A STUDY OF THE MECHANICAL AND MICROCIRCULATORY PROPERTIES IN SKIN SUBJECT TO VENOUS ULCERATION

By

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Abstract

In chronic venous insufficiency (CVI), numerous changes occur in the skin consequent to impaired venous flow. These changes which include oedema, result in the skin being prone to ulceration. The cause of ulceration is not clear, different hypotheses were proposed, but none accepted. Unrelieved oedema is associated with impaired healing. Cutaneous oedema of the lower extremities is produced by a disturbance in the state of near equilibrium that involves capillaries, lymphatics and interstitium. A change in the cutaneous properties is expected with the presence of oedema.

The aim of this work was to investigate changes in the cutaneous mechanical and microcirculatory properties in oedematous tissues. Non-invasive durometry, uniaxial extensometry and laser Doppler flowmetry were chosen for the measurements.

Durometry and extensometry were found reliable. In controls, measurements demonstrated regional variations in the mechanical properties, and differences with age. In the elderly, microvascular response to a minor challenge was impaired, as was the postural vasoconstrictive response.

Studies on patients with CVI (with frank ulcers and without) showed an increase in hardness index and a reduction in both extensibility and relaxation indices. Microvascular response to a minor challenge was impaired but an intact postural vasoconstrictive response was found.

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Dedication

To my parents
For who I am, I owe it to them

Acknowledgement

I am truly grateful to a lot of people whom encouraged me while I was working on the thesis:

All my patients and volunteers, whom without these studies would not be carried out.

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My daughters Rafif, Rahif and Reef who thought the world of their mother.

List Of Abbreviations

The abbreviations used throughout this thesis have been defined when they appear for the first time. Wherever possible the standard abbreviation has been used.

A-mode or A-scan	Amplitude mode
ABPI	Ankle brachial pressure index
ANOVA	Analysis of variance
A.U.	Arbitrary units
B-mode	Brightness mode
C	The speed of wave
C	Velocity of light
C^0	Degrees Centigrade
Conc	Concentration
COP_i	The interstitial fluid colloid osmotic pressures
COP_{pl}	The plasma colloid osmotic pressures
CV	Coefficient of variation
CVI	Chronic venous insufficiency
ECM	Extra cellular matrix
FF	Fluid filtration
F	Female
Fe	Non-time dependent extension force
f_o	Observed frequency
f_s	Frequency of initial beam
Fpeak	Force at maximum extension
Fv	Time dependent extension force
HRT	Hormone replacement therapy
IFP	Interstitial fluid pressure
K	Capillary filtration coefficient
LASER	Light Amplification by the Stimulated Emission of Radiation
LDF	Laser Doppler flowmetry
M	Male
min	minute
MHz	Mega Hertz
MRI	Magnetic resonance imaging

ml	millilitre (10^{-3}) litre
mm	millimetre (10^{-3}) meter
mmHg	millimetre mercury
MSb	The variability between subjects
MSG	Mercury strain-gauge plethysmograph
MSw	The variability within subjects
m^2	meter squared
N	Newtons
NHS	National Health Service
nm	nanometre (10^{-9}) meter
P	Precision
Pa	Pascal
P_a	Arterial Pressure
PC	Personal Computer
P_c	Capillary hydrostatic pressures
Pca	Capillary pressure at the arterial end
Pcv	Capillary pressure at the venous end
P_i	Interstitial fluid hydrostatic pressures
P_v	Venous pressure
PPG	Photoplethysmography
PRG	Phleborheoplethysmography
PUVA	Photochemotherapy with long-wave ultraviolet radiation
RBC	Red blood cell
R	Reliability
r_a	Precapillary resistance
r_v	Postcapillary resistance
ROI	Region of intrest
s or sec	Seconds
sd	Standard deviation
SEM	Scanning electron microscopy
θ	The microvasular barrier reflection coefficient to proteins
T-test	Student T-test
$TcPO_2$	Transcutaneous oxygen tension
TAM	Transmission acoustic microscopy

TEM	Transmission electron microscopy
TWL	Transepidermal water loss
μ or μm	micrometer (10^{-6}) meter
v_o	The vector velocities of the observer
v_{os}	The relative velocity of the source with respect to the observer
v_s	The vector velocities of the source
W	Watt

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Oral Presentations:
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Hammad, L. Roberts, G. Mani, R. Some Effects of Edema on Peripheral Tissues in Patients with Chronic Venous Ulcers. 8th European Tissue Repair Meeting, Copenhagen, August 1998.

Hammad, L. Roberts, G. Mani, R. Tissue Visco-Elasticity Changes with Age and Venous Hypertension. 3rd meeting on Measurements in Wound Healing, Southampton. March 1999.

Posters:
Hammad, L. Roberts, G.H. Mani, R. Shearman, C.P. Uniaxial Extensometry: A Non-invasive Assessment of Tissue Tensile Strength. 1st meeting on Measurements in Wound Healing, Southampton March 1996.

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Hammad, L. & Mani, R. Uniaxial Extensometry and Durometry- Two Techniques of Measuring Some Mechanical Properties of Cutaneous Tissues. 3rd Meeting on Measurements in Wound Healing, Southampton, 1999

Chapter One: Introduction

Venous leg ulcer healing is complicated by oedema (Prasad et al. 1990), which is a symptom not a disease. Oedema occurs as a result of venous hypertension, which in turn disturbs Starlings equilibrium that governs fluid filtration from capillaries resulting in the presence of excess fluid in the interstitium.

1.1 Venous ulcers

Leg ulceration is a common problem that affects 1.5-3% of the population and costs the National Health Service between £230-400 million annually (Effective Health Care 1997). Leg ulcers cause considerable restriction of activities and in some cases loss of employment (Callam et al. 1988). Marchesi (1986) stated that "ulceration results from necrosis occurring as the sequel to cell destruction by toxins and poisons or from interference with blood supply". Dale defined leg ulcer as "Open sore below the knee anywhere on the leg or foot which take more than 6 weeks to heal" (Dale et al. 1983).

The majority of leg ulcers are of venous aetiology, other examples of chronic wounds include diabetic foot ulcers, pressure sores, skin lesions in leprosy or as a consequence of other disorders such as malignancy or infection. Approximately 80-95% of leg ulcers are vascular in origin (Morison and Moffatt 1994), chronic venous hypertension and arterial disease being the principal causes. The association of leg ulcers with venous diseases is strong and ischaemic disease alone or with venous insufficiency account for 20% of total cases of leg ulceration (Effective Health Care 1997). Other causes, which amount to no more than 2-5% of the total, include neuropathy, infection, malignancy, lymphoedema, vasculitis, trauma and self inflicted (Morison and Moffatt 1994).

Venous ulcers are usually oval in shape with sloping edges and appear mostly in the gaiter skin above the ankle joint (Lancet 1982), figure 1.1. They are the sequel of a series of changes in skin and subcutaneous tissues, which include skin thickening, pigmentation and oedema. Browse stated that "venous ulceration is caused by the disorganisation of the microcirculation that is induced by prolonged and unrelieved venous hypertension (Browse, 1986). Venous ulcers are associated with chronic insufficiency (CVI). High venous pressure in the lower extremities, which occurs as a result of valvular incompetence is often associated with deep vein thrombosis (Browse et al. 1988), and superficial and/or deep venous incompetence may lead to ulceration (Cornwall et al. 1986). Occasionally, either developmental abnormalities in the valve or abnormality of the venous wall may result in CVI (Sandeman and Shearman 1999).

Figure 1.1 Venous leg ulcers are usually found in the gaiter region of the ankle.

The cause of venous ulceration is ill understood. Venous stasis was suggested as a cause for ulceration (Homans 1917), but the presence of high oxygen content found in the femoral venous blood taken from limbs with varicose veins led to the rejection of this hypothesis (Blalock 1929). Blalock (1929) concluded that the total blood flow through limbs with venous ulcers was increased, which was supported by other studies (Abramson and Fierst 1942, Piulachs and Vidal-Barraquer 1953). It was suggested that high concentration of oxygen in venous blood in ulcerated legs resulted from "a shunting of blood directly from the arterioles to the venules, largely avoiding the capillary bed" (Holling et al. 1938). The concept of arterio-venous shunting was supported by the reduced time needed for contrast media injected arterially to appear in veins of patients with ulcers (Haimovici et al. 1966), and the increase in the cutaneous temperature which was recorded in the post-thrombotic limbs (Haeger and Berglan 1963). However the increased levels of radioactive labeled-macroaggregates of albumin in the ulcer-bearing skin ran contrary to the arterio-venous shunting concept as a cause of venous ulcer formation (Lindemayer et al. 1972).

Both ulceration and lipodermatosclerotic changes were suggested to result from an alteration in the local capillary bed consequent to calf pump failure (Browse 1986). Increased capillary permeability and concentration of fibrinogen were reported in an animal model of venous hypertension (Burnand et al. 1982, Leach and Browse 1985), as well as in patients with lipodermatosclerosis (Burnand et al. 1981). These led to the proposal that fibrin cuffs that formed around capillaries barred nutrient transport leading to venous ulceration (Browse 1986). Other hypotheses for skin ulceration include oedema around the capillaries barring nutrient transport (Fagrell 1982), white blood cell accumulation in tissues (Coleridge Smith et al. 1988), increased skin tension (Chant 1990) and growth factor traps (Falanga and Eaglstein 1993).

The discontinuity of fibrin cuff around capillaries (Falanga and Eaglestein 1993) and the presence of growth factors in the ulcer fluid (Stacey and Trengove 1999) do not support these two hypotheses as a cause for venous ulceration. The increase prevalence of ulceration in CVI but not in lymphoedema put some doubt on the increase in tension hypothesis, whereas the lack of conclusive link between neutrophil activation and venous ulceration weaken the white cell hypothesis. The absence of a conclusive links between the above hypotheses and ulceration, with trauma being mentioned by many patients as the initial cause of skin breaking suggests the possibility of other causes for ulcer formation.

Venous ulcer is a sequel of CVI, where skin changes follows the increase in venous and capillary permeability and leads to oedema formation. Changes in cutaneous tissues include thickening, pigmentation, induration and later lipodermatosclerosis. The relationship between oedema and these changes is not clear neither is the role of oedema in venous ulceration. Figure 1.2 outline proposed changes in the cutaneous tissues that lead to ulceration.

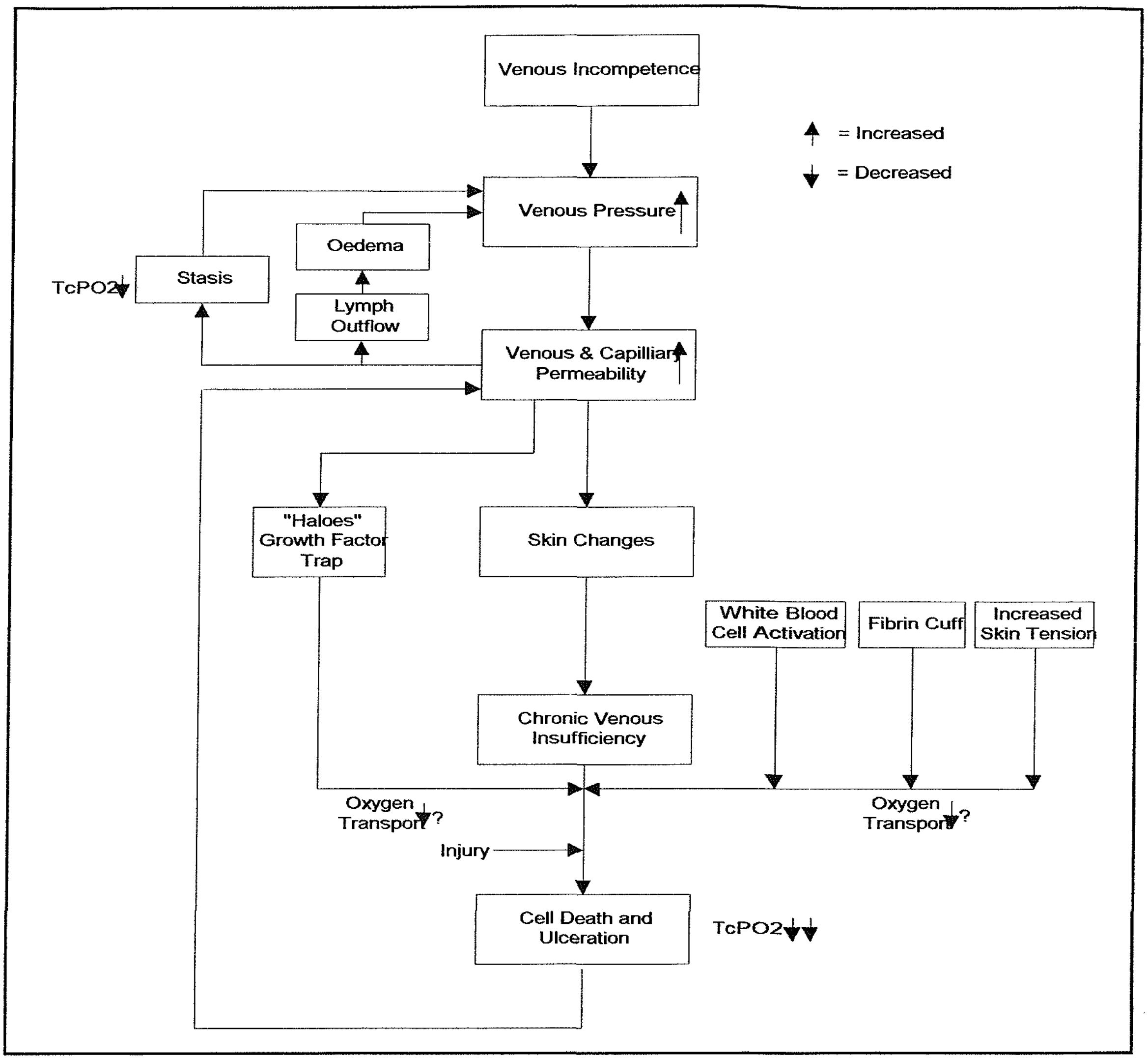


Figure 1.2 Proposed changes that lead to venous ulceration, modified from Mani (1988).

The reduction in TcPO2 around venous ulcers (Mani 1998) suggests decreased oxygen transport, and changes in the cutaneous tissue introduced by the increase in veins and capillaries permeability may contribute to the reduction of TcPO2 and result in the chronicity of the venous ulcer. These changes, which affect the skin and increase its prevalence of ulceration are discussed in the following sections.

1.2 Chronic venous Insufficiency

Chronic venous insufficiency (CVI) is characterised by the impairment of the return of venous blood to return to the right atrium. CVI is caused by calf pump failure, as a result of a combination of superficial venous incompetence, communicating vein leakage or outflow tract obstruction or incompetence (Browse et al. 1988). This leads to oedema, eczema, pigmentation, thickening and fibrosis (lipodermatosclerosis) of the skin of the lower leg, and often ulceration. Although ulceration is related to tissue death, Browse et al. (1988) referred to lipodermatosclerosis and atrophie blanche as "the visible evidence of slow tissue death and replacement with scar tissue".

Other changes reported include dilated and tortuous capillaries both in a canine model (Burnand et al. 1982) and in patients with venous hypertension (Mourad et al. 1989) with increased permeability to large molecules (Burnand et al. 1982). The deposition of fibrin around capillaries in CVI was associated with decreased fibrinolysis, and was suggested as a cause of venous ulceration as stated earlier (Browse 1986). A change in cutaneous extensibility (Mourad et al. 1988) and an impaired control of the microcirculation during standing was found in extremities suffering from CVI (Allen et al. 1988 and Gniadecka et al. 1991). In lipodermatosclerosis a reduction in $TcPO_2$ (Clyne et al. 1985) and an increase in cutaneous hardness was found (Romanelli and Falanga 1995). Gniadecka (1996) found differences in the location of oedema in CVI, cardiac insufficiency and lymphoedema. The presence of oedema in the papillary dermis in lipodermatosclerotic skin as opposed to the reticular dermis in the case of cardiac insufficiency and the uniform distribution in lymphoedema, was suggested to be associated with leg ulceration. Clearly a number of changes occur which may be expected to affect the elasto-mechanicl and microcirculatory properties of tissues at risk of ulceration.

1.3 Oedema

Staub and Taylor (1984) defined oedema as "an abnormal accumulation of liquid in cells, tissues or cavities of the body". Oedema can be acute and/or chronic. Causes of acute oedema include allergic reaction, burns and acute pulmonary oedema following acute left heart failure. Two models for chronic oedema involve lymphatic obstruction and right heart failure. Oedema is categorised by its origin and is used in this thesis to distinguish between different causes of oedema that occur in the interstitial space.

Interstitial oedema could result from any factor that elevates the interstitial fluid pressure above 0mmHg. In the presence of a negative interstitial fluid pressure (IFP), the change in the interstitial fluid volume is minimal (figure 1.3), as a result of Starlings equilibrium, where filtration from capillaries equal absorption by capillaries and lymphatics (Guyton 1981). When the IFP rises from a negative value, the increase in the flow of lymph produces a safety factor to prevent oedema formation (Guyton 1981), if IFP rises to atmospheric pressure a sudden increase in the volume occurs.

An increase in the IFP occurs as a result of plasma protein deficiency (hypoperotenemia), lymphatic obstruction and a disturbance in the vascular system (vasogenic oedema). Hypoproteinemia caused by malnutrition, failure to synthesis proteins in the liver (cirrhosis) and rapid escape of plasma protein from blood (nephrosis) reduces plasma protein concentration, increases net filtration and raises interstitial pressure (Guyton 1981).

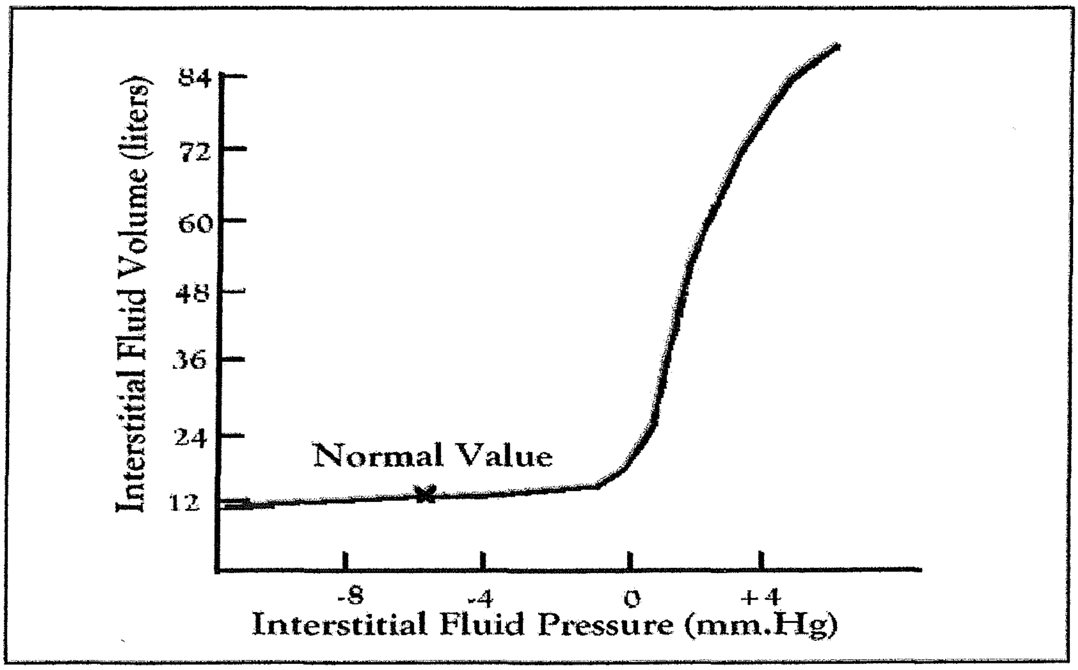


Figure 1.3 Pressure volume curve of interstitial space. After Guyton (1981).

Dysfunction of the lymphatic system results in lymphoedema. Factors which affect the ability of the lymphatic system to collect excessive interstitial fluid and proteins includes physical obstruction of the lumen of existing lymph vessels as in filariasis, incompetence of the segmented valve and destruction of lymph vessel or nodes following mastectomy. In addition paralysis of lymphatic smooth muscle, reduced tissue motion, elevated after load with venous hypertension and congenital defects would affect the ability of the lymphatic system to collect excess fluid and proteins.

Vasogenic oedema involves alteration in the intravascular Starling force and a change in the characteristics of the microvascular barrier (Guyton 1981). Capillaries are narrow vessels that connect arterioles and venules. The primary function of capillaries is to permit the exchange of nutrients and waste between the blood and tissue cells. Starling stated that under normal conditions a state of near equilibrium exists at the capillary membrane, whereby the amount of fluid filtering outward through the arterial end of capillaries equals the quantity of fluid returned to the circulation by absorption at the venous end of capillaries. If the near-equilibrium between forces at the capillary membrane is changed, a disturbance in fluid filtration will either produce an increase in filtration or absorption, and the rise in filtration will be balanced up to a limit by lymphatics, beyond which, fluid starts accumulating in tissues.

Capillary hypertension and inflammation are the initial insults that lead to the formation of such oedema. Capillary hypertension originates from increased venous or arterial pressures, arteriolar dilation, venous constriction or venous obstruction. The most common cause of vasogenic oedema is venous hypertension, since any rise in arterial pressure is counter balanced by the high pre to post capillary resistance ratio, which produces minimal increase in transcapillary fluid filtration, figure 1.4.

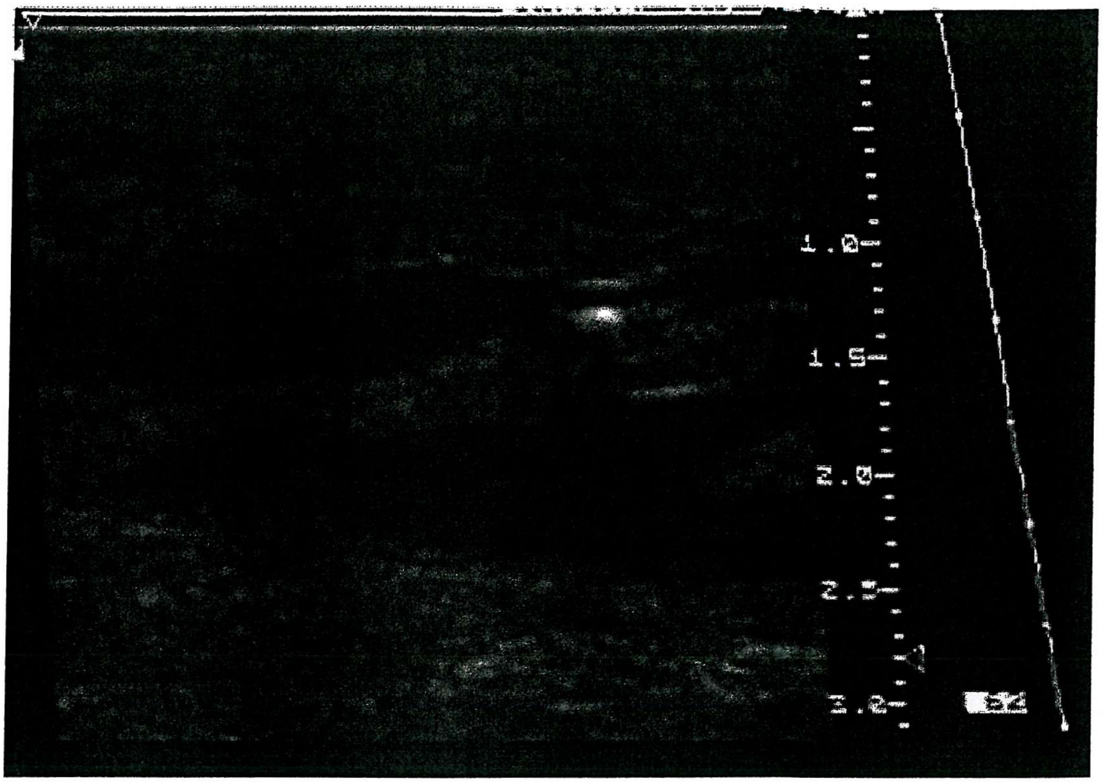


Figure 1.4 A sonographic image of oedema in the gaiter region of the ankle in patient with CVI using 7.5MHz ultrasound probe. Hypoechoic areas in the image are pockets of oedema both in superficial and deeper areas.

Conditions which affect capillary pressures, include left heart failure resulting in pulmonary oedema, retention of fluid by kidneys, right heart failure, chronic venous insufficiency and deep vein thrombosis. Inflammation occurs in tissue in response to injury, whether it is caused by bacteria, trauma, chemical insult and heat, it involves the release of vasoactive chemicals such as histamine and bradykinin which alter vascular tone and endothelial porosity (Sparks et al. 1984). It results in the rapid formation of interstitial oedema due to a reduction in arterial resistance, dilation of arterioles and precapillary sphincters, and an increase in interstitial volume and matrix hydration.

Clinically oedema is classified subjectively and graded in a scale of 1 to 4, a scale of +1 suggests that oedema is barely detectable and +4 means the extremity has swollen to 1.5 to 2 times normal volume. In the case of chronic oedema, tissue expands with ease allowing severe oedema to develop at lower atmospheric pressure i.e. +4 oedema occurring at 0.0 mmHg instead of class +1. The phenomenon is called delayed compliance or stress-relaxation of the tissue space, figure 1.5 (Guyton 1981).

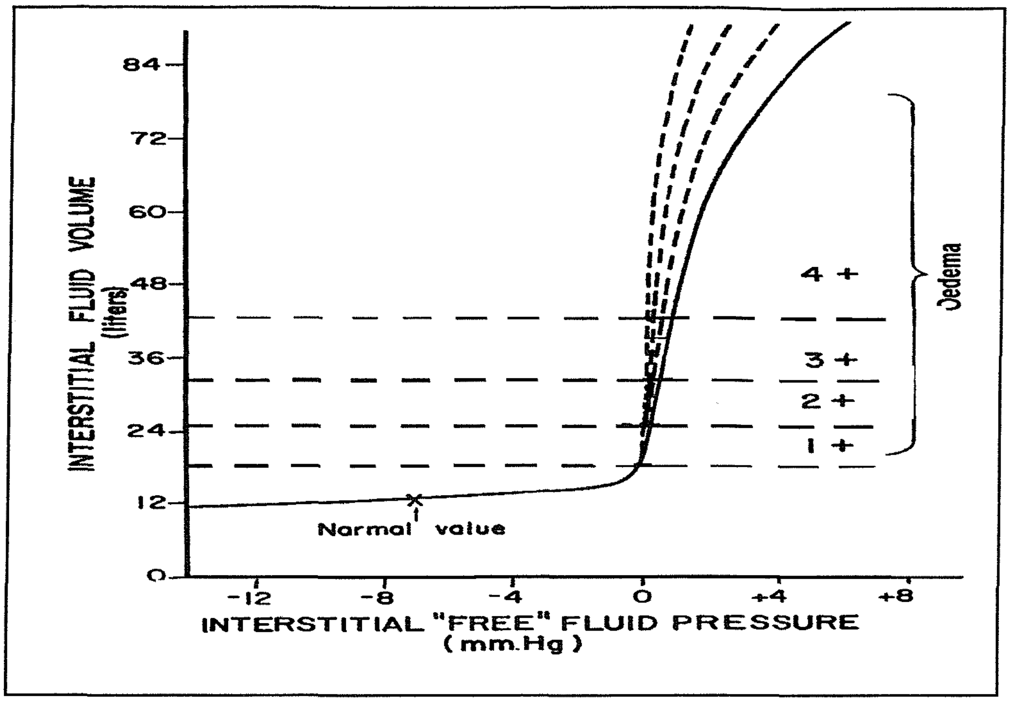


Figure 1.5 The effect of prolonged oedema on the pressure-volume curve of the interstitial space. After Guyton (1981).

In the presence of excess fluid in the interstiitium, which consists primarily of fibers (collagen and elastin), polysaccharides, structural glycoproteins and ground substance (Comper 1984), the gel, which forms the ground substance of the interstitium, traps any excessive amounts of fluid and starts to swell. Once the gel has swollen more than 30% to 50%, the entanglements of the glycoproteins begin to break up and free fluid develops which form channels in the tissue allowing fluid to flow freely, thus causing pitting oedema. In the case of trauma or infection, the free fluid coagulates forming non-pitting (brawny) oedema. Clinically, oedema is assessed by the extent of pitting caused by finger pressure. Objectively, tape measurement of the circumference of the leg can be used and yields clues to swelling. Water displacement plethysmograph measures changes in limb volume and was used to show effects of elevation (Mowbray 1989). Tissue electrical impedance, was used to measures the change in the conductive properties following oedema removal (Wheeler et al. 1972 and Barnes et al. 1992). Veraart used infrared photosensors to detect the outline of limbs (Varaat and Neumann

1992). The above techniques measure gross changes in limb volume without assessing the location.

More advanced methods such as ultrasound and magnetic resonance imaging (MRI) were used to locate and quantify oedema (Querleux et al. 1988b, Gniadecka 1995, Gniadecka and Quistorff 1996). In the cutaneous tissues, excess fluid was found to accumulate beneath the epidermis Querleux et al. 1988b and Gniadecka 1996), measurement of dermal oedema using high frequency ultrasound had a good correlation with the relative fat/water content obtained using magnetic resonance spectroscopy (Gniadecka and Quistorff 1996). After comparing ultrasound with MRI, it was suggested that ultrasonography was preferred for reasons of high sensitivity, resolution and resources effectiveness (Querleux, 1988b and Gniadecka 1996). Gniadecka reported an association between venous ulceration and the location of oedema, as oedema was located in the upper dermis in lipodermatosclerosis compared to lower dermis in cardiac insufficiency and a uniform distribution in lymphoedema (Gniadecka 1996).

1.4 Skin

The skin is the heaviest single organ of the body, accounting for about 16% of total body weight and displaying in adults 1.2-2.3 m^2 of surface to the external environment. The skin forms a protective barrier against bacterial invasion, dehydration and harmful light rays. In addition, it helps to maintain homeostasis by thermoregulatory secretory activity providing an important route for the transmission of information about the external environment and prevents excessive loss of inorganic and organic compounds.

Skin structure and thickness varies widely in different areas of the body. It is composed of an epithelial layer, (the epidermis), ectodermal in origin, and a layer of connective tissue of mesodermal origin, (the dermis). Beneath the dermis lies a loose connective tissue that contains a pad of adipose cells, (the hypodermis or subcutaneous tissue) which although not considered part of the skin, binds skin loosely to the subjacent tissue. Epidermal derivatives include hair, nail, sebaceous and sweat glands, figure 1.6. Two major types of solid structure are present in skin. These are Type I collagen, which endows tissue with tensile strength and structural stability, the other being glycoproteins which are composed of approximately 98%

hyaluronic acid and 2% protein. In addition to collagen, elastin forms the other fibrous components of skin, although less abundant than collagen.

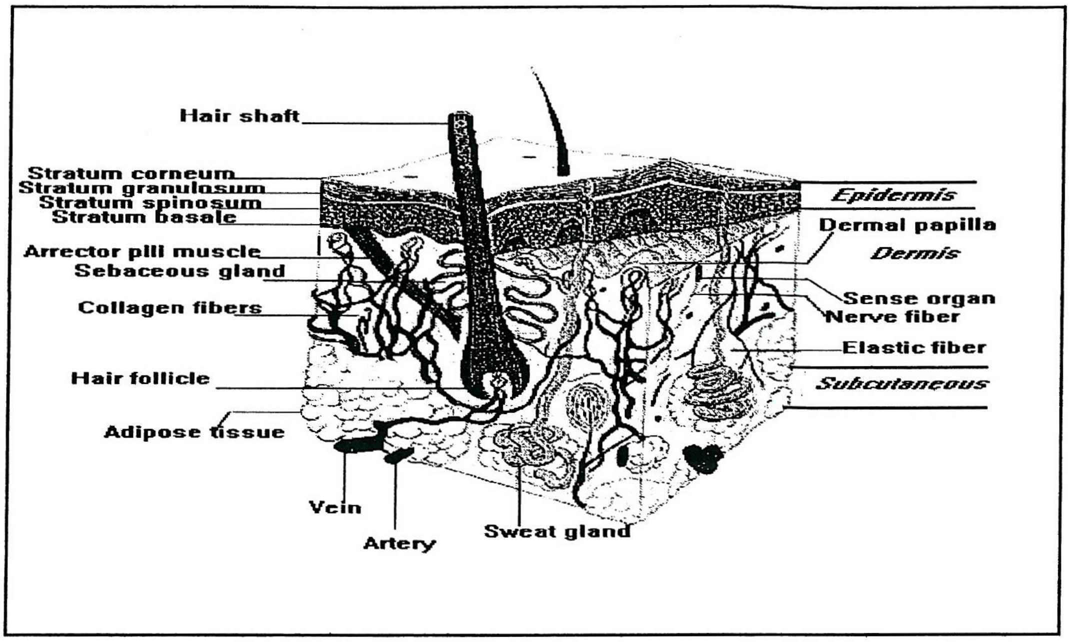


Figure 1.6 Skin Structure. After Miller-Keane (1992).

The epidermis consists mainly of stratified squamous keratinized epithelium, keratinocytes, and three less abundant cell types: melanocytes, Langerhans's cells and Merkel's cells, which are responsible for skin colour, processing cutaneous antigens to lymphoid cells present in the epidermis, and which serve as sensory mechanoreceptors respectively. From the dermis outward, the epidermis consists of five layers. Stratum basale and Stratum spinosum are related to as the germinative layer responsible for the constant renewal of epidermal cells. Stratum granulosum contain lamellar granules that act as a barrier to penetration by foreign material, stratum lucidum is present in thick skin only and stratum corneum consists of 15-20 layers of flattened non-nucleated cells whose cytoplasm is filled with keratin.

The dermis is composed of two distinctive layers, the outermost papillary layer and the deeper, reticular layer. It contains connective tissue, which supports the epidermis and binds it to the subcutaneous tissue with a very irregular surface, having many projections (dermal papillae) which project into the concavities between the epidermal ridges. These projections are believed to reinforce the dermal epidermal junction. The papillary dermis is composed of loose thin connective tissue with thin bundles of collagen and elastin fibers. Special collagen fibrils (anchoring fibrils) insert into the basel lamina providing the binding method between dermis and epidermis. The reticular dermis is composed of a thick, irregular and dense connective tissue with more fibres and fewer cells than the papillary layer. It comprises interlaced collagen fibers (mainly type I collagen) which display a waviness with a network of supporting elastin fibers. The waviness of the collagen fibers and the elastin become gradually thinner toward the papillary dermis (Junqueira et al. 1989).

The cutaneous nerves have efferent autonomic fibers that supply the smooth muscle of hairs, blood vessels, sweat and sebaceous glands, together with afferent somatic fibers of general sensation. The lymph vessels of the skin form a plexus at the junction of the dermis and the superficial fascia. This plexus receives finger-like vessels from the papillae, which drains into lymph vessels, which accompany the superficial arteries and veins. The structure of the vascular bed of the skin varies considerably from one area to another in the human body. In most areas, blood enters the skin through small arteries penetrating the subcutaneous tissue. One small artery branches into several precapillary arterioles, which divide into terminal capillary loops located in every skin papilla. Veins and venous plexuses form the network, which transports blood from the skin to the heart, figure1.7.

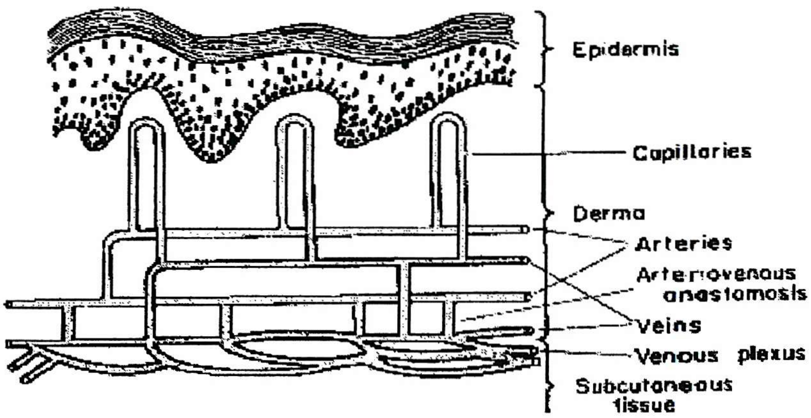


Figure 1.7 The cutaneous vascular system. After Guyton (1981).

Circulation through the skin serves two major functions: first, body temperature regulation, which takes approximately 85% of total blood flow to the skin. Secondly, skin nutrition served by the usual nutritive arteries, capillaries and veins. Vascular structures concerned with heating the skin consist principally of (a) venous plexuses which hold large quantities of blood that can heat up the surface of the body and (b) arterio-venous anastomoses that allow the blood to be shunted from the arterioles to the venous plexi. The arterio-venous anastomoses are found principally in the volar surfaces of the hands and feet, the lips, the nose and the ears, which are areas of the body most often exposed to maximal cooling.

The flow required to regulate body temperature changes markedly in response to the rate of metabolic activity of the body and the temperature of the surroundings. Under normal cool conditions the blood flow to the skin is about 400ml/minute in the average adult. This can decrease to as little as 50ml/minute in severe cold or it can increase to as much as 2.8litre/minute if the skin is heated to maximum vasodilation. The amount of blood, which flows through the skin, is controlled by nervous mechanisms. The temperature control centre of the hypothalamus produces vasoconstrictor and vasodilator mechanisms. The vasoconstrictor effect is due to the secretion of norepinephrine from the sympathetic vasoconstrictor fibers, which keeps the arterio-venous anastomoses totally closed and control the amount of flow in the nutritive vessels. The basic mechanism, which activates vasodilation, is not clear, although maximum blood flow through the skin is associated with sweating, which suggests that the secretion of acetylcholine from the sympathetic fibers to activate sweat glands have a vasodilating effect (Guyton 1981). Local control of skin blood flow is demonstrated mainly when pressure is applied to the skin. A hyperaemic effect is noted due to the increased flow to that area balancing the diminished availability of nutrients to the tissue during the duration of the force (Guyton 1981).

Changes occur in cutaneous tissues with age, with the presence of pathology and with the application of treatment. As the average life expectancy increases, cutaneous ageing occurs among other changes, which affect our body tissues. Aged skin is characterised by dryness, roughness and wrinkles, and unfortunately these changes among other body changes result in the elderly being prone to ulceration (Effective Health Care 1997) and delayed wound healing (Bolognia et al. 1993).

Cutaneous ageing involves one or two of the following three processes, chronologic (intrinsic) ageing, actinic (extrinsic) damage and hormonal influence. Intrinsic ageing is a direct process of age and genetic factors, it is mainly confined to sun-protected area and characterized by cutaneous atrophy (Kligman et al.1988) with the loss of elasticity (Gilchrest, 1982), slowed metabolic activity and no evidence of inflammation (Lavker 1995).

The extrinsic process or photodamage occurs as a result of chronic exposure to ultraviolet radiation (UVR). Although it involves hypertrophy due to the inflammatory mechanism initially, severely photoaged skin may be even more atrophic than equally aged sun-protected skin. Photodamage is responsible for the more profound cutaneous alteration such as roughness, hyperpigmentation, thickened epidermis with increased melanogenesis, twisted and dilated microvasculture, laxity and deep wrinkles as a result of massive elastosis and collagen degeneration (Gilchrest and Yarr 1992). Histological and biochemical studies revealed that while intermolecular cross-linkage of collagen fibers increases with age as well as by UVR irradiation reducing the solubility of collagen in aged skin, a significant increase in glycosaminoglycans is attributed mainly to photodamage (Miyachi and Ishikawa 1998). Microscopic studies demonstrated that deep wrinkles on sun-exposed areas, which do not disappear with stretching are slightly protected from solar elastosis which affect surrounding tissues and maintain them as permanent wrinkles (Tsuji et al. 1986).

In women, hormonal ageing, as a result of postmenopausal oestrogen deficiency, is considered the third contributor to the process of ageing. It seems that hormone replacement therapy (HRT) have a role in the treatment of this type of ageing, as HRT was found to reverse the reduction in skin thickness and to limit the growth of facial hair (Vaillant and Callens 1996).

1.5 The aims of the thesis

From the literature, different hypotheses were proposed to explain the causes of venous ulceration, but the absence of a conclusive link between these hypotheses and skin ulceration, weaken these hypotheses.

The role of oedema in venous ulcers is not clear, careful study of the wound healing literature revealed that oedema complicates ulcer healing (Prasad et al. 1990). Oedema is a symptom of CVI, and the presence of oedema is thought to occur not only from a disturbance in the macrocirculation but as well as from changes in the microcirculation (Allen et al. 1988). Although the presence of extra fluid in the skin changes cutaneous viscoelasticity, the relationship between oedema and other skin changes which accompany CVI had not been clarified.

The aims of this study were: to identify suitable methods of measuring relevant mechanical and microcirculatory changes in the skin, and to use these methods to examine effects that are associated with chronic vasogenic oedema.

Chapter Two: Techniques available for the assessment of the cutaneous properties

2.1 Techniques for assessing the structure and composition of cutaneous tissues

Skin differs greatly in structure, composition and appearance from site to site. The state of a person's wellbeing is reflected on skin appearance, such appearances may be affected by diseases. Techniques for assessing skin appearance include the non-invasive photography and surface impression (Fasc et al. 1964) through indirect methods such as the use Harpenden callipers and radiography for measuring cutaneous thickness (Shuster 1975 and Lawrence and Shuster 1985). Invasive methods depend on histological examination of tissue samples and, biopsies, using at first light (Pearce and Grimmer 1972) and later electron and scanning acoustic microscopy methods (Quaglino et al. 1996 and Kolosov et al. 1987). Recently ultrasonography, ultrasound backscatter microscopy and magnetic resonance imaging (MRI) were used to obtain information from the cutaneous tissues non-invasively (Murakami and Miki 1989, Turnbull et al. 1995 and Querleux et al. 1988b).

2.1.1 Skin surface impression

The demand for urgent treatment of burns inflicted during the Second World War, which coincided with the developments in plastic surgery, renewed interest in research of skin surface characteristics. Fasc et al. (1964) devised a system to be used as the base for different replica techniques, which used acetone-soluble film, laid on a glass slide, with high adhesive properties. The film was attached to the skin until it dried, later it was carefully and evenly removed. Marks and Dawber (1971) used ethyl cyanoacrylate, which adheres firmly to both the skin and the glass slide in the presence of small quantities of water, to obtain not only a surface pattern but also a specimen of stratum corneum. The skin replicas were inspected, photographed and later examined either with light or with electron microscopy. Photographic enlargement demonstrated the geometric pattern of skin creases, which vary with site, and allowed the relatively inelastic stratum corneum to accommodate for deformation up to a limit (Schellander and Headington 1974).

Ferguson and Barbenel (1981) investigated the relationship between surface patterns and directional extensibility of skin. Surface impressions were taken using silicone rubber before and during uniaxial extension while a suction device was employed to assess the extensibility and the anisotropic behaviour of cutaneous tissues. They demonstrated, that the grooves and ridges within the surface where responsible for the functional epidermis reserve that allowed the epidermis to stretch prior to stretching or disturbing the epidermal cells. A relationship was found between skin extensibility and the degree of folding of the epidermal surface.

Quan et al. (1997) applied measurement of skin surface roughness assessment in addition to other techniques to differentiate between photodamage and ageing in human skin non-invasively. Skin roughness impressions were made using silicon rubber and a profilometer. A difference in skin roughness between young and old subjects and a difference between sun-exposed and sun-protected sites in the older group was found, with the increase in roughness related to chronological ageing.

2.1.2 In-vitro assessment of cutaneous structure and composition

Thickness measurements from fixed tissues were subject to errors from shrinkage and distortion resulting from the fixing process. The conditions under which samples were studied also influenced results, it was suggested that early measurements of skin thickness were erroneously high (Kligman 1969 and Whitton 1973).

Light microscopy was used to measure thickness and changes due to age and pathology, but the advent of electron microscope demoted the use of the former. Brown used scanning electron microscopy (SEM) to study fibrous arrangement in human skin (Brown 1971). Although SEM magnification (X100,000) was less than transmission electron microscopy (TEM) (X1, 000,000), the ability to examine thicker specimens ~20μm compared to the 100nm used for the latter, and the relatively simple preparation needed, allowed the study of fibrous arrangement in strained skin specimens. Brown measured an increase in the size of reticular dermal fibers which was attributed to age. Extending the skin resulted, in flatting the epithelial layer initially followed by epidermal cell elongation and the straightening and later alignment of the dermal fibers. Quaglino et al. (1996) examined the influence of age, sex and body region on various dermal structures and reported a slow increase in the size of collagen bundles and loss in the functional properties of elastin, due to an increase in fibers size with age.

Acoustic microscopy was used in two modalities to examine tissues in vitro. In transmission acoustic microscopy (TAM) an ultra thin sample was placed between two transducers. Kolosov et al. (1987) who examined human skin and mouse liver, using 450MHz TAM, found the stratum corneum to be highly attenuating compared to the malpighian layer, with a variation in attenuation in the dermis attributed to different dermal components. Barr et al. (1991) examined different neoplastic and cutaneous inflammatory tissue specimens using reflective acoustic microscopy at 600 and 800MHz crystals, the ultrasound waves being reflected by a 6μm sample. In the different types of tumours studied, specific diagnosis was possible, inflammatory conditions were more puzzling.

Light scattering was used to measure the size and orientation of collagen bundles (Ferdman and Yannas 1993). Light passing through a narrow slit will undergo diffraction. The narrower the width of the slit relative to the wavelength of light, the wider the range of angles into which the light is diffracted. Helium neon laser was used as the light source with the bundles of collagen acting like narrow slits scattering light between 1° to 6°. Birefringence is another technique to examine collagen bundles optically. It relies on shining polarised light on a thin sample of tissue, rotating the sample through set stages and using image processing to estimate the orientation and crimping of collagen bundles (Ho et al. 1996).

2.1.3 Non-invasive assessment of cutaneous structure and composition

Techniques such as soft tissue radiography (Meema et al. 1964), pulsed ultrasound (Allexander and Miller 1979) and MRI (Querleux et al. 1988b) are non-invasive methods of measuring thickness in vivo. Ultrasound backscatter microscope was able to yield data on different cutaneous layers (Turnbull et al. 1995). Although ultrasound was used to examine tissue structure and thickness, the ability to investigate the mechanical behaviour of tissues is one of its potentials (Parker et al. 1989).

Shuster et al. (1975) used radiography and biochemistry to examine dermal thickness and composition respectively, demonstrated a direct relationship between skin collagen and dermal thickness, a reduction in collagen with age and reduced collagen quantities in females. The authors proposed that the variation in collagen density would limit the use of dermal thickness as a measure of collagen content in diseases.

The first reported study on the use of ultrasound in measuring skin thickness was published by Alexander and Miller (1979), which highlighted the simplicity as well as inherent accuracy of the method. They compared A-scans with X-rays measurements of skin and showed a very good correlation between the two methods. Tan et al. (1981 and 1982) examined the potential of using A-scan measurements to grade skin thinning resulting from cortisteriod therapy, and found a good correlation between ultrasound values and Xeroradiography. The studies also showed that age and sex affected skin. It was found that ultrasound and radiographic measurements of thickness were lower than values obtained with histology, which was attributed to the loss of skin tension in-vitro (Tan et al. 1982).

Rukavina and Mohar (1979) reported the use of ultrasound imaging to study deep skin tumours with the help of a commercial ophthalmic scanner, the results lead to the development of B-scan imaging using a plastic film transducer. Miyauchi and Miki (1983) identified the importance of such cutaneous acoustic parameters as velocity before using ultrasound. Lawrence and Shuster (1985) compared ultrasound with Harpenden callipers to measure skin thickness, and found that ultrasound yielded consistently lower values. The higher values obtained by callipers were attributed to subcutaneous fat not easily separated using the latter.

Serup (1984a, b, c, d, and e) studied changes in skin thickness in different skin disorders using A-scan ultrasound at 15MHz. In the acrosclerosis study, he showed the advantages of ultrasound for the measurement of skin-phalanx distance for diagnosis (Serup 1984a). In patient with morphoea, measurements of the pigmented spot thickness, with no sign of scleroderma, he demonstrated relative and absolute reductions in values compared to control sites (Serup 1984b). In the sclerotic plaques, an increase in thickness was found when compared to regional controls (Serup 1984c). Serup studied allergic reaction (Patch-testing) using A-scans with laser Doppler flowmetry and suggested that ultrasound could identify weak reaction as a relative increase in thickness (Serup 1984d). The same author reported that using ultrasound to quantify the skin-prick histamine weals added an extra dimensional information especially in small and medium size weals (Serup, 1984e).

Hoffmann et al. (1992a) studied malignant melanomas by assessing thickness and density using 20MHz B-scan mode and compared values with histology. They reported a significant correlation between the methods although ultrasound over-estimated the thickness. This discrepancy was attributed to the presence of sub-tumour inflammatory infiltrates and other hypo-echoic structures in the region of tumour. Edwards (1984) described the construction of an ultrasonic instrument for the measurements of different cutaneous layers thickness using A-scan and B-scan in his PhD thesis. He presented a method for calculating acoustic impedance for stratum corneum and the epidermis from the amplitude of the reflected echoes. Edwards proposed the method for initial assessment as well as diseases progress. The same authors characterised skin tumours, basal cell carcinoma (BCC), dermatofibromas and hypertrophic scars (fibrosis), moles, and intraepidermal epitheliomas (IEE), using different A-scan parameters such as amplitude, density, regularity of echoes, and amplitude of echoes beneath the tumour (Edwards et al. 1989).

Querleux et al. (1988a) developed a 25MHz ultrasonic scanner, B-scan images were produced later from A-scans that were digitised, processed, and stored in electronic memory. With an axial resolution of less than 0.1mm, they were able to identify different parts of the dermis. Later they compared sonographic images with images taken from a modified 0.1 Tesla MRI system (Querleux et al. 1988b), and concluded that shorter acquisition times made ultrasound the better technique for localising different skin components. Although, the authors favoured ultrasound as a technique for investigating cutaneous structure and related changes, they identified MRI for biochemical and physiological studies.

Richard et al. (1993) examined the water content of different skin components and the effects of age using MRI. In both young and old subjects and within the sun-protected area, different skin components could be differentiated, epidermal mobile water was found to be at least twice as abundant as dermal mobile water. In the aged group, an increase in the amount of total water content of the dermis was found and was related to the increase in the mobile water of the upper dermis in elderly. Gniadecka and Quistroff

(1996) assessed in-vivo dermal water using high-frequency ultrasound and MRI, a good correlation between the two techniques was found in the forearm of healthy volunteers, but higher values were obtained in the presence of histamine-weals using ultrasound compared to MRI.

Murakmi and Miki (1989) used 25MHz and 40MHz B-scanner to examine different skin components. They identified the Malpighian layer of the epidermis as an echolucent zone beneath a strongly echogenic linear corneo-malpighian junction in normal palms and soles. Turnbell et al. (1995) used acoustic microscopy to examine the skin in vivo. They demonstrated the ability to investigate not only skin tumours but non-malignant cutaneous disorders as well. Ultrasound has also been used for monitoring and investigating different wound healing models to measure wound thickness, re-epithelialization, formation of granulation, and the rate of healing (Turnbell et al. 1995).

Goans et al. (1977) used 3MHz and 13MHz A-scans to measure burn depth in-vivo in porcine skin immediately post burn and up to 14days later using 1720m/sec as the velocity of ultrasound in porcine skin. From the A-scans, they could identify the necrotic-viable tissue interface, which was confirmed by histology. They recommended ultrasound for the determination of early excision and skin grafting of deep dermal and full thickness burns (Goans et al. 1977). In an animal model, Brink et al. (1986) examined the possibility of measuring burns depth in-vitro. The burn-adjacent tissues interface could be identified, with a significant correlation between ultrasound measurement and histology. In a human model, Pugliese et al. (1992) used punch biopsy to create wounds in 15 volunteers, and calculated the volume of each wound using wound depth, internal, and external diameter from ultrasound images. They demonstrated the delay in wound healing in aged skin. Cryosurgery which is used for the treatment of malignant epithelial tumours, was used as a model for wound healing (Hoffmann et al. 1992b and 1993), with the ultrasound being used to calculate the volume of the tumours, which was essential for determining the freezing temperature, and number of freezing cycles.

Cutaneous changes occur with age and include thinning loss of elasticity, laxity and pigmentation. Sonographic examination of the cutaneous tissue of the elderly, described the presence of a sub-epidermal low echogenic band (De Rigal et al. 1989, Hoffmann et al. 1991, 1992a and Gniadecka et al. 1994d, 1994e). With age, an increase in the size of the band, which was related partially to photoageing due to its prominent appearance in the dorsal aspect of the forearm was found (De-Rigal et al. 1989). They suggested that the presence of the band was due to the reduction of the sup-epidermal elastic plexus, which caused fragmentation and clumping of fibers in the upper dermis. By relating low echogenic pixels obtained from ultrasound images of the cutaneous tissues to the amount of water present, Gniadecka et al. found an age-related diurnal change of the dermal fluid content (Gniadecka et al. 1994d and 1994e).

Oedema was demonstrated as an increase of the size of the subepidermal low echogenic band in lipodermatosclerosis (Gniadecka 1995). This band expanded during the day, the expansion was reversed with the application of leg compression. Gniadecka (1996) also demonstrated that oedema was located in the upper dermis in the lipodermatosclerotic skin, compared to lower dermis in cardiac insufficiency and a uniform dermal distribution in lymphoedema.

2.2 Techniques available for measuring the mechanical properties of skin

Skin acts as a mechanical barrier between the interior of the body and the outside world, but is required to glide and stretch during body movement and the resistance to mechanical force is necessary. The skin exists under tension in the in-vivo environment and the ability to resist mechanical forces is different between different sites and direction and is found to be dependent on rate of loading. In addition, the return of skin to a pre-strained position, after the removal of load is time dependent.

Different techniques were used to examine the cutaneous mechanical properties. Principally, a load is applied to the skin and either the resistance or the cutaneous creep or relaxation was measured. Cutaneous creep measures the change in length in response to a pre-determined load and relaxation measures the load require to stretch skin to a given length (Millington and Wilkinson 1983).

2.2.1 Indentation test

Spheres and flat discs were used as indentors to compress skin and either the force or recovery time were measured and related to skin stiffness. Christensen et al. (1977) used an indentor to measure the stiffness of skin, which was influenced by hydration. An indentor was used to examine skin hardness in scleroderma (Falanga 1995), lipodermatosclerosis (Romanelli and Falanga 1995) and chronic venous insufficiency (Le Blanc et al. 1997). In scleroderma and lipodermatosclerosis, results suggest a relationship between the skin severity score and the hardness measurements (Falanga 1995, Romanelli and Falanga 1995). Whereas the presence of oedema in CVI, had no significant effect on cutaneous hardness (Le Blanc et al. 1997).

2.2.2 Torsional test

The test involves the application of a torque parallel to the skin surface and measuring the resultant deformation. This technique allows the quantification of several parameters such as immediate extensibility and recovery, viscoelastic deformation, elastic recovery, creep and relaxation time (Escoffier et al. 1989) but does not account for skin anisotropic characteristics (Payne 1991).

Leveque et al. (1980) studied in-vivo, the effects of age and sex on skin extensibility using a device to apply a torque. Results indicated a maximum skin thickness around the age of forty, a decrease in extensibility with age, with female skin being less extensible than that of males. Leveque's results were in accord with the findings of Quaglino et al. (1996), who used electron microscopy to evaluate the ultrastructure of the dermis and observed a reduction in collagen with age, though sex difference were minimal. De Rigal and Leveque (1985) used the same technique to measure stratum corneum extensibility in vivo. They demonstrated an increase in skin extensibility with hydration, attributed to an increase in stratum corneum contribution, with the effect of a moisturiser on the cutaneous mechanical properties, being temporary.

Escoffier et al. (1989) using ultrasound and torsional force on the ventral forearm, showed that skin maintained its thickness and extensibility up to the seventh decade as opposed to its elasticity, which decreased from an early age. In addition skin thickness was significantly different between sexes.

2.2.3 Suction test

The application of a negative pressure (suction) to create a central displacement is the principle of the suction device. Both in-vitro and in-vivo biaxial measurements of skin properties may be tested. Sample preparation and storage for in-vitro tests should be considered where skin specimens are likely to dehydrate at room temperature (Jansen and Rottier 1958). The skin has a 'memory' for previous mechanical loading and so the smallest possible forces should be used in excising the skin and removing the subcutaneous fat. The inability of the suction cup to identify or quantify anisotropy as uniaxial extension resulted in the application of a pre-tensioning device which eliminated skin tension in-vivo (Alexander and Cook 1977).

The shape of the skin under suction is dependent on the aperture geometry. With a circular aperture; a spherical cap is produced (Cua et al. 1990). In vivo tensile testing with the suction device demonstrated a marked age dependency as the magnitude of the elasticity decreased with age (Gniadecka et al. 1994b, Cua et al. 1990 and Takema et al. 1994). Cua et al. (1990) attributed the change found with age to the alteration in the elastic fiber network. Takema et al. (1994) investigated elastic properties and thickness of human skin using suction and A-mode ultrasound. They reported a decrease in the ventral aspect of the forearm skin thickness with age, by comparison a significant increase was found in the skin over the forehead. In addition, skin elasticity was found to decrease with age in both sites, as a result of chronological and photoageing. Gniadecka et al. (1994b) reported an increase in elasticity around the ankle region in young volunteers compared to aged controls. They argued that the presence of diurnal variability in distensbility and elasticity in young persons only, suggests poor compensation for gravitational stress in the elderly. Cua et al. (1990) highlighted the variability in elastic properties between different body regions using suction. However, the difference between the sexes were not statistically significant for most regions (Cua, 1990).

The possibility of visualising tissue displacement with suction was examined by Diridollou et al. (1998), the system comprised a suction device built within an ultrasound scanner. With suction, fluid filtration was found in the subcutaneous area. This was suggested to contribute to the loss of skin recovery when returned to atmospheric pressure and confirmed the non-elastic nature of the skin. They concluded that the major contributor, in the case of suction, to the cutaneous resistance is the dermis.

2.2.4 Tissue elastography

Sonoelastography is a technique based on the principle that by exciting an object with a known vibration, structures with different stiffness within the object will respond with different motion based on their shape, homogeneity and density (Parker et al. 1989). These motions are displayed as a map of relative stiffness of the imaged area. The technique, which is in its infancy, has the potential to detect early changes in tissue observed in tumour development (Varghese and Ophir 1998a and 1998b, Kallel et al. 1998).

2.2.5 Extension test

Uniaxial and biaxial measurements of skin may be performed in-vitro or in-vivo. This test requires specimen to be longer than the grips of the tester for uniaxial tests and the reverse for biaxial tests. For in-vitro studies and as in the suction test, conditions under which measurements are taken should always be stated, since similar difficulties of specimen collection, storage, and preparation are encountered in this form of testing, as this would affect the measured properties. Results obtained from in-vitro tests are not comparable with in-vivo measurements, since excised skin is no longer in the same state of tension, nor is it affected by the presence of interstitial fluids or the attachment to the underlying tissue.

However, Vlasblom (1967) showed that for small deformations in the plane of the skin in-vivo, the contribution of the subcutaneous tissue is relatively unimportant. Thus, uniaxial and torsional measurements may be considered to determine these properties of the dermis. Factors affecting tests in-vivo, include the attachment area, type of adhesion, force applied on the skin by the instrument weight, body position, skin anisotropy and most importantly, the device should not cause discomfort or permanent damage.

Kenedi (1964), Forrester et al. (1969) and Daly and Odland (1979) described three regions in a non-linear stress-strain curve obtained from an in-vitro uniaxial skin extension. Daly and Odland (1979) proposed that, the three different phases were related with the alignment of different fibers. The first phase was associated with a very large strain at low stress, controlled by the fine network of elastin fibers in the dermis. An intermediate region (second phase) was thought to arise from the random network of collagen fibers beginning to align in the direction of the applied stress. In the third phase, all the fibers were involved but little deformation occurred. The age related changes did not present themselves in the dermal collagen fibers stiffness (third phase) but in the loss of elasticity (first phase).

In a study of the mechanical properties of both human and rabbit cutaneous tissues in-vitro, Pan et al. (1998) examined changes in the acoustic properties induced with the application of transverse stress. While both cutaneous creep and stress relaxation processes were classified as logarithmic function, Young's modulus was found to increase logarithmically with strain and linearly with stress. The ultrasonic attenuation coefficient decreased with an increase in strain, leading to an improved penetration and signal strength observed in B-scan. A significant increase in the backscatter coefficient as a function of strain was only observed at 30MHz, such findings suggested that the reorganisation of cutaneous fibers may occur at a scale smaller than the ultrasound wavelength used. No change in the speed of sound with increasing strain was observed, although it demonstrated a tendency to increase with age.

Gunner et al. (1979) demonstrated using uniaxial extension, a difference in thickness and extensibility between normal skin and skin with severe atrophy consequent to steroid therapy. The effect of Prednisolone on skin extensibility was found to be non-significant whereas. Whereas preliminary results had demonstrated that photochemotherapy with long-wave ultraviolet radiation for psoriasis treatment showed trends of decreased extensibility (Gunner et al. 1981). Mourad et al. (1988) investigated cutaneous mechanical properties in the gravitational syndrome using a modified version of the Gunner extensometer. They characterised the extension phase with two parameters, a non-time dependent extension force (Fe) and time dependent extension force (Fv). Fv exhibited a statistical significance attributable to the change in skin stiffness consequent to pathological changes. During the relaxation phase, a statistical significance was present in the time constant of the time dependent force between the groups, and a good correlation with the clinical index for disease severity.

Quan et al. (1997) used uniaxial extensometry, ultrasound and skin surface roughness in addition to clinical and histological assessments to differentiate between photodamage and chronological ageing. A decrease in skin thickness was found in the elderly compared to young group. The loss of skin elasticity was related to photodamage more than chronological damage, the difference between the elderly and the young group was statistically significant in both sun-exposed and sun-protected sites (Quan et al. 1997).

2.3 Techniques available for measuring the skin microcirculation

In patients with CVI, oedema forms as a result of the disturbance in the Starling equilibrium, which effects filtration, and absorption in the microcirculation. Direct measurements of cutaneous blood flow include radioactive techniques through to measurements of reflected laser light using the Doppler principle. Indirect techniques measure changes in the filtration rate.

2.3.1 Radioisotope studies

Radioisotope clearance measurements of cutaneous blood flow are done by injecting a bolus of isotonic saline labelled with radioactive substances usually Xenon (Xe^{133}), Iodine (I^{125}) or Technetium (Tc^{99m}) dermally and studying its uptake by blood. The exponential decay (clearance) of the radioactivity from the site or organ is measured by either a scintillating counter or a gamma camera and is an accurate measure of local blood flow (Sejrsen 1968). The technique was used to study subcutaneous blood flow in both extremities during positional changes and exercise (Nielsen et al. 1988). A reduction in the flow in both extremities was found when the head was tilted up while the body remained in the supine position, while leg exercise at nearly erect position increased the flow within the lower extremity. In addition, a vasodilatory response was noted in the thigh and calf region in response to the change in metabolic rate. Bendtsen et al (1992) devised a miniature silicon diode matrix detector capable of detecting not only low Gamma energy but as well, X-ray radiation, for the measurements of cutaneous washout of Xe^{133}. The increased sensitivity and the ability to detect geometry changes, was suggested to be an advantage during exercise, where motion artefacts increase. This method is quantitative but with hazards from radiation. In addition, serial or repeated tests are rarely possible.

2.3.2 Capillaroscopy and fluorescence videomicroscopy

Capillary microscopy uses a low magnification microscope attached to a video camera to visualise blood flow in the dermal capillaries (Fagrell et al. 1977). The advancement in the optical field lead to the introduction of fiberoptic video microscopy to evaluate cutaneous capillaries, through the use of optical sensors attached by a flexible fiberoptic system connected to a TV monitor (Thulesius 1992). Tooke et al. (1983) measured blood flow in the nailfold area and reported a positive correlation between capillary blood cell velocity and laser Doppler output. But the presence of a reduced fall in laser Doppler output after venous occlusion compared to capillary blood cell velocity resulted in the authors suggesting the ability of the laser Doppler to measure blood flow in deeper vessels.

The intravenous injection of a fluorescent dye, Na-fluorescein, provided a method to quantify transcapillary and interstitial diffusion and to depict lymphatic microvessels. However, an anaphylactic reaction after dye injection limited its uses in human studies (Bollinger 1986) Although capillaroscopy provided a non-invasive assessment of individual capillaries, it required total immobilisation of the measured site and proved to be time consuming, minimising its use.

In chronic venous insufficiency a reduction in capillary density was suggested to contribute to the pathogenesis of leg ulceration (Allen et al. 1988). Variations in capillary density found within the ulcer area and adjacent tissues were suggested to reflect the state of tissue healing (Gschwandtner et al. 1999). As low capillary density was found in the in non-granulating areas compared to areas with granulation, and the presence of higher number of capillaries in non-ulcerated skin both adjacent and distant to the ulcer.

2.3.3 Plethysmography

Plethysmography detects the change in the dimension of the limb induced by the change in vascular volume. A variety of transducers have been used to detect such changes including mercury strain-gauge (MSG), photoplethysmography (PPG), phleborheograph (PRG), water and air plethysmography.

MSG was used to measure temporal changes in circumference in response to small stepped changes in applied pressure (Michel and Moyses 1987 and Gamble et al. 1992 and 1993). Changes in vascular compliance occur first and are distinguishable from a slower change attributed to tissue compliance. Mason and Giron (1982) measuring calf volume changes during treadmill exercise found less reduction in leg volume in patients with moderate-to-severe obstructive venous outflow compared to patients with minimal or no obstruction.

When the technique was applied during exercise and with elevation with and without occlusion, a good correlation with invasive ambulatory venous pressure and with ascending and retrograde venography was found (Schanzer et al. 1984). Roberts et al. (1986) assessed the reproducibility of the technique in volunteers at rest and after exercise, and suggested the ability of the technique to monitor pathological changes through serial measurements. An increase in capillary filtration and calf blood flow were found in the presence of deep venous thrombosis, attributed to the presence of a local inflammation process which was suggested to over-rule the increase in venous pressure and contribute to oedema formation (Seem and Stranden 1990). When the effect of long term bed rest , 42 days 6^{o} head-down, on venous hemodynamics was assessed in controls using MSG with venous occlusion, alteration in the leg vascular compliance was found as a result of impairment of venous emptying capacities and arterial flow (Louisy et al. 1997).

Photoplethysmography is an optical technique that relies on detecting the backscattered or reflected light to measure instantaneous changes in the blood supply to the skin (Hertzman 1938). PPG and PRG record the changes in blood volume but not the outflow when multiple pneumatic cuffs are placed on the thigh, calf and foot. Limb volume fluctuations are recorded during respiration and during compression of the foot or calf. In the presence of venous thrombus, limb volume did not decrease significantly distal to pneumatic compression (Barnes 1982).

Water displacement plethysmography was used to demonstrate an increase in foot swelling after eight hours of sitting (Noddeland and Winkle 1988). Although the increase was present in both active and immobilised foot, the rate of swelling was significantly higher in the inactive foot. Whereas Mowbray (1989), found a reduction in leg volume in both controls and patients with CVI after elevation associated with a decreasing trend of $TcPO_2$ and increasing trend in blood flow.

Impairment in the venous hemodynamics, which manifests itself as an increase in venous filling index and the residual volume fraction in addition to a reduction in the ejection fraction, was found in acute lipodermatosclerosis (Greenberg et al. 1996). Results suggested that both chronic and acute lipodermatosclerosis had an underlying venous pathology. Van-Geest et al. (1998) using air plethysmography found a reduction in capillary filtration rate, 6 weeks after stripping the greater saphenous vein due to insufficiency. The reduction in the filtration rate was suggested to reflect an improvement in the microcirculation. When the effect of lymphoedema on venous dynamics was examined, Kim et al. (1999) found an increase in the ambulatory venous pressure, venous volume and venous filling index and a decrease in ejection fraction in the affected leg. The change in the venous return, in lymphoedema was suggested to aggravate soft tissue oedema. Yang et al. (1999) found an improvement in the calf muscle pump function with exercises in patients with CVI demonstrated as an increase in the ejection fraction and a decrease in residual fraction despite the absence of changes in venous reflux.

2.3.4 Laser Doppler flowmetry (LDF)

A laser light is delivered to the skin and the backscatter is returned to a detector by optical fibers. Light reflected from RBC, which is Doppler shifted, is detected and processed to give an output in millivolts or arbitrary units which is linearly proportional to RBC flux. The RBC flux is related to the product of average speed and concentration of moving red blood cells in the tissue sample volume. Laser Doppler flowmetry is an established technique, used to examine changes in the cutaneous dermatology (Hughes et al. 1987) and pharmacology (Murrell and Taylor 1959).

The major drawback of the LDF is the variation in the RBC flux from comparable sites between individuals, from different sites in the same individual, and even from the same site in the same individual at intervals of hours, days, and weeks (Tenland et al. 1983). Other factors influencing measurements include skin temperature, mental activity and psychological state (Berardesca et al. 1991).

Braverman et al. (1990) investigated the effect of the probe position on the RBC flux and the flux wave pattern and found a correlation of these two elements with the type of microvascular element beneath the probe. High flux pulsatile patterns were found at areas with ascending elastic arterioles and their immediate branches in the centre. Low flux with pulsatile flow patterns with minimal or no vasomotor activity at areas above the edge of an elastic arteriole and low flux with a non pulsatile pattern at areas composed of primarily capillaries and post-capillary venules. Tooke et al. (1983) assessed human skin circulation at rest, following the release of arterial occlusion and during venous occlusion using LDF and dynamic capillaroscopy. Results displayed certain significant differences despite broad comparability in the pattern of responses recorded by the two techniques. These differences were related to the ability of the LDF to record blood flow in deeper blood vessels as well as to the superficial nutritional capillaries.

Hughes et al. (1987) compared point thermometry, LDF and ultrasound Doppler against biopsy to determine the malignant nature of the cutaneous lesions. They demonstrated a significant difference in blood flow measured with LDF, between benign and malignant lesions.

Hassan et al. (1986a, 1986b, 1988 and 1990) used LDF to investigate the postural vasoconstrictive response in the human foot studying the effects of such stimuli as indirect heat, combined oral contraceptive and the menstrual cycle on the response. They proposed that the response is triggered by a local neurogenic mechanism with some contribution from a local myogenic response, in addition to a centrally elicited sympathetic component (Hassan et al. 1988). A diminished response in the feet of volunteers was found with indirect heating, combined oral contraceptive and during the luteal phase of the menstrual cycle. It was suggested that indirect heat resulted in the partial release of sympathetic vasoconstrictor tone, which over-rode the postural control of vascular tone. This response was reported to be diminished in patients with CVI (Allen et al. 1988 and Gniadecka et al. 1991) and in the elderly controls (Gniadecka et al. 1994a). It was proposed that this impairment would predispose oedema formation.

Sindrup et al. (1987) showed a significant increase in LDF flux in skin surrounding venous leg ulcers. An abolished response and preserved vasomotion was found in patients with sickle cell anaemia, which prevented infarction by allowing the passage of stiff sickle RBC (Gniadecka et al. 1994c). Measurements of reactive hyperaemia following a certain period off arterial occlusion, was used to distinguishing between patients with peripheral arterial obliterative disease and controls (Kvernebo et al. 1989).

The laser Doppler imager permits microcirculatory flow studies without physical contact with tissues and sampling larger areas. The technique has a potential in burn depth assessment (Niazi et al. 1993) and in the studies of cutaneous allergic reaction and inflammation (Clough and Church 1997). Despite the variation in the LDF flux within and between individuals effecting its reproducibility, the technique offers a simple approach to measure capillary blood flow. Minimal patient preparation and the absence of side effects are some of the advantages that resulted in the popularity of the technique for measuring cutaneous blood flow.

Although this section is devoted to laser Doppler flowmetry, the use of ultrasound for the measurements of microcirculation, which is still in its infancy, will be briefly mentioned. Christopher et al. (1996 and 1997) devised a continuous-wave 40MHz ultrasound Doppler system for the measurements of cutaneous blood velocity and later a pulsed-wave 50MHz Duplex ultrasound system was capable of detecting blood flow of 5mm/s in arterioles and venules.

2.4 Measurements of transcutaneous oxygen tension ($TcPO_2$)

Oxygen diffuses out of the cutaneous capillaries into the interstitial space and surrounding skin cells. Some of this oxygen undergoes cellular metabolism, while the rest is distributed throughout the skin, which gives rise to a " cutaneous oxygen tension" (Rooke 1992).
The amount of oxygen that reaches the surface of skin reflects the difference between oxygen delivery from blood capillaries and consumption. Skin surface measurements of oxygen, transcutaneous oxygen tension ($TcPO_2$) is measured using a modified Clarke electrode. The sensors detect a current generated at the cathode consequent to the breakdown of free oxygen molecules during chemical interaction with hydroxyl ions in an aqueous electrolyte (Huch et al. 1973).

$TcPO_2$ was used to assess the severity of peripheral arterial disease (Batay-Csorba et al 1987). In patients with claudication, $TcPO_2$ was low and severely decreased in patients with ischemia at rest compared to normal extremities (Ohge et al. 1981). Predicting tissue viability was another clinical application of $TcPO_2$. The ability to predict flap viability and amputation level is established as $TcPo_2$ above 40mmHg predicts healing and viability (Rooke 1992). In the presence of venous ulcer, $TcPo_2$ at the ulcer edge was low compared to identical sites on controls (Mani et al. 1989), an increase in $TcPo_2$ was found with the ulcer in the healing phase (Klori et al. 1988). Mani (1995) proposed that, there could be a resistance to oxygen diffusion in patients with CVI and oedema may be "a resistive element". Mani's suggestion was based on the increase in $TcPO_2$ when oedema is removed from ulcerated leg by bandaging or elevation.

2.5 Transepidermal water loss (TWL)

The stratum corneum acts as a water store, water enters by absorption from the environment which is related directly to ambient relative humidity, by diffusion from the dermis and by lateral movements from the helically coiled distal tubules of sweat glands (Steinmetz and Adams 1981). In the absence of profuse sweating and high humidity, TWL refers to the rate at which water migrates from the viable dermal tissues through the layers of stratum corneum to the external environment (Miller et al. 1981). This approach was used to study causes of dry skin (Cardillo and Morganti 1994), the restoration of barrier function in wounded skin (Malten and Thiele 1973) and in the evaluating of occlusive properties of topical preparation (Berube and Berdick 1974).

Direct measurements of TWL involve the use of flow hygrometry, to measure the water vapour concentration over a fixed area of skin in the presence of a flowing gas stream (Aly et al. 1978). Other indirect method involves measuring the relative change in the amount of water vapour in a defined volume of air, in contact with a fixed area of skin (Miller et al 1981). Water is present in the skin in two states: either as 'free' water (available to dissolve electrolytes), which accounts for about 20% of the water in the skin or 'bound' water (not available to dissolve electrolytes), which accounts for 80% of the total water stored (Yates 1971).

2.6 Techniques used in this thesis

From the study of the literature presented above, it was apparent that oedema increased tissue pressure, which in turn might affect the elasto-mechanical properties of skin. The effects of unrelieved oedema on tissue perfusion were not clear.

To examine changes in the cutaneous elasto-mechanical properties, durometry and extensometry were selected. The presence of oedema introduces change in cutaneous properties such as hardness, described clinically as induration. The durometer is a non-invasive and non-destructive technique used to measure hardness of a sample and the instrument will be used in this thesis to examine changes in cutaneous hardness associated with the presence of oedema.

With the presence of excess fluid in tissue, changes in cutaneous viscoelasticity occur. Cutaneous viscoelasticity is dependent on composition and thickness, both thought to be affected by the presence of oedema, being clinically manifested as an increase in thickness and induration. Uniaxail extensometry is a non-invasive technique capable of measuring skin extensibility and relaxation, both related to viscoelasticity.

It was suggested that in CVI, cutaneous oedema occur as a result of disturbances in the macrocirculation and the microcirculation environments (Burnand et al. 1981 and Mourad et al. 1989). The increase in capillary numbers and permeability found in CVI would aggravate oedema presence, but seems unable to promote ulcer healing and suggest some deficiency in tissue perfusion (Sindrup et al. 1987). From the different techniques available to examine the cutaneous microcirculation, laser Doppler flowmetry was selected to be used in this thesis, the technique will examine the microcirculation during the application of a minor stimulus (cutaneous stretching with the extensometer) and to study the postural vasoconstrictive response. The advantages of the technique lay in the ability to use the LDF during uniaxial extensometry and to monitor a specific region of interest during and after movement (passive leg lowering)., in addition to the minimum patient preparation required.

The techniques used to examine the mechanical properties of skin and its microcirculation were selected for their availability and non-invasiveness. The reproducibility studies and the measurement protocols are described in the succeeding chapter. All work reported on controls and patients were done after obtaining prior Ethics approval, and informed consent.

Chapter Three: Techniques and the measurement protocol used in this thesis

3.1 Durometry: Assessment of skin hardness

3.1.1 Equipment

Durometers are used in the non-destructive hardness measurement of rubber, plastic and other non-metallic materials. A durometer, Model 1600, type 00 (Rex Gauge company, IL) was used for the measurement of skin hardness. The 1600 model has a spring-loaded indentor and a circular dial, type 00 is recommended for use with light foams, sponge rubber gels and animal tissues. Its 35mm diameter foot-plate provides a large contact area. A standard 226gm weight was used to apply a constant load. The total weight of the instrument including the standard weight used was 416gm. A rubber block was used to check the calibration of the durometer before use. Figure 3.1 shows this durometer.

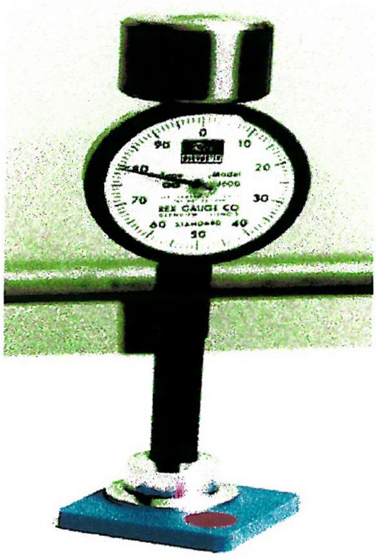


Figure 3.1 The durometer, Rex Gauge company ™, Model 1600, type 00 was used for skin hardness measurements. The foot-plate and standard weight were used to improve repeatability of the measurements. The blue rubber block was used as a reference for the calibration.

The force (Newtons) required to indent the skin using the durometer was calculated using equation 3.1 supplied by the manufacturer for type 00 durometer (Appendix 1).

$$\text{Force (N)} = 0.203 + 0.00908H_{00} \quad \textbf{Equation 3.1}$$

Where H_{00} =hardness reading on type 00 durometer

3.1.2 Skin hardness measurement protocol

Skin hardness measurements with the durometer were done on the forearm and the gaiter regions of the ankle. Subjects were resting in the supine position with the shoulder in a 45^0 abduction position with the elbow joint in an approximately 100^O extension, the hips were adducted and test leg externally rotated through 45^0. The extremity under examination was supported in position using a pillow made of polystyrene beads. The room temperature was controlled between 21-24^{0}C in an environment free from draught and noise, figure 3.2.

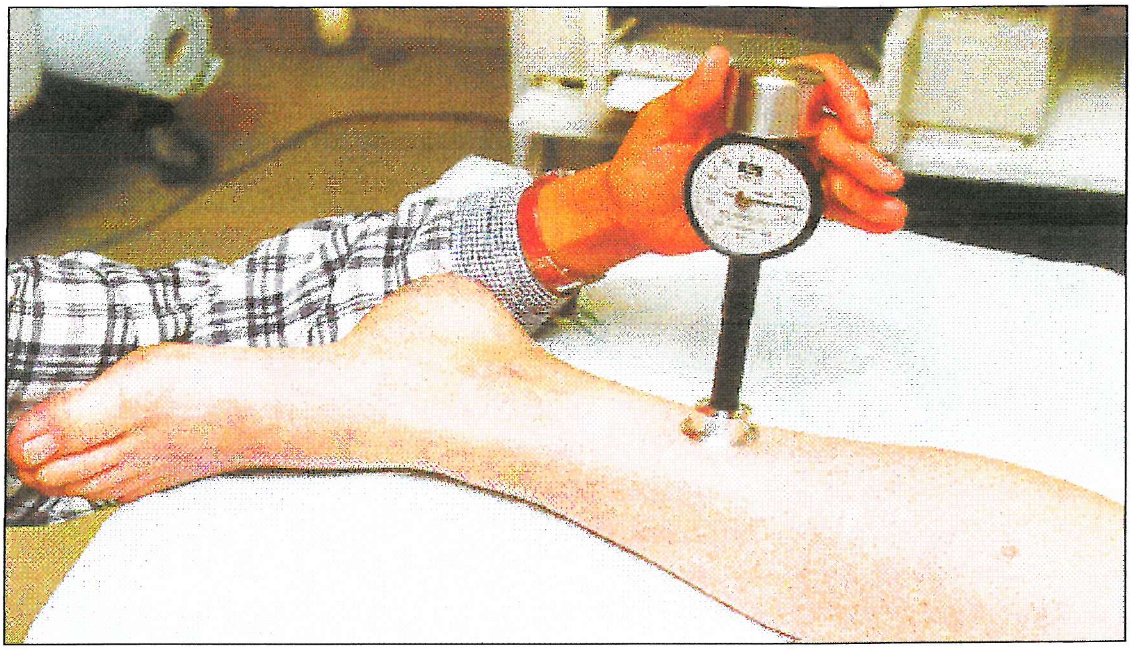


Figure 3.2 Skin hardness measurements in the gaiter region of the ankle, 10cm above medial malleolus, the leg is externally rotated and supported using a pillow made of polystyrene beads. The hardness measurements were obtained with the durometer resting on the area by gravity.

In the gaiter region of the ankle, three sites were chosen for hardness measurements, 5cm and 10cm superior to medial malleolus and midway between the medial malleolus of the ankle and the medial condyles of the tibia. On the volar aspect of the forearm, measurements were made at three locations, 5cm and 10cm inferior to the antecubital fossa and midway between the antecubital fossa and the wrist joint, as depicted in figure 3.3. When in use, the durometer was rested on the skin without exerting any external force.

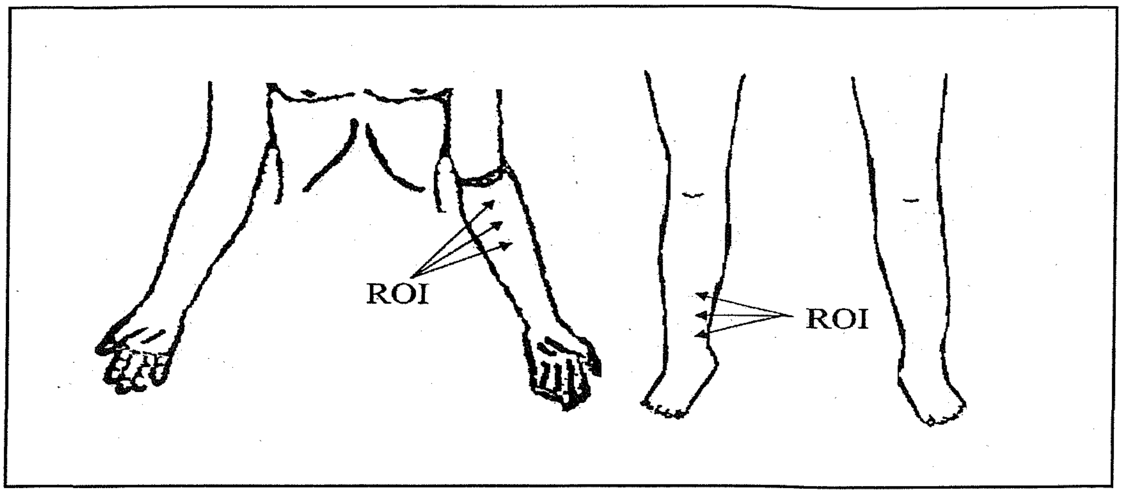


Figure 3.3 Regions of interest (ROI) used for measuring cutaneous hardness within each extremity

Durometry values were expressed initially as cutaneous hardness (Newtons) and later as hardness indices. The indices were derived by dividing data obtained from the three leg regions by data obtained from the three sites in the forearm, table 3.1.

Hardness Indices	Derived from cutaneous hardness (Newtons) measured at :
1	5cm superior to medial malleolus/ 5cm inferior to the antecubital fossa
2	10cm superior to medial malleolus/ 10cm inferior to the antecubital fossa
3	Midway between the medial malleolus of the ankle and the medial condyles of the tibia/ midway between the antecubital fossa and the wrist joint

Table 3.1 Deriving hardness indices from cutaneous hardness (Newtons) measured in the forearms and legs.

A hardness index is a ratio of skin hardness obtained in the leg to forearm, used to examine the effect of age, sex and disease on hardness in the absence of a method to examine skin thickness and its contribution to cutaneous hardness.

3.1.3 Reproducibility studies on asymptomatic controls

The biomechanical properties of cutaneous tissues were examined extensively in the in-vitro environment. With new in-vivo techniques being introduced, it is essential to examine the properties of the new technique, with an aim to understand the sources of variation and errors. These properties include the validity, variability and the reliability of the technique. The validity of a new technique is calculated by comparing it with established technique (gold standard) (Altman and Bland 1983). Variability of a technique, investigates sources of variation, "true biological variation" as well as measurements errors, and temporal variation (Coltan 1974). The true biological variation refers to "all factors that tend to make one individual different from other" while measurement error refer to "all factors that tend to produce differences with different measurements of the same phenomenon". Temporal variation relates to "all factors that produce variation in observation within an individual from one time to another" (Coltan 1974).

In clinical measurements, the first two sources of variation are examined by replicate measurements, where measurement error may be determined from within subject variability and true biological variation from between subjects variability, although it contains a component of measurement error (Coltan 1974). The coefficient of variation for the technique, related to the degree of spread of series of observation is calculated (Coltan 1974). The reliability of the technique is calculated from the component of variance due to random error plus the component of variance due to error-free variability between subjects (Fleiss 1986).

Aim

To assess the repeatability in the performance of the durometer.

Method

7 asymptomatic volunteers (3M, 4F, age ranges 27-50, mean age 38.6 years) with no known skin or peripheral vascular disorders were studied. The protocol described earlier in section 3.1.2 was used and the measurements were repeated at the same time of the day on five consecutive days.

Statistical analysis

The variability within (MSw) and between (MSb) subjects were examined using the analysis of variance test (Anova-test) (Coltan 1974). The coefficient of variation of the technique (CV) was also calculated, (Coltan 1974).

$$\mathrm{CV} = \frac{SD}{mean} * 100 \qquad \textbf{Equation3.2}$$

The reliability R composed of variance due to random error (σ_e^2), plus the component of variance due to error-free variability between subjects (σ_T^2), was also calculated, equation 3.3, (Fleiss 1986).

$$R = \frac{\sigma_T^2}{\sigma_T^2 + \sigma_e^2} \quad \text{..................................} \textbf{Equation 3.3}$$

Results

Variability within and between subjects and the reliability for the six locations tested are presented in table 3.2. With the individual measurements presented in appendix 2.

Location	Within subjects (MSw)	Between subjects (MSb)	Significance	Coefficient of Variation %CV	Reliability R%
5cm inferior to antecubital fossa	2.750E-04	57.42E-04	P < 0.001	6.78	79.56
10cm inferior to antecubital fossa	4.829E-04	137.6E-04	P < 0.001	6.91	84.67
Mid forearm	9.908E-04	358.8E-04	P < 0.001	8.64	87.58
5cm superior to medial malleolus	7.844E-04	50.06E-04	P < 0.001	6.97	51.85
10cm superior to medial malleolus	4.676E-04	109.3E-04	P < 0.001	5.27	81.64
Mid leg	4.434E-04	243.3E-04	P < 0.001	5.55	91.57

Table 3.2 Within and between subject variances and reliability of the durometer technique in the measurement of skin hardness.

Variability between subjects was greater than that within subjects in both forearms and legs.

3.2 Uniaxial extensometry: assessment of cutaneous tissue extensibility and relaxation

3.2.1 Equipment

A Cutech extensometer was used to apply a uniform extension to the skin in-vivo. The extensometer arms, one fixed and the other movable, where driven apart by means of a motor driven lead screw, at a controlled rate of 37.5% in 8 seconds, figure 3.4. The extension rate was based on previous work, which suggested that in-vivo stretching of

10mm in length skin sample a further 3-4mm was not uncomfortable for subjects and provided reasonable limit for comparison (Gunner et al. 1979).

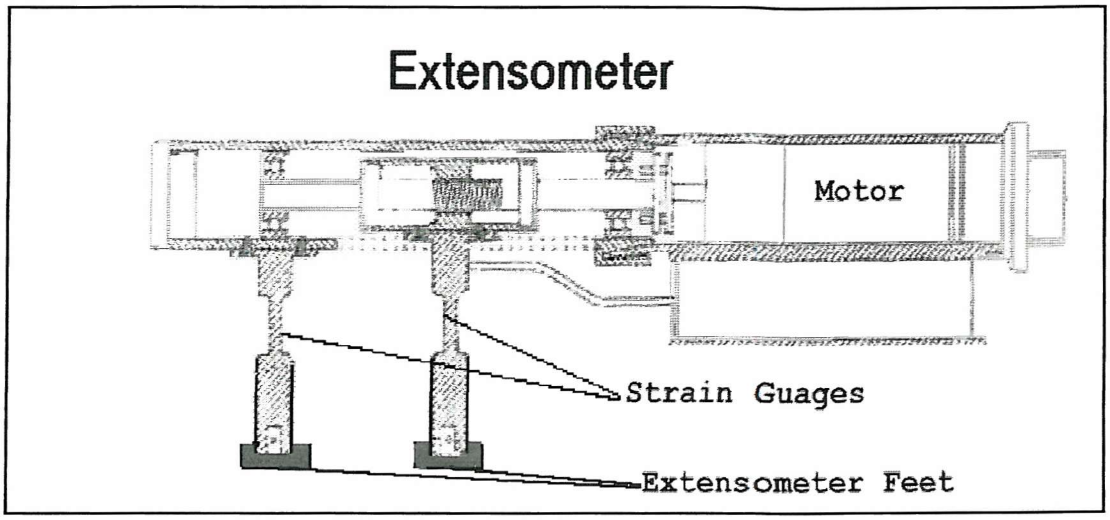


Figure 3.4 A diagrammatic scheme of the extensometer. The movable extensometer arm (nearer to the motor) is driven by a motor, at a controlled rate of 37.5% in 8 seconds and the force exerted during uniaxial extension is measured by a pair of strain gauges bonded to each of the arms.

The extensometer feet were glued to the surface of skin using cyanoacrylate adhesive and held parallel to the surface plane taking care to avoid either pressure or suction. The instrument was held in position by a retort clamp, figure 3.5.

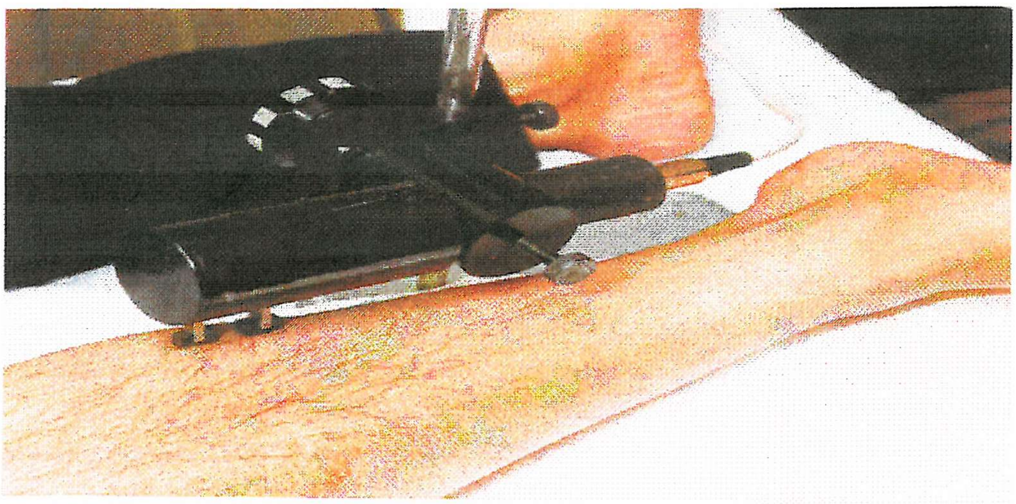


Figure 3.5 Uniaxial extensibility/relaxation measurement on the medial aspect of the leg. The extensometer feet were glued to the skin using cyanoacrylate adhesive, without applying pressure or suction.

The force exerted on the skin during uniaxial extension was measured by two strain gauges bonded to each of the arms. Data was acquired and stored in a personal computer (PC) using an analogue to digital converter, figure 3.6.

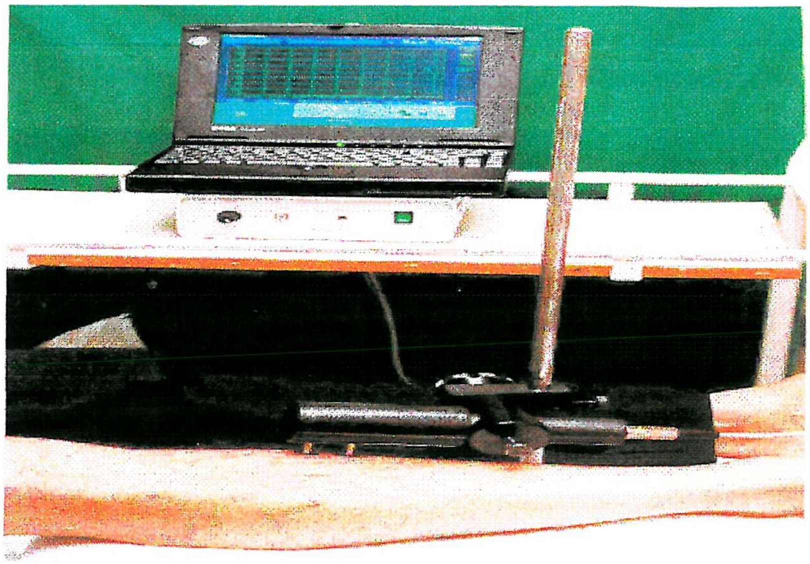


Figure 3.6 The extensometer and data acquisition system.

3.2.2 Extensometer calibration

The extensometer was calibrated using a standard weight of 502 gram attached to one extensometer arm where 1gm force is equivalent to 1mV, figure 3.7. The calibration was done daily.

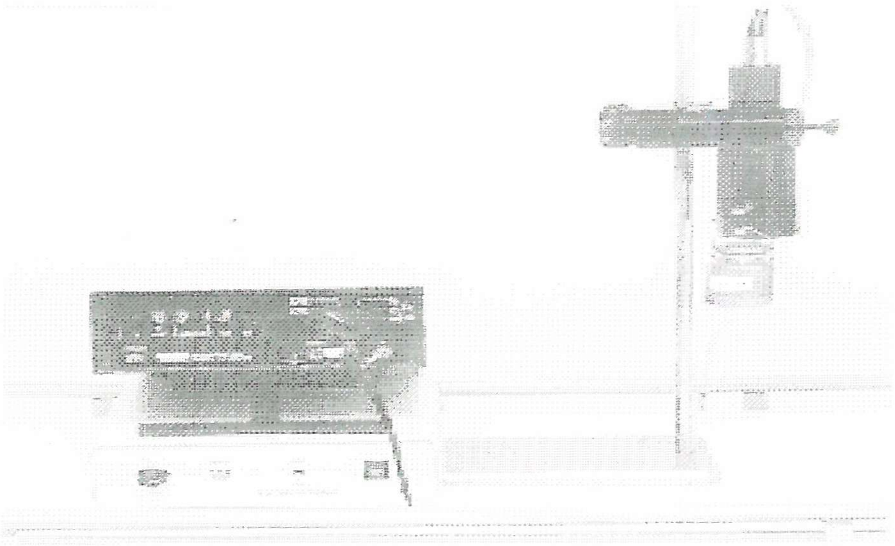


Figure 3.7 Calibration of the extensometer output, a 502gm weight is equivalent to 502mV output.

3.2.3 The extension protocol

Subjects were resting in the supine position with the shoulder in a 45^0 abduction position with the elbow joint in a 100° extension and supported in position with a pillow made of polystyrene beads. When measurements were conducted in the gaiter region of the ankle, the hips were adducted and test leg externally rotated through 45^0 and supported using the same pillow Skin sites were shaved when necessary, cleaned and degreased. Once dry, the extensometer feet were attached using cyanoacrylate adhesive. The skin over the gaiter region of the ankle, midway between the medial malleolus of the ankle and the medial condyles of the tibia, and the volar aspect of the forearm, 5cm inferior to the antecubital fossa, were studied, figure 3.8.

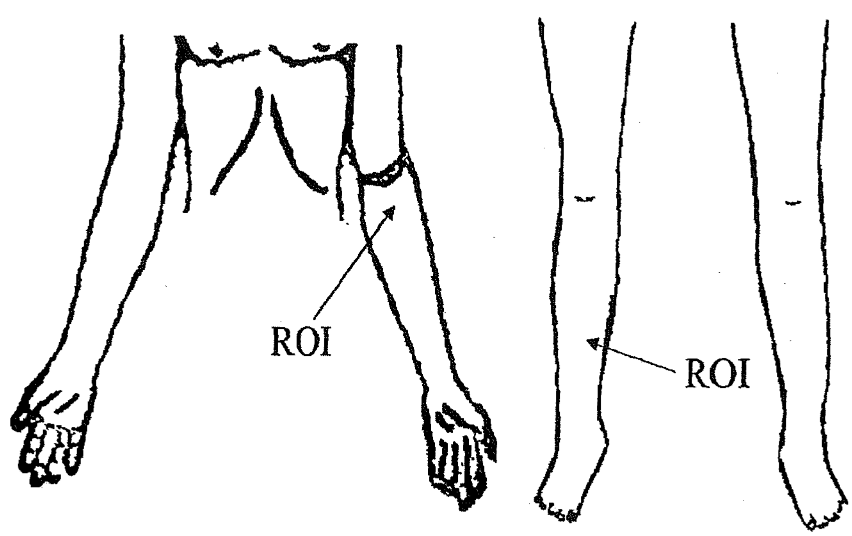


Figure 3.8 Region of interest =ROI used for applying extension/relaxation in both extremities

Cutaneous stretching parallel to Langer's lines were always performed, figure 3.9. The room temperature was controlled between 21-24^{0}C in an environment free from draught and noise.

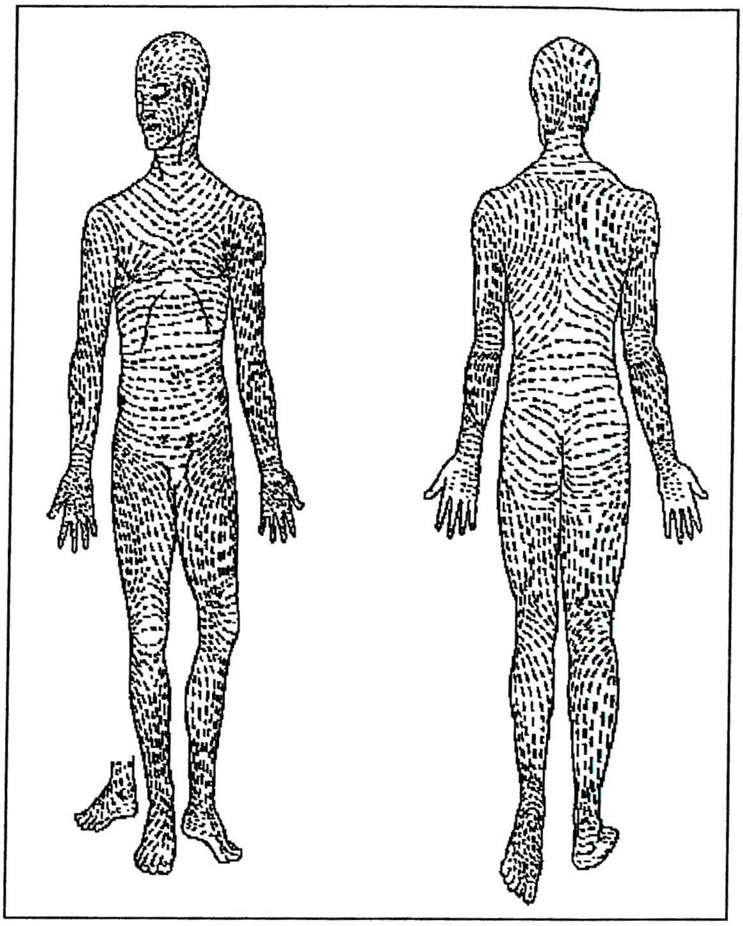


Figure 3.9 A map of Langer's (cleavage) lines of the skin.
After Cox (1941)

3.2.4 The extension curve

Data was acquired and stored in the PC. A typical extension/relaxation curve is presented graphically in figure 3.10. The force-extension curve comprised two phases, 'Extension Phase' lasting 8 seconds and 'Relaxation Phase'. The curve was described by two parameters: Force at maximum extension in Newtons (Fpeak) and time taken to reach 0.696Fpeak, recorded in seconds (Relaxation time) during the relaxation phase. Analysis of data showed the relaxation phase to follow a single exponential decay (Mani 1994), and data are presented in a logarithmic fashion (natural logarithm).

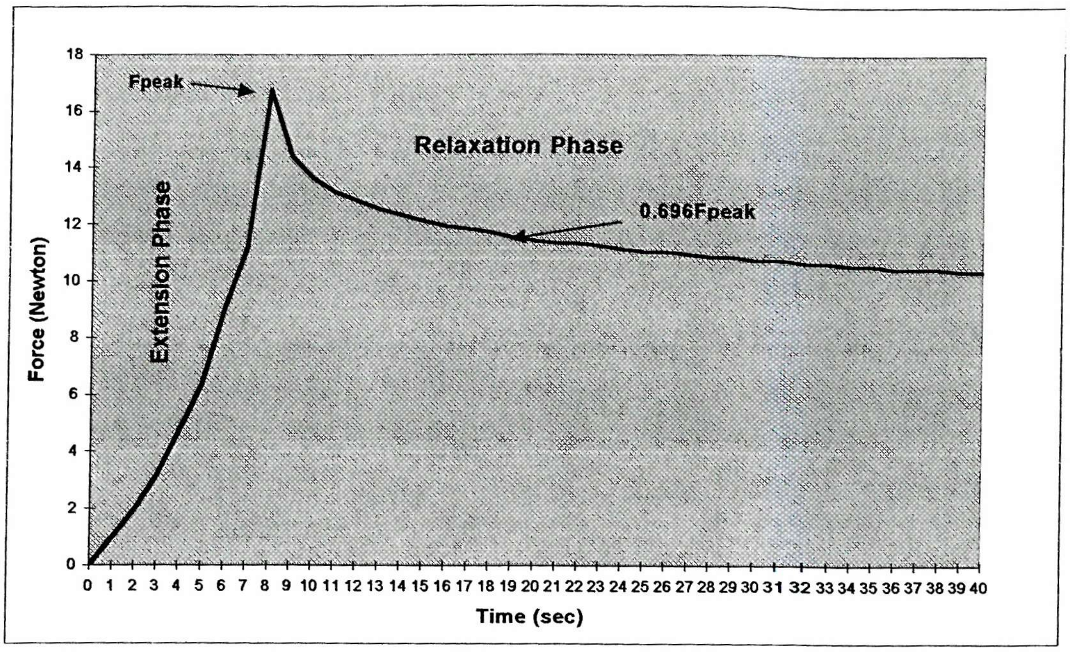


Figure 3.10 An extension/relaxation curve obtained from asymptomatic control leg.

Later, indices for extensibility and relaxation were calculated by dividing data obtained from the leg region by that from the forearm, table 3.3.

Extensibility index	Log (Fpeak obtained from midway between the medial malleolus of the ankle and the medial condyles of the tibia / Fpeak obtained from 5cm inferior to the antecubital fossa)
Relaxation index	Log (Relaxation time obtained from midway between the medial malleolus of the ankle and the medial condyles of the tibia / Relaxation time obtained from 5cm inferior to the antecubital fossa)

Table 3.3 Extensibility and relaxation indices were derived from Fpeak (Newtons) and relaxation time (s) measured in the forearms and legs.

Prior to examining the reproducibility of the extensometer, the effects of repetition and Langer's line on the mechanical properties were examined. As previous researchers did not address the effects of repetition and Langer's line on the mechanical properties (Gunner et al. 1979, Mourad 1987 and Quan et al. 1997), results would contribute to the setting of the measurements protocol.

3.2.5 The effect of repetition

Aim

To study the effect of repetition on the cutaneous mechanical properties.

Method

A group of thirteen asymptomatic controls (8M, 5F, mean age 38.9 years, age range 23-63 years) were included in the study. The exclusion criteria were swelling of the leg and ankle, diabetes, skin disorders treated with steroids, myocardial infarction, pregnancy, cancer or other terminal illness. The protocol discussed in section 3.2.3 was used. Three extensions/relaxation cycles were done on both forearms and legs. 10 minutes were allowed between cycles to permit recovery. Data are presented in appendix 3, table 3.4 as mean and standard deviation (±1sd) and graphically in figures 3.11 and 3.12.

Statistical analysis

One-factor repeated measure Anova was used to evaluate the differences between the three measurements and paired sample T-test was applied to examine for the presence of a statistical difference between two measurements.

Results

Data from 4 legs were excluded due to artefacts.

Parameters (natural log)	Location	First extension	Second extension	Third extension	Significance
Fpeak	Forearm (N=13)	1.58 ±0.55	1.42 ±0.52	1.34 ±0.47	P=0.001
	Leg (N=9)	2.69 ±0.38	2.46 ±0.36	2.43 ±0.34	P < 0.001
Relaxation time	Forearm (N=13)	3.05 ±0.39	4.04 ±0.93	3.71 ±0.093	P=0.005
	Leg (N=9)	3.5 ±0.84	4.6 ±0.84	4.85 ±0.97	P< 0.001

Table 3.4 The effect of repetition on force at maximum extension (Fpeak) and relaxation time

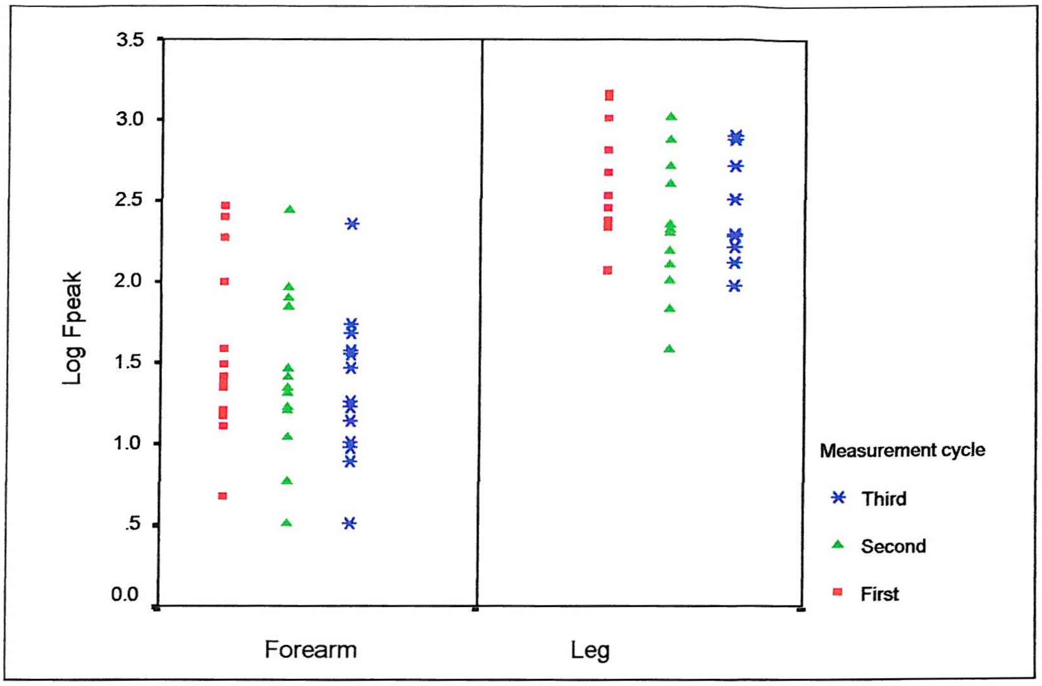


Figure 3.11 The effect of repetition on force at maximum extension (Fpeak) in both forearms and legs. A significant reduction in Fpeak was found in both extremities after the first extension/relaxation cycle despite the 10-minute recovery time between cycles.

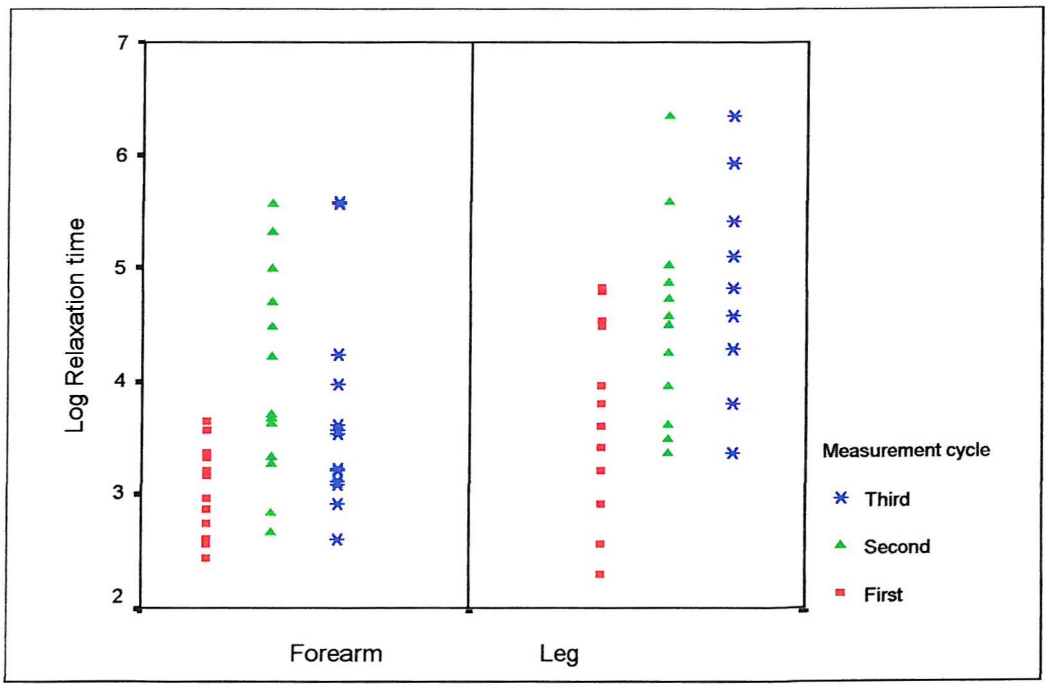


Figure 3.12 The effect of repetition on relaxation time in both forearms and legs. A significant increase in relaxation time was found after the first extension/relaxation cycle, in both extremities.

3.2.6 The effect of collagen orientation.

Aim

To examine the effect of skin anisotropy by orthogonal extensometry.

Method

A group of thirteen asymptomatic controls were recruited (3M, 10F, age range 18-64 years). The exclusion criteria were the same as in previous study. The protocol described in section 3.2.3 was used on the first day. On the second day, the same sites were tested but in an orthogonal direction, using the same procedure. Data are presented in appendix 4, table 3.5 as mean ±1sd and graphically in figures 3.13 and 3.14.

Statistical analysis

The effect of changing the extension axis on the force at maximum extension (log Fpeak) and log relaxation time was examined within both forearms and legs using paired sample T-test.

Result

N is the number of measurement included in the analysis, data with artefacts were excluded.

Parameters (natural log)	Location	Parallel to Langer's lines stretching	Perpendicular to Langer's lines stretching	Significance
Fpeak	Forearm (N=11)	1.30 ± 0.44	0.33 ± 0.53	P < 0.001
	Leg (N=13)	2.71 ± 0.26	1.86 ± 0.3	P < 0.001
Relaxation time	Forearm (N=10)	2.69 ± 0.33	3.61 ± 0.94	P=0.01
	Leg (N=12)	2.73 ± 0.5	2.61 ± 0.21	P=0.44

Table 3.5 The effect of skin anisotropy (changing the extension plane from parallel to perpendicular with respect to Langer's lines) on the force at maximum extension and relaxation time.

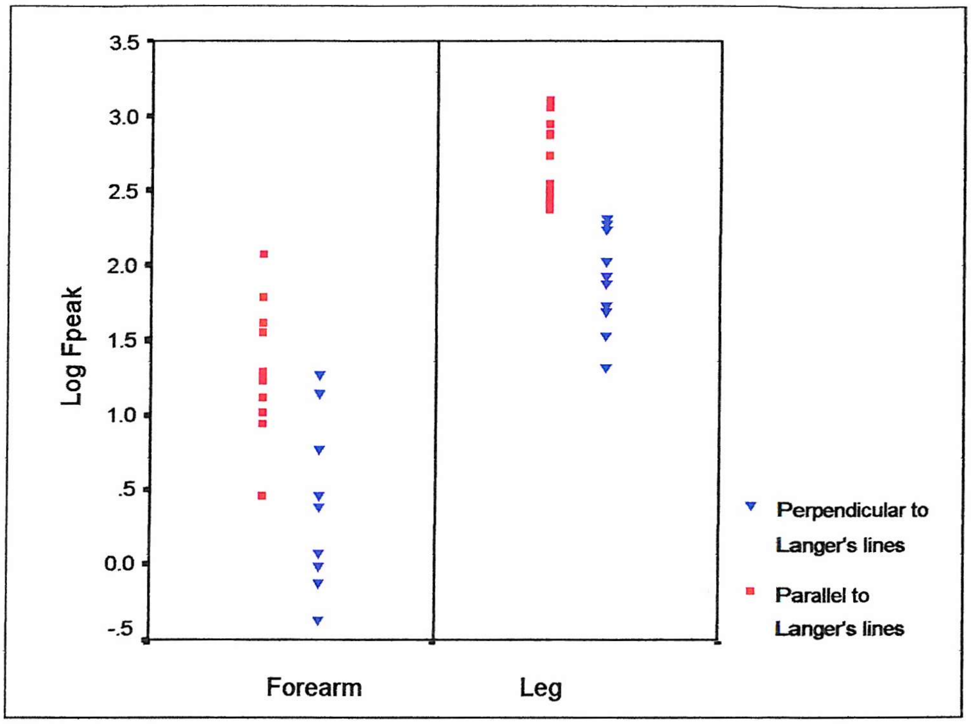


Figure 3.13 The effect of Langer's lines on Fpeak in both forearms and legs. Perpendicular to Langer's lines, a significant reduction in Fpeak was found in both extremities.

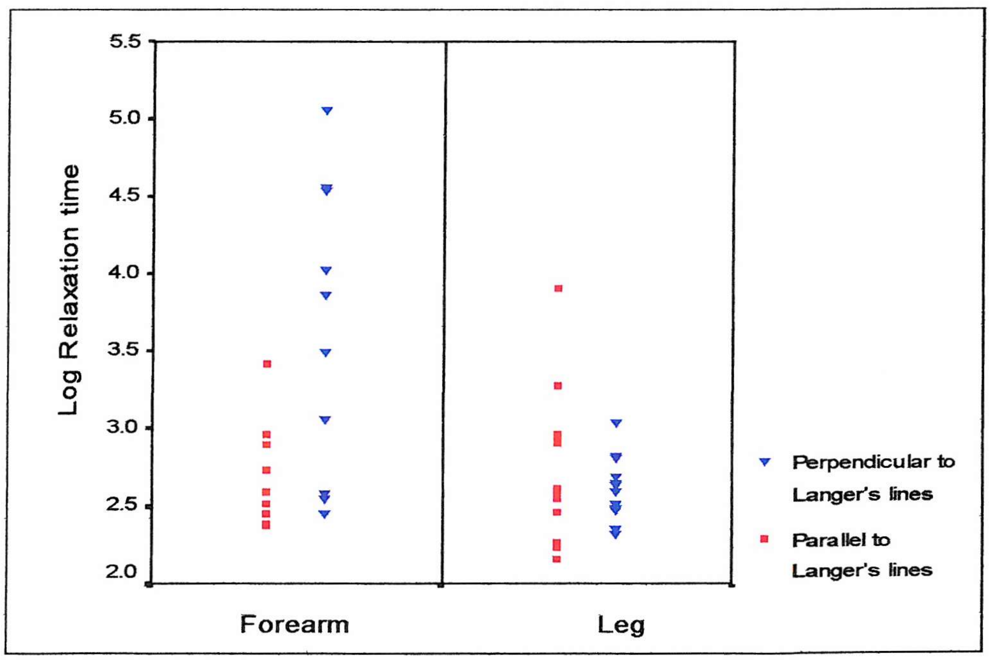


Figure 3.14 The effect of Langer's lines on relaxation time in both forearms and legs. Perpendicular to Langer's lines, a significant increase in relaxation time was found in the forearm only.

3.2.7 Reproducibility studies on asymptomatic controls

Aim

To determine the reproducibility of the extensometer.

Method

The study was carried out on the skin over forearms and legs in 5 asymptomatic volunteers (4M, 1F, age ranges 21-63, mean age 42.4 years). The exclusion criteria were similar to previous study, the measurement protocol described in section 3.2.3 was used. Measurements were repeated on five consecutive days at the same time of the day.

Statistical analysis

Sources of variation and the equation used for calculating the reliability were discussed in section 3.1.3. The variability within (MSw) and between (MSb) subjects was examined using the analysis of variance test (Anova-test).

Result

Variability within and between subjects and the reliability in the forearms and legs are presented in table 3.6. With the individual measurements presented in appendix 5.

Parameter (Log)	Location	Within subjects (MSw)	Between subjects (MSb)	Significance	Coefficient of Variation CV%	Reliability R%
Fpeak	Forearm	0.055	0.242	P=0.01	15.39	40.7
	Leg	0.021	0.294	P<0.001	5.54	72.2
Relaxation time	Forearm	0.195	0.227	P=0.36	15.02	3.2
	Leg	0.167	0.272	P=0.27	13.10	11.1

Table 3.6 Within and between subject variances in the measurement of force at maximum extension (Fpeak) and relaxation time, and the reliability of the technique.

Analysis of variance showed the variability between subjects to be greater than that within subjects in forearms and legs, though only statistically significant within Fpeak in both extremities.

3.2.8 Uniaxial extensometry: A comparative study between extensometry and durometry on asymptomatic controls

It was difficult to determine a method that would validate either extensometry or durometry. As both methods measure the mechanical properties of cutaneous tissues, a comparison between these two methods was carried out.

Aim

To examine the association between hardness measurement obtained with the durometer, and Fpeak and relaxation time extracted from extension-relaxation curve within the same site.

Methods

The protocols for durometry and extensometry were described earlier in sections 3.1.2 and 3.2.3. Both measurements were done on the same visit; in forearms at 5cm inferior to antecubital fossa. On legs, measurements were done on the medial aspect midway between the medial malleolus and medial condyles of the tibia. Initially durometry was done first, followed by uniaxial extensometry. 25 asymptomatic controls (6M, 19F, mean age 67.7 years, age range 51-83 years) were studied using protocols described in section (3.88 and 3.888). The exclusion criteria applied previously were used in this study. Data are presented in appendix 6, table 3.7 and graphically in figures 3.14a and 3.15.

Statistical analysis

Outliers were removed before determining the degree of association between measurements. The association between cutaneous hardness, force at maximum extension and relaxation time were calculated using Pearson's correlation coefficient.

Location	Cutaneous hardness X log Fpeak	Cutaneous hardness X log relaxation time
Forearm (5cm inferior to antecubital fossa)	r =0.58 (P= 0.012)	r =0.133 (P= 0.576)
Leg (middle of the medial aspect of the leg)	r =0.4 (P= 0.048)	r =0.25 (P= 0.228)

Table 3.7 The degree of association between cutaneous hardness, force at maximum extension (log Fpeak) and relaxation time (log relaxation time) after the removal of outliers.

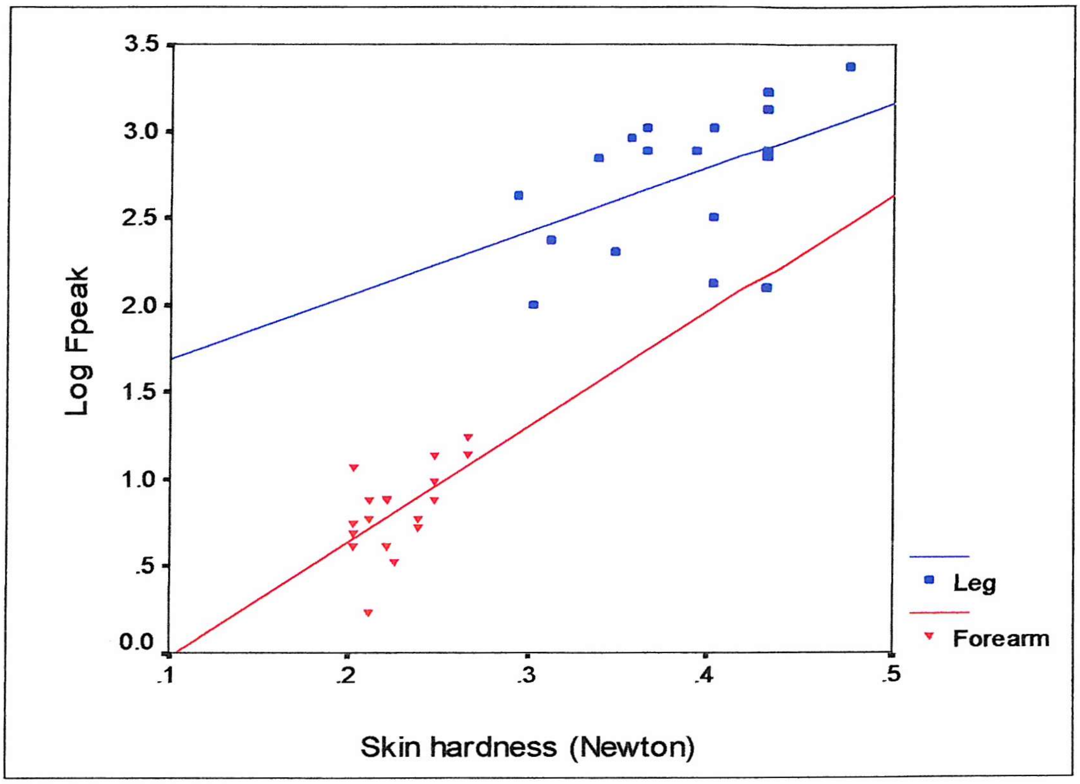


Figure 3.14a The association between cutaneous hardness and force at maximum extension. An association was found between cutaneous hardness and log Fpeak in the forearm (r =0.58, P= 0.012) and the leg (r=0.4, P= 0.048).

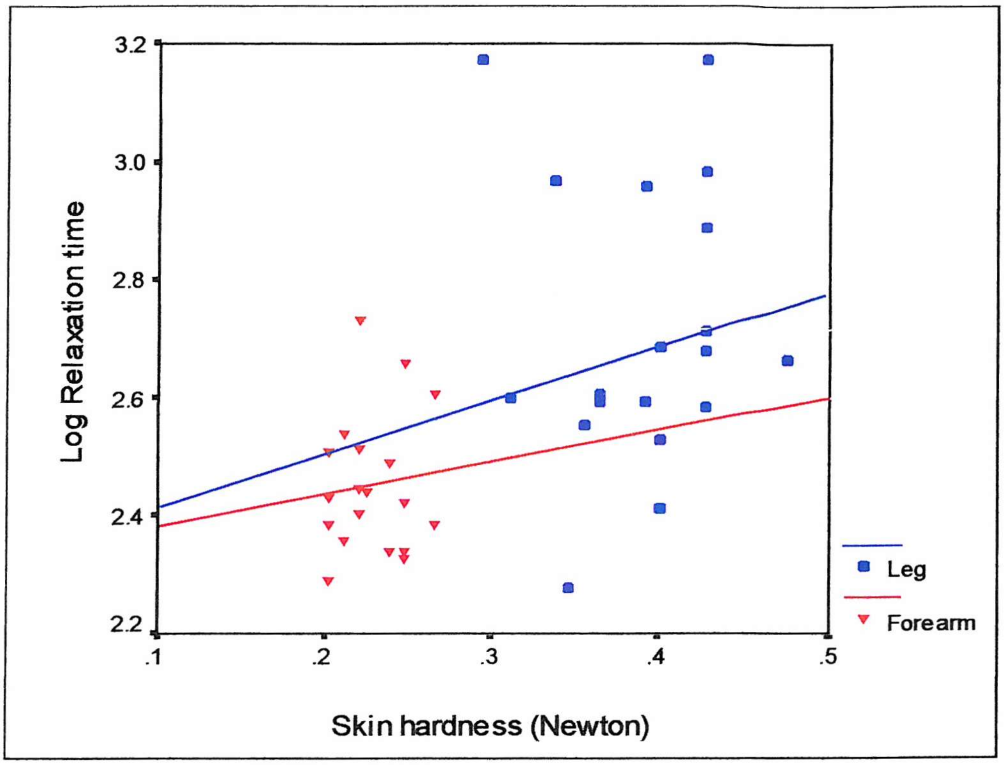


Figure 3.15 The association between cutaneous hardness and relaxation time was poor.

3.3 Laser Doppler flowmetry: assessment of cutaneous microcirculation

3.3.1 Laser

The word LASER is an acronym for Light Amplification by the Stimulated Emission of Radiation. Laser light is produced when light, electric discharge or radio frequency energises a medium. The excitation of atoms by the external stimulus results in electrons moving from the ground state into higher orbit (excited state). A photon, the basic unit of light is released when these electrons fall back to the original orbit (ground state). A substance has the potential to become a lasing medium, suitable for producing laser light, if it can have more atoms in the excited state than in its resting energy state 'population inversion'. In the presence of population inversion, a photon from an initial spontaneous decay stimulates each excited atom in its path to emit a photon entirely identical to itself in frequency, wavelength, amplitude, phase and direction, which results in the emission of laser light from the medium.

Three particular properties are responsible for the difference of laser light from ordinary light; coherence, collimation and monochromaticity. The light photons are in phase with each other, travel in the same direction, as well as being parallel to each other, leading to a minimum loss of power along the laser beams. The emitted photons in the laser beam are all of the same wavelength and hence of the same colour.

3.3.2 Interactions of laser with tissues

In tissues, absorption, scattering and reflection attenuate laser light, and laser light interactions can be classified into thermal and non-thermal interactions. Absorption increases exponentially with the length of the material, each tissue has its characteristic optical absorption spectra; generally, absorption results from the chromophores (colouring agents) and is highly dependent on wavelength. Tissues and haemoglobin absorb ultraviolet and blue light but transmit red light, whereas water transmits well in the visible region.

Reflection occurs when the surface of the sample is planer and optically polished, which is not necessity the case in tissues. With scattering, a fraction of the laser beam does not continue in its original straight path but is deflected to other directions. The scattered light undergoes further reflection and scattering, until it is either absorbed or escapes from the sample.

3.3.3 The Doppler effect

The Doppler shift is the change in the perceived frequency when there is a relative movement between the source and the observer. It was first described by Johann Christian Doppler (1803-1853) in his famous paper 'On the Coloured Light of Double Stars and Some Other Heavenly Bodies' (Doppler 1843) and the correct elementary formula for motion of source or observer along a line between them, appeared in the same article, equation 3.3.

$$f_o = f_s \frac{C - v_o}{C - v_s} \qquad \text{Equation 3.3}$$

Where f_o is the observed frequency,

f_s is the frequency of initial beam,

C is the speed of wave and v_o and v_s are the vector velocities of the observer and the source.

The Doppler principle was used to assess blood flow in the macrocirculation (Doppler ultrasound) as well as the microcirculation (laser Doppler). The spectral purity of laser makes it practical to detect small frequency shifts resulting from this motion.

The Doppler effect in optics is explained in terms of Einstein's theory of relativity, which states that the speed of light is constant in all reference frames, that light needs no material medium for its propagation and its speed, relative to the source or observer, is always the same. Therefore, it is only the relative motions between the observer and the source that determines the Doppler shift frequency (Magnin 1986), equation 3.4.

$$f_d = [f_s(1 - v_{os}/C)/\sqrt{1 - (v_{os}/C)^2}] - f_s \qquad \text{Equation 3.4}$$

Where f_d is the Doppler shift frequency,

f_s is the frequency of initial beam,

v_{os} is the relative velocity of the source with respect to the observer and C is the velocity of light.

When the reflector i.e. RBC moves, the returning light will undergo a Doppler shift that is twice that predicted by the equation, since the RBC acts as both the observer as well as the source. For direct back scattering, one must actually scale the frequency shift by the cosine of the angle between RBC velocity and the line connecting the object to the receiver.

3.3.4 Equipment

The MBF3D laser Doppler monitor (Moor Instruments, U.K.) has a continuous wave laser radiation generated by a semiconductor laser diode operating at a wavelength of 780 to 820nm with a maximum accessible power of 1.5mW. Light is emitted with an angular spread of approximately 30°; the numerical aperture of the 200μm silica glass fiber is 0.25. Fiber optic probes are used to deliver light to the tissue surface, and to collect a portion of backscattered light. At a distance of 200mm from the fibre end, the average power density is approximately 0.2μW/mm² and the maximum power density is approximately twice the average. For an optic probe output power of 1.5mW, the measured power through a 7mm-diameter aperture at a distance of 200mm from the probe end, is approximately 14μW. Data can be stored in the laser Doppler system or in a PC for further analysis, figure 3.16. The MBF3D allows for the selection of a sampling rate and in these studies, a sample rate of 20 sample/second was chosen.

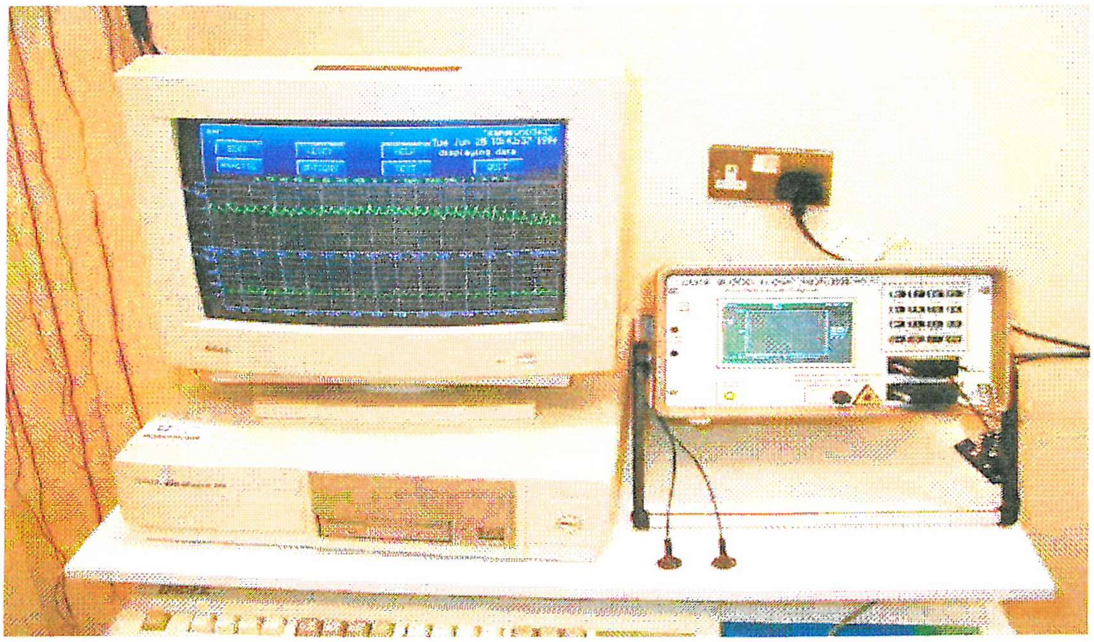


Figure 3.16 The MBF3D laser Doppler monitor used for cutaneous microcirculation study. Laser light is delivered to the skin and collected by optic probes. The output signal is stored in the PC and displayed as flux (Arbitrary units).

3.3.5 LDF output

The backscattered component of the reflected light, which undergoes frequency shifting, is processed to produce the flux, a parameter related to the movement and concentration of red blood cells, figure 3.17. The flux is related to the product of average speed and concentration of moving RBC in the tissue sample volume.

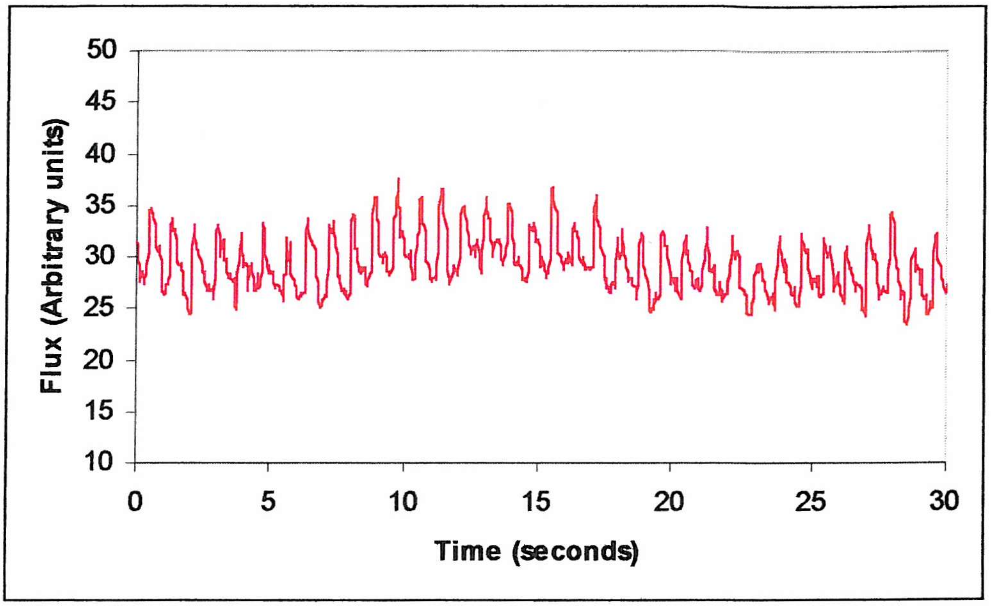


Figure 3.17 The LDF output, where the backscattered light signal is processed and displayed as Flux. The change in the flux with cardiac cycle was measured at the pulp of the big toe using MBF3D laser Doppler

3.3.6 Probe Calibration

The laser output power may vary between probes and could change over time. A standard reference, provided by the manufacturer was used to calibrate individual probes at regular intervals as recommended by the manufacturer.

3.3.7 The LDF protocol

In order to assess changes in blood flow in tissues subject to ulceration, it was planned to study local control of the microcirculation and changes in blood flow during extension/relaxation. Local control of blood flow derived through an intact postural vasoconstrictive response had been described as an oedema-preventive mechanism. Measurements were conducted in a room with a controlled temperature between 21-24 ^{0}C in an environment free from draught and noise, after a minimum period of 30 minutes acclimatisation, 2 hours after the last food or drink. The probes were attached to the skin using double-sided adhesive discs and probe pressure on site was minimal.

3.3.7.1 The measurement protocol for blood flow changes during extension/relaxation

When the cutaneous microcirculation during skin stretching were examined, the LDF probe was positioned between the extensometer feet and secured in place with Velcro strap. This permitted examining the microcirculation as well as skin extensibility and relaxation in the same experiment, figure 3.18.

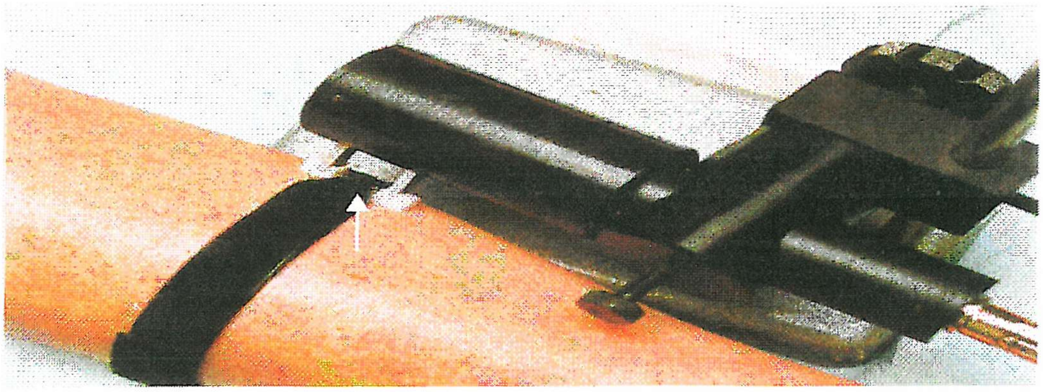


Figure 3.18 The position of the LDF probe between the extensometer feet (white arrow), permitting the monitoring of the microcirculation before and after the application of skin extension/relaxation.

The region of interest (ROI) examined were identical to the cutaneous extension-relaxation study, figure 3.8. Baseline measurement of the LDF parameters, prior to skin stretching were recorded for a minimum of 1minute, followed by measuring the change in the microcirculation during the extension and relaxation phases. A typical change in the flux during extension and relaxation is presented in figure 3.19.

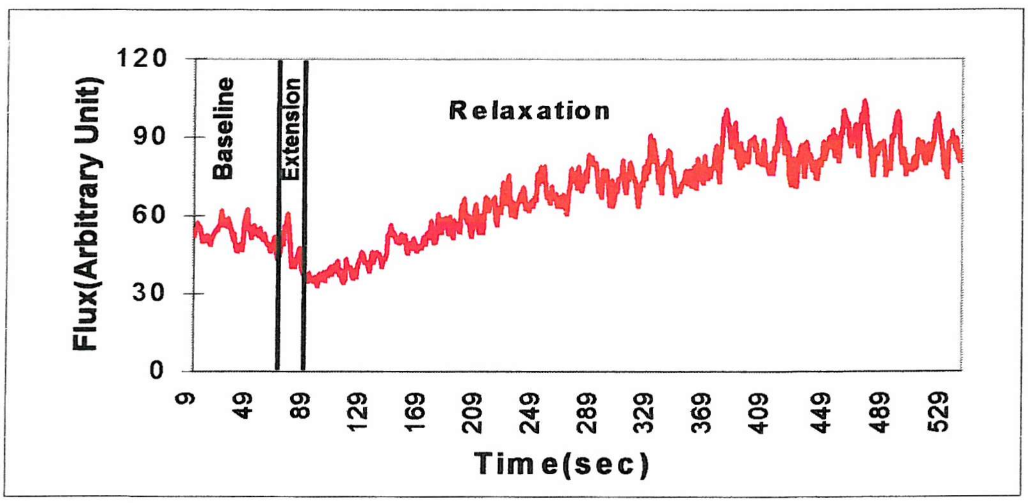


Figure 3.19 Changes in the cutaneous microcirculation with the application of skin extension/relaxation in a control leg. A drop in the flux occurred in the 1st minute of relaxation, followed by a steady increase above baseline level.

During cutaneous extension, an increase in flux occurs, followed by a sudden drop below baseline level. In the relaxation phase, a steady increase in flux was found. At the end of relaxation phase (4 minutes in forearm and 8 minutes in the leg), the flux increase was noted to be above baseline level.

3.3.7.2 The measurement protocol for blood flow changes with passive leg lowering

When the postural vasoconstrictive response was examined, the LDF probes were attached to the pulp of the big toes with a double-sided adhesive ring, this site was chosen to provide the maximum drop from heart level. With the subjects resting in the supine position, baseline measurement was acquired for a minimum of one minute. Followed by a passive leg lowering of approximately 50cm below the heart level for two minutes, while the rest of the body and the contralateral foot remaining in the supine position, figure 3.20. After the two minutes period of passive leg lowering, the extremity was returned to the supine position followed by the lowering of the other leg.

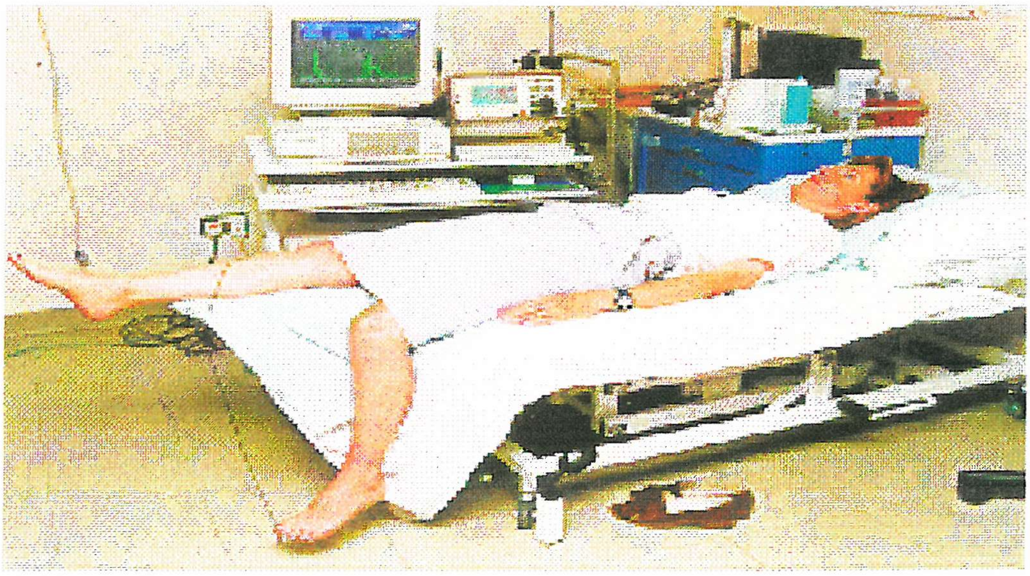


Figure 3.20 The postural vasoconstrictive response, subject positioning and the equipment used. The LDF probe was attached to the pulp of the big toe, which was lowered passively 50cm from the supine position.

A typical diagram of the changes in the LDF flux with passive leg lowering is presented in figure 3.21. A reduction in flux, below baseline level, demonstrates the presence of a control restricting the blood flow in the microcirculation.

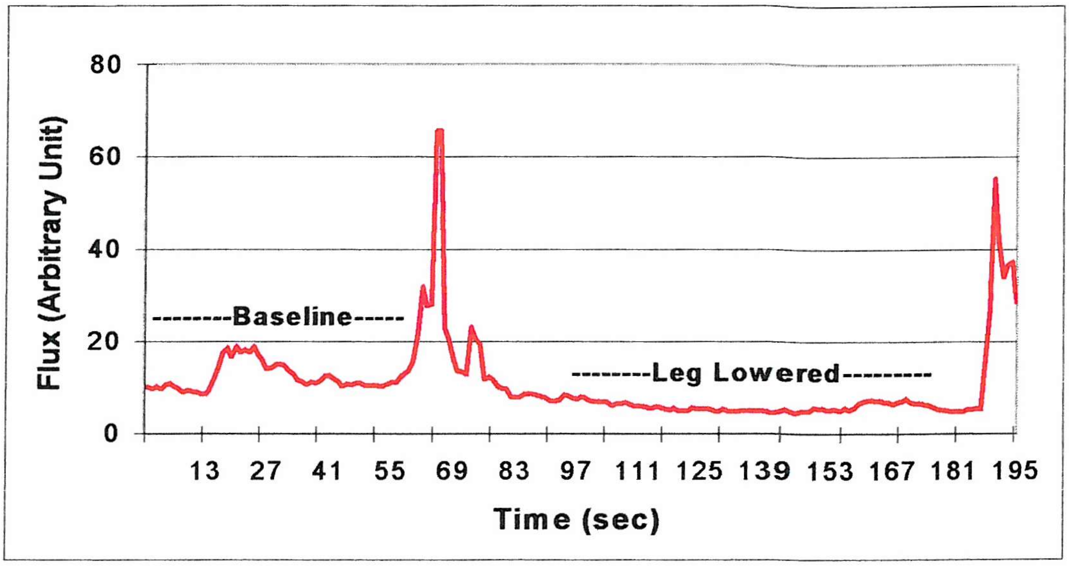


Figure 3.21 The postural vasoconstrictive response, changes in the LDF flux during and after leg lowering from the supine position. Measured at the pulp of the big toe.

The reproducibility of this technique was not repeated in this work, validation studies found variations in flux with location (Tenland et al. 1983). Other factors, such as skin temperature, mental activity and psychological state influenced flux (Berardesca et al 1991). Its use on volunteers and patients follows in the next chapters, due to the variation in flux with location found previously, data were examined both in arbitrary units and as %change with respect to baseline.

3.4 Discussion

The aim of this chapter was to determine suitable protocols in addition to assessing the reliability, reproducibility and validity of the chosen techniques. Durometry and uniaxial extensometry measure mechanical properties while the LDF measures changes in microcirculation.

Although the effects of CVI is mostly felt during standing due to the abnormal increase in venous pressure with gravity, the durometer and extensometer were used on the skin with the extremity under investigation in the supine position. Preliminary trials indicated the difficulty in applying both techniques on extremities in the standing position (durometer and extensometer measurements were dependent on gravity). The ability to use the LDF in both supine and standing position resulted in the microcirculation being assessed both in the supine position (during the application of extension/relaxation with the extensometer) and during standing (postural vasoconstrictive response).

Analysis of durometry data showed the variability between subjects to be significantly greater than within subjects, the coefficient of variation for different sites varied from 5.27% to 8.64% table 3.2. The coefficient of variation is an indicator of the relative spread of the measurement distribution and can be used to determine the precision of the technique (Coltan 1974). The dependence of the CV on the value of the measurement suggested by Bland (Bland 1997) as the presence of a relationship between the mean of paired measurements to their differences were not examined, as measurements were repeated on five consecutive days and not just twice.

The reliability of the data varied from 51.85% to 91.57%, table 3.2. The reliability of a technique examines the contribution of the random error (measurement error) to the variation between subject. A reliability approaching unity indicates a small contribution of random error to the measurements, whereas reliability near zero suggests the opposite. With the durometer, the reliability was found to increase proximal to the ankle and further from elbow joint. It was observed that the CV was lower proximal to the elbow joint whereas the reliability increased distally. In the gaiter region of the ankle, low CV value was equivalent to higher reliability. The discord between CV and reliability in the forearm seems to arise from the dependence of CV on the mean of measurements, where larger CV is obtained with larger values. Both CV and reliability are statistical parameters used to describe the repeatability of the technique, CV is commonly used and quoted while reliability examine the ratio of measurement error to biological variations. Findings suggest that both parameters could be used simultaneously to study the repeatability of a technique.

When using the durometer, it was important to check it before every measurement and this was not time consuming and relatively simple to achieve. Data analysis also indicated that expressing durometer readings as an index of leg site over forearm was more reliable (table 3.1), presumably due to smoothing of variations at individual sites. This was adopted for this work except when the regional variations in cutaneous hardness were examined.

Uniaxial extensometry required careful preparation of sites and methodology. The shape of the extension-relaxation curve was attributed to the viscoelastic properties of the cutaneous tissues, figure 3.9. With elastic materials such as rubber, the force required to stretch it in a specific time, has a linear relationship with the increase in the sample length, the deviation from total elasticity in the case of cutaneous tissue was contributed to the viscous element present. Tissue viscoelasticity were attributed to fibers (collagen and elastin) and the gel-like ground substance. With extension, the change in the fiber dimensions that would be accompanied by ground substance displacement and may result in the non-linearity in the extension phase. During the relaxation phase, the force required to stretch the skin diminishes due to the ability of skin to adapt, probably as a result of a change in the fibre dimensions and a further displacement of ground substance.

From the extension/relaxation curve, force at maximum extension (Fpeak) as well as a parameter of relaxation were examined. Relaxation time was measured as the time taken to reach 0.696 of the initial value, since the decay of the force at maximum extension was characterized as a single exponential. Extensometer data were expressed as indices for the work presented in this thesis as for the durometer, except when the effect of location was examined.

Repeat experiments at the same site, revealed that skin was subject to pre-conditioning, table 3.4, Fpeak was significantly reduced after the first extension/relaxation cycle in both forearms and legs ($F=0.001$ and < 0.001 respectively, repeated measure Anova). In contradiction, relaxation time was significantly increased ($P=0.005$ and $P < 0.001$ respectively, repeated measure Anova). The above differences in Fpeak and relaxation time may result from lack of full recovery within the ten minutes period between cycles. From just this experiment, it is difficult to relate the lack of recovery to a specific skin component.

The reduction in Fpeak ($P= 0.009$, 0.001 respectively, Paired sample T-test) and the increase in relaxation time ($P< 0.001$ and $=0.02$ respectively, Paired sample T-test) were statistically different between the first and second cycle in forearms and legs. Whereas no statistical difference in Fpeak ($P=0.095$ and 0.438, Paired sample T-test) and time

(P=0.357 and 0.239, paired sample T-test) were found between the second and the third cycle in both forearms and legs.

The statistical differences, within both parameters, between the first and second cycle, and the absence of differences between the second and the third cycle, suggests that skin can be preconditioned (the skin's ability to adapt to deformation) with the application of two extension cycles. Also, it suggests that only the first measurement should be taken as a true representative of a pre-strained skin extensibility and relaxation. Skin should be allowed time to recover from previous measurement if repetition is needed. This is considered important when the effect of collagen fibers orientation and the reproducibility of the technique are examined. To allow for skin recovery after the 1st extension/relaxation cycle, cutaneous extension/relaxation perpendicular to Langer's lines were not conducted on the same day but applied on the next day, and when the reproducibility of the technique were examined, measurements were conducted on consecutive days.

When extensometry tests were done along and orthogonal to Langer's Lines, it was observed that force at maximum extension was reduced significantly on forearms and legs ($P<0.001$, Paired t-test), table 3.5. This is attributed to orientation of collagen fibers in cutaneous tissues. It is difficult to isolate any effects due to elastin in these data, but since the proportion of collagen/elastin fibers is greater the observed changes are thought to represent the response of the former. Collagen fibres are made up of hundreds of finer fibrils and each fibril, in turn, is made up of several triple helical spiralled collagen molecules twisted into coils, which results in collagen fibers resisting extension in a manner similar to coils. The structure of collagen fibers allow it to change dimension in response to the application of a mechanical force, and the force needed to elongate this collagen fibre cable would be larger than needed to separate aggregated fibers and the above finding seems to support this thought.

Relaxation times were statistically significantly increased on forearm skin (P=0.01, Paired t-test) perpendicular to Langer's lines. This may be because the act of extension may be affecting ground substance as well as the fibers. On legs this parameter was not statistically significant in different directions (P=0.444, Paired sample T-test).

When the reproducibility of the technique for measuring cutaneous Fpeak and relaxation time were examined, results demonstrated that, although between subjects variability were greater than within subjects in both extremities, it was statistically different only with Fpeak ($P=0.01$ and < 0.001, Anova, in forearms and legs), table 3.6. The CV varied between 5.54% to 15.39%. The technique was more reliable when measuring Fpeak in both forearms and legs ($R=40.7\%$ and 72.2% respectively), but less reliable when relaxation time were examined (3.2% and 11.1% in forearms and legs). The large CV and reduced reliability with the relaxation time compared to Fpeak, despite being measured with the same instrument simultaneously, suggest that relaxation time is influenced by factors others than ones affecting Fpeak, possibly being affected by time. When measuring Fpeak in the leg, CV was small (5.54%) and reliability value was of higher order (72.2%) compared to the forearm, table 3.6.

Comparisons of durometer and extensometer data were done since neither could be validated against a "gold standard". On forearm and leg skin, durometer data were well correlated with extensometer force at maximum extension ($r=0.58$, $P=0.012$ and $r=0.4$, $P=0.048$ respectively), table 3.7. When relaxation times were compared against durometer hardness data, there was a lack of correlation on both forearms and legs.

The correlation between durometer hardness data and force at maximum extension suggest that the methods yield similar though not identical data. This is to be expected since the former is a point measurement of the "yield" of tissues while the latter stretches a volume of tissue that is likely to be different to that tested by durometry. Since the two methods were relatively easy to use and acceptable to subjects, but not identical, both were adopted with the protocols described to study elasto-mechanical behavior of cutaneous tissues in succeeding chapters.

Several factors may affect the mechanical properties measured by the two techniques, skin hydration, composition and thickness are characteristic of individual. However, technical consideration will also affect the measured value. Pressure applied, the durometer area of foot attachment, deviation from perpendicular position for the durometer, orientation with respect to Langer's lines, type of adhesion used, the area of foot attachment, speed of feet separation are some factors that would influence the measurements. Generally hardness measurement should be avoided over bony parts, as the unavailability of sufficient soft tissues results in the durometer measuring bone hardness. The change in natural tension with different body position would affect measurement.

3.5 Conclusion

Skin is a viscoelastic and anisotropic material, which possesses a memory for mechanical properties. The force/deformation relationship is not linear and the skin requires time for recovery. The two techniques and the protocol used, for examining the mechanical properties of cutaneous tissues, were considered reproducible and suitable for further studies. The reliability of the durometer increases further from bony areas, whereas the reliability of the extensometery to measure skin extensibility is greater in the leg region compared to the forearm. The LDF offers a simple non-invasive method for examining the cutaneous blood flow. Those techniques were used in further studies as reported in the succeeding chapters.

Chapter Four: Studies on asymptomatic controls

Since the elderly are prone to ulceration, it was considered important to study differences due to site, sex and age on skin properties. Durometry, extensometry and LDF studies were carried out on asymptomatic controls to examine the effects of location, sex and age on mechanical and microcirculatory properties of skin. The studies were presented in a similar order to the previous chapter, findings are discussed later at the end of this chapter.

4.1 Subjects selection

Asymptomatic controls were recruited from hospital staff, medical students, the community, relative of patients and patients attending the eye clinic in Southampton General Hospital. Advertising for volunteers were placed in different areas of the hospital and were sent to public places in the community. The study was explained to the candidates and their question answered. Volunteers were asked to fill a clinical history questionnaire to examine their suitability for the study, appendix 37. Volunteers whom did not have a past or present history of swelling of the leg and ankle, DVT, diabetes, varicose veins, heart problems, skin disorder treated with steroids, pregnancy, cancer or any terminal illness, were considered suitable to be included in the control group.

Eighty asymptomatic controls were recruited over 3years duration. Variations in number of subjects within each study was due to the unavailability of the durometer and the LDF at the beginning of the study, table 4.

Name of the study	Number of asymptomatic controls included in the study
Skin hardness	54 Subjects
Cutaneous extensibility and relaxation	80 Subjects
Cutaneous microcirculation during skin extension/relaxation	53 Subjects
The postural vasoconstrictive response	52 Subjects

Table 4 Number of asymptomatic controls included in each study.

4.2 Skin hardness studies

Method

A group of 54 asymptomatic controls (18M, 36F, mean age=51.9 years, age range 21-83years) were studied. The protocol described in section 3.1.2 was used in the forearms and legs. Data are presented in appendices 7-10, as median (min & max) in tables 4.1-4.4 and graphically in figures 4.1-4.4.

Statistical analysis

Data from one forearm were not available for analysis (the subject did not give permission for measurements in the forearm due to the presence of a burning scar). The changes in cutaneous hardness with location were examined using Friedman test, by examining the differences in hardness (Newtons) measurements from the three locations in each extremity. To assess the differences in skin hardness between upper and lower extremities, hardness measurements from the forearm were compared to data obtained from an equivalent site in the leg using Wilcoxon test.

The Mann-Whitney test was used to examine the differences in hardness indices between males and females. Kruskal-Wallis and Mann-Whitney tests were used to examine the influence of age on the same parameters. Data were divided in to six groups according to their age and gender, and the combined effects of age and sex on hardness indices were examined using Kruskal-Wallis test.

Results

Forearm (N=53)		Leg (N=54)		Significance
5cm inferior to antecubital fossa	0.24 (0.2 & 0.38)	5cm superior to medial malleolus	0.43 (0.31& 0.52)	**P<0.001**
10cm inferior to antecubital fossa	0.29 (0.2 & 0.47)	10cm superior to medial malleolus	0.4 (0.29 & 0.54)	**P<0.001**
mid forearm	0.31 (0.2 & 0.58)	mid leg	0.36 (0.2 & 0.49)	**P=0.004**
Significance	**P<0.001**		**P<0.001**	

Table 4.1 Regional variation in skin hardness (Newtons) within the same extremity and between extremities measured in asymptomatic controls.

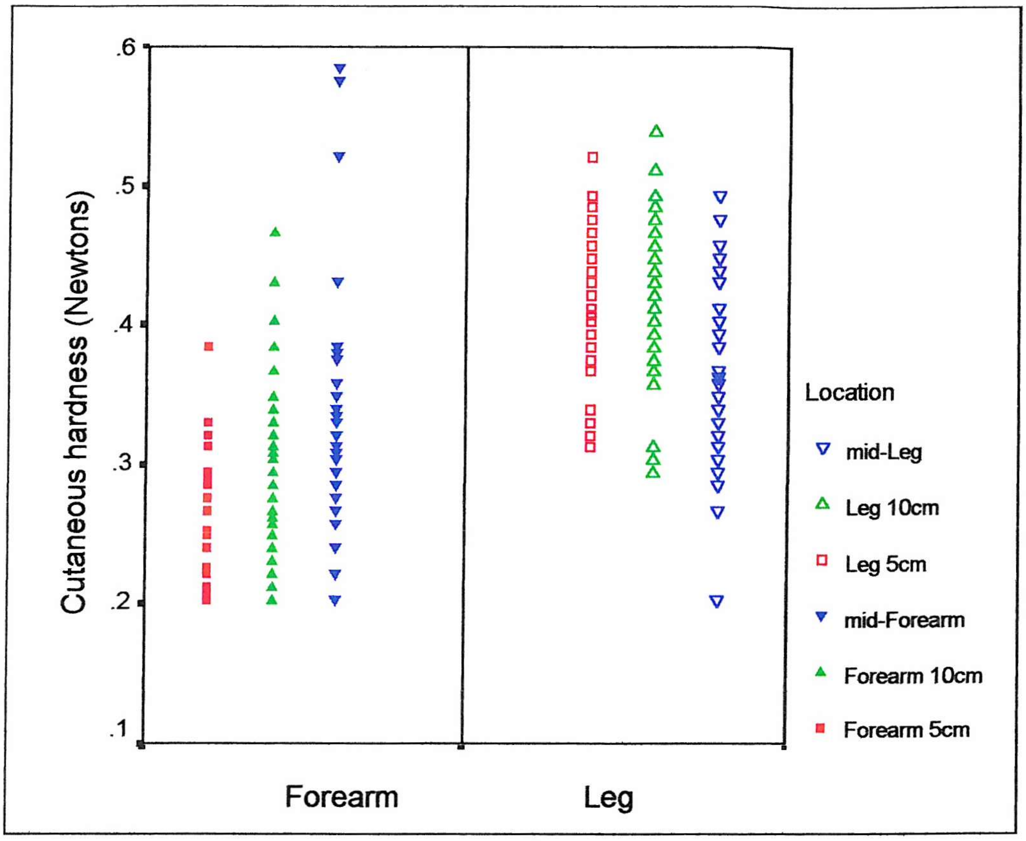


Figure 4.1 Regional variation in cutaneous hardness, measured in asymptomatic controls. In the medial aspect of the forearm, a significant increase in cutaneous hardness was found distal to the elbow joint. In the medial aspect of the leg, a significant reduction was found proximal to the ankle joint.

Hardness Indices	Male N=18	Female N=35	Significance
hardness index 1	1.65 (1 & 2.34)	1.72 (1.17 & 2.39	P=0.645
hardness index 2	1.33 (0.82 & 2.09)	1.56 (1.03 & 2.43)	**P=0.002**
hardness index 3	1.11 (0.46 & 1.46)	1.29 (0.82 & 1.94)	**P=0.006**

Table 4.2 Difference in hardness indices (leg/arm) between males and females.

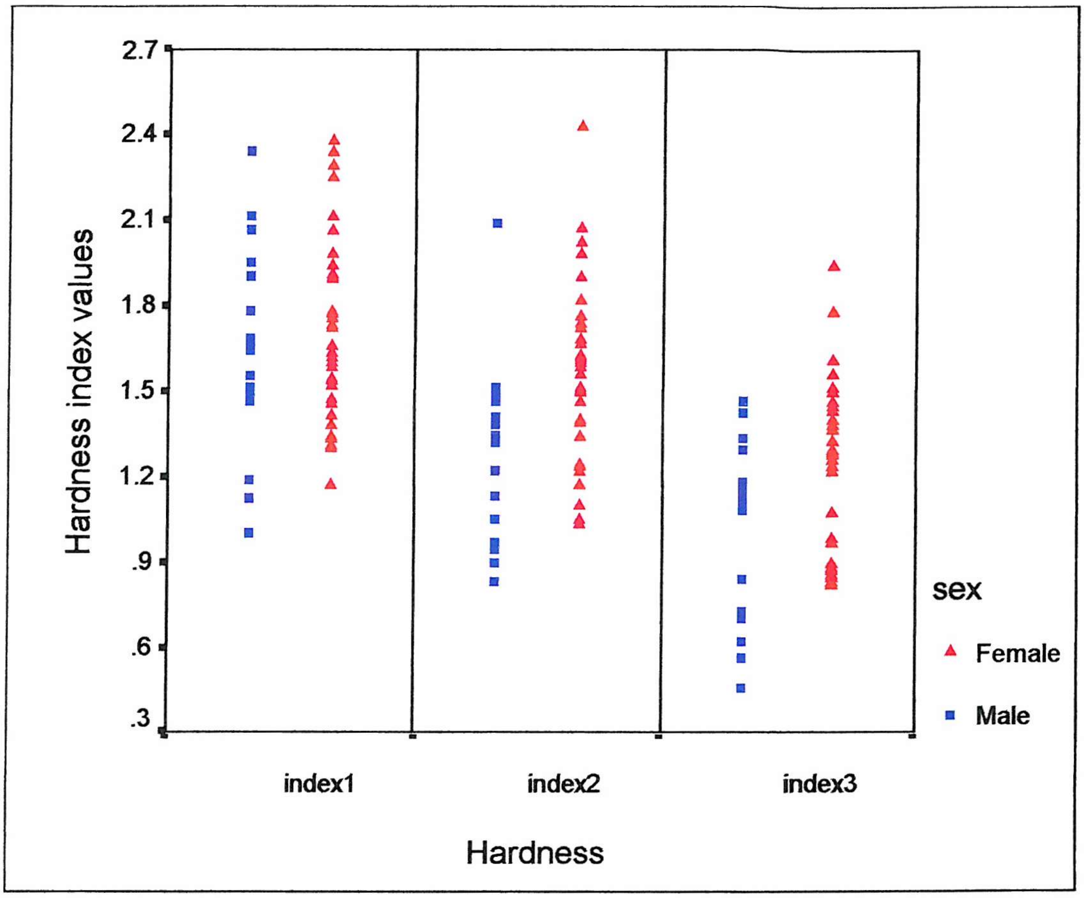


Figure 4.2 The difference in hardness indices between sexes. A significant increase in hardness (index 2 and 3) were found in females compared to males.

Location	21-40years N=20	41-60years N=10	61-90years N=23	Significance
hardness index 1	1.54 (1 & 2.39)	1.62 (1.12 & 2.34)	1.78 (1.3 & 2.25)	P=0.104
hardness index 2	1.22 (0.94 & 1.6)	1.33 (0.82 & 1.74)	1.67 (1.38 & 2.43)	**P<0.001**
hardness index 3	0.88 (0.56 & 1.47)	1.13 (0.46 & 1.49)	1.38 (1.08 & 1.94)	**P<0.001**

Table 4.3 The effect of age on skin hardness indices measured in asymptomatic controls.

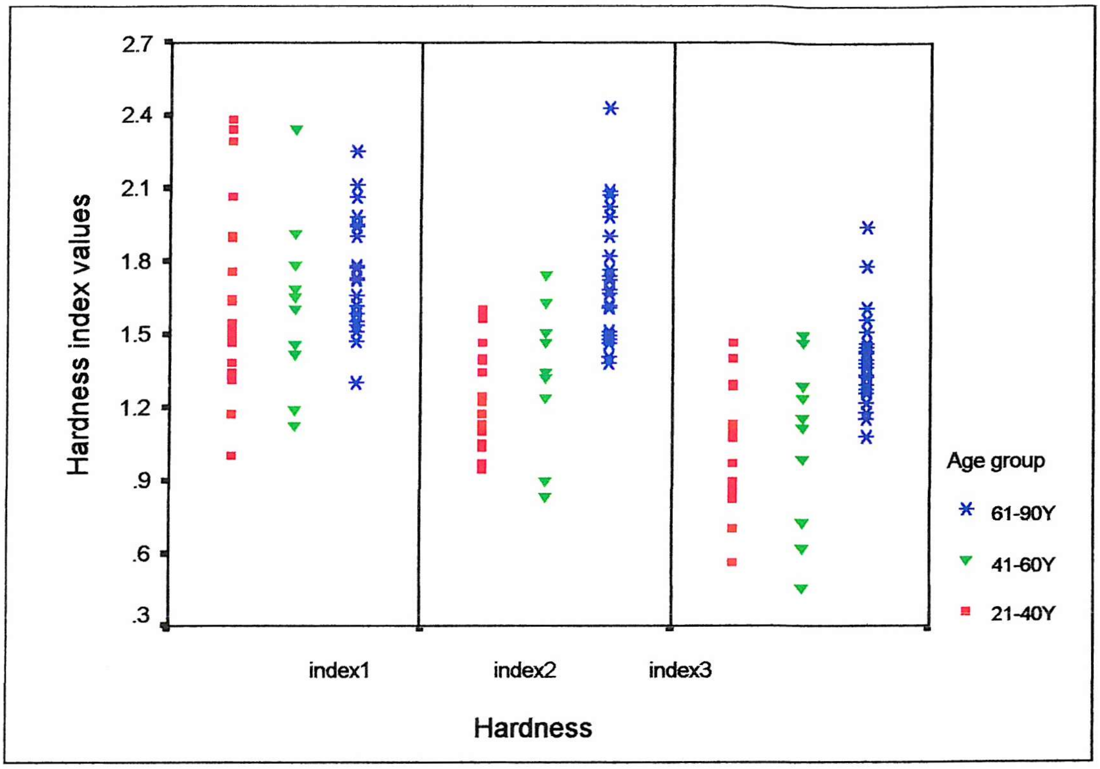


Figure 4.3 The effect of age on skin hardness indices measured in asymptomatic controls. A significant increase in hardness (index 2 and 3) was found with age in asymptomatic controls.

	21-40Y Male N=6	21-40Y Female N=14	41-60 Y Male N=5	41-60 Y Female N=5	61-90 Y Male N=7	61-90 Y Female N=16	Significance
hardness index 1	1.5 (1 & 2.07)	1.55 (1.17 & 2.39)	1.65 (1.12 & 2.34)	1.6 (1.41 & 1.91)	1.91 (1.51 & 2.11)	1.76 (1.3 & 2.25)	P=0.368
hardness index 2	1.01 (0.94 & 1.22)	1.29 (1.03 & 1.6)	1.32 (0.82 & 1.47)	1.5 (1.23 & 1.74)	1.46 (1.38 & 2.09)	1.73 (1.49 & 2.43)	**P<0.001**
hardness index 3	0.77 (0.56 & 1.13)	0.89 (0.82 & 1.47)	0.73 (0.46 & 1.15)	1.28 (0.99 & 1.49)	1.3 (1.08 & 1.46)	1.41 (1.22 & 1.94)	**P<0.001**

Table 4.4 The combined effect of age and sex on skin hardness indices measured in asymptomatic controls.

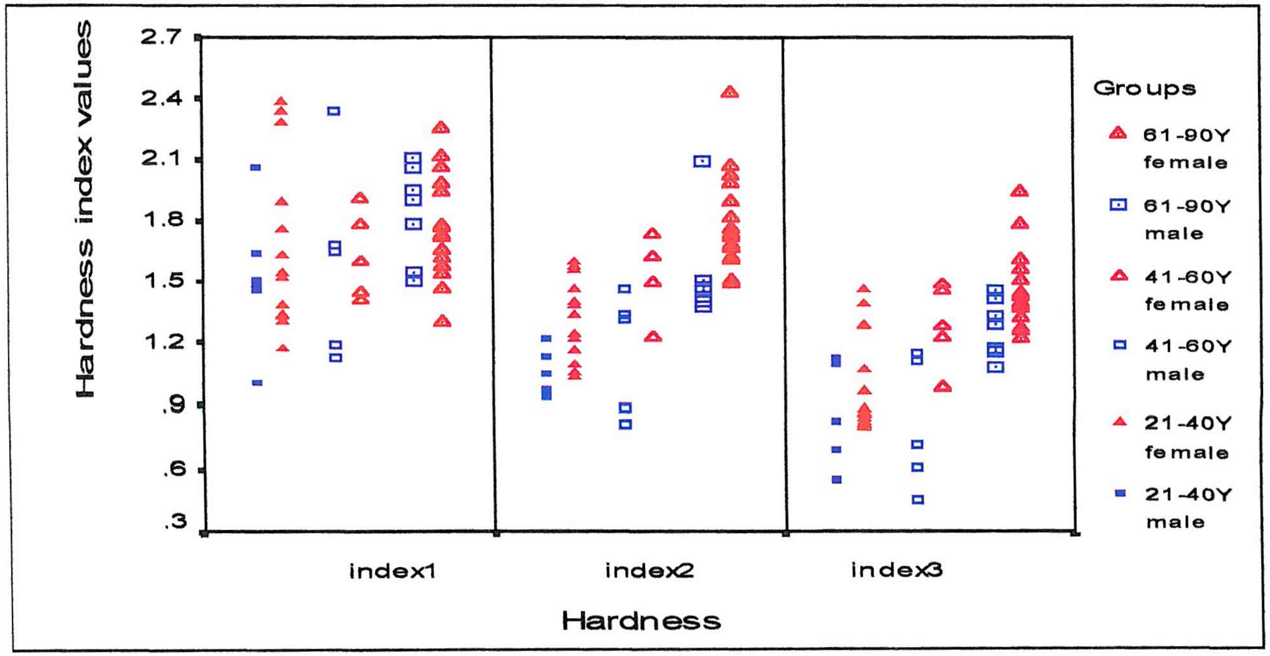


Figure 4.4 The combined effect of age and sex on skin hardness indices. A significant increase in cutaneous hardness (index 2 & 3) in the females compared to males and with age in both sex groups.

4.3 Cutaneous extensibility and relaxation studies

Method

A group of 80 asymptomatic controls (29M, 51F, mean age 48.3 years, age range 18-83 years) were studied. The exclusion criteria were skin disorders treated previously with steroids, pregnancy, diabetics, CVI, known heart disorders, cancer and other terminal illness. After acclimatisation and area identification the same extension protocol described in section 3.2.3 was used in the forearms and legs. Data are presented in appendix 11-14, in tables 4.5-4.8 as mean ± 1sd for Fpeak and as median (min & max) for relaxation time and displayed graphically in figures 4.5-4.8.

Statistical analysis

Regional variations in both Fpeak and relaxation time were examined using Paired sample T-test and Wilcoxon test. Independent sample T-test and Mann-Whitney test were used to examine differences between sexes in extensibility and relaxation indices. Changes with age and the combined effect of age and sex on extensibility and relaxation indices were examined using Anova-test and Kruskal-Wallis tests.

Results

Data from 4 forearms and 9 legs were excluded, eight subjects dropped from the study due to shortage of time whereas the inability to glue the extensometer feet took place in three extremities. Measurements were discontinued due to erythema in one patient, the probe was detached in one subject and the presence of involuntary movement in one subject forearm was the cause of discarding the data.

Location	Log Fpeak	Log Relaxation time
Forearm	1.21±0.64	2.58 (2.15 & 4.35)
Leg	2.73±0.35	2.78 (2.16 & 6.4)
Significance	**P<0.001**	**P<0.001**

Table 4.5 Regional variation in force at maximum extension (Fpeak) and relaxation time.

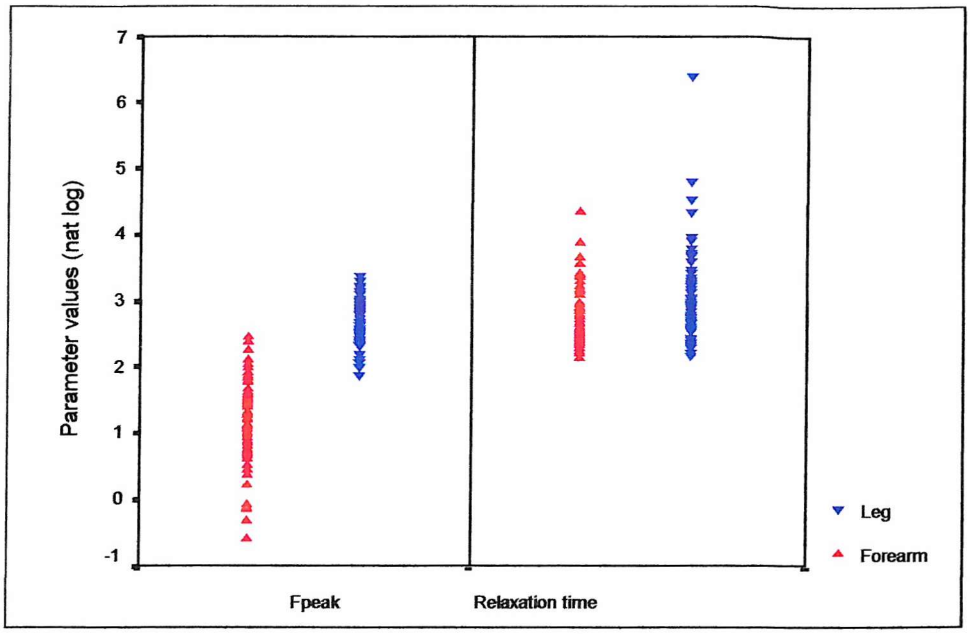


Figure 4.5 Regional variation in Fpeak and relaxation time. A significant increase in both Fpeak and relaxation time were found in legs compared to forearms of asymptomatic controls.

Indices	Male (N=24)	Female (N=43)	Significance
Extensibility	1.35±0.61	1.61±0.64	P=0.106
Relaxation	0.17 (-0.57 & 3.24)	0.26 (-1.98 & 1.87)	P=0.67

Table 4.6 The differences in extensibility and relaxation indices between sexes

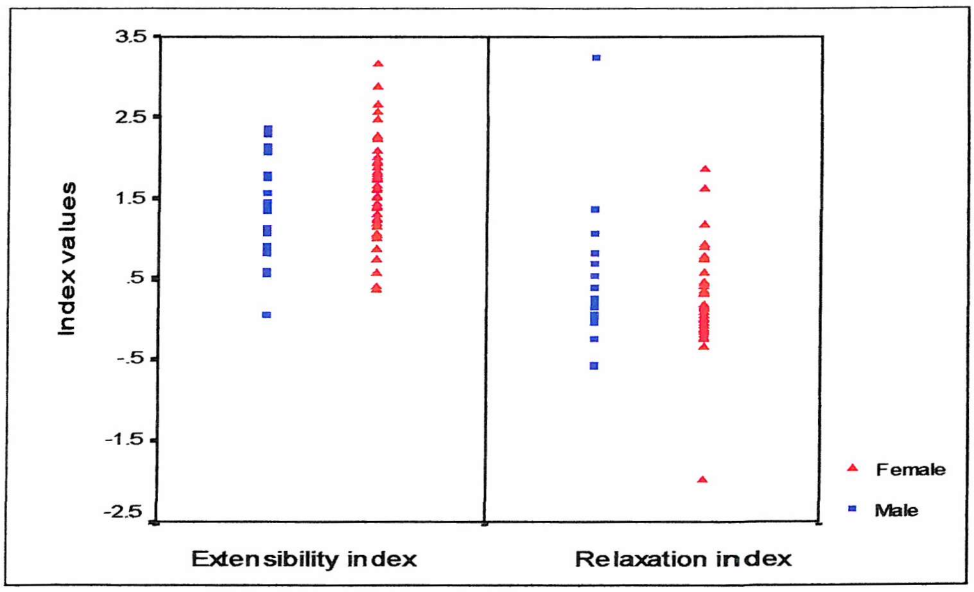


Figure 4.6 Differences in extensibility and relaxation indices according to sex. Non-significant differences in extensibility and relaxation indices were found between males and females controls.

Indices	21-40 years (N=25)	41-60 years (N=20)	61-90 years (N=22)	Significance
Extensibility	1.26±0.48	1.28±0.56	2.02±0.59	P<0.001
Relaxation	0.2 (-0.57 & 1.62)	0.13 (-0.55 & 3.24)	0.22 (-1.98 & 0.88)	P=0.96

Table 4.7 The effect of age on skin extensibility and relaxation indices measured in asymptomatic controls.

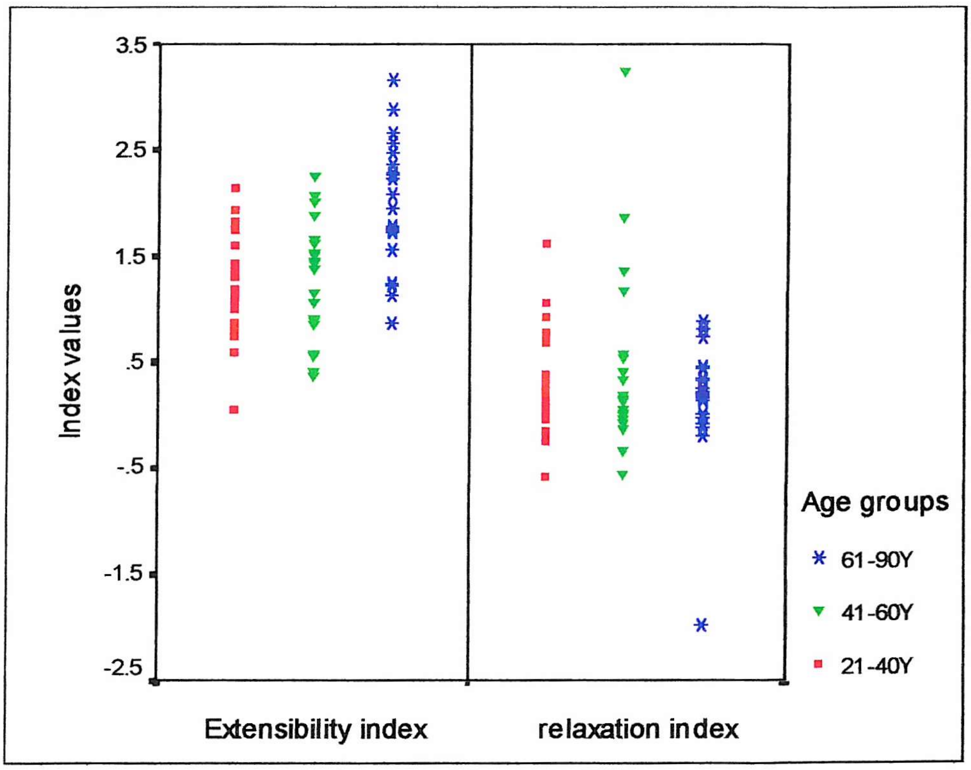


Figure 4.7 The effect of age on skin extensibility and relaxation indices measured in asymptomatic controls. A significant increase in extensibility index in the elderly was found, whereas the change in relaxation index with age was statistically non-significant.

Indices	21-40Y Male N=11	21-40Y Female N=14	41-60 Y Male N=14	41-60 Y Female N=6	61-90 Y Male N=7	61-90 Y Female N=15	Significance
Extensibility	1.15±0.57	1.35±0.38	1.12±0.55	1.34±0.58	1.85±0.43	2.09±0.64	**P<0.001**
Relaxation	0.14 (-0.57 & 1.05)	0.33 (-0.24 & 1.62)	0.27 (-0.55 & 3.24)	0.13 (-0.33 & 1.87)	0.19 (-0.01 & 0.82)	0.34 (-1.98 & 0.88)	P=0.92

Table 4.8 The combined effect of age and sex on skin extensibility and relaxation indices measured in asymptomatic controls.

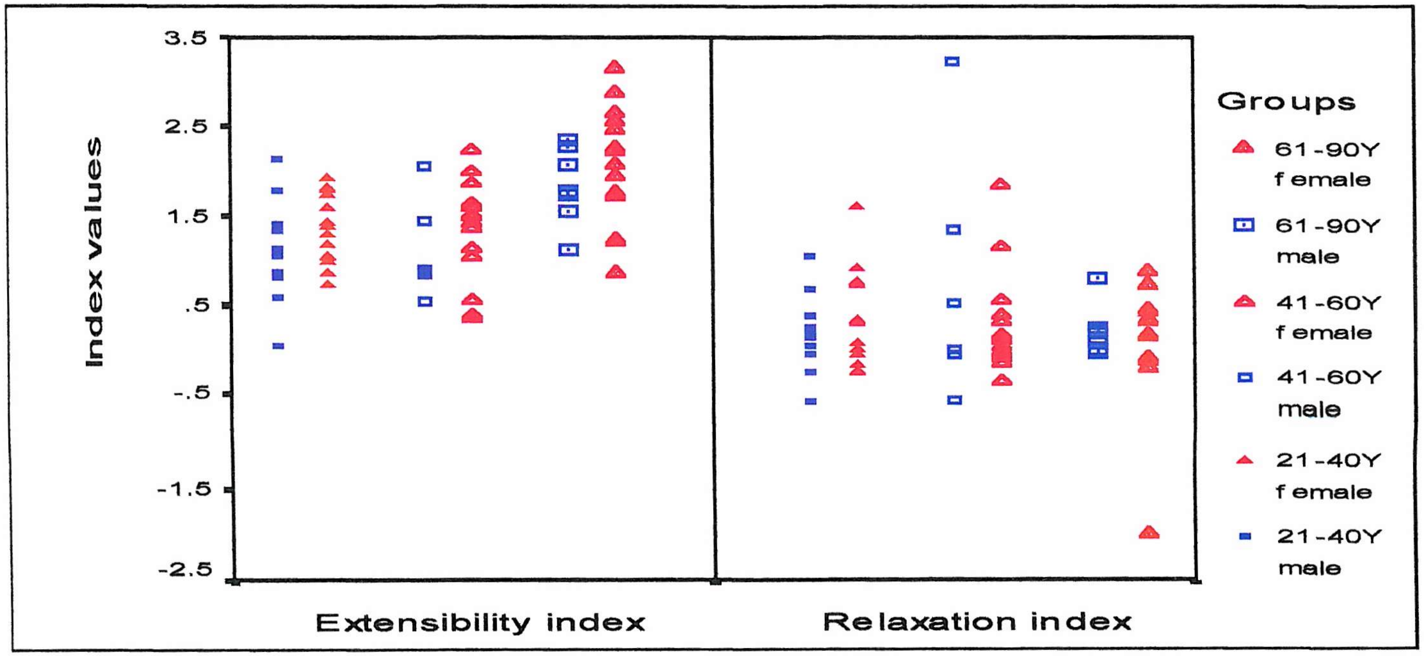


Figure 4.8 The combined effect of age and sex on skin extensibility and relaxation indices measured in asymptomatic controls. A significant increase in extensibility index was found in elderly within each sex group. Changes in relaxation index were not significant.

4.4 Changes in the cutaneous microcirculation during skin extension/relaxation.

Method

A group of 53 asymptomatic controls (24M, 29F, mean age 49.9 years, age range 22-74 years) were studied. The exclusion criteria were skin disorders treated previously with steroids, pregnancy, diabetes, CVI, known heart disorders, cancer and other terminal illness. Both forearms and legs were tested; changes in the cutaneous microcirculation were examined during the application of cutaneous extension/relaxation. The protocols used for cutaneous microcirculation measurement, section 3.3.7.1, and cutaneous extension, section 3.2.3 were used. Data are presented in appendices 15-22, in tables 4.9-4.16 as median (min & max) and displayed graphically in figures 4.9- 4.22.

Statistical analysis

The mean of the flux, during baseline, extension phase and during 1 minute interval of the relaxation phase were calculated for both extremities. During the process of cutaneous extension and relaxation, data were examined in its original form in arbitrary units (A.U.) and as a %change in flux = $(\text{flux}_{\text{extension-relaxation}} - \text{flux}_{\text{baseline}})*100/\ \text{flux}_{\text{baseline}}$. A positive %change in flux suggests a rise in flux above baseline level and a negative %change in Flux suggest a drop in flux below baseline level. In addition, the slopes of the %change in flux, during the extension-relaxation phases and during the relaxation phase were studied. It was noted that during the 8 seconds extension phase, the flux reached a peak and then dropped below the baseline, so the time for the flux to peak during the extension phase in seconds was examined.

The effect of cutaneous stretching on the microcirculation were evaluated using Friedmen test, a non-parametric method equivalent to one sample repeated measure analysis, within forearms and legs. Differences between sexes were examined using Mann-Whitney test and Kruskal-Wallis test was used to examine the effect of age on the cutaneous microcirculation. The combined effects of sex and age on the cutaneous microcirculation were examined using Kruskal-Wallis test.

Results

Data from 4 forearms and 11 legs were excluded from the analysis, due to the unavailability of insufficient data during the relaxation phase (≥4 minutes in the forearm & ≥8 minutes in the leg).

Forearm (N=49)		Flux (A. U.)	%change in Flux
Baseline		33.00 (9.50 & 188.50)	
Extension		41.60 (17.30 & 188.40)	24.80 (-17.79 & 150.94)
Relaxation	1min	38.00 (15.10 & 138.60)	13.48 (-66.80 & 131.58)
	2min	43.80 (18.90 & 163.90)	37.07 (-55.53 & 200.91)
	3min	51.40 (17.20 & 181.70)	43.88 (-48.02 & 235.34)
	4min	45.40 (21.50 & 194.10)	50.00 (-45.06 & 257.49)
Significance		**P<0.001**	**P<0.001**

Table 4.9 The effect of cutaneous extension/relaxation on the microcirculation within the forearm of asymptomatic controls.

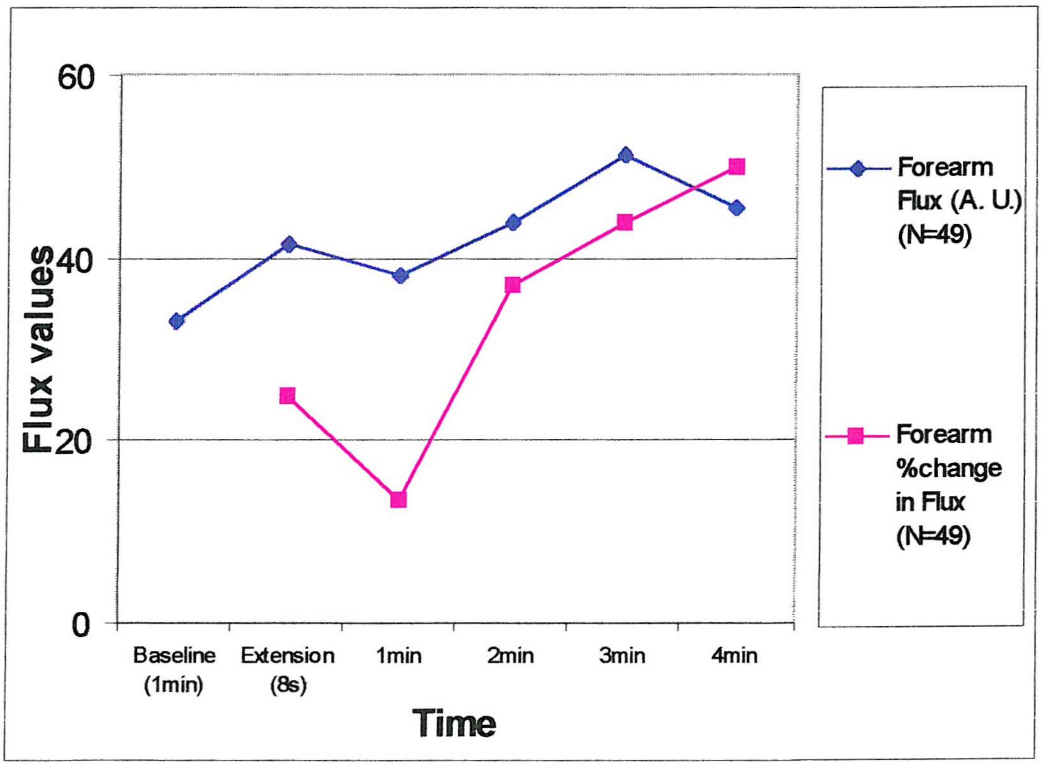


Figure 4.9 The cutaneous microcirculation (flux in arbitrary units and %change in flux) measured in controls forearm before and after the application of cutaneous extension/relaxation.

Leg (N=42)		Flux (A. U.)	%change in Flux
Baseline		25.45 (12.00 & 60.40)	
Extension		29.90 (15.80 & 70.70)	27.45 (-19.56 & 247.06)
Relaxation	1min	17.75 (7.00 & 58.00)	-19.49 (-67.90 & 36.18)
	2min	24.20 (10.90 & 80.00)	-.85 (-57.93 & 82.13)
	3min	26.05 (12.50 & 80.50)	19.21 (-50.25 & 156.18)
	4min	28.70 (13.10 & 110.20)	27.56 (-53.20 & 177.66)
	5min	31.05 (13.10 & 131.90)	26.87 (-41.13 & 178.27)
	6min	33.70 (13.90 & 147.70)	35.59 (-46.80 & 291.57)
	7min	36.05 (13.90 & 165.20)	34.58 (-53.20 & 335.39)
	8min	35.90 (12.60 & 176.40)	53.09 (-55.91 & 313.48)
Significance		**P<0.001**	**P<0.001**

Table 4.10 The effect of cutaneous extension/relaxation on the microcirculation within the leg of asymptomatic controls.

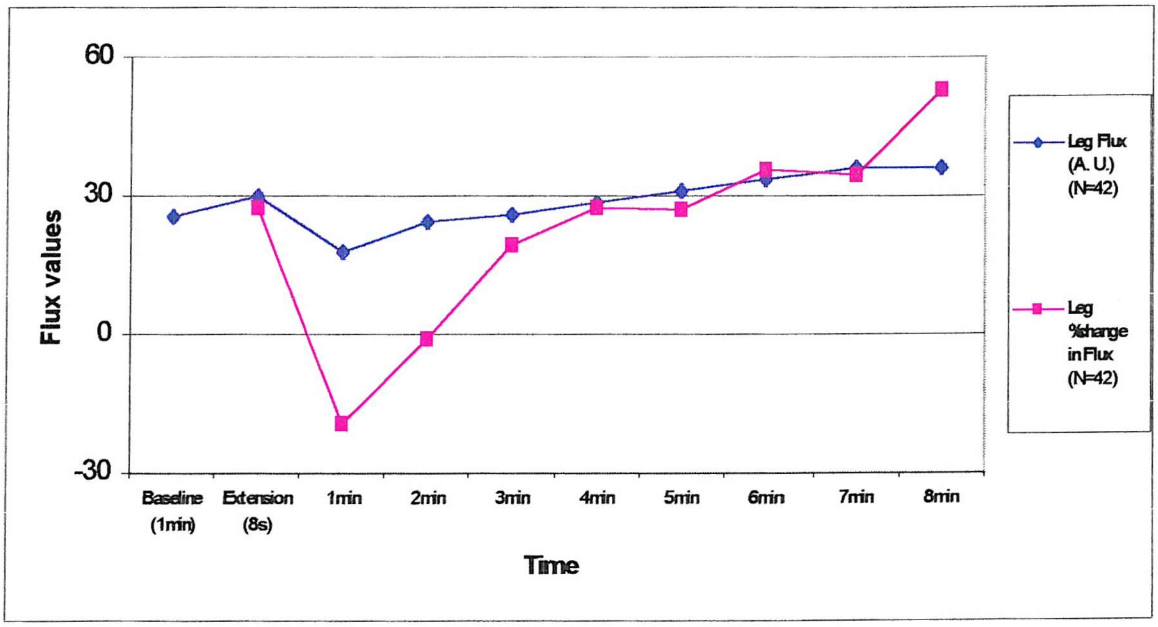


Figure 4.10 Changes in the cutaneous microcirculation (flux in arbitrary units and as %change in flux) with the application of cutaneous extension/relaxation, measured in controls legs.

Forearm		Flux (A. U.)			%change in Flux		
		Male (N=21)	Female (N=28)	Significance	Male (N=21)	Female (N=28)	Significance
Baseline		34.00 (13.3&188.5)	32.55 (9.5&156.5)	P= 0.473			
Extension		45.70 (19.9&188.4)	41.15 (17.3&146.5)	P=0.544	26.97 (-15.13&75.70)	24.54 (-17.79&150.94)	P=0.904
Relaxation	1min	41.70 (15.1&138.6)	35.55 (16.4&118.4)	P=0.385	11.68 (-32.51&120.26)	18.76 (-66.80&131.58)	P=0.443
	2min	44.60 (18.9&163.9)	41.95 (21.1&135.3)	P=0.585	21.84 (-16.67&200.91)	42.01 (-55.53&200.00)	P=0.249
	3min	54.90 (20.6&181.7)	45.35 (17.2&154.0)	P=0.84	40.77 (-26.05&234.24)	46.17 (-48.02&235.34)	P=0.258
	4min	45.80 (21.5&194.1)	44.95 (22.0&174.1)	P=0.824	48.45 (-13.20&163.94)	54.71 (-45.06&257.49)	P=0.225
Time to reach peak		5.00 (1.0&8.0)	4.00 (0.50&8.00)	P=0.464			
slope % change in flux (ext-4min)					7.72 (-13.98&39.45)	10.77 (-14.58&61.38)	P=0.332
slope % change in flux (1min-4min)					9.95 (-5.42&27.29)	11.55 (-3.86&63.12)	P=0.258

Table 4.11 Differences between sexes in cutaneous microcirculation within the forearm before and during extension/relaxation, measured with LDF in asymptomatic controls.

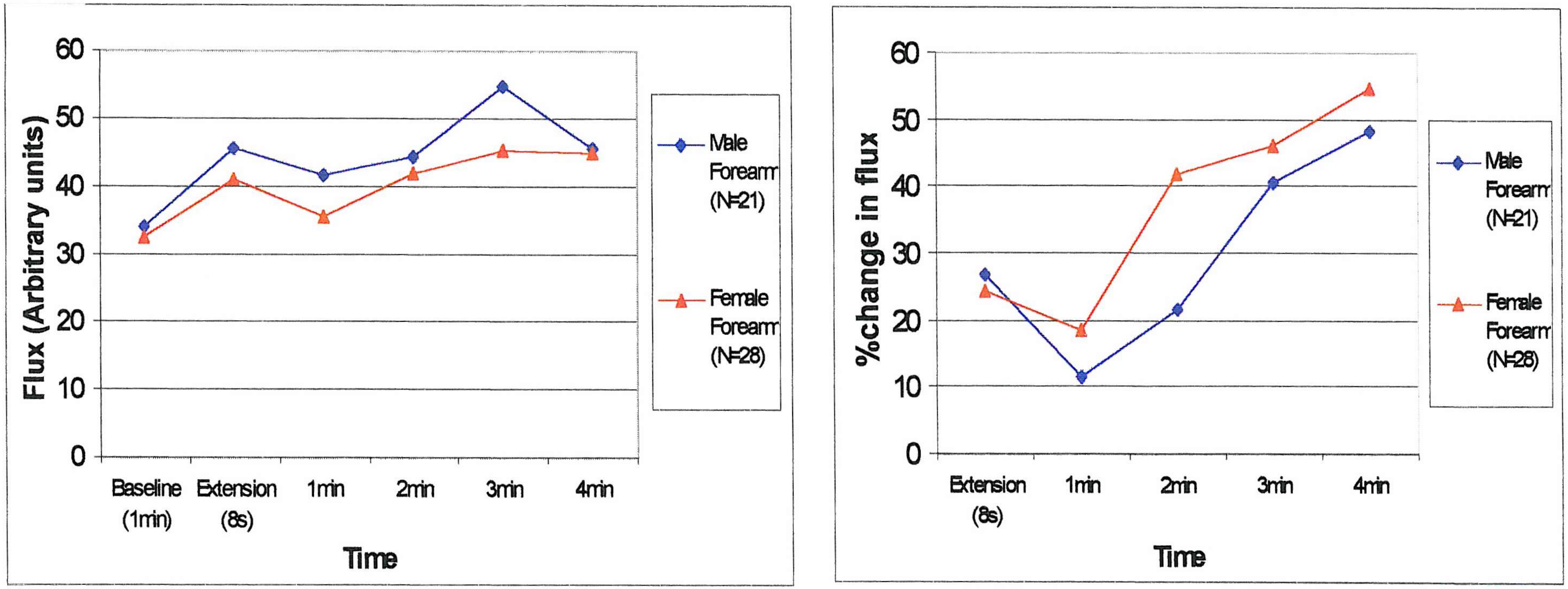


Figure 4.11 Differences between sexes in cutaneous microcirculation (flux in arbitrary units and as %change in flux) within the forearm before and during extension/relaxation, measured with LDF in asymptomatic controls. Non-significant differences were found between males and females in the forearm cutaneous microcirculation.

Leg		Flux (A. U.)			%change in Flux		
		Male(N=18)	Female (N=24)	Significance	Male (N=18)	Female (N=24)	Significance
Baseline		26.00 (13.5 & 49.4)	25.45 (12.0 & 60.4)	P=0.559			
Extension		33.25 (16.8 & 67.4)	29.70 (15.8 & 70.7)	P=0.77	27.45 (-11.39 & 247.06)	26.44 (-19.56 & 131.62)	P=0.76
Relaxation	1min	17.10 (7.0 & 58.0)	19.20 (8.7 & 39.3)	P=0.703	-21.16 (-65.76 & 27.91)	-16.43 (-67.90 & 36.18)	P=0.416
	2min	21.55 (10.9 & 80.0)	28.40 (11.4 & 55.8)	P=0.593	-14.73 (-55.67 & 71.43)	3.33 (-57.93 & 82.13)	P=0.213
	3min	24.05 (12.5 & 80.5)	31.20 (13.5 & 78.6)	P=0.394	-6.63 (-50.25 & 110.00)	23.72 (-42.80 & 156.18)	P=0.099
	4min	25.90 (14.1 & 110.2)	33.60 (13.1 & 96.1)	P=0.297	9.08 (-53.20 & 132.49)	46.68 (-40.22 & 177.66)	P=0.093
	5min	25.95 (13.1 & 131.9)	35.90 (13.7 & 111.0)	P=0.178	0.49 (-41.13 & 178.27)	42.21 (-37.27 & 169.10)	**P=0.025**
	6min	28.05 (14.0 & 147.7)	39.15 (13.9 & 108.0)	P=0.213	13.27 (-46.80 & 211.60)	56.65 (-35.42 & 291.57)	P=0.071
	7min	29.45 (13.9 & 165.2)	41.15 (14.2 & 122.1)	P=0.098	17.18 (-53.20 & 248.52)	66.23 (-26.57 & 335.39)	**P=0.04**
	8min	27.60 (12.6 & 176.4)	43.20 (15.8 & 127.4)	P=0.109	24.72 (-55.91 & 272.15)	70.78 (-27.31 & 313.48)	**P=0.027**
Time to reach peak		4 (1 & 6)	3.5 (1 & 8)	P=0.809			
slope % change in flux (ext-8min)					3.13 (-18.83&33.21)	8.35 (-5.15 & 40.15)	P=0.064
slope % change in flux (1min-8min)					7.06 (-1.15&37.12)	12.12 (-0.80 & 45.31)	**P=0.029**

Table 4.12 Differences between sexes in the cutaneous microcirculation within the leg before and during cutaneous extension/relaxation, measured with LDF in asymptomatic controls.

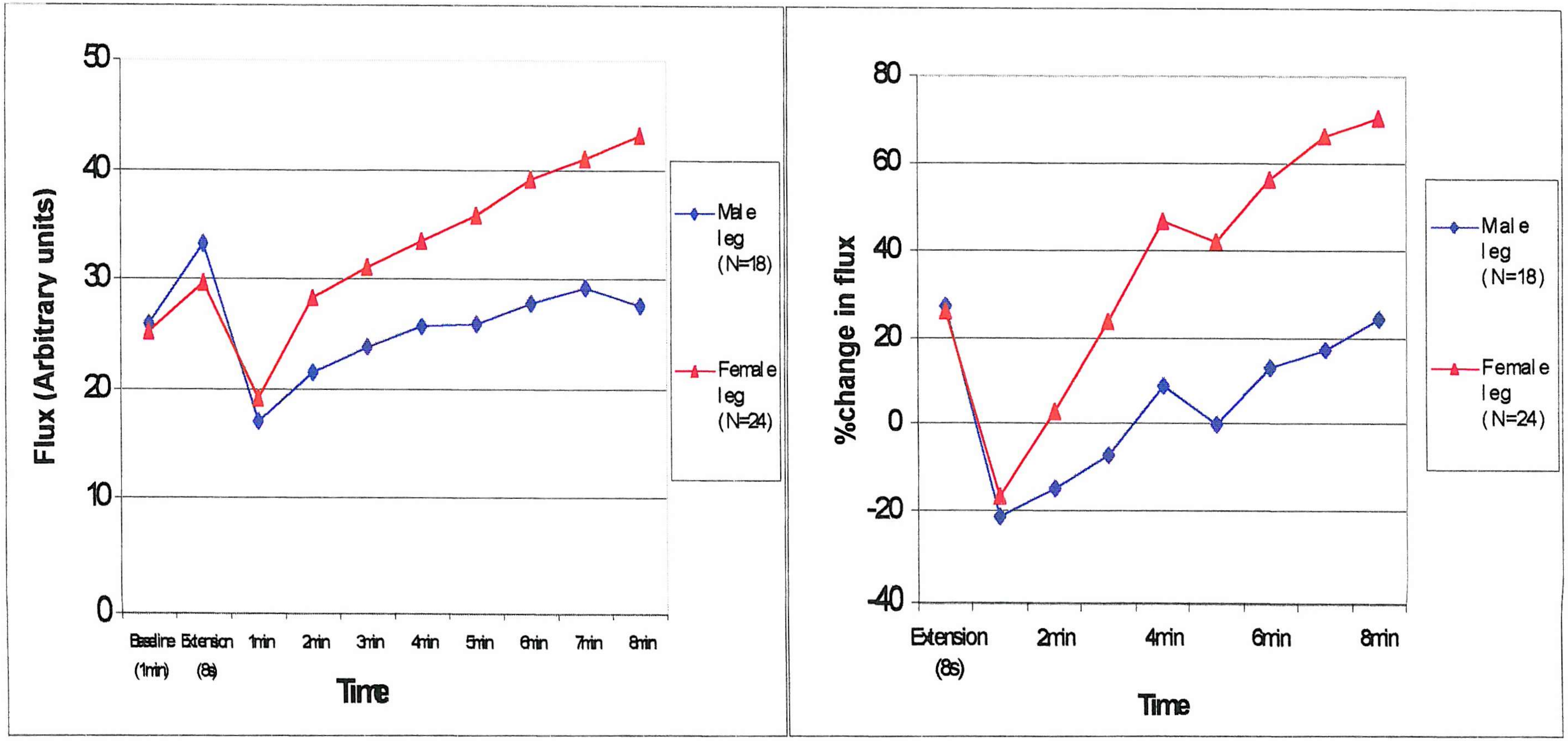


Figure 4.12 Differences between sexes in the cutaneous microcirculation within the leg before and during cutaneous extension/relaxation, measured with LDF in asymptomatic controls. Data are presented as flux (A.U.) and as %change in flux, a significant differences between males and females were found in the %change in flux at 5, 7 & 8 minutes.

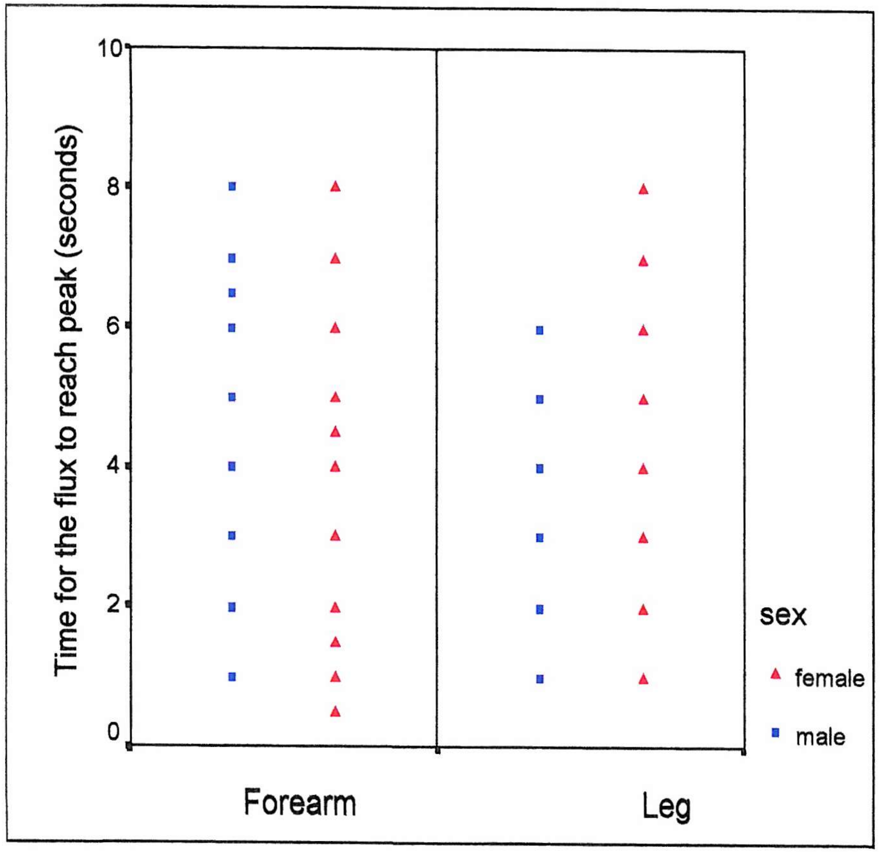


Figure 4.13 Differences between sexes in the time required for the flux to peak during extension. Non-significant differences between males and females were found in both extremities.

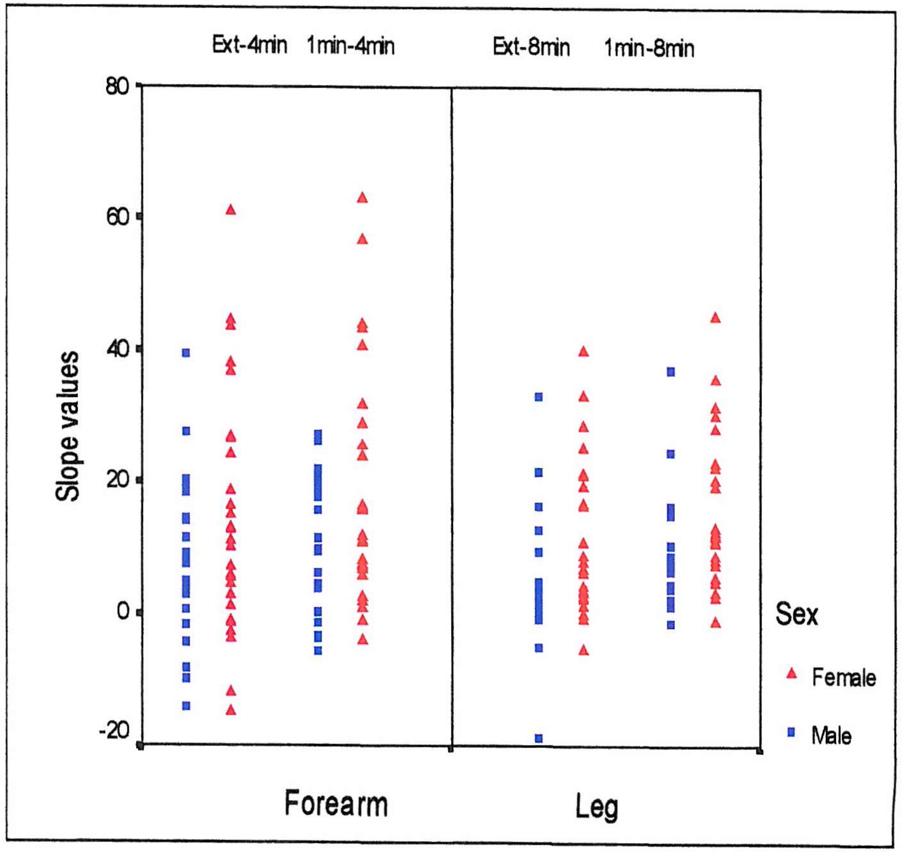


Figure 4.14 Differences between sexes in the slopes of the %change in flux measured in both extremities. Significant differences between males and females in the slope of the %change in flux measured between 1min-8min in the leg, whereas in the forearms, the differences between sexes were statistically non-significant.

Forearm		Flux (A. U.)				%change in Flux			
		21-40y N=16	41-60y N=13	61-90y N=20	Significance	21-40y N=16	41-60y N=13	61-90y N=20	Significance
Baseline		33.00 (13.30&188.5)	22.90 (9.50&65.7)	36.30 (20.20&156.50)	P=0.157				
Extension		40.05 (19.90&188.4)	40.90 (17.30&88.7)	46.75 (21.90&146.50)	P=0.609	25.63 (-15.13&93.23)	52.54 (-17.79&150.94)	16.68 (-6.39&50.00)	**P=0.017**
Relaxation	1min	38.25 (15.10&138.6)	32.20 (16.40&59.9)	39.10 (19.40&118.40)	P=0.314	26.03 (-32.51&113.64)	38.43 (-66.80&131.58)	6.04 (-24.35&48.28)	P=0.248
	2min	54.70 (18.90&163.9)	37.40 (22.50&74.4)	43.30 (21.10&135.30)	P=0.163	62.70 (-16.01&200.91)	69.87 (-55.53&200.00)	15.61 (-15.07&84.48)	**P=0.04**
	3min	65.15 (20.60&181.7)	41.40 (26.30&93.80)	47.70 (17.20&154.00)	P=0.192	59.47 (-6.65&234.24)	80.79 (-48.02&235.34)	25.03 (-26.05&125.86)	**P=0.024**
	4min	73.45 (21.50&194.1)	42.90 (27.70&97.10)	45.35 (22.00&174.10)	P=0.157	63.90 (-2.46&257.49)	87.34 (-45.06&193.16)	26.18 (-16.92&224.57)	**P=0.032**
Time to reach peak(s)		5 (1 & 8)	4 (4 & 8)	4 (1 & 8)	P=0.765				
slope % change in flux (ext-4min)						14.12 (-9.73&61.38)	12.89 (-14.58&43.84)	3.73 (-11.77&44.83)	P=0.073
slope % change in flux (1min-4min)						17.07 (1.21&63.12)	15.77 (-1.27&43.38)	7.43 (-5.42&57.03)	**P=0.04**

Table 4.13 The effect of age on cutaneous microcirculation in the forearm before and during the application of cutaneous extension/relaxation, measured with LDF in asymptomatic controls.

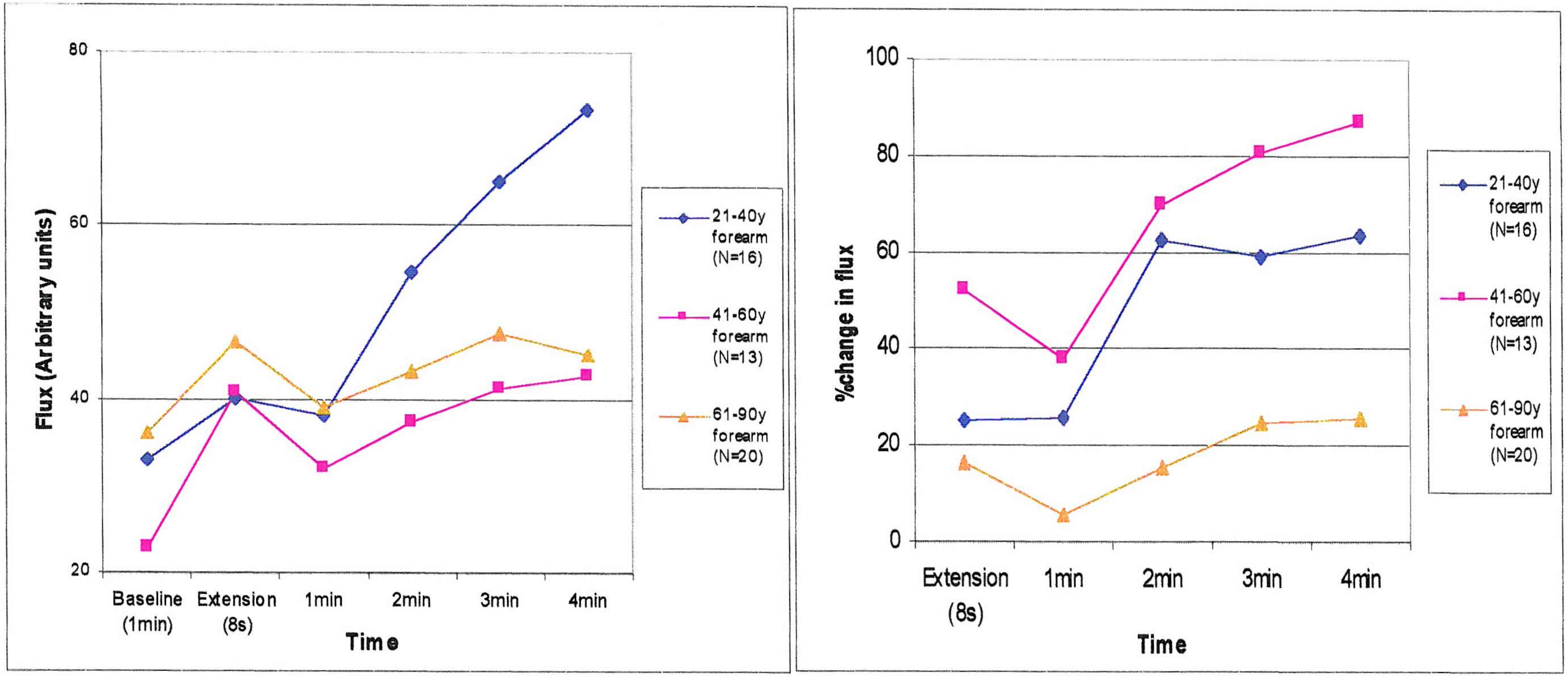


Figure 4.15 The effect of age on the forearm cutaneous microcirculation before and during the application of cutaneous extension/relaxation, measured with the LDF in asymptomatic controls. Data are presented as flux (A.U.) and as %change in flux, a significant decrease in the %change in flux with age was found at 2, 3 & 4 minutes.

Leg		Flux (A. U.)				%change in Flux			
		21-40y N=13	41-60y N=11	61-90y N=18	Significance	21-40y N=13	41-60y N=11	61-90y N=18	Significance
Baseline		30.10 (12.0&60.4)	25.40 (13.5&55.8)	19.80 (13.5&38.4)	P=0.168				
Extension		38.60 (15.8&70.7)	28.20 (18.7&67.4)	29.25 (16.8&67.4)	P=0.318	21.2 (-4.44&63.93)	38.27 (-19.56&105.84)	27.45 (-19.24&247.06)	P=0.732
Relaxation	1min	20.70 (7.0&44.1)	19.40 (8.7&58.00)	17.25 (10.30&42.2)	P=0.688	-26.13 (-65.76&27.91)	-17.01 (-67.90&22.36)	-20.20 (-62.06&36.18)	P=0.688
	2min	27.80 (12.0&52.3)	23.70 (11.4&80.00)	23.70 (10.90&55.8)	P=0.71	-4.92 (-55.67&71.43)	1.02 (-57.93&68.78)	-0.23 (-32.30&82.13)	P=0.561
	3min	27.90 (12.50&64.80)	26.10 (14.2&80.50)	25.65 (13.50&73.5)	P=0.94	3.83 (-50.25&101.66)	33.16 (-42.80&69.83)	20.84 (-25.78&156.18)	P=0.182
	4min	26.80 (14.10&72.20)	28.30 (16.2&110.2)	29.15 (13.10&80.8)	P=0.952	-0.39 (-53.20&100.00)	40.80 (-40.22&132.49)	41.72 (-18.23&177.66)	P=0.095
	5min	32.10 (16.10&78.90)	31.70 (17.0&131.9)	30.20 (13.10&75.5)	P=0.977	2.32 (-41.13&120.60)	35.77 (-37.27&178.27)	41.11 (-29.95&169.10)	P=0.206
	6min	38.20 (18.50&82.9)	35.10 (17.5&147.7)	32.70 (13.90&83.0)	P=0.985	17.21 (-46.80&115.61)	39.42 (-35.42&211.60)	55.80 (-25.13&291.57)	P=0.203
	7min	38.50 (18.90&87.70)	36.30 (19.9&165.2)	35.75 (13.90&84.7)	P=0.92	18.88 (-53.20&114.29)	53.28 (-26.57&248.52)	70.98 (-25.67&335.39)	P=0.147
	8min	42.90 (17.4&83.3)	35.60 (19.7&176.4)	35.90 (12.6&111.2)	P=0.983	49.02 (-55.91&131.67)	70.97 (-27.31&272.15)	68.44 (-2.62&313.48)	P=0.313
Time to reach peak		3 (2&6)	4 (1&8)	4 (1&7)	P=0.43				
slope % change in flux (ext-8min)						3.75 (-4.92&16.65)	5.11 (.12&33.21)	7.46 (-18.83&40.15)	P=0.337
slope % change in flux (1min-8min)						8.21 (1.23&20.32)	10.92 (1.72&37.12)	11.65 (-1.15&45.31)	P=0.343

Table 4.14 The effect of age on cutaneous microcirculation within the leg before and during cutaneous extension/relaxation, measured with LDF in asymptomatic controls.

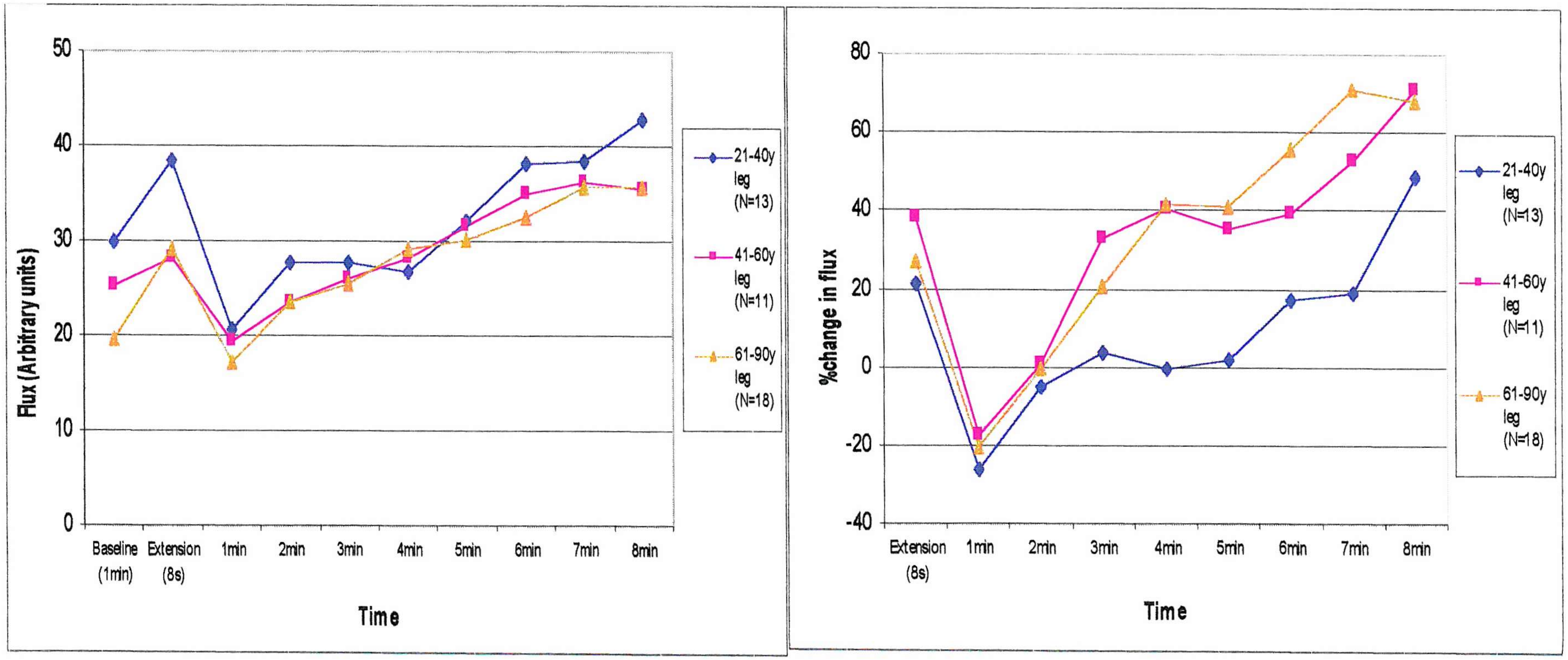


Figure 4.16 The effect of age on cutaneous microcirculation within the leg before and during cutaneous extension/relaxation, measured with LDF in asymptomatic controls. Non-significant differences were found in the leg cutaneous microcirculation with age. Data are presented as flux (A.U.) and as %change in flux.

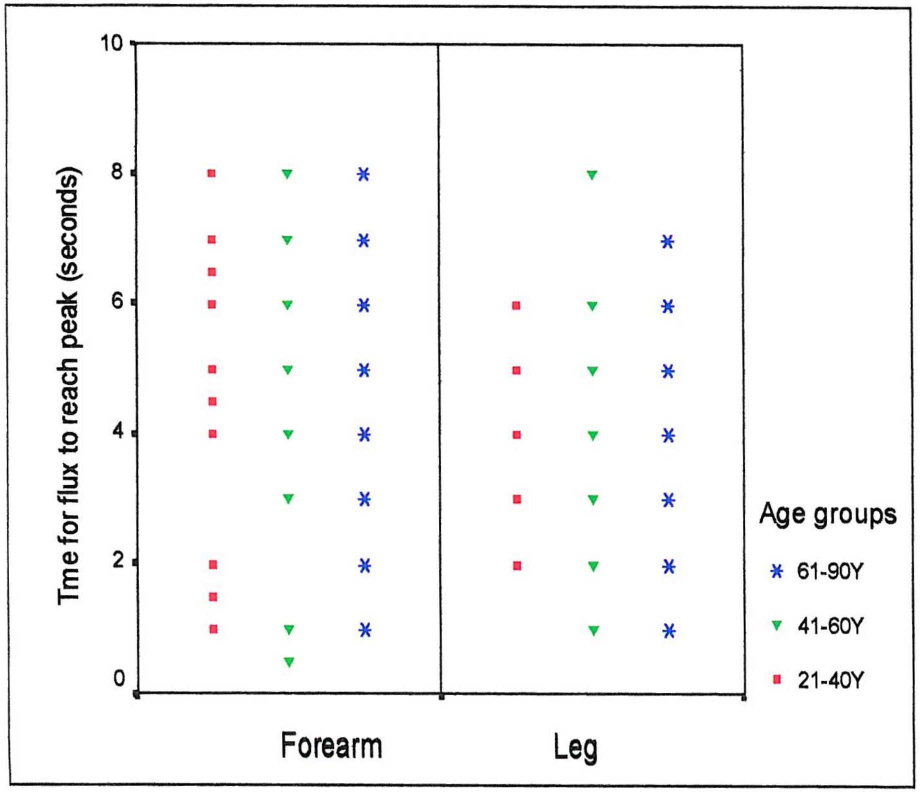


Figure 4.17 The effect of age on the time required for the flux to peak during the extension phase. Non-significant difference between the three groups was found in both extremities.

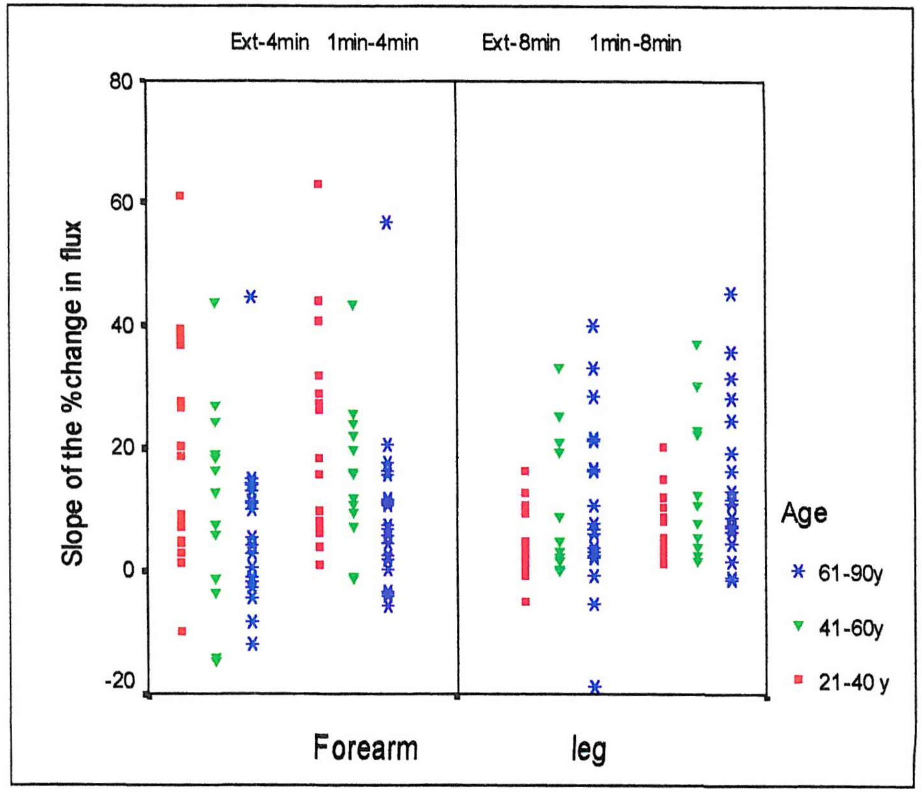


Figure 4.18 The effect of age on the slopes of the %change in flux measured in both extremities. Significant reduction in the slope of the %change in flux measured between 1min-4min of relaxation phase in the elderly forearm. In the leg, the effect of age was not statistically significant.

Forearm	Flux (A. U.)							%change in Flux						
	21-40y		41-60y		61-90y		Significance	21-40y		41-60y		61-90y		Significance
	Male	Female	Male	Female	Male	Female		Male	Female	Male	Female	Male	Female	
Baseline	36 (13.3&188.5)	32.55 (19.2&52.9)	33.75 (22.7&65.7)	21.2 (9.5&54.6)	34 (26.3&87.9)	40.2 (20.2&156.5)	P=0.351							
Extension	38.8 (19.9&188.4)	40.05 (30.7&69.8)	55.2 (37.1&88.7)	36 (17.3&60)	45.7 (33.5&100.5)	55.3 (21.9&146.5)	P=0.434	21.82 (-15.13&59.11)	28.12 (2.71&93.23)	57.99 (35.01&75.70)	51.13 (-17.79&150.94)	14.33 (1.92&44.16)	19.02 (-6.39&50.00)	P=0.096
Relaxation 1min	37.15 (15.1&138.6)	38.25 (32&71.4)	51.85 (32.2&59.9)	31.2 (16.4&58.3)	39.9 (26.5&88.5)	38.3 (19.4&118.4)	P=0.265	20.68 (-32.51&113.64)	29.61 (-25.47&84.38)	29.23 (-9.04&120.26)	38.43 (-66.80&131.58)	3.58 (-16.40&27.95)	8.50 (-24.35&48.28)	P=0.599
Relaxation 2min	48.5 (18.9&163.9)	59.35 (36&90.3)	61.05 (29.5&74.4)	32.8 (22.5&58.2)	43.8 (31.5&76)	42.8 (21.1&135.3)	P=0.225	47.89 (-16.01&200.91)	79.10 (14.61&158.30)	66.28 (-16.67&127.75)	69.87 (-55.53&200.00)	10.29 (-13.54&47.47)	16.18 (-15.07&84.48)	P=0.131
Relaxation 3min	58.2 (20.6&181.7)	69 (39&108.6)	63.3 (28.9&93.8)	39.1 (26.3&59.7)	44 (37.3&65)	52.4 (17.2&154.)	P=0.299	54.28 (-6.65&234.24)	104.21 (39.70&212.55)	82.44 (-18.36&143.61)	80.79 (-48.02&235.34)	9.71 (-26.05&90.57)	28.86 (-14.85&125.86)	P=0.101
Relaxation 4min	65.05 (21.5&194.1)	79.4 (38.7&122.7)	66.55 (3.9&97.1)	38.6 (27.7&56.8)	44.9 (37.9&76.3)	62.4 (22.174.1)	P=0.204	58.65 (-2.46&163.94)	118.41 (34.85&257.49)	93.99 (-12.71&146.70)	87.34 (-45.06&193.16)	16.84 (-13.20&62.61)	31.21 (-16.92&224.57)	P=0.117
Time to reach peak	5.75 (1&8)	3.25 (1&7)	3 (1&6)	5 (0.5&8)	5 (2&8)	4 (1&8)	P=0.6							
slope % change in flux (ext-4min)								8.93 (-9.73&39.45)	22.73 (1.52&61.38)	13.05 (-13.98&18.99)	12.89 (-14.58&43.84)	0.75 (-8.18&14.44)	5.80 (-11.77&44.83)	P=0.255
slope % change in flux (1min-4min)								12.83 (4.12&27.29)	30.58 (1.21&63.12)	14.73 (-1.27&22.15)	15.77 (-0.92&43.38)	4.55 (-5.42&20.63)	7.73 (-3.86&57.03)	P=0.162

Table 4.15 The combined effect of age & sex on cutaneous microcirculation within the forearm before and during the application of cutaneous extension/relaxation, measured with LDF in asymptomatic controls. No significant differences were found between the groups.

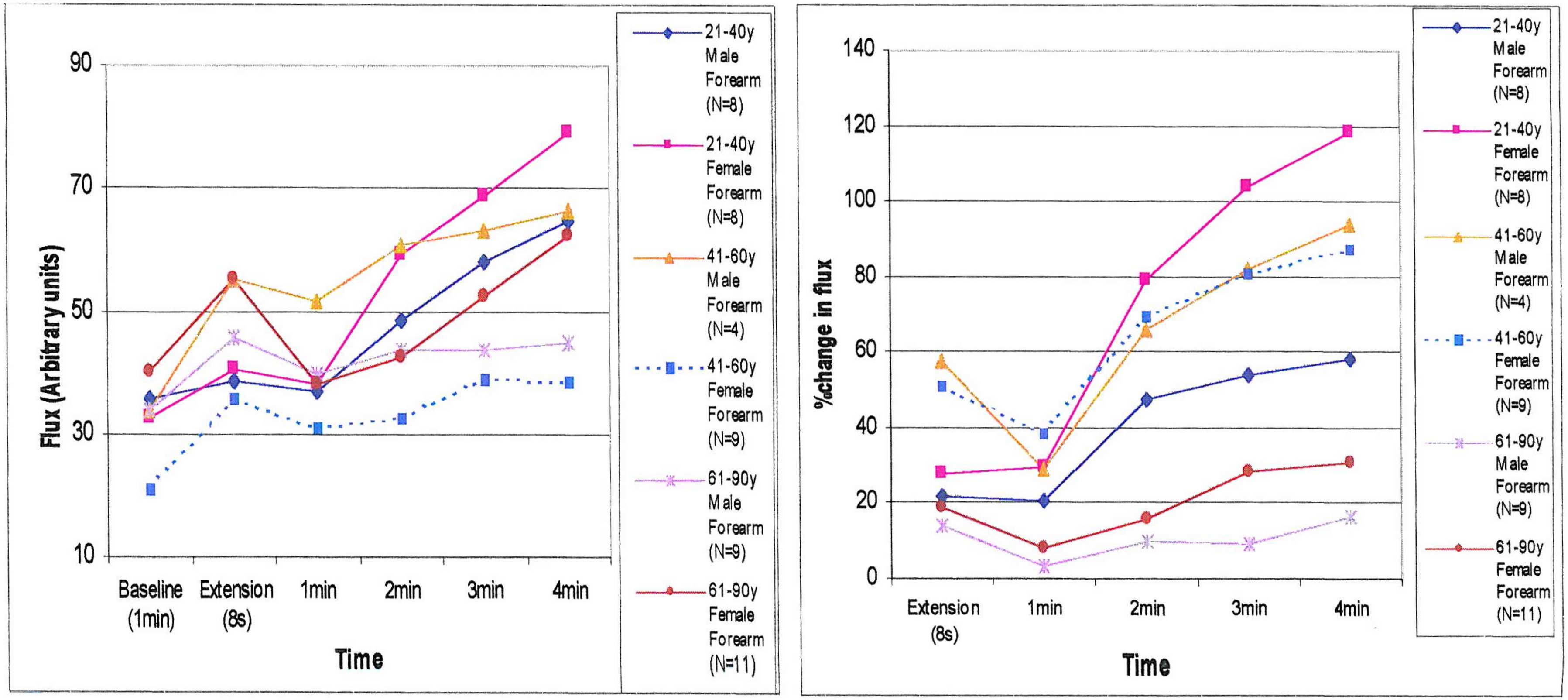


Figure 4.19 The combined effect of age & sex on cutaneous microcirculation (flux & %change in flux) in the forearm before and during skin extension/relaxation, measured with the LDF in asymptomatic controls. No significant differences were found between groups.

Leg		Flux (A. U.)							%change in Flux						
		21-40y		41-60y		61-90y		significance	21-40y		41-60y		61-90y		significance
		Male	Female	Male	Female	Male	Female		Male	Female	Male	Female	Male	Female	
Baseline		35.35 (18.0&49.4)	26.4 (12&60.4)	35 (20.1&47.4)	25.4 (13.5&55.8)	19.2 (13.5&38.4)	20.60 (14.3&36.9)	P=0.419							
Extension		43.95 (17.2&58.9)	38.6 (15.8&70.7)	35.05 (23.1&67.4)	28.2 (18.7&46.7)	28.25 (16.8&64.9)	29.25 (18.1&67.4)	P=0.75	23.70 (-4.44&43.66)	21.21 (-2.82&63.93)	21.01 (-11.39&42.19)	38.27 (-19.56&105.84)	27.45 (-4.95&247.06)	34.99 (-19.24&131.62)	P=0.977
Relaxation	1min	18.95 (7&44.1)	24.5 (10.5&39.3)	24.1 (13.2&58)	16.6 (8.7&38.2)	14.85 (10.3&42.2)	19.2 (12.2&37.1)	P=0.633	-35.17 (-65.76&27.91)	-26.13 (-47.68&-3.92)	-21.36 (-41.59&22.36)	-17.01 (-67.90&-2.36)	-21.16 (-48.64&20.57)	3.30 (-62.06&36.18)	P=0.77
	2min	24.1 (12&51.6)	31.9 (13.4&52.3)	30.75 (17.5&80)	19.8 (11.4&55.8)	17.95 (10.9&55.8)	28.4 (13.4&53)	P=0.631	-14.63 (-55.67&71.43)	-4.92 (-29.47&33.73)	-1.17 (-22.57&68.78)	1.02 (-57.93&33.86)	-16.00 (-32.30&59.43)	14.49 (-26.02&82.13)	P=0.479
	3min	28.95 (12.5&60.7)	27.9 (17.2&64.8)	32.2 (16.8&80.5)	26.1 (14.2&78.6)	20.65 (14.7&73.5)	35.55 (13.5&70.9)	P=0.74	-6.93 (-50.25&101.66)	3.83 (-32.28&43.33)	5.18 (-25.66&69.83)	34.60 (-42.80&60.63)	-6.63 (-25.78&110)	47.11 (-6.50&156.18)	P=0.208
	4min	30.6 (14.1&60.2)	26.8 (19.8&72.2)	32.7 (23.6&110.2)	24.9 (16.2&96.1)	23.4 (16.9&69.1)	43.7 (13.1&80.8)	P=0.518	-3.43 (-53.20&100.00)	-0.39 (-24.67&65.00)	22.61 (-21.73&132.49)	46.92 (-40.22&88.58)	9.08 (-18.23&102.22)	83.88 (-8.39&177.66)	P=0.124
	5min	32.65 (16.1&66.4)	32.1 (23.2&78.9)	29.55 (24.6&131.9)	31.7 (17&111)	22.9 (13.1&75.5)	46.65 (13.7&75.2)	P=0.529	-1.74 (-41.13&120.60)	25.88 (-20.70&93.33)	18.36 (-29.54&178.27)	39.30 (-37.27&134.81)	-0.25 (-29.95&122.22)	100.17 (-4.20&169.10)	P=0.077
	6min	36.1 (18.5&64.9)	38.2 (21.9&82.9)	31.45 (23.9&147.7)	37.0 (17.5&108)	25.75 (14&81)	45.15 (13.9&83)	P=0.581	16.77 (-46.80&115.61)	19.67 (-17.05&102.50)	22.03 (-25.95&211.60)	57.48 (-35.42&174.07)	9.16 (-25.13&131.43)	90.90 (-2.80&291.57)	P=0.166
	7min	35.3 (18.9&64.5)	38.5 (22&87.7)	31.5 (26.1&165.2)	39.5 (19.9&122.1)	26.2 (13.9&84)	46.85 (14.2&84.7)	P=0.42	17.12 (-53.20&114.29)	20.22 (-26.49&110.00)	24.16 (-23.42&248.52)	61.88 (-26.57&192.59)	17.49 (-25.67&151.85)	102.12 (-0.70&335.39)	P=0.089
	8min	42.7 (17.4&73.9)	42.9 (27.8&83.3)	33.9 (25.6&176.4)	35.6 (19.7&127.4)	24.6 (12.6&87.4)	46.45 (15.8&111.2)	P=0.468	36.50 (-55.91&115.95)	56.58 (-16.56&131.67)	21.81 (-12.24&272.15)	71.53 (-27.31&163.70)	12.23 (-32.62&168.15)	110.07 (10.49&313.48)	P=0.124
Time to reach peak		3 (2&6)	3 (2&6)	4 (1&6)	4 (1&8)	5 (1&6)	3.5 (1&7)	P=0.781							
slope % change in flux (ext-8min)									3.38 (-4.92&12.75)	3.75 (-0.57&16.65)	3.48 (0.37&33.21)	8.88 (0.12&25.39)	3.14 (-18.83&21.79)	13.82 (-5.15&40.15)	P=0.216
slope % change in flux (1min-8min)									6.37 (1.23&15.16)	8.21 (3.36&20.32)	5.94 (1.72&37.12)	12.57 (2.68&30.39)	7.07 (-1.15&24.77)	16.41 (-0.80&45.31)	P=0.183

Table 4.16 The combined effect of age & sex on cutaneous microcirculation within the leg before and during cutaneous extension/relaxation measured with LDF in asymptomatic controls. No significant differences were found between groups.

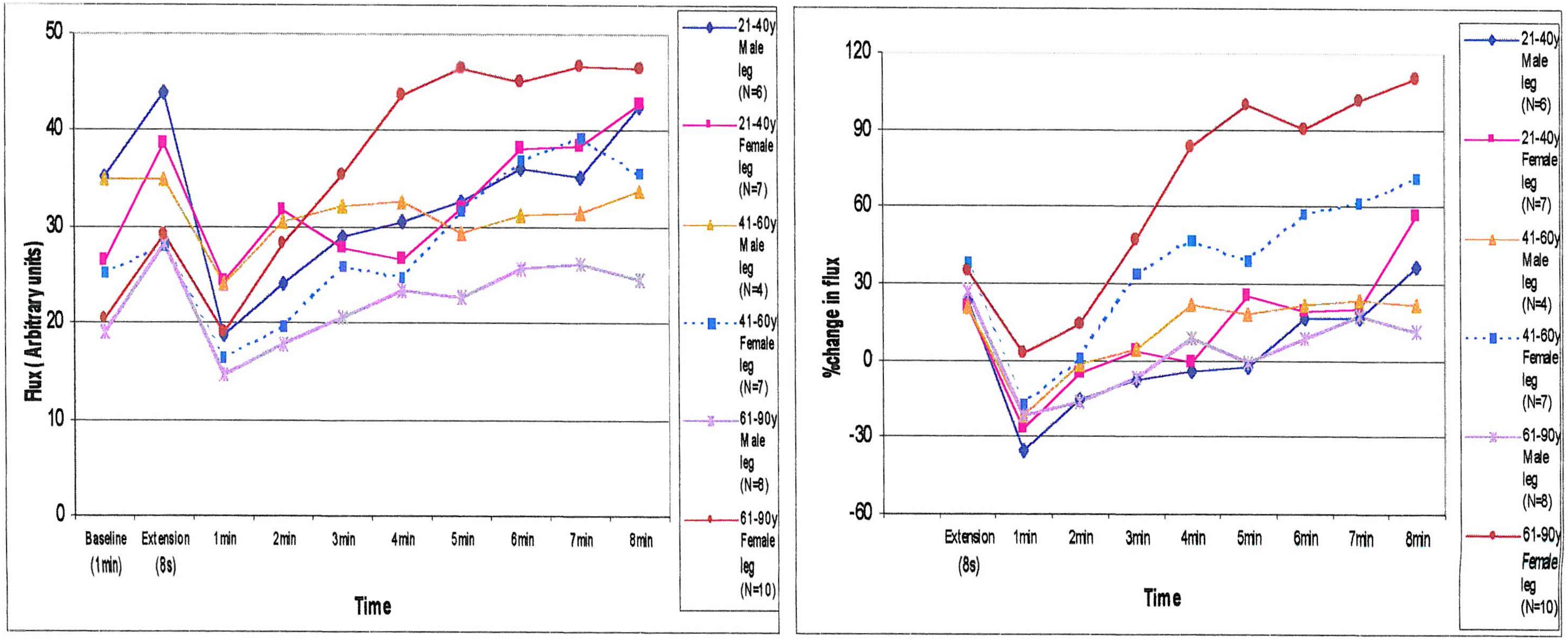


Figure 4.20 The combined effect of age & sex on cutaneous microcirculation (flux & %change in flux) in the leg before and during cutaneous extension/relaxation measured with LDF in asymptomatic controls. No significant changes with age or between sexes were found between groups.

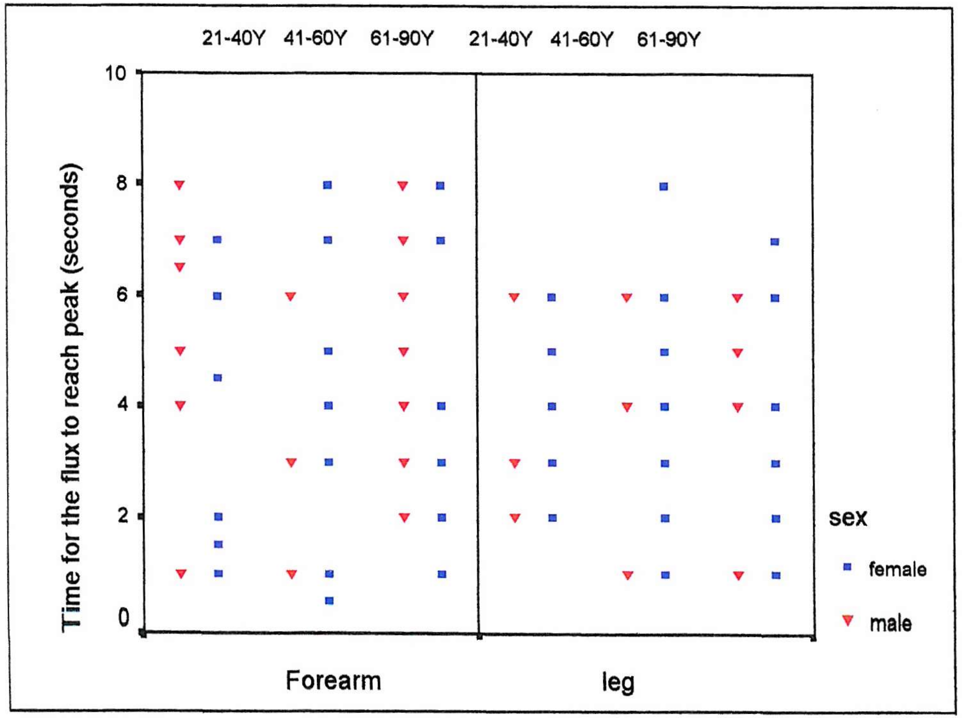


Figure 4.21 The combined effect of age & sex on time required for the flux to peak during extension phase in both extremities. Non-significant differences in the time required for the flux to peak during the extension phase were found in both extremities.

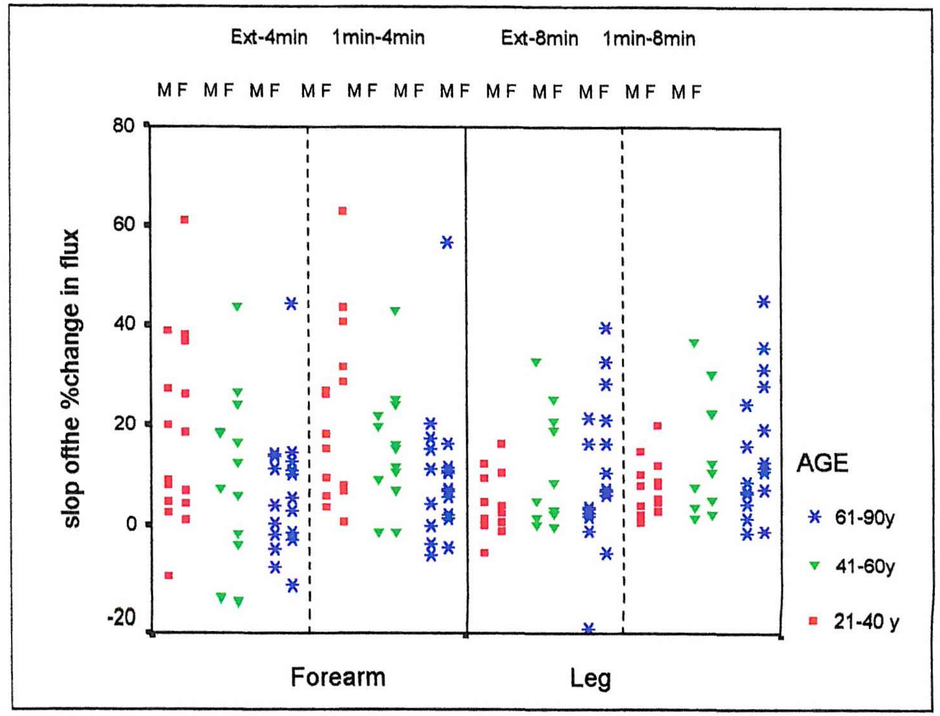


Figure 4.22 The combined effect of age & sex on the slopes of the %change in flux, measured in both extremities. Non-significant effects of age and sex on the slope of the %change in flux measured at extension-relaxation and during the relaxation phase in both extremities.

4.5 The postural vasoconstrictive response

Method

A group of 52 asymptomatic controls (22M, 30F, mean age 47.2 years, age range 21-74 years) were studied. The exclusion criteria were skin disorders treated previously with steroids, pregnancy, diabetes, CVI, known heart disorders, cancer and other terminal illness. The protocol described previously in section 3.3.7.2 was used in this study. Data from 104 legs were included in the analysis, and presented in appendices 23-26, in tables 4.17- 4.20 as median (min & max) and graphically in figures 4.23- 4.32.

Statistical Analysis

Mean baseline flux ($Flux_{bl}$) (over 1 minute), the drop in flux with leg lowering at 5,10,15,20,30 seconds ($Flux_{drop\ at\ 5,10,15,20,30}$) and the mean value between 60-120 seconds ($Flux_{drop\ at\ 90s}$) were extracted. Data were examined in arbitrary units (A.U.) and as a %drop in Flux [$(Flux_{bl} - Flux_{drop})*100/ Flux_{bl}$]. A positive %drop in flux implied a reduction in blood flow on leg lowering and a negative %drop in flux indicated an increase in blood flow with leg lowering. The gradient or slopes of the %Flux, between 5 seconds and 90 seconds and between 10 seconds and 90 seconds and the time needed for the flux to reach baseline values after leg lowering were also calculated.

Changes in the microcirculation during and after passive leg lowering were examined using Friedman test. Mann-Whitney test was applied to examine differences in the response between sexes. Kruskal-Wallis and Mann-Whitney tests were used to examine both the effect of age and the combined effect of age and sex on the response.

		Flux (A. U.)	% drop in Flux
Baseline		41.10 (5.70 & 542.60)	
Lowering	5s	49.90 (9.60 & 792.70)	-15.62 (-414.29 & 77.43)
	10s	41.10 (6.00 & 723.10)	8.11 (-256.39 & 80.61)
	15s	34.20 (6.40 & 723.80)	7.07 (-180.45 & 83.83)
	20s	28.20 (5.00 & 483.00)	21.11 (-151.04 & 87.22)
	30s	21.80 (3.90 & 506.60)	31.44 (-118.97 & 93.91)
	90s	19.70 (4.10 & 377.20)	47.08 (-121.85 & 87.38)
Significance		**P<0.001**	**P<0.001**

Table 4.17 The postural vasoconstrictive response. Changes in the cutaneous microcirculation with passive leg lowering measured in the pulp of the big toe of asymptomatic controls. The flux is presented both in arbitrary unit's (A.U.) and as %drop in flux.

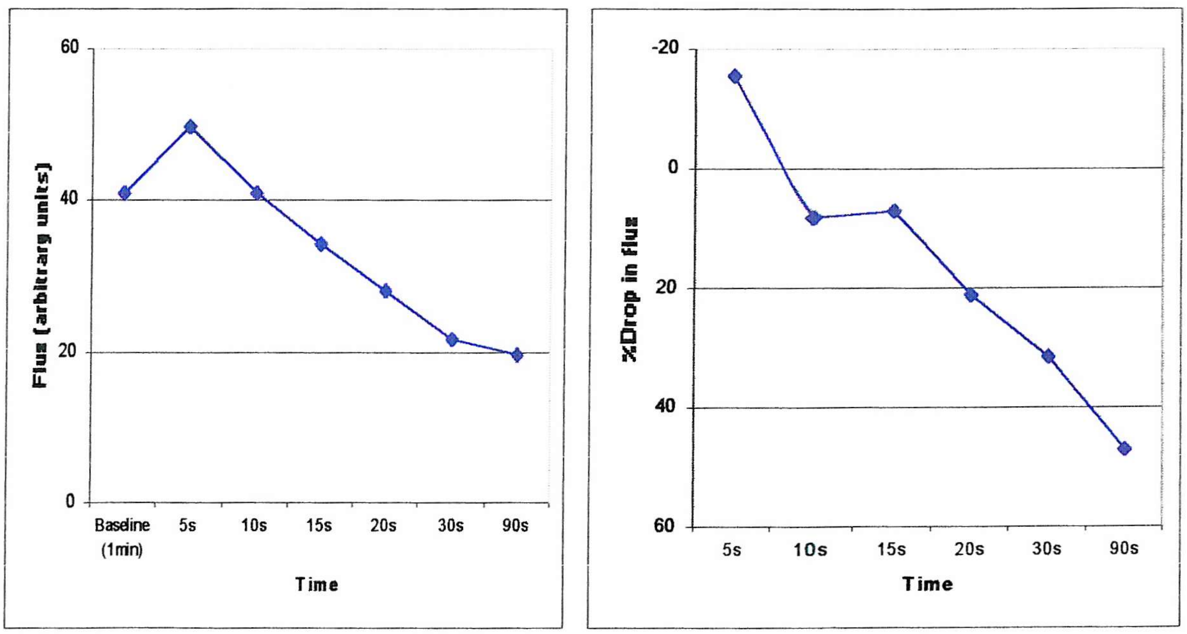


Figure 4.23 The postural vasoconstrictive response. Significant changes in the cutaneous microcirculation with passive leg lowering measured in the pulp of the big toe of asymptomatic controls. Data are presented as flux (A. U.) and %drop in flux.

		Flux (A. U.)			% drop in Flux		
		Male (N=44)	Female (N=60)	Significance	Male (N=44)	Female (N=60)	Significance
Baseline		50.4 (5.7 & 218.6)	33.4 (5.8 &542.6)	P=0.534			
Lowering	5s	49.1 (9.6 & 237.7)	51.6 (11 & 792.7)	P=0.815	-3.50 (-350.46&69.68)	-18.82 (-414.29&77.43)	P=0.34
	10s	41.75 (9.3 & 190.5)	40.3 (6 &723.1)	P=0.752	15.14 (-253.13&80.61)	1.90 (-256.39&77.16)	P=0.378
	15s	36.05 (7.7 & 155.5)	31 (6.4 & 723.8)	P=0.59	13.40 (-170.18&71.17)	5.71 (-180.45&83.83)	P=0.35
	20s	36.85 (5 & 213.3)	22.55 (7.5 & 483)	P=0.258	21.11 (-151.04&77.47)	21.16 (-112.50&87.22)	P=0.813
	30s	28.7 (3.9 & 223.6)	18.55 (5.2 & 506.6)	P=0.132	28.37 (-82.46&77.34)	32.89 (-118.97&93.91)	P=0.445
	90s	25.7 (4.1 & 176.1)	15.7 (4.3 & 377.2)	P=0.091	40.91 (-121.85&85.32)	52.86 (-99.66&87.38)	**P=0.016**
Time to reach baseline (s)		6 (1 & 120)	8.5 (1 & 120)	P=0.305			
slope % drop in flux (5s-90s)					0.4532 (-0.36&2.47)	0.6396 (-0.30&3.98)	**P=0.022**
slope % drop in flux (10s-90s)					0.3400 (-0.98&2.52)	0.5289 (-0.43&2.86)	**P=0.035**

Table 4.18 The postural vasoconstrictive response, differences between males & females during passive leg lowering as measured with LDF in asymptomatic controls

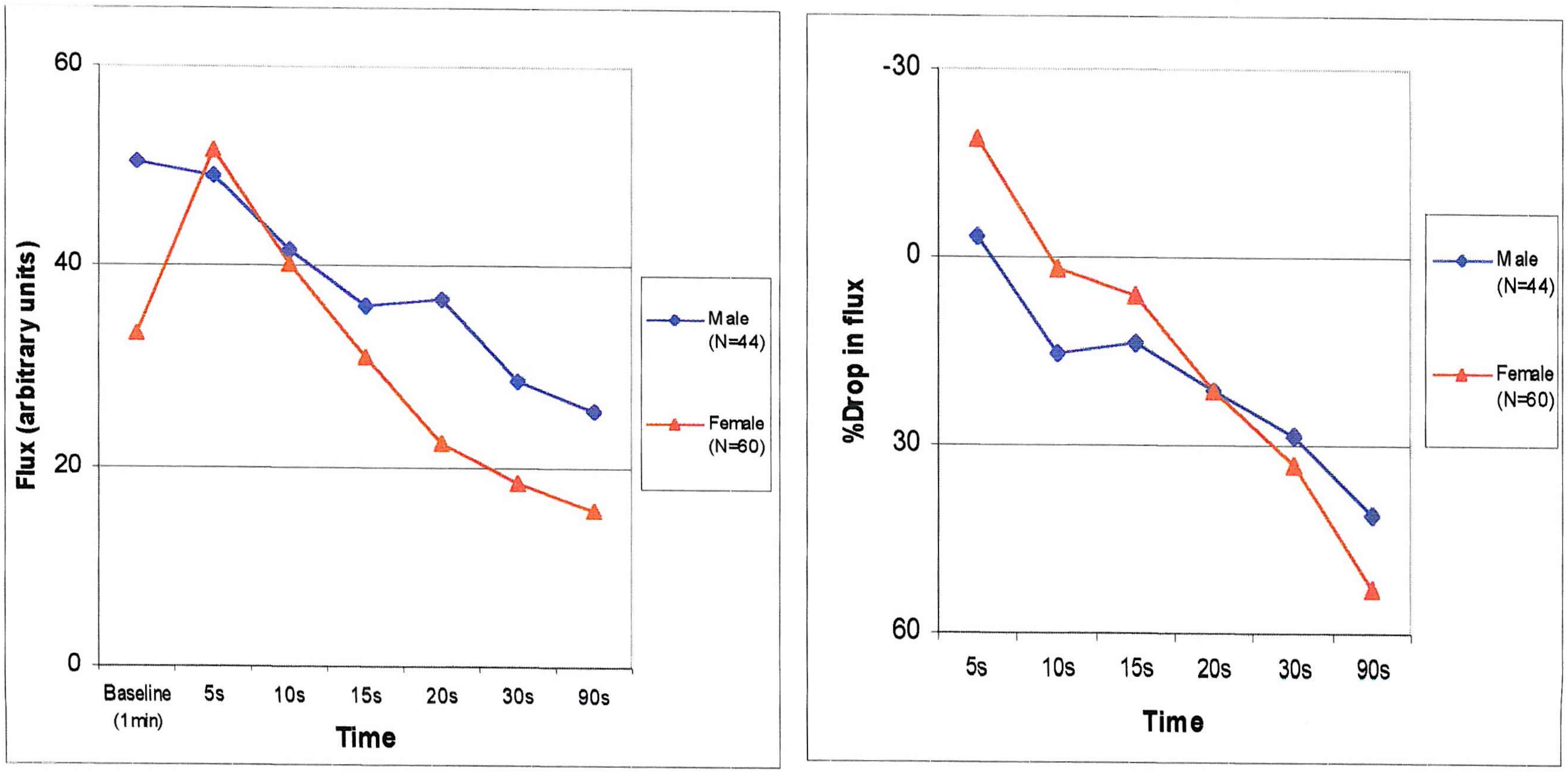


Figure 4.24 The postural vasoconstrictive response, differences between males & females during passive leg lowering, measured with LDF in asymptomatic controls. A significant increase in the %drop in flux was found in the females at 90s.

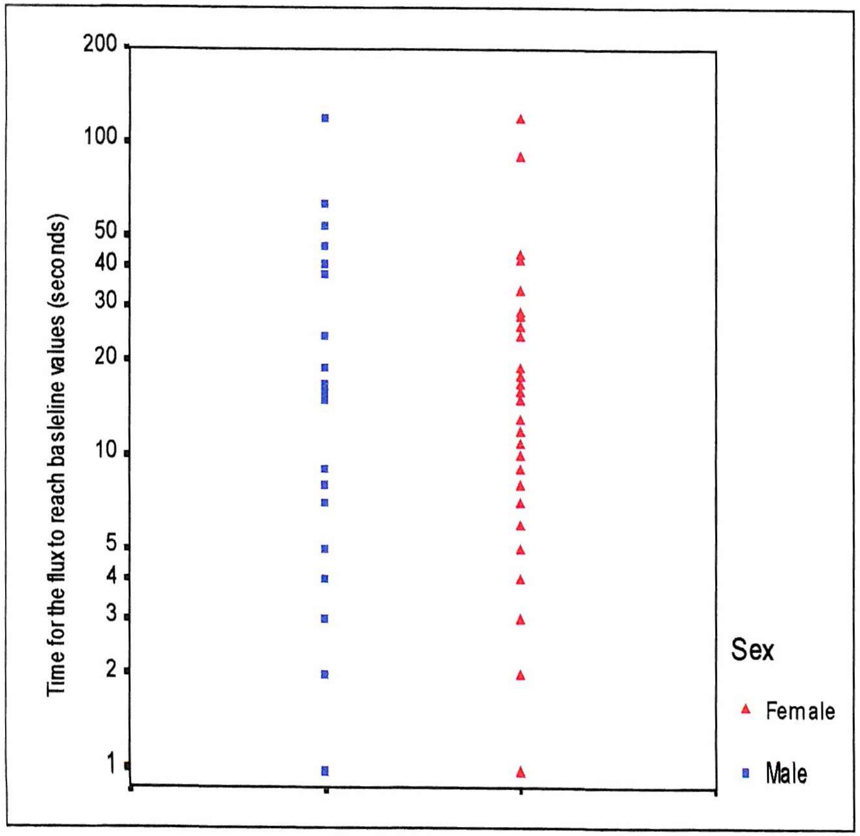


Figure 4.25 The postural vasoconstrictive response, differences between males & females controls in the time required for the flux to reach baseline values after leg lowering. Non-significant differences between sexes were found.

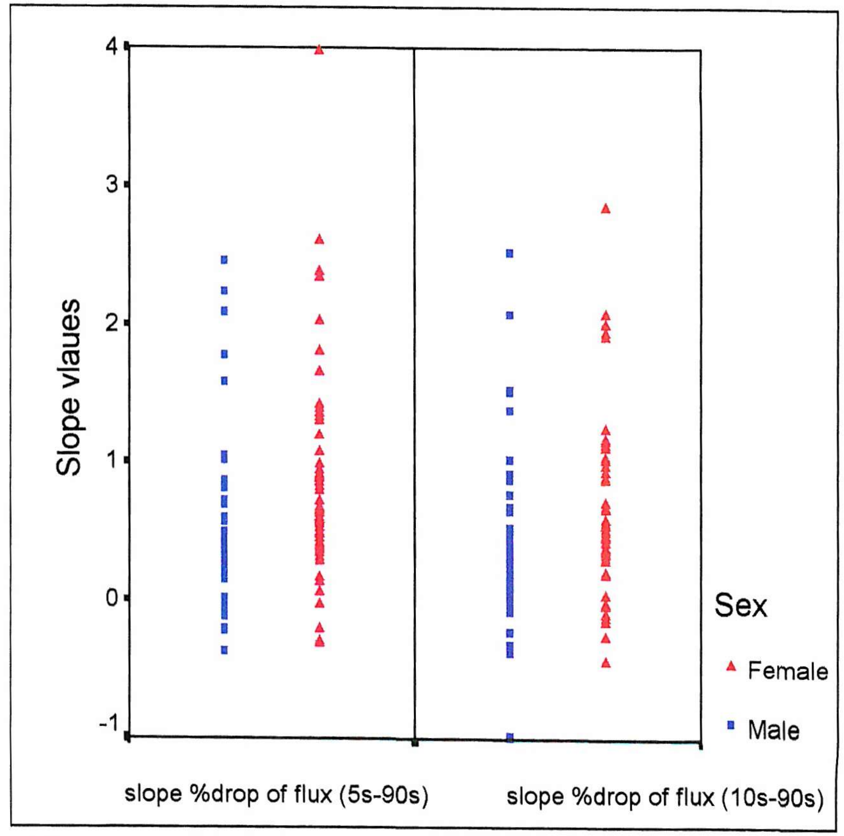


Figure 4.26 The postural vasoconstrictive response, differences between males & females controls in the slopes of the %drop in flux. Significantly higher slopes were found in the female's controls.

		Flux (A. U.)				% drop in Flux			
		21-40y (N=36)	41-60y (N=32)	61-90y (N=36)	Significance	21-40y (N=36)	41-60y (N=32)	61-90y (N=36)	Significance
Baseline		27 (7.1 & 215.5)	30.65 (5.7 & 247.4)	61.5 (5.8 & 542.6)	**P=0.026**				
Lowering	5s	54 (9.6 & 178.9)	36.95 (11 & 255.3)	59.4 (12.3 & 792.7)	P=0.053	-27.57 (-414.29 & 52.4)	-13.40 (-213.77&40.7)	-11.11 (-350.46&77.43)	P=0.432
	10s	40.05 (9.3 & 111.7)	29.4 (6 & 224.6)	49.75 (7.5 & 723.1)	P=0.099	-10.28 (-256.39&72.26)	7.53 (-142.51&60.86)	18.80 (-156.19&80.61)	P=0.193
	15s	33.6 (9.4 & 227.1)	25.4 (6.4 & 269.9)	39.65 (8.3 & 723.8)	P=0.087	-0.82 (-180.45&83.83)	15.05 (-170.18&71.07)	11.94 (-133.18&72.63)	P=0.190
	20s	25.5 (5 & 213.3)	21.7 (7.3 & 272)	36.95 (8.4 & 483)	**P=0.023**	9.19 (-151.04&87.22)	28.49 (-49.12&65.44)	16.39 (-118.35&77.47)	P=0.206
	30s	20.55 (3.9 & 182.2)	15.85 (5.2 & 216)	34.75 (7.7 & 506.6)	**P=0.012**	25.85 (-77.08 & 91.7)	32.29 (-82.46&76.36)	30.64 (-118.97&93.91)	P=0.707
	90s	11.25 (4.1 & 138.6)	12.4 (4.3 & 89.2)	34 (4.8 & 377.2)	**P=0.005**	47.99 (-121.85&85.32)	56.40 (-89.47&84.44)	30.43 (-99.66&87.38)	**P=0.048**
Time to reach baseline		10.50 (1&42)	7 (1&120)	5 (1&120)	P=0.474				
slope % drop in flux (5s-90s)						0.6231 (-0.36&3.98)	0.6112 (0.03&2.62)	0.412 (-0.29&2.24)	**P=0.040**
slope % drop in flux (10s-90s)						0.5981 (-0.98&2.86)	0.4609 (-0.03&2.01)	0.3458 (-0.31&1.12)	**P=0.019**

Table 4.19 Differences with age in the postural vasoconstrictive response measured with LDF in the big toe of asymptomatic controls.

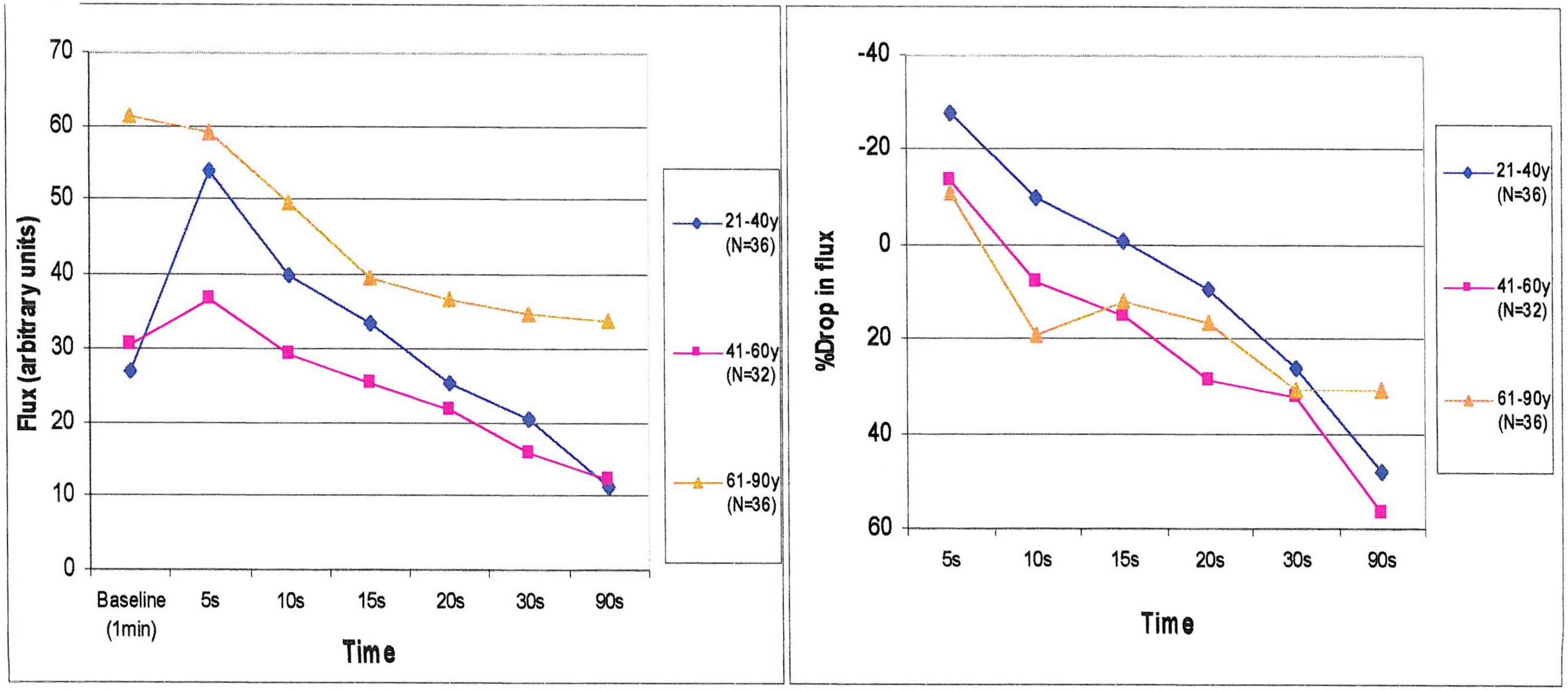


Figure 4.27 The postural vasoconstrictive response, differences with age in the flux (A.U.) and %drop in flux measured with LDF in the big toe of asymptomatic controls. A significant increase with age was found in the flux at baseline, 20s, 30s and at 90s. As well as a significant decrease in the %drop in flux at 90s.

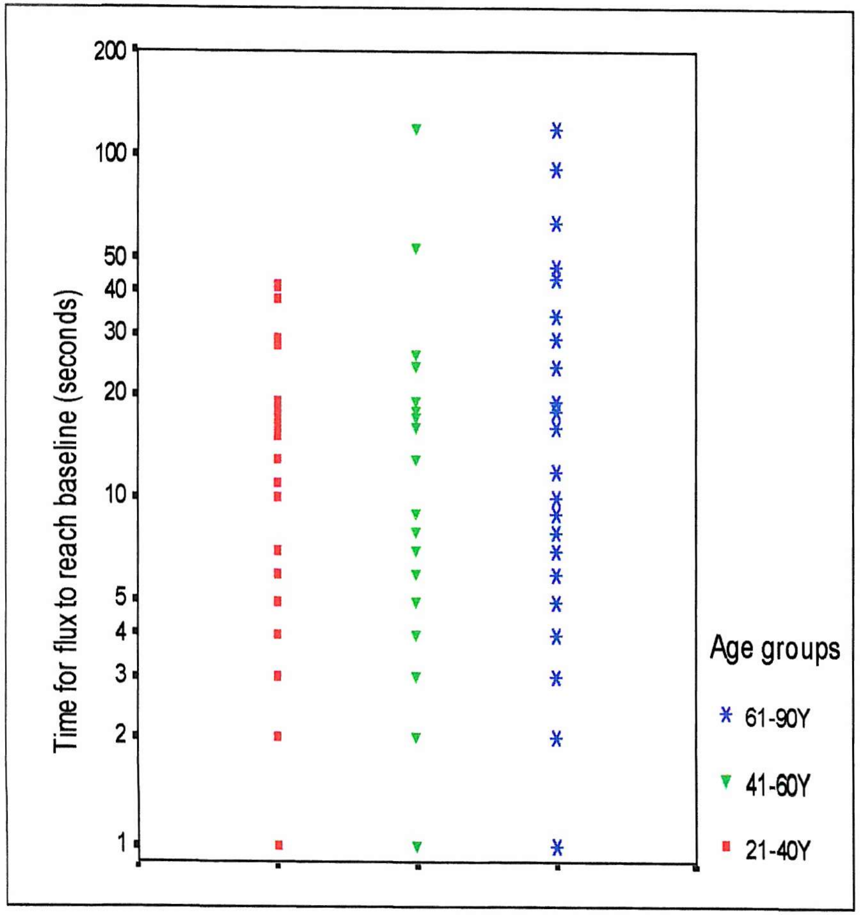


Figure 4.28 The postural vasoconstrictive response, differences with age in the time required for the flux to reach baseline values after leg lowering measured with LDF in the big toe of asymptomatic controls. With age, non-significant differences in the time was found.

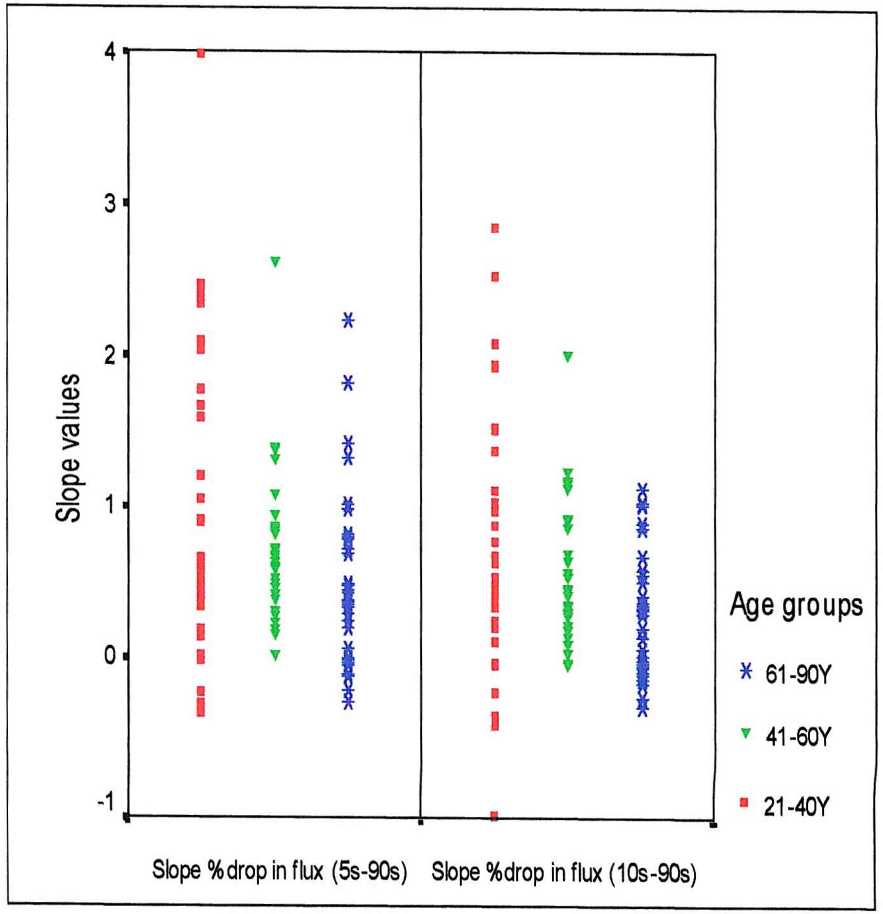
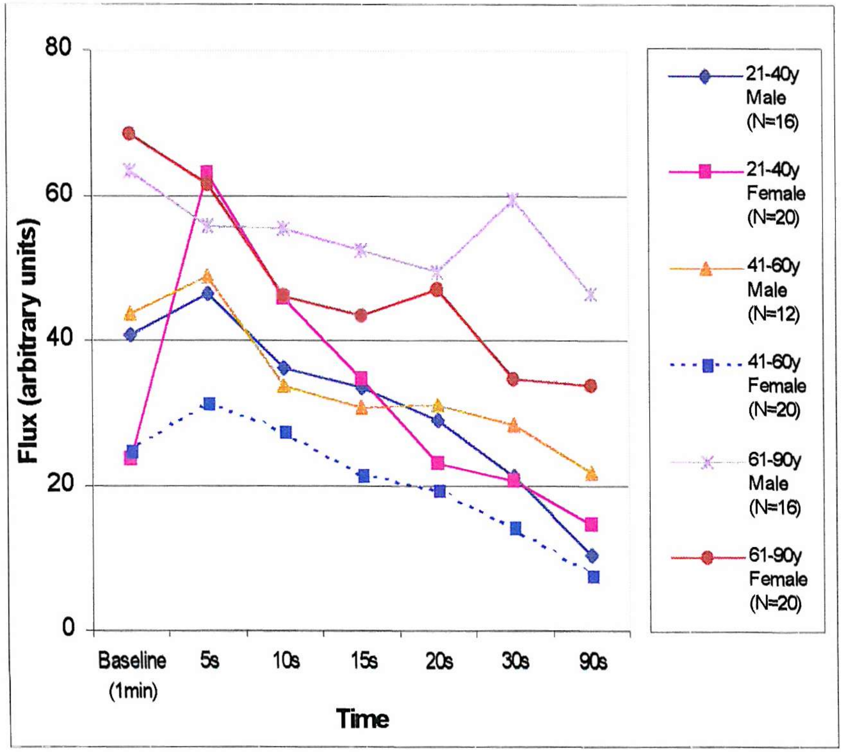


Figure 4.29 The postural vasoconstrictive response, differences with age in the slope of %drop in flux measured between 5s-90s & 10s-90s. Significant reductions in both slopes of the %drop in flux with age.

		Flux (A. U.)							% drop in Flux						
		21-40y		41-60y		61-90y		Significance	21-40y		41-60y		61-90y		Significance
		Male	Female	Male	Female	Male	Female		Male	Female	Male	Female	Male	Female	
Baseline		40.85 (7.1&179.8)	21.20 (9.1&215.5)	43.9 (5.7&147.8)	27.7 (8&247.4)	63.45 (10.9&218.6)	56.85 (5.8&542.6)	P=0.181							
Lowering	5s	46.5 (9.6&116.3)	58.80 (12.8&178.9)	48.9 (14.1&179.4)	31.7 (11&255.3)	56 (14.4&237.7)	61.05 (12.3&792.7)	P=0.276	-13.52 (-183.33&52.40)	-27.57 (-414.29&32.53)	-24.78 (-201.75&40.70)	-9.91 (-213.8&3 8.05)	1.67 (-350.46&69.68)	-33.73 (-220.4&77.43)	P=0.611
	10s	36.45 (9.3&111.7)	43.35 (11.8&103.9)	34 (9.6&118.6)	29.4 (6&224.6)	55.5 (12&190.5)	46.2 (7.5&723.1)	P=0.459	-11.28 (-253.13&66.00)	-10.28 (-256.39&72.26)	10.20 (-68.42&50.76)	-5.30 (-142.51&60.86)	19.42 (-156.19&80.61)	15.89 (-99.50&77.16)	P=0.532
	15s	33.6 (9.4&155.5)	34.9 (9.6&227.1)	30.9 (7.7&117.3)	24.95 (6.4 &269.9)	52.6 (15.9&146.2)	36.9 (8.3&723.8)	P=0.366	4.11 (-165.74&71.17)	-4.41 (-180.45&83.83)	16.60 (-170.18&52.77)	15.05 (-64.67&71.07)	26.14 (-62.39&61.47)	6.82 (-133.18&72.63)	P=0.410
	20s	29.15 (5&213.3)	22.30 (8.7&161.5)	31.4 (7.3&101.9)	21.4 (7.5&272)	49.6 (10.7&172.4)	33.15 (8.4&483)	P=0.129	10.86 (-151.04&67.39)	9.19 (-112.50&87.22)	29.37 (-49.12&52.57)	27.83 (-35.93&65.44)	16.17 (-118.35&77.47)	16.57 (-82.76&69.72)	P=0.649
	30s	21.25 (3.9&182.2)	19.80 (6.7&82)	28.5 (6.9&98.7)	14.4 (5.2&216)	59.45 (11.1&223.6)	29 (7.7&506.6)	**P=0.044**	33.78 (-77.08&73.09)	16.81 (-35.14&91.70)	14.44 (-82.46&76.36)	45.12 (4.0&71.32)	22.16 (-50.13&77.34)	33.18 (-118.97&93.91)	P=0.524
	90s	10.65 (4.1&114)	11.65 (5.5&138.6)	22.1 (5.7&89.2)	7.75 (4.3&88.3)	46.7 (9.1&176.1)	29.95 (4.8&377.2)	**P=0.014**	43.27 (-121.85 &85.32)	50.67 (-41.00&80)	45.08 (-89.47&63.48)	62.98 (25.07&84.44)	26.04 (-16.49&81.87)	46.44 (-99.66&87.38)	**P=0.020**
Time to reach baseline (s)		6 (1&41)	11 (1&42)	7 (2&120)	7 (1&26)	4 (2&64)	5.5 (1&120)	P=0.562							
slope % drop in flux (5s-90s)									0.5947 (-0.36&2.47)	0.6696 (-0.30&3.98)	0.5376 (0.03&.88)	0.6624 (0.17&2.62)	0.3035 (-0.20&2.24)	0.4857 (-0.29&1.82)	**P=0.039**
slope % drop in flux (10s-90s)									0.5015 (-0.98&2.52)	0.6722 (-0.43&2.86)	0.2762 (-0.03 &.92)	0.5465 (0.05&2.01)	0.1085 (-0.31&1.03)	0.3680 (-0.25&1.12)	**P=0.019**

Table 4.20 The postural vasoconstrictive response, the combined effect of age & sex on cutaneous microcirculation during passive leg lowering as measured with LDF in asymptomatic controls.



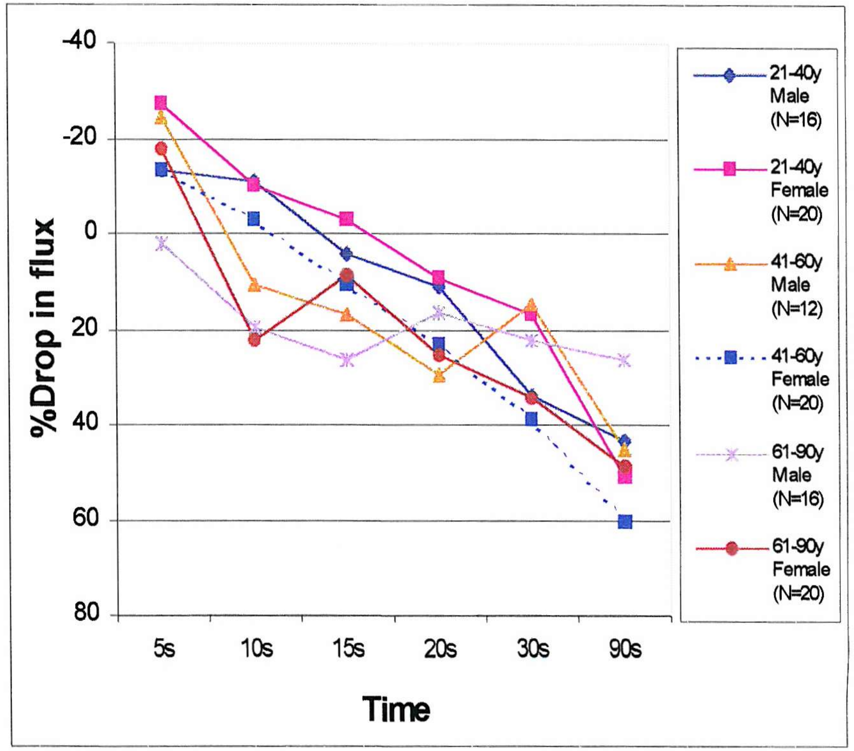


Figure 4.30 The postural vasoconstrictive response, the combined effect of age and sex on the flux and %drop in flux. A significant increase in the flux at 30s and at 90s was found in the two elderly groups, as well as a significant decrease in the %drop in flux at 90s.

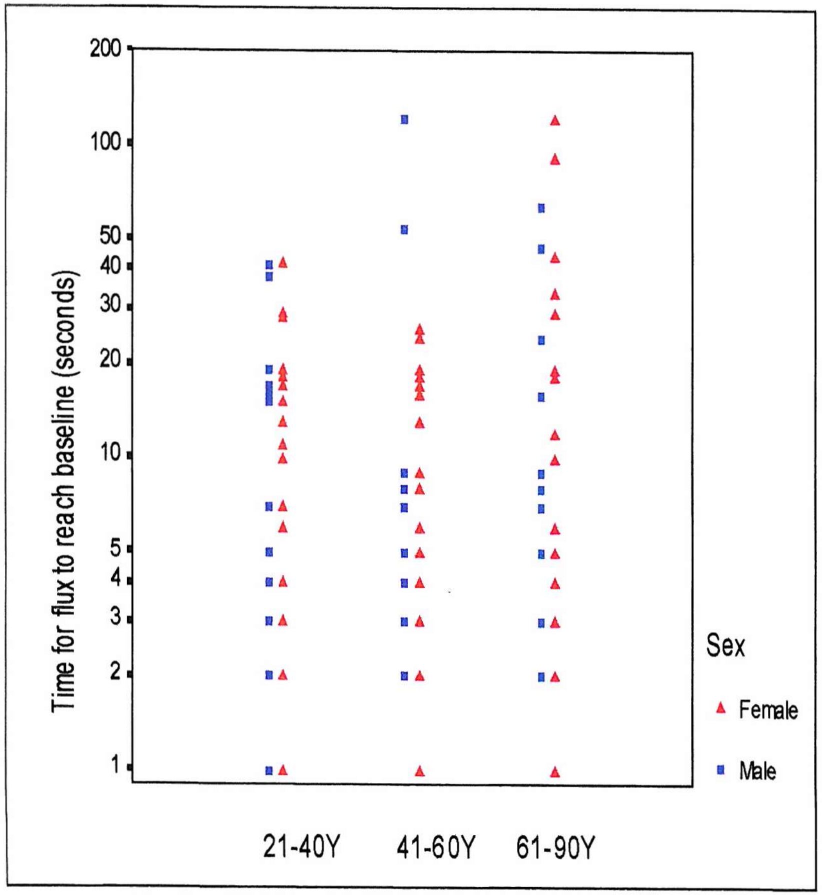


Figure 4.31 The postural vasoconstrictive response, the combined effect of age and sex on the time required for the flux to reach baseline values after leg lowering. Non-significant differences in the time were found.

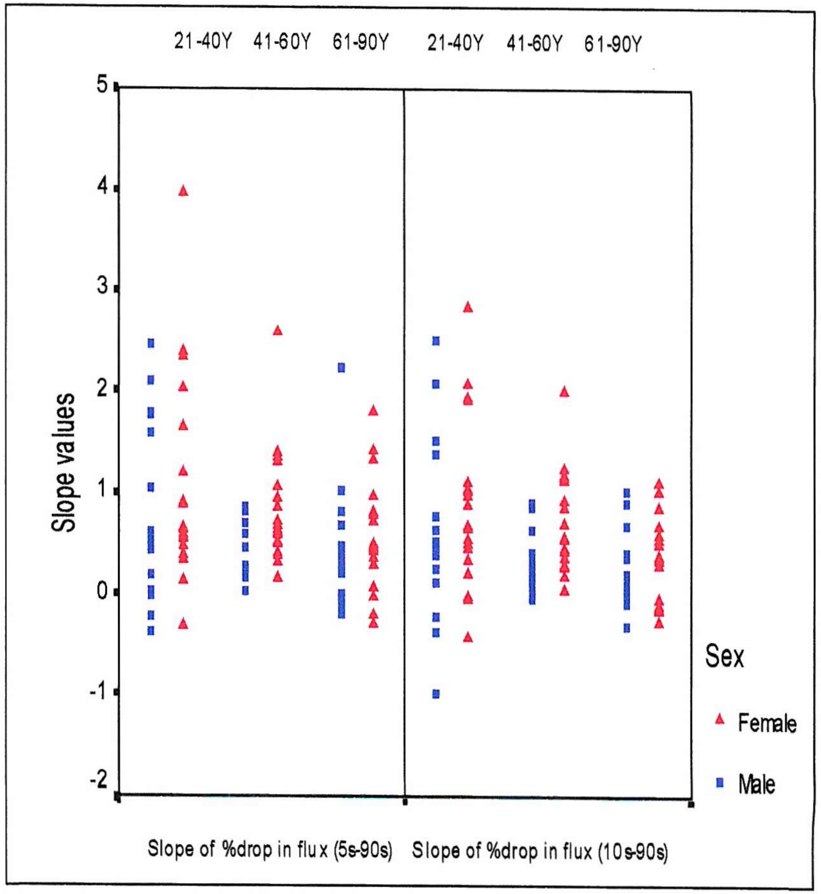


Figure 4.32 The postural vasoconstrictive response, the combined effect of age and sex on the slopes of %drop in flux measured between 5s-90s & 10s-90s. Significant reduction in the slopes of the %drop in flux with age was found.

4.6 Discussion

The aim of this chapter was to assess changes in different groups with location, sex and age using the durometer, extensometer, and the LDF to measure changes in the microcirculation.

4.6.1 Durometer findings

The differences in hardness values at corresponding sites were statistically significant on forearms and legs. On the forearm, a significant increase in the cutaneous hardness (Newtons) was found distal to the elbow joint, compared with a significant reduction proximal to the ankle joint in the leg ($P<0.001$ both extremities, Friedman test). The differences in hardness between the two extremities were statistically significant when similar sites in location from the joints (the elbow and the ankle) were examined ($P<0.001$, <0.001 & $=0.004$, Wilcoxon test), table 4.1. The increase in hardness proximal to the ankle joint and distal to the elbow could be related to differences in cutaneous structures and thickness; as well the volume and the type of underlying tissues present. This assumption was considered because of the inability to assess individual effect of each layer on hardness measurements, although it was reported that contribution from different skin layers to indentation was identified using ultrasound imaging (Kawchuk and Elliott 1998).

Hardness indices were higher in females ($P=0.002$ at Hardness index 2 & $P=0.006$ at hardness index 3 respectively, Mann-Whitney), table 4.2. The difference in hardness index 1 between males and females were statistically non-significant. Differences in composition and thickness of tissues could be expected to influence hardness values. Skin thickness, composition and muscle/fat ratio are different between sexes and this may account for the significant differences in hardness indices between sexes. It might be preferable in the future to include skin thickness measurement with any test for cutaneous hardness.

Examination of the effects of age on hardness indices revealed an increase in the elderly group, table 4.3. These were statistically significant in comparison with both other age groups at hardness index 2 ($P<0.001$ & 0.001, Mann-Whitney) & hardness index 3 ($P<0.001$ & 0.005, Mann-Whitney). The increase in hardness indices with age is similar to the reduction of elasticity reported previously using suction (Gniadecka et al. 1994b). This may be influenced by age-related changes in composition of fibers, ground substance and thickness (Quaglino et al. 1996).

When the combined effects of age and sex on hardness indices were examined, tables 4.4, significant differences were found within hardness indices 2 & 3 only ($P<0.001$, Kruskal-Wallis test). This may be attributed to the increase in hardness in females compared to males within each age group, and to the increase in hardness with age within the same sex group.

4.6.2 Extensometer findings

Force at maximum extension Fpeak and relaxation time were both increased in legs compared with forearms ($P<0.001$, paired T-test and Wilcoxon test) and suggests site dependency, table 4.5. Differences in cutaneous thickness and composition would affect extensometer data, as well as the contributions of skin tension and the tissue underneath i.e. fat & muscle.

As for durometer data, when the indices for extension and relaxation were derived and examined for differences between males and females, differences between sexes were statistically non-significant, table 4.6. Extensibility index was increased in the elderly compared to other groups ($P<0.001$, independent sample t-test) but not between the young and middle age groups ($P=0.928$, independent sample t-test). Relaxation index was found to be minimally affected with age, table 4.7. The minimal effect of age on relaxation is in contrast with Quan et al. (1997) findings, where an increase in τ (a parameter measured during the relaxation time/skin thickness) was established in the elderly. The increase in τ in Quan et al. study was probably related to the observed decrease in skin thickness.

Extensibility index alone was significantly affected by age and sex ($P<0.001$, Anova), table 4.8. The significance in extensibility index was attributed to the effect of age more than sex as the differences between males and females within the same age group were statistically non-significant for all three age groups (P=0.326, 0.431 & 0.322, respectively, Independent sample T-test). These observations could be the reflection of viscoelastic changes consequent to changes in the structure and composition of cutaneous tissues. The increase in extensibility index with age (i.e. decrease in extensibility) is in overall agreement with the increase in hardness measured by durometry.

4.6.3 Cutaneous microcirculation during skin extension/relaxation

Changes in the LDF flux during extension/relaxation (and with passive leg lowering) were analyzed both in arbitrary units and as a change with respect to baseline i.e. %change in flux (%drop in flux). In addition, the rate of the %change in flux over a set period of time (slope) and the time to reach either peak or baseline values were examined.

When the skin was stretched 37.5% in 8seconds, a transient increase in the cutaneous blood flow occurred, followed by dropping during the 1st minute of relaxation in both extremities. After the 1st minute of relaxation, there was a steady increase, which elevated the flux values at 4 minutes in the forearm and 8 minutes in the leg. In both extremities, the change in the flux during extension and relaxation were statistically significant ($P<0.001$, Friedmen test), table 4.9 & 4.10. These changes showed the ability of the cutaneous circulation to respond to this challenge.

In female legs, the recovery of the microcirculation (%change in flux) was significantly higher than males at different time points, the recovery rate (slope of %change in flux between 1min-8min) was also faster, table 4.12. However the differences on forearms were not statistically significant, table 4.11. The lack of a difference between sexes in the forearms was different from the legs, and was attributed to shorter (4minutes) monitoring time. Differences between sexes in the leg region were found between 5th and 8th minutes of relaxation, although, the absence of variations between sexes in the cutaneous microcirculation in the forearms could not be excluded.

With age, this recovery was low and slow in the elderly; this was statistically significant on forearm skin, table 4.13, though not on legs, table 4.14. The above significant difference in the forearms, are attributed to lower %change in flux at 2min, 3min & 4min of the relaxation phase in the elderly compared to the young group (P=0.007, 0.007, 0.009 respectively, Mann-Whitney test). Percentage change in flux considered between ext-4min & 1min-4min were significantly lower in the elderly (P=0.026 & 0.024 respectively, Mann-Whitney test). The differences between middle-age group and elderly was limited to a significant lower %change in flux found during the extension phase in elderly, (P=0.006, Mann-Whitney test). The presence of a significantly lower %change in flux in the elderly could be related to the inability of the elderly skin and its microcirculation to adapt to external stretching. The presence of differences in the microcirculation with age in the forearm but not in the leg, may result from a genuine lack of age effect on the leg microcirculation. Although it may arise from the 37.5% extension rate in 8 seconds being insufficient to examine changes in the cutaneous microcirculation with age. Factors that may effect the elderly cutaneous microcirculation include dilated microvasculture (Gilchrest and Yarr 1992), cutaneous atrophy (Kligman and Lavker 1988), the loss of cutaneous elasticity (Gilchrest 1982) and a slowed metabolic activity (Lavker 1995).

When the combined effect of age and sex on the cutaneous microcirculation was examined, no significant differences between the groups were found in both extremities, table 4.15 & 4.16. This may result from the absence of significance between sexes in the forearms and the absence of differences according to age in the middle of the leg region. As it was easily possible to follow the response in blood flow to a simple challenge, it was decided to extend this test to study patients.

4.6.4 The postural vasoconstrictor response

When the leg was passively lowered, a drop in the blood flow in the pulp of toe was found, table 4.17. The reduction in the flux after the first 5 seconds of leg lowering, were found to be significantly different than baseline (P=0.044, =0.003, <0.001, <0.001, <0.001 respectively, Wilcoxon test). This was consistent with the presence of an intact vasoconstrictor response.

The magnitude of the reduction in flow with leg lowering (%drop in flux) and the rate of the drop (slopes) were greater in the female group. This suggested a better control than in males. Since a positive postural vasoconstrictive response is stated to protect from oedema formation. The above finding was surprising and their was no guidance in the literature to explain the above. Hassan et al. (1990) studied the postural vasoconstrictive response in pre-menopausal females and reported variations through the menstrual cycle, but did not examine differences between sexes.

The results of analysing the postural vasoconstrictive response data, showed that the response was attenuated in the elderly group compared to others, table 4.19. The presence of high flux during the supine position (baseline) and after leg lowering in the elderly could be attributed to the dilated and twisted microvasculture (Gilchrest and Yarr 1992), which may affect the functional properties of the cutaneous microcirculation. The increased transparency of the thin senile skin might enhance penetration of laser light and possibly increase flux values.

The postural vasoconstrictive response is stated to depend on an intact pre-capillary sphincter, which in turn limits a rise in capillary hydrostatic pressure. This limits filtration, protecting from oedema formation. The impairment in the response found in the elderly is in accord with Gniadecka et al. (1994a), who also studied this response in the elderly. Since the elderly are prone to venous ulceration, this test was carried out on patients as reported in the succeeding chapter.

When the combined effect of age and sex was examined, differences between young male controls and young female controls were statistically non-significant. Differences in the response between elderly male controls and elderly female controls were statistically non significant. A significant reduction in both the %drop and the rate of %drop was found in middle-aged males compared to females of equivalent age. It suggests the presence of a better drop in flux in the female group compared to male controls. With the increase prevalence of ankle swelling in females, this finding was surprising and further investigation is required to examine the cause of the difference. A significant increase in flux (after dependency) in elderly females compared to middle-aged female group was found. These findings confirm the presence of differences between sexes and the effect of age on the postural vasoconstrictive response and should be considered when the effects of CVI and venous ulcers on the postural vasoconstrictive response are examined.

4.7 Conclusion

All three techniques were well tolerated by subject volunteers. No adverse effects were seen. On the above basis, all were used to examine changes in the mechanical and microcirculatory properties of skin affected by the presence of CVI and venous ulcers.

Chapter five: Studies in patients with CVI

In order to examine changes in the mechanical and microcirculatory properties in skin prone to venous ulceration, a final set of studies were performed and presented in the same order as in the previous chapter.

5.1 Subject selection

Patients with CVI with and without venous ulceration were recruited from patients attending the surgical and dermatology clinics. After explaining the study to the candidates and their question answered, they were asked to fill a clinical history questionnaire to examine their suitability for the study, appendix 37. Volunteers whom have a past or present or history of swelling of the leg and ankle, DVT and ulcers but without a history of diabetes, heart problems, skin disorder treated with steroids, pregnancy, cancer or any terminal illness, were considered for the patients group. A duplex scan of the venous system was performed to confirm the presence of CVI. In the presence of CVI and an ulcer, patients with an ankle/brachial index ≤ 0.9 were excluded due to the presence of ischaemia. Table 5 outlines number of CVI patients with and without venous ulceration and asymptomatic controls included in each study.

Name of the study	Number of subjects included in the study		
	CVI only	Venous ulcer	Asymptomatic controls
Skin hardness	30	14	30
Cutaneous extensibility and relaxation	68	22	58
Cutaneous microcirculation during skin extension/relaxation	42	21	44
The postural vasoconstrictive response	40	23	40

Table 5.0 Number of subjects included in each study.

5.2 Skin hardness studies

Method

A group of 44 patients with CVI were included in the study. All patients had evidence of deep venous incompetence in duplex examination. Of the 44 patients, 30 had CVI only (6M, 24F, age range 35-86 years, mean age 63.5 years) while 14 patients (5M, 9F, age range 46-76 years, mean age 74 years) had frank venous ulcers. The exclusion criteria for the control and patient groups were discussed in section 4.1 and 5.1 respectively. The protocol described in section 3.1.2 was used in the study. Data are presented in appendices 27 & 28, tables 5.1-5.3 as median (min & max) and graphically in figures 5.1-5.3.

Statistical analysis

Data from CVI patients (with frank ulcers and without) were compared with asymptomatic controls (N=30, 6M, 24F, age range 37-83 years, mean age 63.1 years) and examined for statistical significance using the non-parametric Kruskal-Wallis and Mann-Whitney tests. Changes with CVI were examined in the elderly only (CVI=20 & venous ulcer=12) and compared to age matched asymptomatic controls (N=20) using the same statistical methods as above. Changes with CVI were examined in the elderly males (CVI= 4 & venous ulcer=3) and females (CVI= 16 & venous ulcer=8). Data was compared to age matched asymptomatic controls males (N=4) and females (N=16) using the above statistical methods.

Results

In patients with venous ulcers, hardness indices 1 and 2 were calculated in 12 subjects and hardness index 3 in 10 cases only. In the elderly patients with venous ulcers, hardness index 1 was calculated in 11 patients, hardness index 2 in 10 patients and hardness index 3 in 8 patients, because it was occasionally difficult to measure cutaneous hardness in the proximity of the ulcer. In elderly male patients with venous ulcers, hardness index 3 was calculated in 2 patients. In elderly female patients with venous ulcers hardness index 2 was calculated in 7patients, hardness index 3 in 6patients.

Hardness indices	Controls	CVI only	Venous ulcer	Significance
Index 1	1.78 (1.12& 2.39)	1.95 (1.27&3.37)	2.32 (1.07&3.46)	**P=0.007**
Index 2	1.62 (1.10&2.43)	1.55 (1.05&2.48)	1.89 (1.23&3.19)	P=0.089
Index 3	1.35 (0.61&1.94)	1.35 (0.90&2.55)	1.53 (0.81&2.07)	P=0.476

Table 5.1 Changes in hardness indices in patients with CVI.

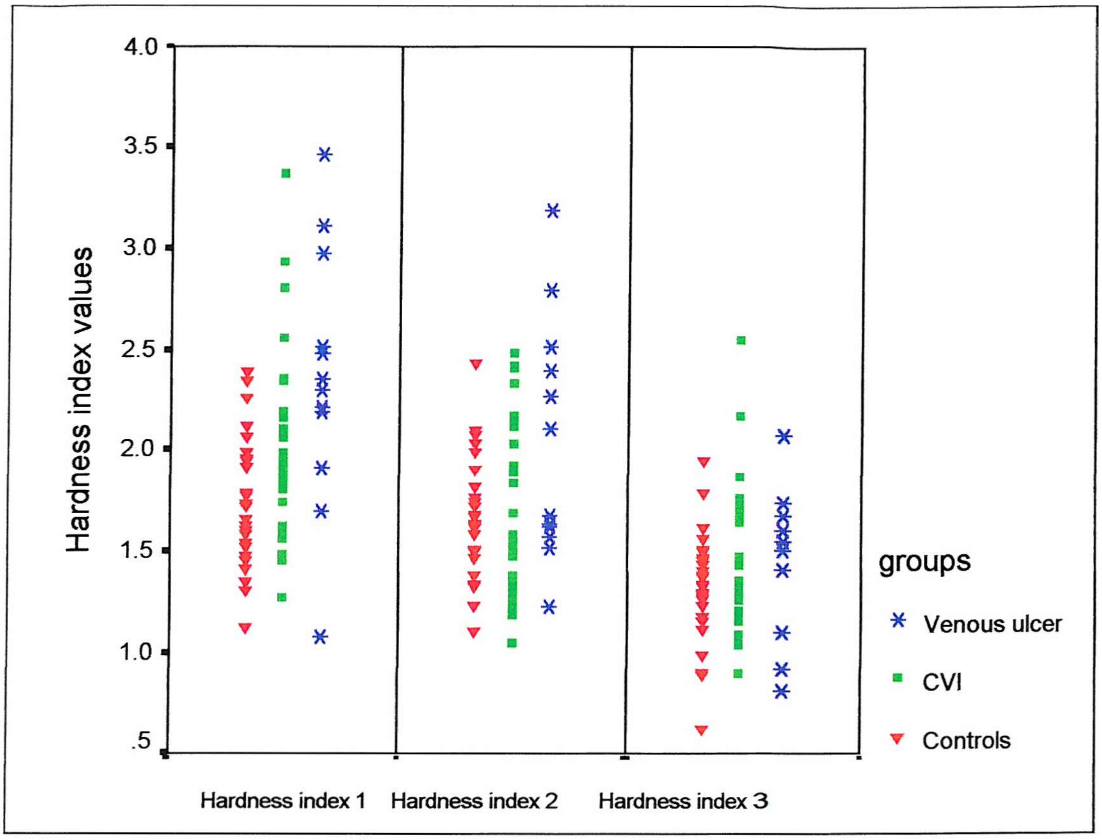


Figure 5.1 Changes in hardness indices in patients with CVI. A significant increase in hardness index 1 in the presence of venous ulcer compared to controls and CVI, in addition to a significant increase in hardness index 2 in the presence of venous ulcer compared to controls.

Hardness Indices	In the elderly (61-90Y)			Significance
	Controls	CVI only	Venous ulcer	
Index 1	1.78 (1.30&2.25)	2.09 (1.46&3.37)	2.35 (1.07&3.46)	**P=0.01**
Index 2	1.70 (1.38&2.43)	1.91 (1.19&2.48)	2.18 (1.23&3.19)	P=0.15
Index 3	1.38 (1.16&1.94)	1.46 (1.09&2.55)	1.56 (0.92&2.07)	P=0.426

Table 5.2 Changes in hardness indices in elderly patients with CVI.

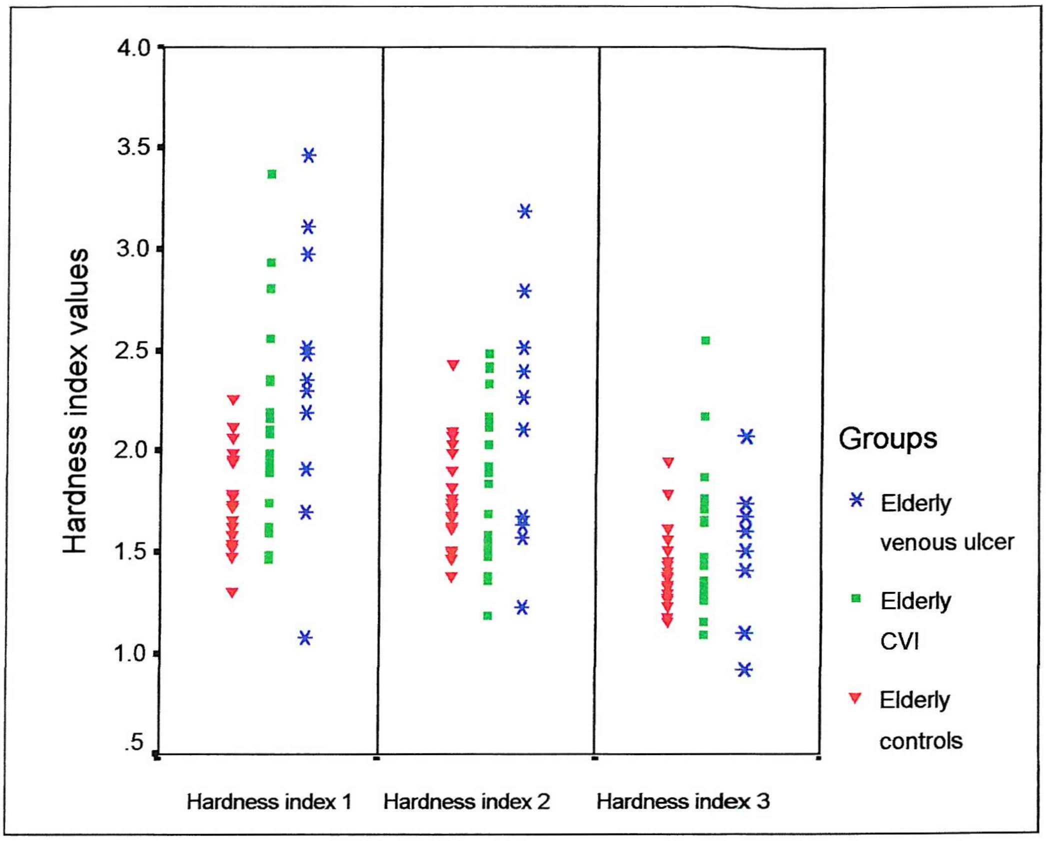


Figure 5.2 Changes in hardness indices in elderly patients with CVI. Significant increase in hardness index 1 in elderly CVI and elderly venous ulcer compared to elderly controls.

Hardness Indices	In the elderly (61-90Y) males				In the elderly (61-90Y) females			
	Controls	CVI only	Venous ulcer	Significance	Controls	CVI only	Venous ulcer	Significance
Index 1	2.01 (1.51 & 2.11)	2.23 (1.59&2.93)	2.35 (1.92&3.46)	P=0.515	1.75 (1.30&2.25)	2.09 (1.46&3.37)	2.39 (1.07&3.12)	**P=0.027**
Index 2	1.49 (1.38 & 2.09)	2.05 (1.19&2.48)	2.11 (1.23&2.79)	P=0.628	1.73 (1.49&2.43)	1.91 (1.36&2.40)	2.26 (1.57&3.19)	P=0.256
Index 3	1.24 (1.16 & 1.33)	1.40 (1.29&1.64)	1.39 (1.10&1.68)	P=0.375	1.41 (1.22&1.94)	1.56 (1.09&2.55)	1.56 (0.92&2.07)	P=0.618

Table 5.3 Changes in hardness indices in elderly male and female patients with CVI.

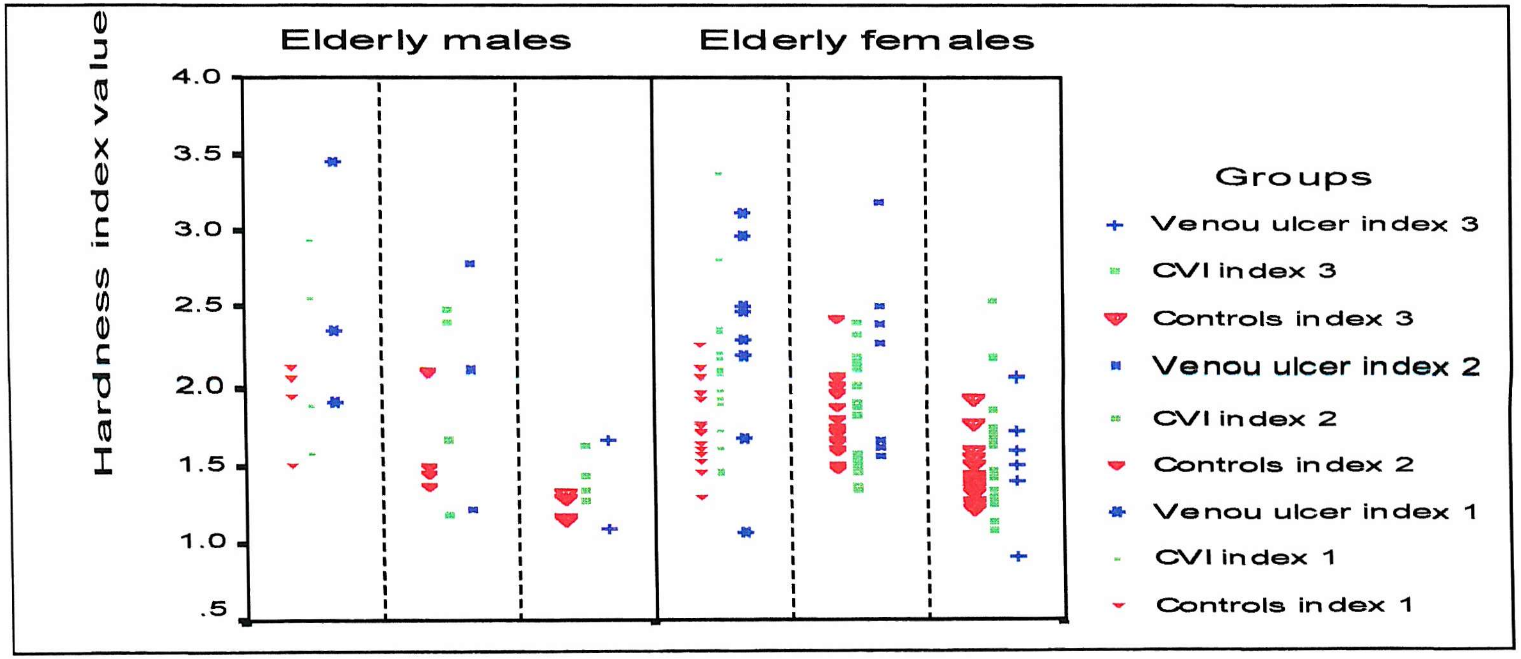


Figure 5.3 Changes in hardness indices in elderly male and female patients with CVI. A significant increase in hardness index 1 in elderly females with CVI and elderly females with venous ulcer compared to elderly female controls.

5.3 Cutaneous extensibility and relaxation studies

Method

A group of 90 patients with CVI, confirmed by Duplex scanning, were studied. Of the 90 patients, 68 patients had CVI (19M, 49F, mean age 59.1 years, age range 25-81 years) but no ulcers at the time of the study, and 22 patients (8M, 14F, mean age 65.95 years, age range 34-85 years) had active venous ulcers. The exclusion criteria used for selecting patients and controls were described in sections 5.1 and 4.1 respectively. The protocol used was described in section 3.2.2. Data are presented in appendices 29 &30, in tables 5.4-5.6 as mean ±1sd for extensibility index or as median (min & max) for relaxation index and graphically in figures 5.4-5.6.

Statistical analysis

Data from patients with and without ulceration were compared to asymptomatic controls (N=58, 18M, 40F, mean age 56.33 years, age range 27-83 years). Parametric tests (Anova-test and Independent sample T-test) were used to examine for statistical significance changes in extensibility index, and the equivalent non-parametric tests (Kruskal-Wallis and Mann-Whitney test) were used for relaxation index. Changes in cutaneous extensibility and relaxation were examined in the elderly patients (CVI=33 & venous ulcer=15) and compared to data obtained from 26 elderly controls using the above statistical tests. Changes in cutaneous extensibility and relaxation were examined in elderly male (CVI=6 and venous ulcer = 4) and female (CVI=20 and venous ulcer = 11) patients. Data were compared to age matched asymptomatic male (N=7) and female (N=15) controls using the above statistical methods.

Result

Extensibility index from 50 controls, 55 CVI and 22 venous ulcer patients and relaxation index from 49 controls, 54 CVI and 22 venous ulcer patients were included in the analysis. In the elderly (61-90Y), extensibility index from 22 controls, 26 CVI and 15 venous ulcer patients and relaxation index from 21 controls, 26 CVI and 15 venous ulcers were included in the statistical analysis. In the elderly males, extensibility and relaxation indices were examined in 7 controls, 6 CVI and 4 venous ulcers. In the elderly females, extensibility index was examined in 15 controls, 20 CVI and 11 venous ulcers, whereas relaxation index was examined in 14 controls, 20 CVI and 11 venous ulcers due to the presence of artefacts.

Indices	Controls	CVI only	Venous ulcer	Significance
Extensibility	1.59±0.66	1.53±0.53	1.43±0.63	P=0.56
Relaxation	0.22 (-1.98 & 3.24)	0.14 (-2.88 & 1.03)	-0.08 (-3.06& .89)	**P=0.005**

Table 5.4 Changes in extensibility and relaxation indices in patients with CVI.

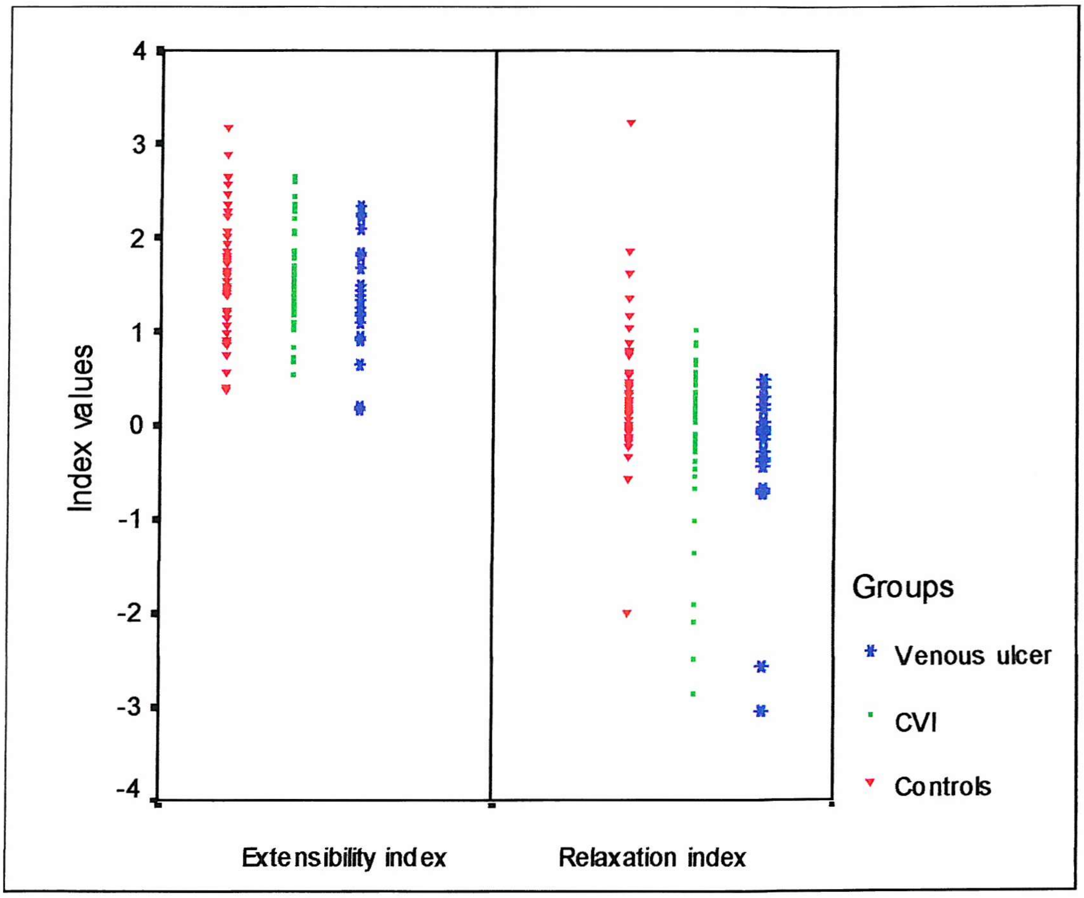


Figure 5.4 The effects of CVI on indices of extensibility and relaxation. A significant reduction in relaxation index in venous ulcer group compared to controls and CVI.

Indices	In the elderly (61-90Y)			Significance
	Controls	CVI only	Venous ulcer	
Extensibility	2.02±0.59	1.63±0.53	1.43±0.68	**P=0.01**
Relaxation	0.22 (-1.98 & 0.88)	0.17 (-2.50 & 0.90)	-0.15 (-2.58 & 0.48)	**P=0.011**

Table 5.5 The effect of CVI on indices of extensibility and relaxation in the elderly.

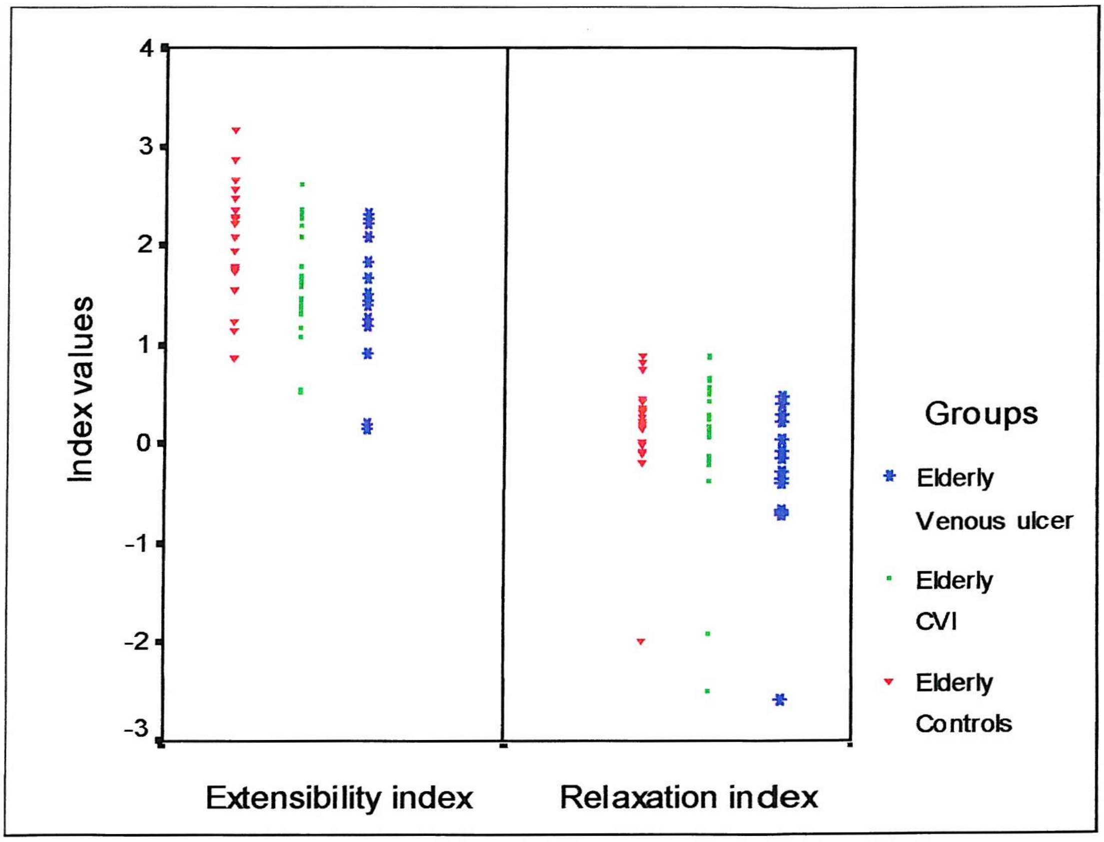


Figure 5.5 The effect of CVI on indices of extensibility and relaxation in the elderly. A significant reduction in extensibility index in elderly CVI (with frank ulcer and without) was found. The relaxation index was significantly reduced in elderly patients with venous ulcer.

Indices	In the elderly (61-90Y) males				In the elderly (61-90Y) females			
	Controls	CVI only	Venous ulcer	Significance	Controls	CVI only	Venous ulcer	Significance
Extensibility	1.85±0.43	1.68±0.53	1.53±0.39	P=0.538	2.09±0.64	1.61±0.54	1.39±0.77	**P=0.019**
Relaxation	0.19 (-0.01&0.82)	0.23 (-0.38&0.90)	-0.02 (-0.15&0.48)	P=0.437	0.34 (-1.98&0.88)	0.17 (-2.50&0.87)	-0.36 (-2.58&0.40)	**P=0.015**

Table 5.6 The effect of CVI on indices of extensibility and relaxation in the elderly males and females.

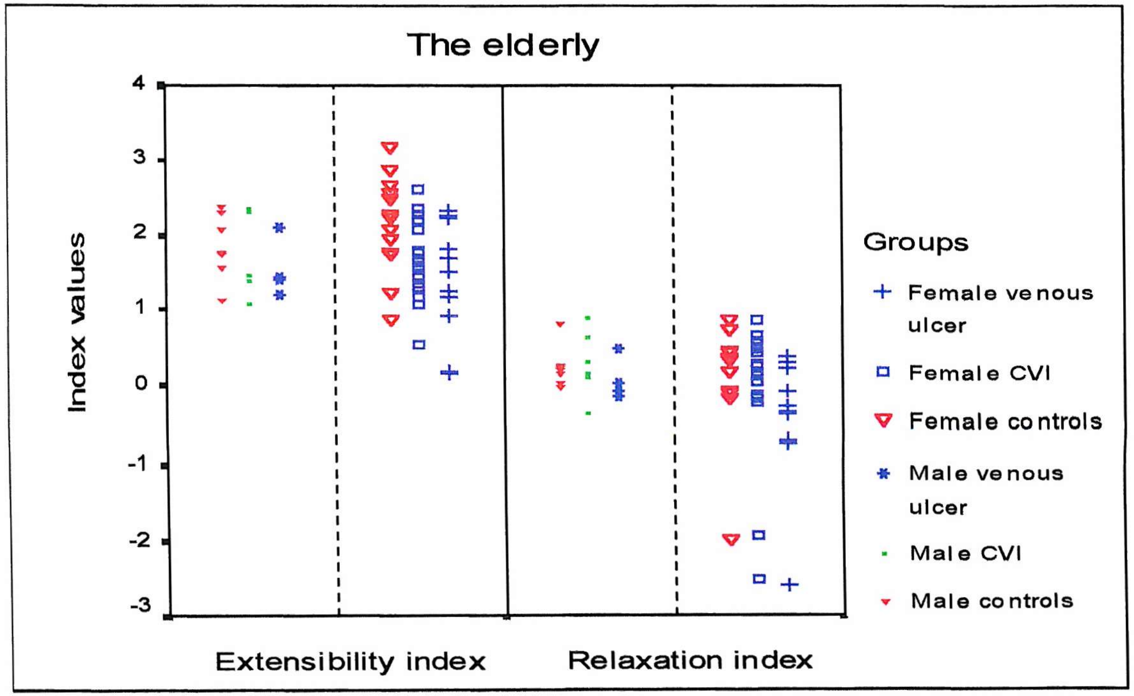


Figure 5.6 The effect of CVI on indices of extensibility and relaxation in the elderly males and females. A significant reduction in extensibility index in elderly females with CVI (with venous ulcer and without) was found. The relaxation index was significantly reduced in elderly female patients with venous ulcer compared to female controls and females CVI.

5.4 Cutaneous microcirculation during skin extension/relaxation studies

Method

A group of 63 patients with CVI, confirmed with Duplex scanning, were studied. Of the 63 patients who attended the research clinic, 42 patients (14M, 28F, mean age 59.1 years, age range 32-81 years) had CVI but no ulcers at the time of the study, and 21 patients (7M, 14F, mean age 65.3 years, age range 34-85 years) had active venous ulcers. The exclusion criteria for patients were discussed previously in section 5.1 and 4.1 respectively. The protocol used for monitoring the microcirculation during the application of cutaneous extension/relaxation were described in section 3.3.7.1. Measurements were conducted on the forearms and mid legs, with the forearms used as a control site. Data are presented in appendices 31-34, tables 5.7-5.12 as median (min & max) and graphically in figures 5.7-5.22.

Statistical analysis

Data from CVI patients (with frank ulcers and without) were compared with asymptomatic controls (N=44, 19M, 25F, mean age 54.34 years, age range 28-74 years) and examined for statistical differences using the non-parametric Kruskal-Wallis and Mann-Whitney tests. Data from the elderly patients (CVI=20 & venous ulcers = 15) were compared to 20 elderly controls using the above statistical methods. Data from the elderly male patients (CVI = 7 & venous ulcer =4) were compared to 9 elderly male controls, data from the elderly female patients (CVI= 13 & venous ulcers =11) were compared to 11 elderly female controls using the above statistical methods.

Results

In both extremities N represent the actual number of subjects in each group included in the analysis due to the unavailability of sufficient data during the relaxation phase (≥4 minutes in the forearm & ≥8 minutes in the leg).

Forearm		Flux (A. U.)				%change in Flux			
		Controls (N=34)	CVI (N=33)	Venous ulcer (N=19)	Significance	Controls (N=34)	CVI (N=33)	Venous ulcer (N=19)	Significance
Baseline		33.55 (9.5&188.5)	26.6 (12.1&121.4)	37.6 (13.4&167.8)	P=0.441				
Extension		46.6 (17.3&188.4)	41.1 (15.7&130.3)	48.8 (22&156.3)	P=0.575	23.41 (-17.79&150.94)	41.63 (-19.07&151.18)	40.51 (-19.61&195.22)	P=0.139
Relaxation	1min	37.4 (15.1&138.6)	31.3 (17.2&115.1)	43.2 (13.8&99.9)	P=0.641	8.77 (-66.8&131.58)	29.88 (-48.65&153.35)	2.99 (-56.79&187.44)	P=0.175
	2min	42.15 (18.9&163.9)	36.7 (14.4&142.9)	45.2 (13.3&125.9)	P=0.743	15.61 (-55.53&200.0)	40.66 (-47.62&241.87)	0.93 (-42.37&222.11)	P=0.120
	3min	43.3 (17.2&181.7)	35.1 (13.5&166.2)	48 (13.2&142.6)	P=0.480	36.59 (-48.02&235.34)	53.53 (-48.88&224.16)	4.17 (-31.72&201.01)	P=0.297
	4min	44.7 (21.5&194.1)	42.4 (13& 182.7)	49.7 (15.4&157.8)	P=0.539	42.95 (-45.06&224.57)	48.06 (-50.13& 73.19)	14.93 (-30.59&205.53)	P=0.405
Time to reach peak		4.25 (0.5&8.0)	4 (1& 8)	4 (2 & 8)	P=0.914				
slope % change in flux (ext-4min)						5.92 (-14.58&44.83)	0.15 (-24.19&61.06)	-1.5 (-19.25&29.1)	P=0.155
slope % change in flux (1min-4min)						10.84 (-5.42&57.03)	4.55 (-13.97&69.20)	3.82 (-26.82&24.15)	P=0.375

Table 5.7 Differences in the forearm cutaneous microcirculation, with the application of cutaneous extension/relaxation, between patients with CVI and controls.

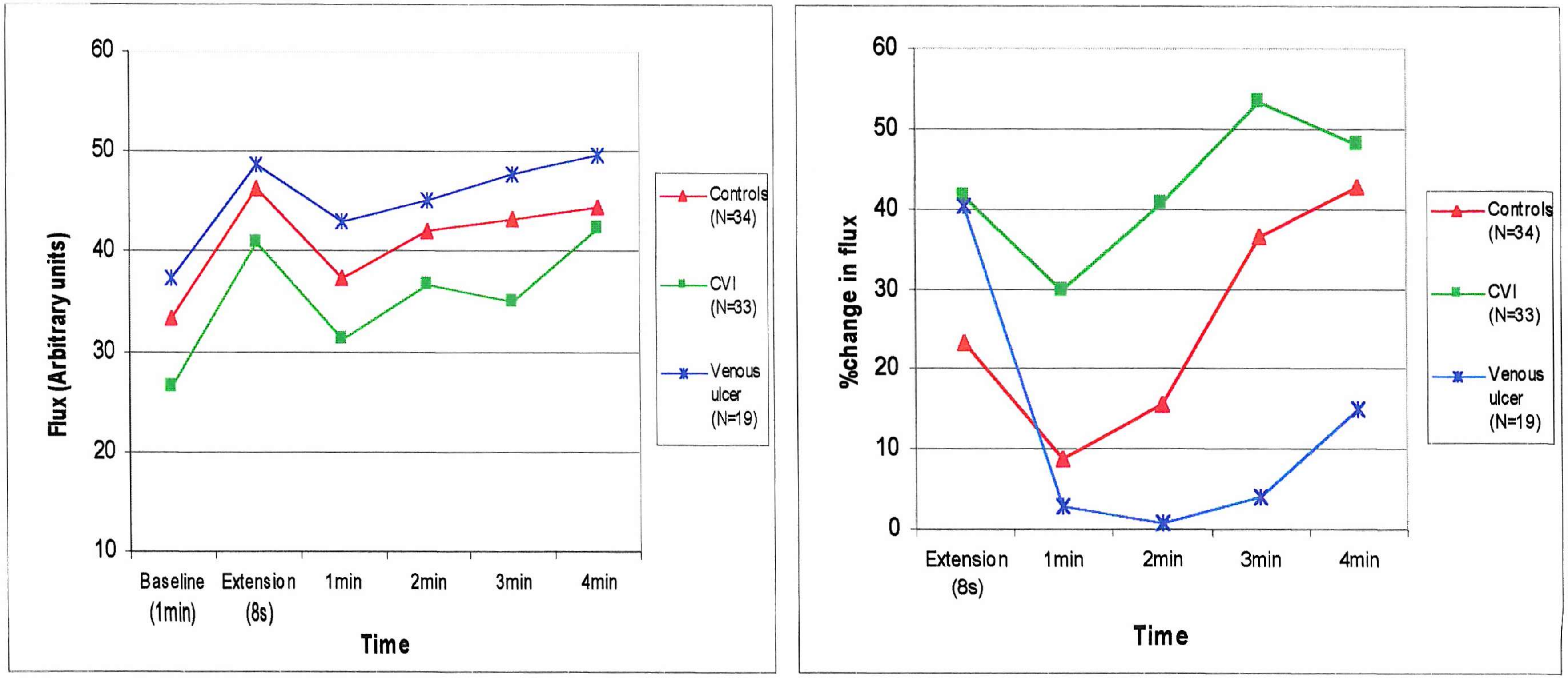


Figure 5.7 Differences in the forearm cutaneous microcirculation (flux and %change in flux) between patients with CVI (with venous ulcers and without) and controls were not statistically significant.

Leg		Flux (A. U.)				%change in Flux			
		Controls (N=35)	CVI (N=34)	Venous ulcer (N=11)	Significance	Controls (N=35)	CVI (N=34)	Venous ulcer (N=11)	Significance
Baseline		25.5 (13.5& 60.4)	27.5 (8.2&175.9)	36.3 (17.4& 142.8)	P=0.077				
Extension		29.8 (16.8& 70.7)	35.95 (11.1&134.8)	37.1 (31.6& 94.4)	P=0.116	26.90 (-19.56&247.06)	18.36 (-46.98&135.29)	17.92 (-33.89& 84.48)	P=0.532
Relaxation	1min	19.4 (8.7& 58)	21.4 (6.90& 79.3)	28.4 (13.3& 73.6)	P=0.167	-18.98 (-67.90& 36.18)	-28.19 (-67.16& 18.82)	-26.52 (-79.90& 26.51)	P=0.201
	2min	26.8 (10.9& 80)	28.5 (7.5& 119.7)	34.2 (15.7& 79.2)	P=0.414	1.02 (-57.93& 82.13)	-11.55 (-44.81& 70.21)	-9.77 (-72.76& 54.39)	P=0.145
	3min	27.9 (13.5& 80.5)	32.05 (7.6& 152.2)	34.3 (16.3& 74.9)	P=0.822	21.81 (-42.80&156.18)	-2.59 (-31.23&107.45)	-6.32 (-68.84& 46.0)	**P=0.022**
	4min	29.2 (13.1&110.2)	32.05 (7.6& 176.1)	33.5 (15.7& 76.7)	P=0.833	34.21 (-40.22&177.66)	7.5 (-26.55&139.36)	-8.27 (-65.76& 43.08)	**P=0.009**
	5min	32.1 (13.1&131.9)	35.9 (7.9& 169.2)	34.6 (17.9& 84.5)	P=0.903	35.77 (-37.27&178.27)	8.52 (-36.83&169.68	2.87 (-62.39& 61.99)	**P=0.046**
	6min	35.1 (13.9&147.7)	40.3 (7.8&1131.6)	32.6 (12.5& 94.3)	P=0.950	49.8 (-35.42&291.57)	18.37 (-52.97&828.3)	-10.19 (-58.89& 83.82	**P=0.016**
	7min	36.3 (13.9& 165.2)	42.65 (8.3& 192.1)	30.9 (12.5& 79.2)	P=0.938	53.29 (-26.57& 335.39)	13.08 (-66.01&184.04)	-12.99 (-55.6& 54.39)	**P=0.004**
	8min	39.3 (12.6&176.4)	36.55 (8.2& 201.1)	32.3 (13.2& 83)	P=0.928	67.14 (-32.62&313.48)	14.78 (-65.44&227.66)	9.06 (-55.81& 49.5)	**P=0.011**
Time to reach peak(s)		4 (1&8)	2 (1&7)	2 (1&6)	**P<0.001**				
slope % change in flux (ext-8min)						6.46 (-18.83& 40.15)	3.7 (-9.09& 29.99)	1.46 (-7.93& 3.51)	**P=0.008**
slope % change in flux (1min-8min)						10.63 (-1.15& 45.31)	6.62 (-7.27& 32.95)	3.07 (-1.77& 6.6)	**P=0.002**

Table 5.8 Changes in the leg cutaneous microcirculation in patients with CVI during extension/relaxation.

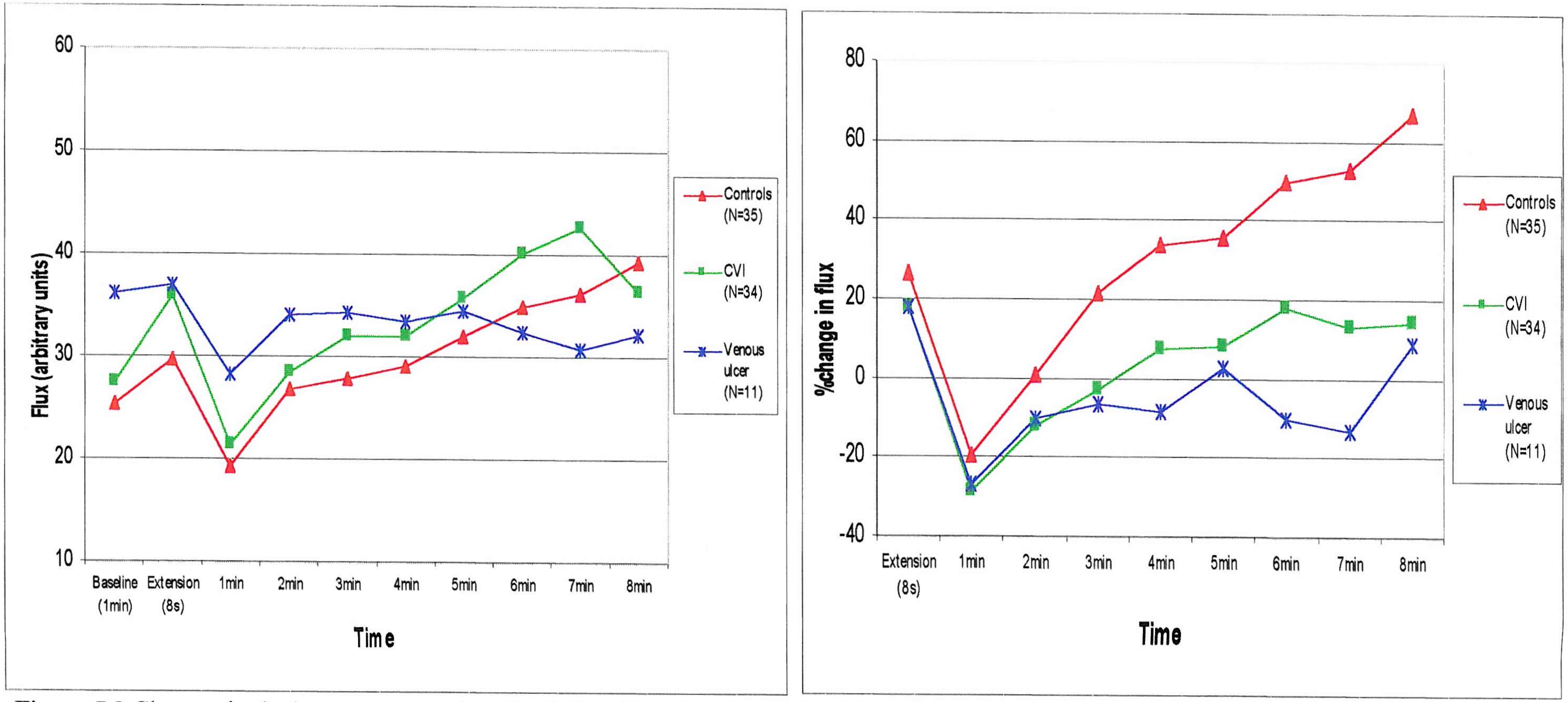


Figure 5.8 Changes in the leg cutaneous microcirculation (flux & %drop in flux) in patients with CVI before and during cutaneous extension/relaxation. A significant increase in the flux (A.U.) at both baseline and extension, and a significant lower %change in flux (3rd –8th min) were found in the venous ulcer group compared to controls. Significant lower %change in flux at 6th & 7th minute was found in the venous ulcer compared to CVI. The difference between CVI and controls was limited to a significant lower %change in flux at 4th minute of relaxation, in the CVI group.

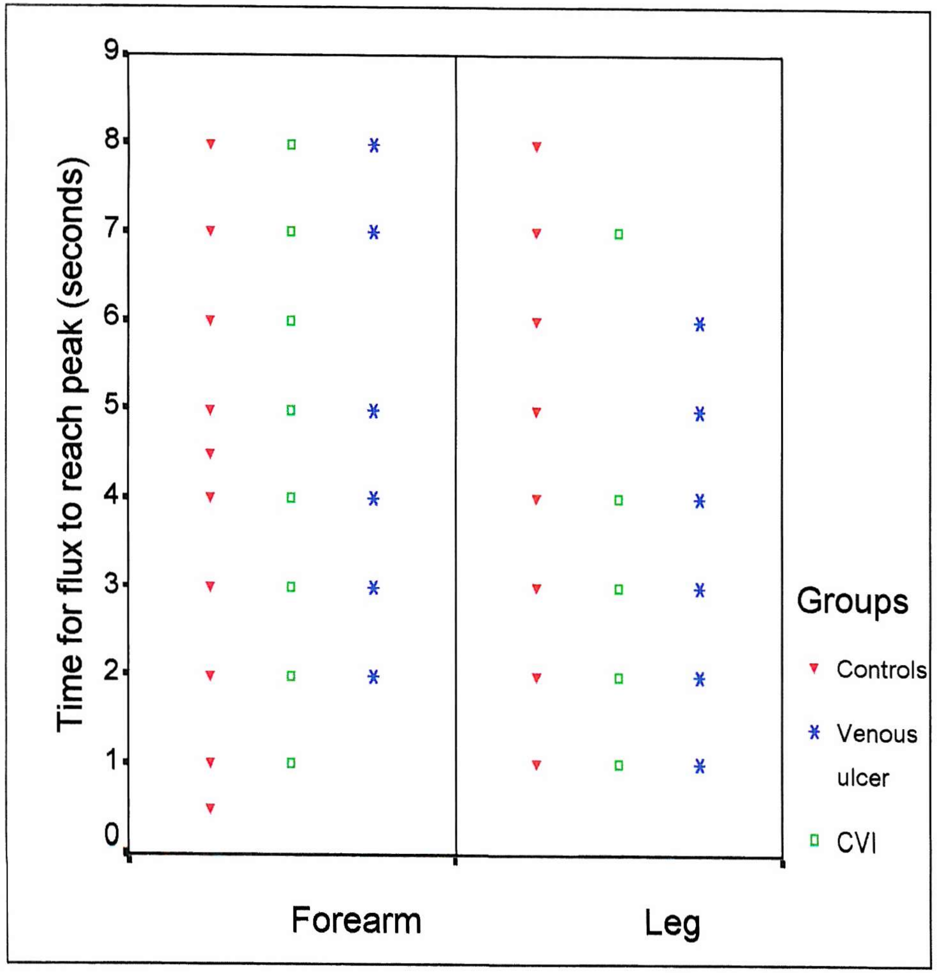


Figure 5.9 Changes in the time required for the flux to reach peak in the extension phase, measured during skin extension/relaxation in patients with CVI (with frank venous ulcers and without) in both extremities. A significant reduction in the time required for the flux to reach peak during extension in the CVI group compared to controls.

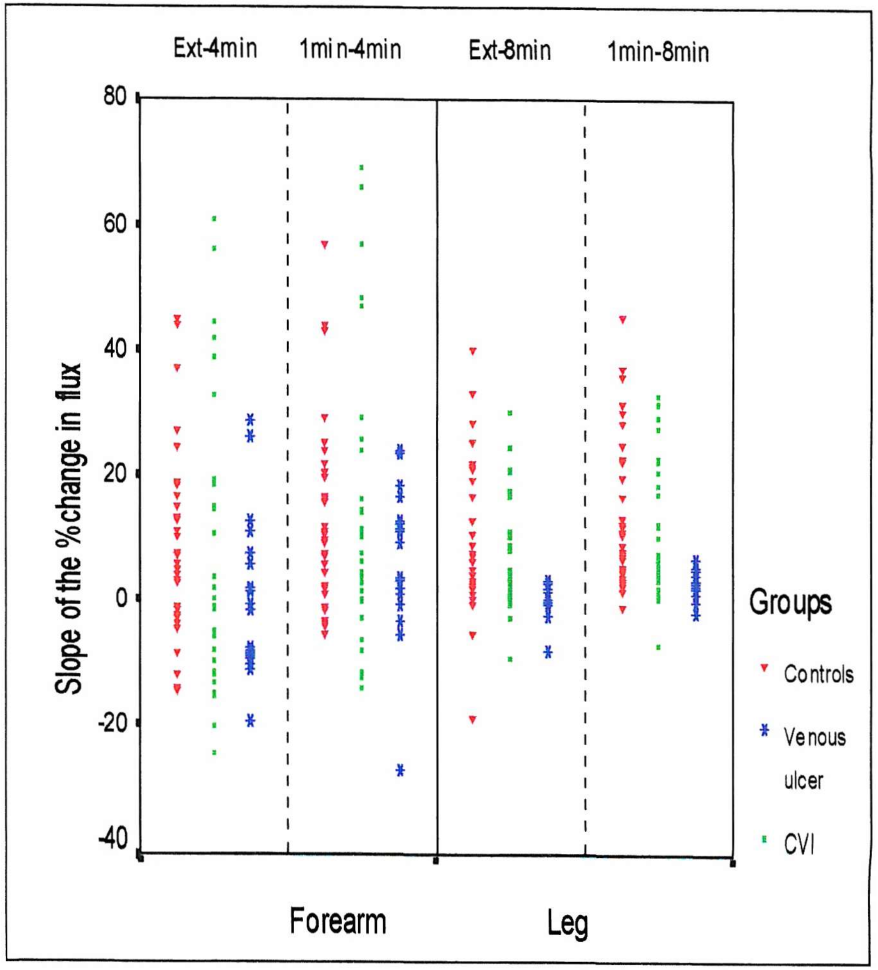


Figure 5.10 Changes in slopes of %change in flux measured during skin extension/relaxation in patients with CVI (with frank venous ulcers and without) in both extremities. Within the venous ulcer group, significantly lower slopes of the %change in flux were found compared to controls and CVI.

Forearm		In the elderly (61-90Y)							
		Flux (A. U.)			Significance	%change in Flux			Significance
		Controls (N=16)	CVI (N=16)	Venous ulcer (N=13)		Controls (N=16)	CVI (N=16)	Venous ulcer (N=13)	
Baseline		38.8 (20.2&156.5)	36 (12.1&121.4)	42.4 (19.6& 167.8)	P=0.528				
Extension		50.7 (21.9&146.5)	42.6 (22.2&130.3)	51.3 (28.8& 156.3)	P=0.649	19.49 (-6.39&50)	40.04 (4.92& 151.18)	40.51 (-19.61& 79.6)	**P=0.025**
Relaxation	1min	40 (19.4&118.4)	38.05 (17.2&115.1)	46.8 (20.9& 99.9)	P=0.744	4.59 (-24.35&48.28)	21.81 (-48.65& 81.20)	-4.43 (-56.79& 76.18)	P=0.195
	2min	42.15 (21.1&135.3)	39.3 (14.4&113.7)	43.6 (16.4& 125.9)	P=0.796	12.67 (-15.07&84.48)	24.88 (-44.62& 139.06)	0.93 (-42.37& 86.86)	P=0.171
	3min	41.9 (17.2&154)	36.5 (13.5& 135.1)	46.7 (16.2& 142.6)	P=0.595	15.69 (-26.05&125.86)	18.01 (-48.88& 169.12)	4.17 (-31.72& 109.80)	P=0.559
	4min	45.15 (22&174.1)	41.7 (13& 142.3	47.3 (22& 157.8)	P=0.584	18.99 (-16.92&224.57)	23.77 (-35.20& 183.47)	13.61 (-30.59& 87.84)	P=0.729
Time to reach peak(s)		4.5 (1&8)	4.5 (1& 8)	3 (2& 8)	P=0.891				
slope % change in flux (ext-4min)						1.09 (-11.77&44.83)	-3.04 (-20.12& 41.83)	-1.5 (-19.25& 13.06)	P=0.297
slope % change in flux (1min-4min)						6.62 (-5.42&57.03)	2.64 (-13.97& 48.17)	3.82 (-26.82& 24.15)	P=0.629

Table 5.9 Differences in the elderly forearm cutaneous microcirculation, with the application of cutaneous extension/relaxation, between patients with CVI with and without ulceration and controls.

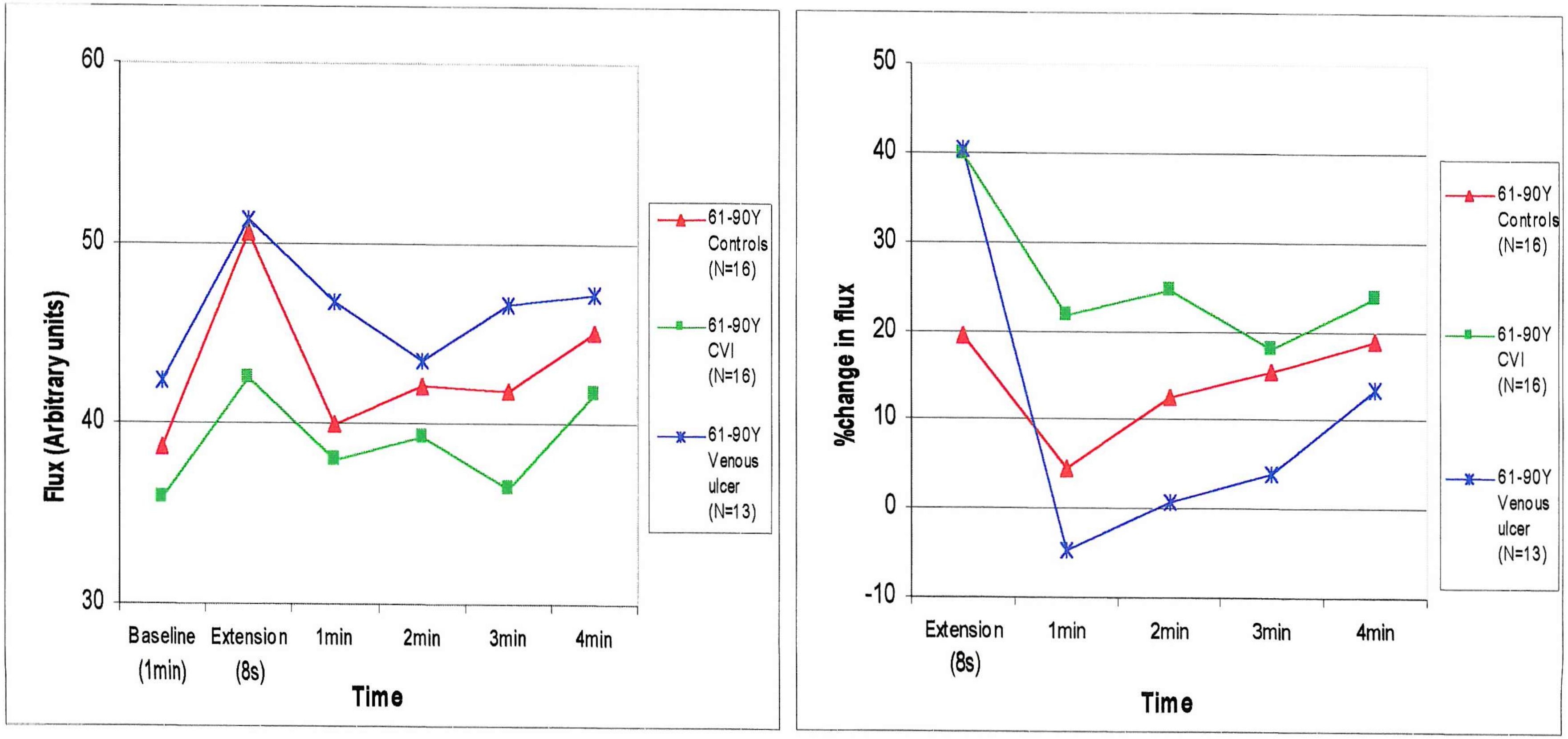


Figure 5.11 Differences in the forearm cutaneous microcirculation (flux & %change in flux) with the application of cutaneous extension/relaxation, between elderly patients with CVI with and without ulceration and elderly controls. The differences were generally non-significant except in the %change in flux during skin extension, as elderly controls exhibit a significant reduction in the %change in flux compared to elderly CVI.

Leg		In the elderly (61-90Y)							
		Flux (A. U.)			Significance	%change in Flux			Significance
		Controls (N=18)	CVI (N=14)	Venous ulcer(N=8)		Controls (N=18)	CVI (N=14)	Venous ulcer (N=8)	
Baseline		19.8 (13.5& 38.4)	29.85 (8.20&175.9)	36.3 (20.2&74.1)	**P=0.046**				
Extension		29.25 (16.8& 67.4)	37.65 (11.1&134.8)	39.6 (31.60&78.8)	P=0.056	27.45 (-19.24& 247.06)	10.46 (-23.37&79.75)	20.53 (-14.98&67.33)	P=0.279
Relaxation	1min	17.25 (10.3& 42.2)	22.6 (6.9&79.3)	26.5 (18.5&73.6)	P=0.071	-20.2 (-62.06& 36.18)	-36.19 (-66.86&11.17)	-21.53 (-61.67&26.51)	P=0.156
	2min	23.7 (10.9& 55.8)	29.35 (7.5&119.7)	30.1 (23 & 79.2)	P=0.238	-0.23 (-32.30& 82.13)	-11.55 (-38.15&70.21)	-4.04 (-52.23&54.39)	P=0.319
	3min	25.65 (13.5& 73.5)	35.65 (7.6&152.2)	30.65 (19.9&74.9)	P=0.648	20.84 (-25.78& 156.18)	-3.53 (-25.69&107.45)	-4.1 (-45.21&46)	P=0.146
	4min	29.15 (13.1& 80.8)	34.15 (7.6&176.1)	30.45 (25.3&76.7)	P=0.852	41.72 (-18.23& 177.66)	-1.74 (-26.55&139.36)	-1.37 (-42.51&43.08)	**P=0.035**
	5min	30.2 (13.1& 75.5)	39.55 (7.9&169.2)	32.55 (27.40&84.5)	P=0.634	41.11 (-29.95& 169.10)	-3.17 (-21.94&169.68)	10.4 (-44.94&61.99)	P=0.154
	6min	32.7 (13.9& 83)	40.3 (7.8&1131.6)	32.45 (26.8&94.3)	P=0.865	55.8 (-25.13& 291.57)	3.74 (-20.68&828.3)	10.98 (-43.32&83.82)	P=0.127
	7min	35.75 (13.9& 84.7)	42.65 (8.3&192.1)	30.85 (27.3&79.2)	P=0.919	70.98 (-25.67& 335.39)	5.21 (-23.07&184.04)	9.4 (-50.61&54.39)	**P=0.035**
	8min	35.9 (12.6& 111.2)	34.35 (8.2&201.1)	32.1 (26.7&83)	P=0.983	68.44 (-32.62&313.48)	9.55 (-25.7&227.66)	16.49 (-39&49.5)	**P=0.049**
Time to reach peak		4 (1&7)	2 (1&7)	3.5 (2&6)	**P=0.017**				
slope % change in flux (ext-8min)						7.46 (-18.83& 40.15)	2.33 (-2.95&29.99)	1.7 (-2.34&2.91)	**P=0.044**
slope % change in flux (1min-8min)						11.66 (-1.15& 45.31)	5.55 (0.48&32.95)	2.68 (-0.23&6.6)	**P=0.034**

Table 5.10 Changes in the leg cutaneous microcirculation in elderly patients with CVI with and without ulceration before and during cutaneous extension/relaxation, measured with laser Doppler flowmetery.

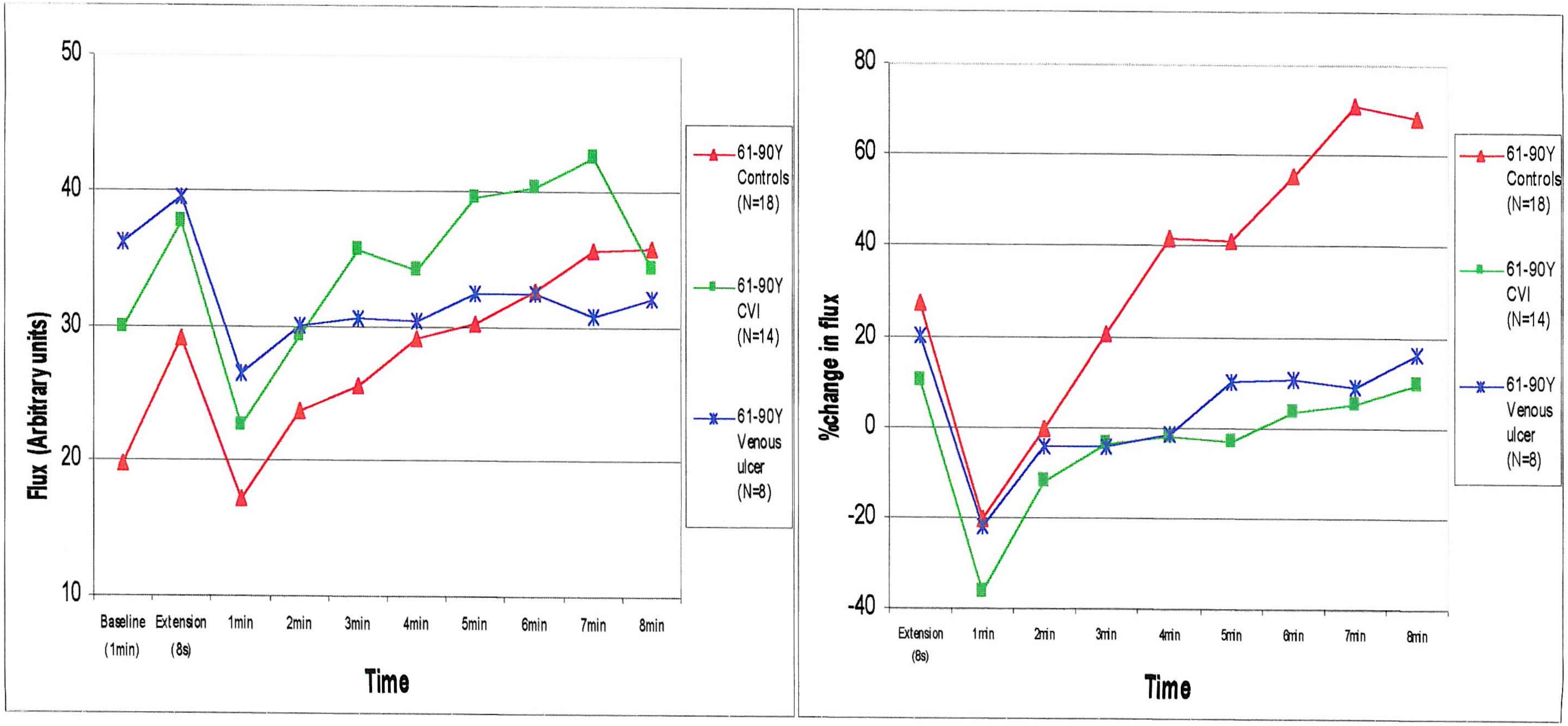


Figure 5.12 Changes in the leg cutaneous microcirculation (flux & %change in flux) in elderly patients with CVI with and without ulceration before and during cutaneous extension/relaxation. A significant lower %change in flux were found during the 4th & 7th minute of relaxation in the elderly CVI group when compared to elderly controls. An increase in flux (A.U.) at baseline, extension, 1st, 2nd minutes of relaxation and lower %change in flux during the 4th, 7th & 8th minute were found in the elderly venous ulcer legs compared to elderly controls.

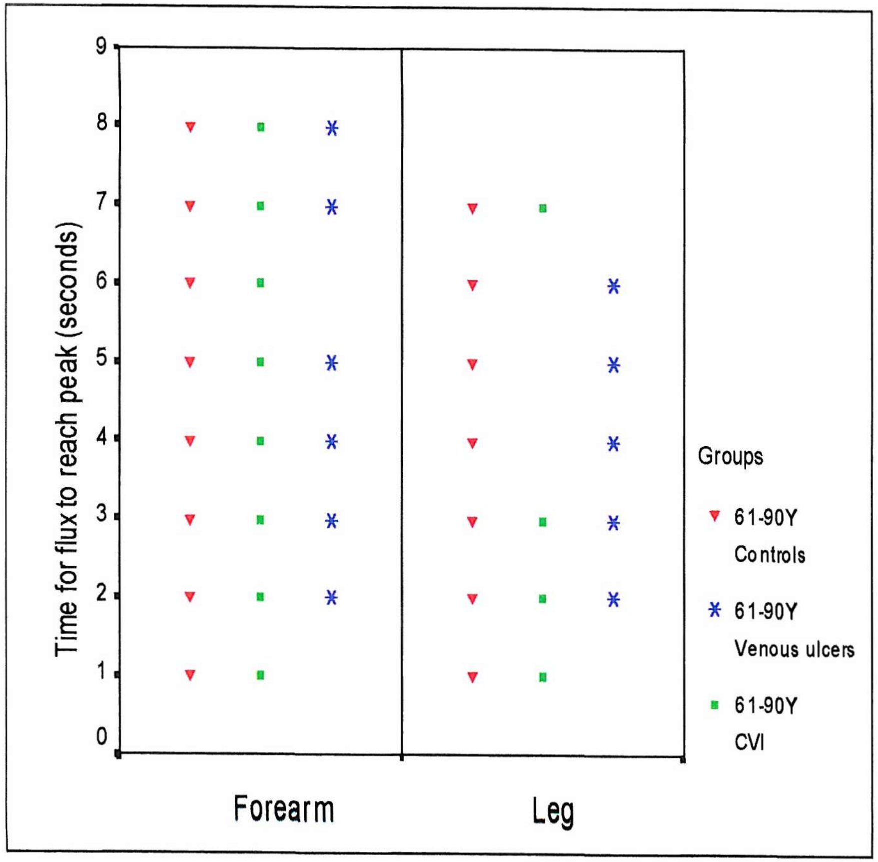


Figure 5.13 Changes in the time required for the flux to reach peak during extension phase in elderly patients with CVI with and without ulceration in both extremities. A significant reduction in the time in the elderly CVI compared to both elderly controls and elderly venous ulcers was found.

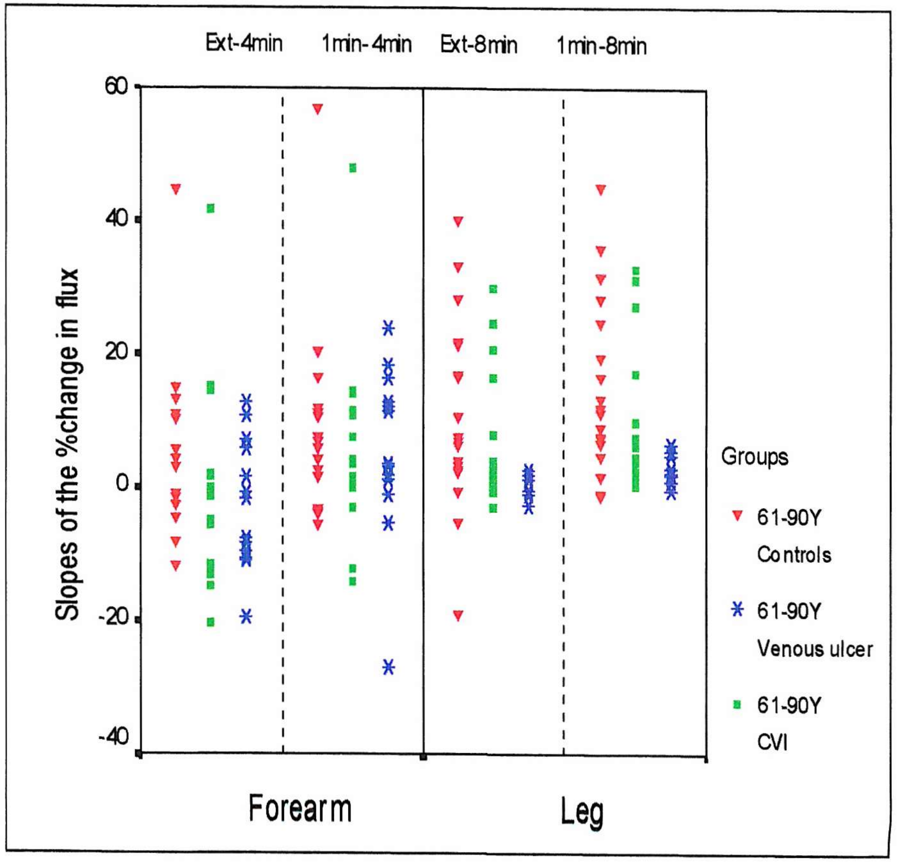
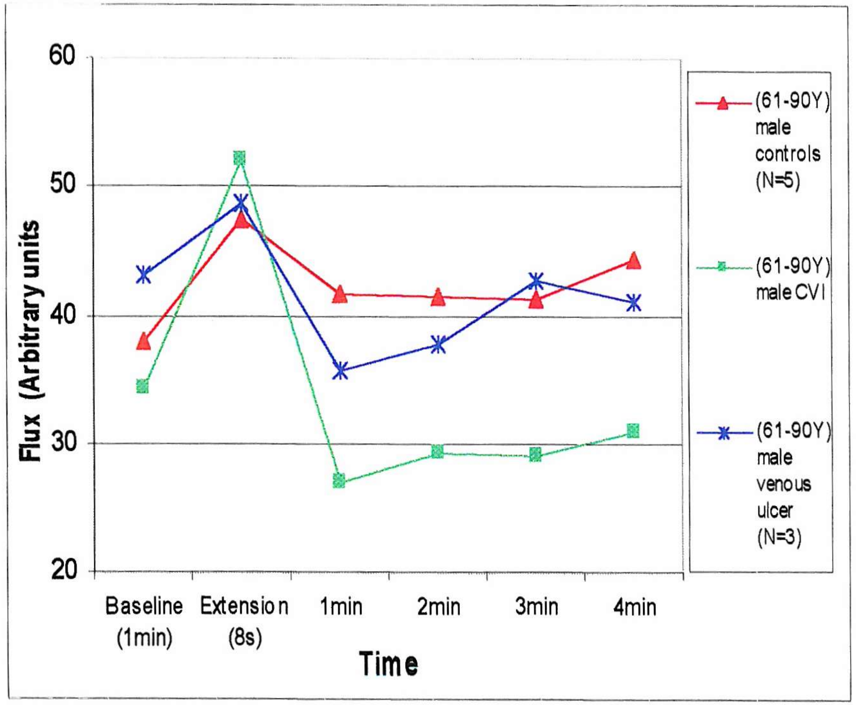


Figure 5.14 Changes in slopes of %change in flux during cutaneous extension/relaxation in elderly patients with CVI with and without ulceration in both extremities. In the leg, both slopes (ext-8min & 1min-8min) were significantly lower in the elderly venous ulcer group compared to elderly controls.

Forearm	In the elderly (61-90Y) male							
	Flux (A. U.)			Significance	%change in Flux			Significance
	Controls (N=5)	CVI (N=4)	Venous ulcer (N=3)		Controls (N=5)	CVI (N=4)	Venous ulcer (N=3)	
Baseline	38.00 (31.7&87.9)	34.35 (17.0&46.4)	43.20 (28.1&55.3)	P=0.778				
Extension	47.50 (38.4&100)	52.20 (38.1&73.0)	48.80 (45.3&65.5)	P=0.933	19.95 (12.9&44.2)	57.71 (38.34&151.18)	51.62 (-11.75&61.21)	P=0.113
Relaxation 1min	41.70 (26.5&88.5)	27.10 (22.7&57.7)	35.80 (23.7&48.8)	P=0.404	0.68 (-16.4&22.65)	27.11 (-48.65&33.53)	-15.66 (-35.26&12.96)	P=0.309
Relaxation 2min	41.50 (31.5&76.0)	29.30 (22.9&72.6)	37.80 (28.6&43.6)	P=0.404	4.80 (-13.54&21.84)	37.68 (-44.62&56.47)	0.93 (-31.65&1.78)	P=0.309
Relaxation 3min	41.40 (37.3&65.0)	29.15 (22.8&75.3)	42.70 (34.9&45.0)	P=0.395	8.95 (-26.05&31.55)	43.57 (-48.88&62.28)	4.17 (-22.78&24.20)	P=0.395
Relaxation 4min	44.40 (37.9&76.3)	30.90 (28.9&68.7)	41.20 (39.1&47.3)	P=0.289	11.47 (-13.20&41.64)	40.21 (-35.20&75.88)	9.49 (-25.50&39.15)	P=0.576
Time to reach peak(s)	6 (3&7)	5.50 (3&7)	3 (3)	P=0.127				
slope % change in flux (ext-4min)					-1.59 (-8.18&4.29)	-8.92 (-14.73&1.94)	-1.50 (-9.31&-.43)	P=0.493
slope % change in flux (1min-4min)					-3.31 (-5.42&20.63)	5.65 (0.04&14.59)	3.82 (-0.72&18.68)	P=0.572

Forearm	In the elderly (61-90Y) female							
	Flux (A. U.)			Significance	%change in Flux			Significance
	Controls (N=11)	CVI (N=12)	Venous ulcer (N=10)		Controls (N=11)	CVI (N=12)	Venous ulcer (N=10)	
Baseline	40.20 (20.2&156.5)	36.00 (12.1&121.4)	41.15 (19.6&167.8)	P=0.699				
Extension	55.30 (21.9&146.5)	41.50 (22.2&130.3)	60.10 (28.8&156.3)	P=0.548	19.02 (-6.39&50.00)	37.89 (4.92&83.47)	34.54 (-19.61&79.60)	P=0.099
Relaxation 1min	38.30 (19.4&118.4)	46.30 (17.2&115.1)	54.30 (20.9&99.9)	P=0.932	8.50 (-24.35&48.28)	17.33 (-13.36&81.20)	1.36 (-56.79&76.18)	P=0.459
Relaxation 2min	42.80 (21.1&135.3)	46.25 (14.4&113.7)	55.15 (16.4&125.9)	P=0.919	16.18 (-15.07&84.48)	19.89 (-14.79&139.06)	3.53 (-42.37&86.86)	P=0.410
Relaxation 3min	52.40 (17.2&154.0)	48.50 (13.5&135.1)	54.45 (16.2&142.6)	P=0.773	28.86 (-14.9&125.9)	4.46 (-20.12&169.12)	-.98 (-31.72&109.8)	P=0.588
Relaxation 4min	62.4 (22.0&174.1)	47.90 (13.0&142.3)	50.65 (22.0&157.8)	P=0.711	31.21 (-16.9&224.6)	15.55 (-23.08&183.47)	15.99 (-30.59&87.84)	P=0.615
Time to reach peak(s)	4 (1&8)	4.5 (1&8)	4.5 (2&8)	P=0.893				
slope % change in flux (ext-4min)					5.80 (-11.77&44.83)	-.58 (-20.12&41.83)	-2.80 (-19.25&13.06)	P=0.346
slope % change in flux (1min-4min)					7.73 (-3.86&57.03)	1.65 (-13.97&48.17)	7.43 (-26.82&24.15)	P=0.325

Table 5.11 Changes in the forearms cutaneous microcirculation in elderly male and female patients with CVI with and without ulceration before and during cutaneous extension/relaxation, measured with laser Doppler flowmetery.



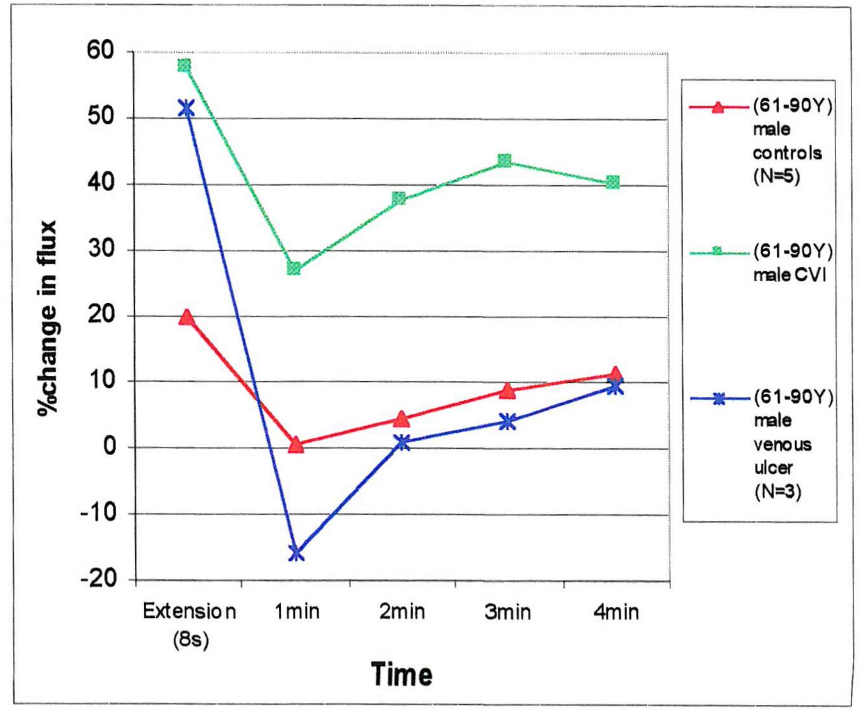


Figure 5.15 Non significant differences in the forearm cutaneous microcirculation (flux & %change in flux) with the application of cutaneous extension/relaxation, between elderly male patients with CVI with and without ulceration and elderly male controls.

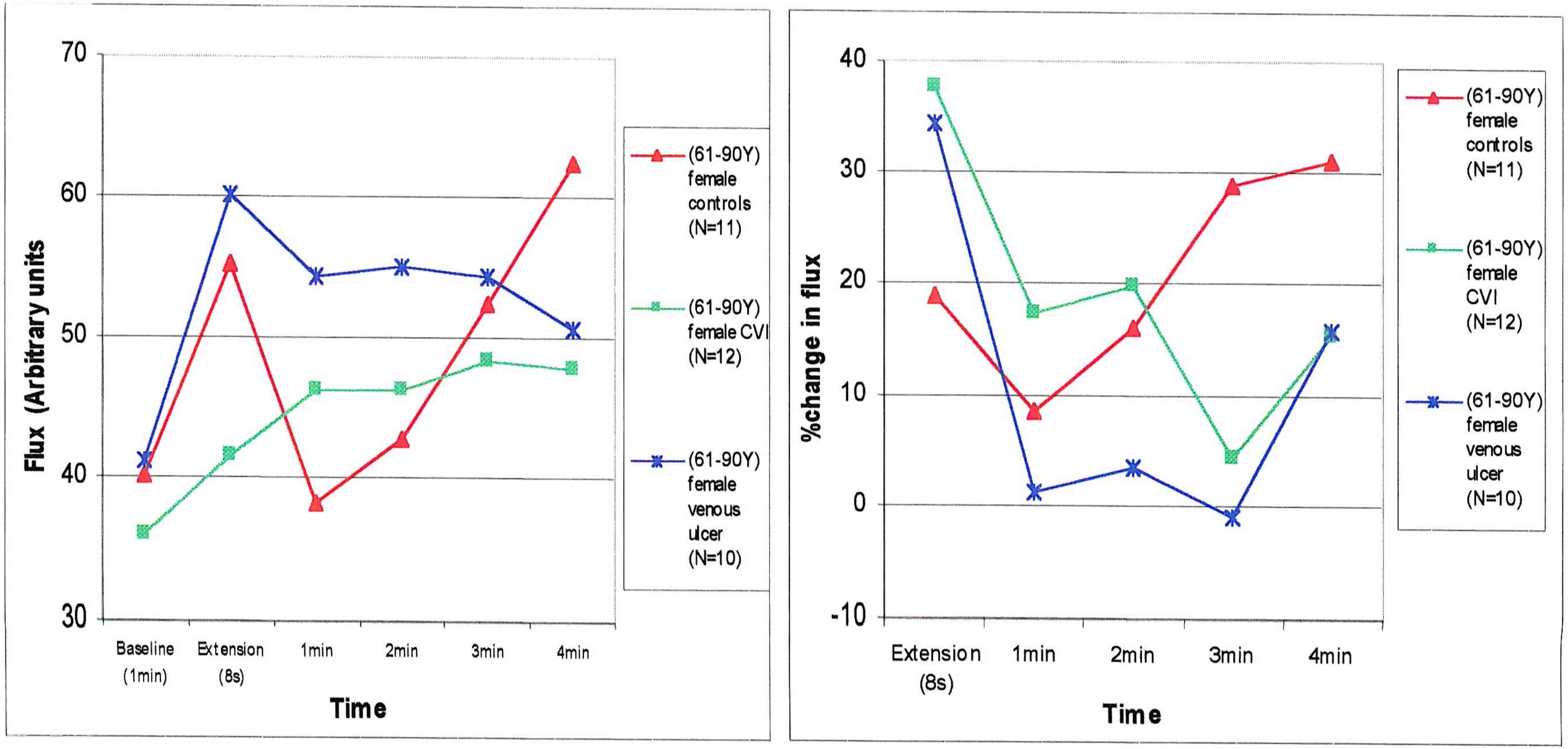


Figure 5.16 Non significant differences in the forearm cutaneous microcirculation (flux & %change in flux) with the application of cutaneous extension/relaxation, between elderly female patients with CVI with and without ulceration and elderly female controls.

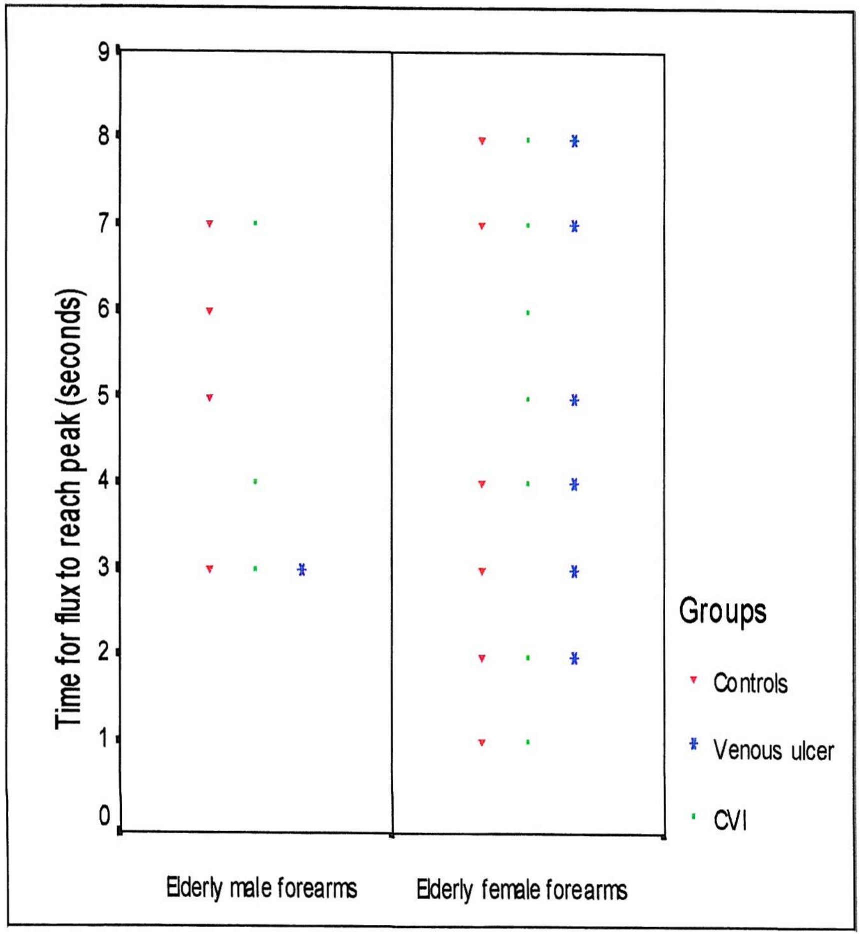


Figure 5.17 In the forearms, a non significant difference in the time required for the flux to reach peak during extension phase was found in elderly male and female patients with CVI (with and without ulceration in both extremities) when compared to elderly male and female controls.

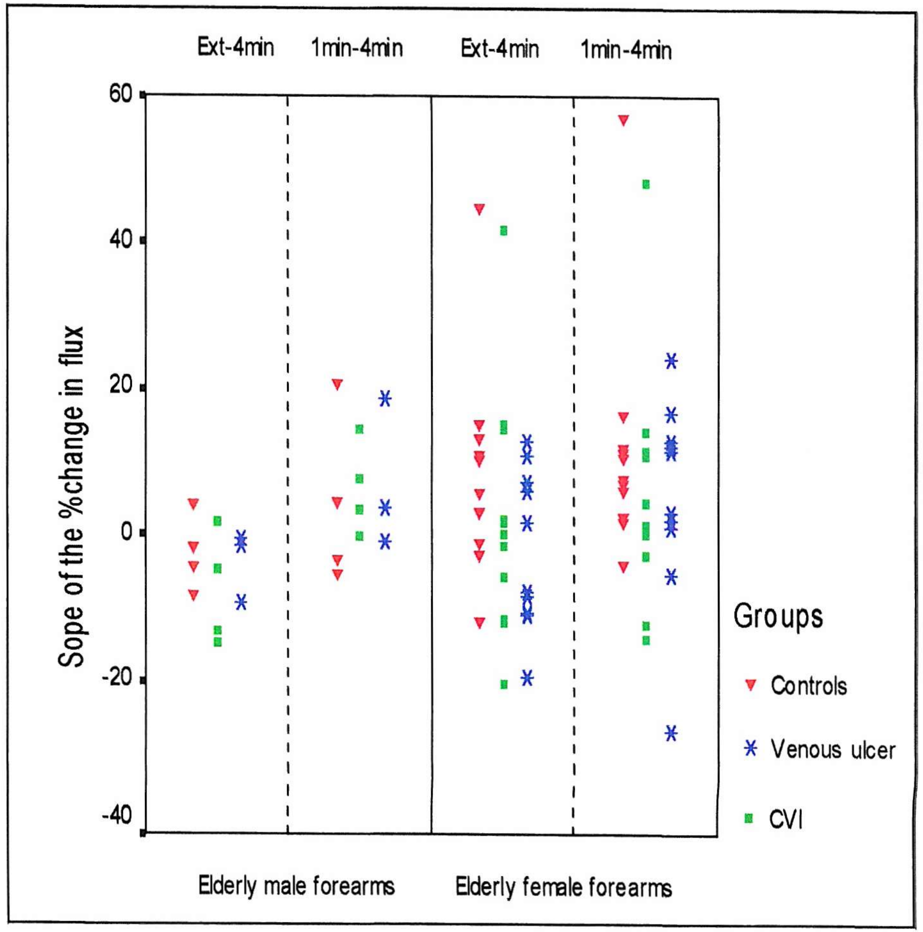


Figure 5.18 In the forearms, non significant differences in both slopes were found in elderly male and female patients with CVI (with and without ulceration in both extremities) when compared to elderly male and female controls.

In the elderly (61-90Y) male

Leg	Flux (A. U.) Controls (N=8)	Flux (A. U.) CVI (N=3)	Flux (A. U.) Venous ulcer (N=1)	Significance	%change in Flux Controls (N=8)	%change in Flux CVI (N=3)	%change in Flux Venous ulcer (N=1)	Significance
Baseline	19.20 (13.5&38.4)	31.80 (15.8&91.9)	27.90	P=0.677				
Extension	28.25 (16.8&64.9)	36.90 (28.4&78.7)	32.90	P=0.455	27.45 (-4.95&247.06)	16.04 (-14.36&79.75)	17.92	P=0.695
Relaxation 1min	14.85 (10.3&42.2)	22.70 (8.9&52.0)	20.50	P=0.741	-21.16 (-48.64&20.57)	-43.42 (-43.67&-28.62)	-26.52	P=0.288
Relaxation 2min	17.95 (10.9&55.8)	27.90 (10.7&91.9)	23.90	P=0.695	-16.00 (-32.30&59.43)	-12.26 (-32.28&.00)	-14.34	P=0.983
Relaxation 3min	20.65 (14.7&73.5)	33.00 (15.2&88.9)	22.50	P=0.584	-6.63 (-25.78&110.0)	-3.26 (-3.80&3.77)	-19.35	P=0.479
Relaxation 4min	23.40 (16.9&69.1)	30.40 (21.0&86.3)	25.30	P=0.565	9.08 (-18.23&102.22)	-4.40 (-6.09&32.91)	-9.32	P=0.538
Relaxation 5min	22.90 (13.1&75.5)	34.50 (30.3&88.7)	29.00	P=0.149	-.25 (-29.95&122.22)	-3.48 (-4.72&118.35)	3.94	P=0.897
Relaxation 6min	25.75 (14.0&81.0)	41.10 (28.3&79.9)	27.40	P=0.328	9.16 (-25.13&131.43)	-11.01 (-13.06&160.13)	-1.79	P=0.784
Relaxation 7min	26.20 (13.9&84.0)	43.80 (28.4&70.7)	29.50	P=0.485	17.49 (-25.67&151.85)	-10.69 (-23.07&177.22)	5.73	P=0.875
Relaxation 8min	24.60 (12.6&87.4)	31.70 (30.7&75.9)	30.90	P=0.565	12.23 (-32.62&168.15)	-3.46 (-17.41&100.63)	10.75	P=0.811
Time to reach peak(s)	5 (1&6)	1 (1&1)	2	P=0.051				
slope % change in flux (ext-8min)					3.13 (-18.83&21.79)	.38 (-.50&20.89)	1.94	P=0.853
slope % change in flux (1min-8min)					7.06 (-1.15&24.77)	1.66 (.48&31.37)	5.09	P=0.944

In the elderly (61-90Y) female

Leg	Flux (A. U.) Controls (N=10)	Flux (A. U.) CVI (N=11)	Flux (A. U.) Venous ulcer (N=7)	Significance	%change in Flux Controls (N=10)	%change in Flux CVI (N=11)	%change in Flux Venous ulcer (N=7)	Significance
Baseline	20.60 (14.3&36.9)	27.90 (8.2&175.9)	36.30 (20.2&74.1)	P=0.117				
Extension	29.25 (18.1&67.4)	38.40 (11.1&134.8)	44.70 (31.6&78.8)	P=0.088	34.99 (-19.24&131.62)	5.71 (-23.37&59.76)	23.14 (-14.98&67.33)	P=0.349
Relaxation 1min	19.20 (12.2&37.1)	22.50 (6.9&79.3)	28.40 (18.5&73.6)	P=0.162	3.30 (-62.06&36.18)	-34.95 (-66.86&11.17)	-16.53 (-61.67&26.51)	P=0.184
Relaxation 2min	28.40 (13.4&53.0)	30.80 (7.5&119.7)	34.20 (23.0&79.2)	P=0.456	14.49 (-26.02&82.13)	-10.83 (-38.15&70.21)	-2.30 (-52.23&54.39)	P=0.169
Relaxation 3min	35.55 (13.5&70.9)	38.30 (7.6&152.2)	34.30 (19.9&74.9)	P=0.971	47.11 (-6.50&156.18)	-4.27 (-25.69&107.45)	-2.68 (-45.21&46.00)	**P=0.034**
Relaxation 4min	43.70 (13.1&80.8)	37.90 (7.6&176.1)	33.50 (26.4&76.7)	P=0.849	83.88 (-8.39&177.66)	.11 (-26.55&139.36)	4.98 (-42.51&43.08)	**P=0.018**
Relaxation 5min	46.65 (13.7&75.2)	44.60 (7.9&169.2)	34.60 (27.4&84.5)	P=0.922	100.17 (-4.20&169.10)	-2.87 (-21.94&169.68)	16.86 (-44.94&61.99)	**P=0.021**
Relaxation 6min	45.15 (13.9&83.0)	39.50 (7.8&1131.6)	32.60 (26.8&94.3)	P=0.896	90.90 (-2.80&291.57)	11.43 (-20.68&828.30)	23.75 (-43.32&83.82)	**P=0.033**
Relaxation 7min	46.85 (14.2&84.7)	41.50 (8.3&192.1)	30.90 (27.3&79.2)	P=0.631	102.12 (-.70&335.39)	9.21 (-16.67&184.04)	13.07 (-50.61&54.39)	**P=0.006**
Relaxation 8min	46.45 (15.8&111.2)	37.00 (8.2&201.1)	32.30 (26.7&83.0)	P=0.713	110.07 (10.49&313.48)	10.39 (-25.70&227.66)	22.22 (-39.00&49.50)	**P=0.004**
Time to reach peak(s)	3.5 (1&7)	2 (1&7)	4 (2&6)	P=0.138				
slope % change in flux (ext-8min)					13.82 (-5.15&40.15)	2.86 (-2.95&29.99)	1.46 (-2.34&2.91)	**P=0.019**
slope % change in flux (1min-8min)					16.41 (-.80&45.31)	6.34 (1.03&32.95)	2.29 (-.23&6.60)	**P=0.008**

Table 5.12 Changes in the legs cutaneous microcirculation in elderly male and female patients with CVI with and without ulceration before and during cutaneous extension/relaxation, measured with laser Doppler flowmetry.

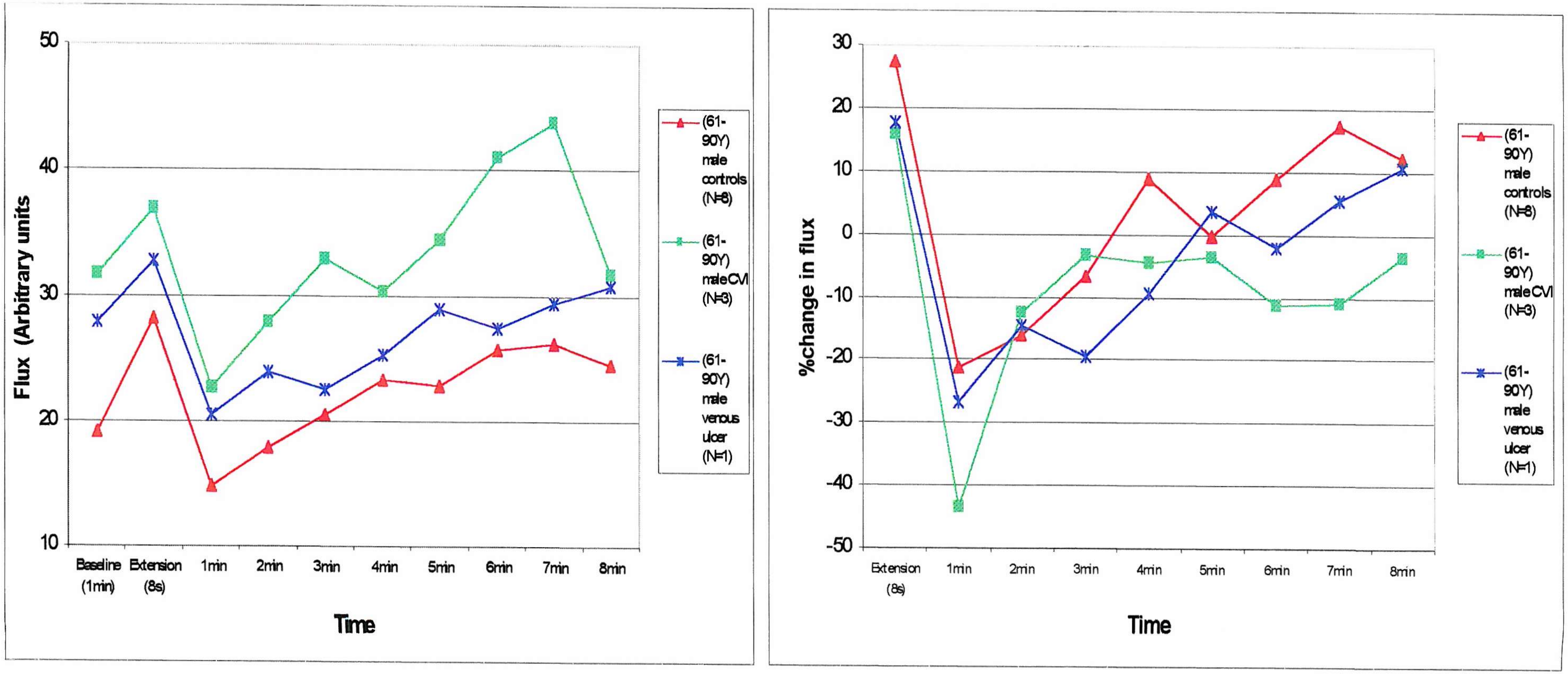


Figure 5.19 Changes in the leg cutaneous microcirculation (flux & %change in flux) in elderly male patients with CVI with and without ulceration before and during cutaneous extension/relaxation. No significant differences were found in the elderly male patients (with and without ulceration) compared to elderly male controls.

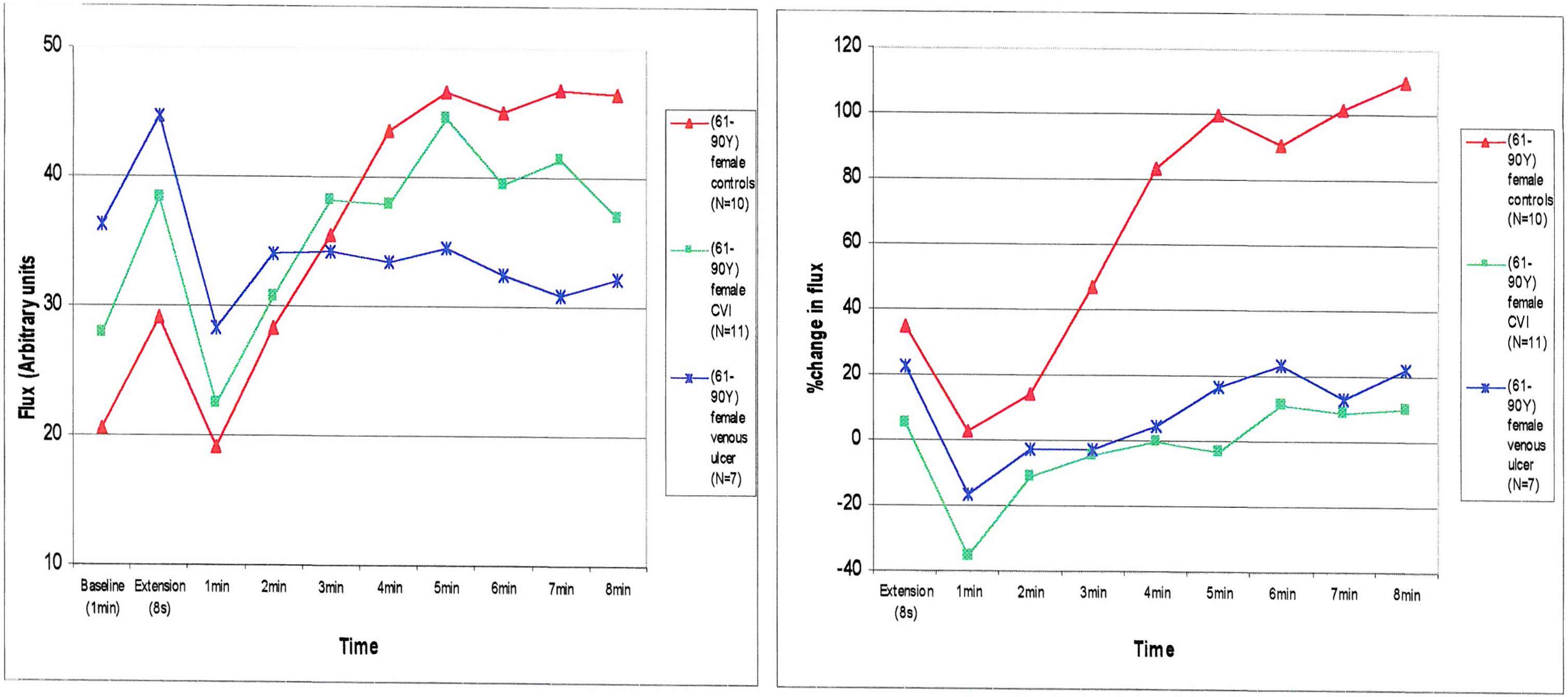


Figure 5.20 Changes in the leg cutaneous microcirculation (flux & %change in flux) in elderly female patients with CVI with and without ulceration before and during cutaneous extension/relaxation. A significant lower %change in flux were found between the 3^{th} - 8^{th} minutes of relaxation in the elderly females with CVI only and elderly females with venous ulcers compared to elderly female controls.

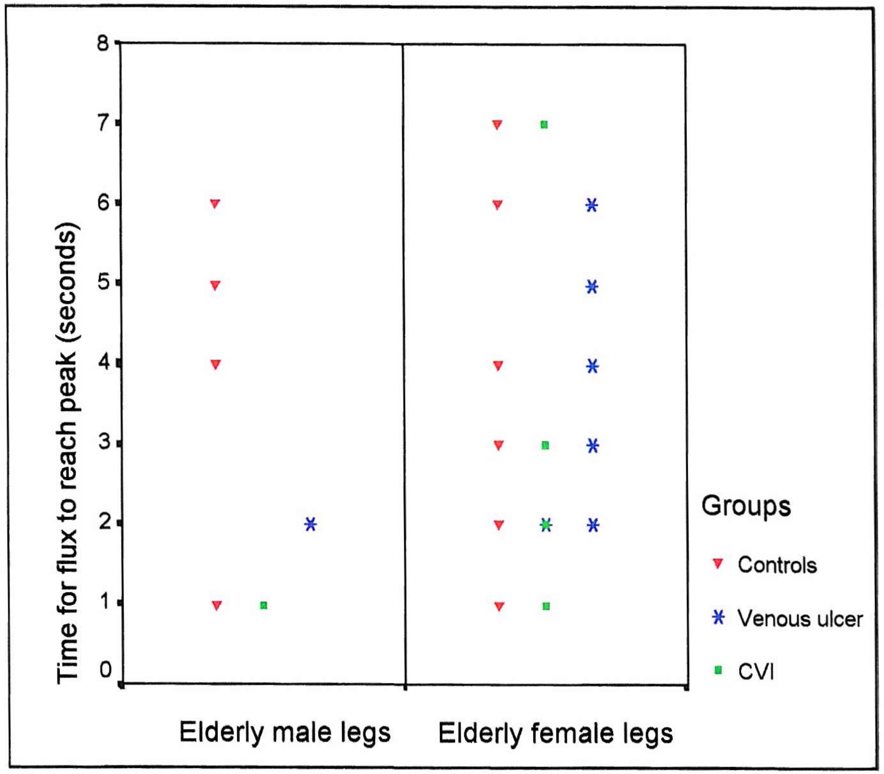


Figure 5.21 The time required for the flux to reach peak during extension phase in the leg region. A significant reduction in the time required for the flux to reach peak during extension phase in elderly male patients with CVI only compared to elderly male controls. Non significant differences in the time were found in elderly females.

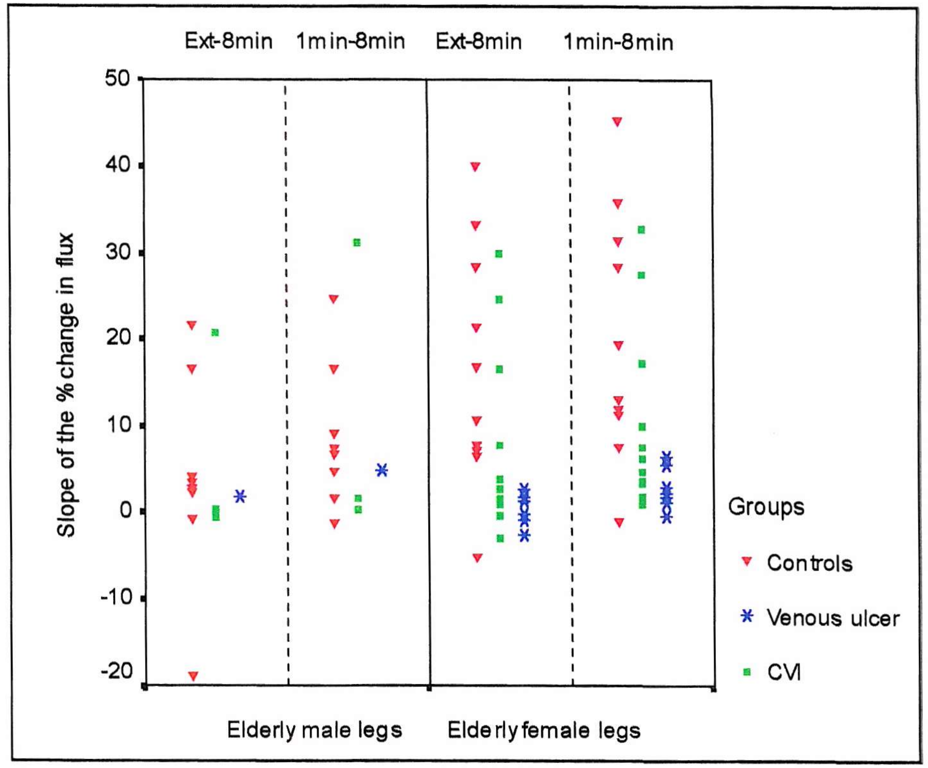


Figure 5.22 The slopes of %change in flux during cutaneous extension/relaxation in elderly male and female patients with CVI with and without ulceration in the leg. Significant lower slopes (ext-8min & 1min-8min) were found in elderly female venous ulcer group compared to elderly female controls. The differences in the elderly male groups were statistically non-significant.

5.5 The postural vasoconstrictor response

Method

A group of 63 patients diagnosed with CVI and confirmed by Duplex scanning, were studied. Of the 63 patients, 40 patients (9M, 31F, mean age 57.7 years, age range 28-81 years) had CVI but no ulcers at the time of the study and 23 patients (8M, 15F, mean age 66.4 years, age range 34-85 years) had active venous ulcers. The exclusion criteria used for selecting patients and controls were described in sections 5.1 and 4.1 respectively. The protocol used for monitoring the microcirculation during passive leg lowering were described in section 3.3.7.2. Data are presented in appendices 35 & 36, tables 5.13-5.15 as median (Min & max) and graphically in figures. 5.23-5.32.

Statistical analysis

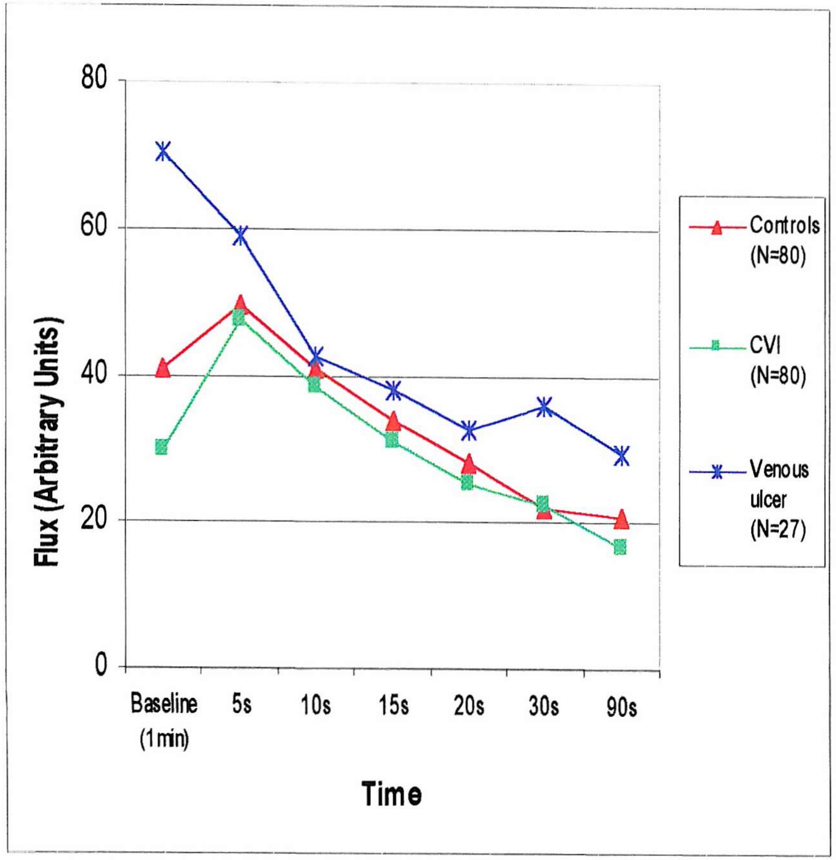
Data acquired from the patients were compared to asymptomatic controls (N=40, 14M, 26F, mean age 52.7 years, age range 23-74 years) and examined for statistical differences using the non-parametric Kruskal-Wallis and Mann-Whitney tests. Data from both extremities in controls and patients with CVI but no ulcers at the time of the study, were included in the analysis. The occurrence of venous ulcers bilaterally in 4 patients resulted in the presence of 27 extremities affected with active venous ulcers.

Changes in the postural vasoconstrictive response were examined in the elderly (61-90Y) patients with CVI and compared to elderly controls using the above statistical methods. Changes in the postural vasoconstrictive response with CVI and venous ulceration were examined in elderly males and females using the above statistical methods.

(N) represents the actual number of extremities within each group included in the statistical analysis.

		Flux (A. U.)				% drop in Flux			
		Controls (N=80)	CVI (N=80)	Venous ulcer (N=27)	Significance	Controls (N=80)	CVI (N=80)	Venous ulcer (N=27)	Significance
Baseline		41.15 (5.7&542.6)	29.85 (6.0&259.4)	70.4 (7.8&202.1)	P=0.154				
Lowering	5s	49.45 (11.0&792.7)	47.45 (8.4&379.6)	59.1 (15.3&268.3)	P=0.807	-18.51 (-350.46&77.43)	-52.87 (-997.14&78.51)	-0.1 (-328.28 &74.15)	**P=0.004**
	10s	41.1 (6.0&723.1)	38.55 (12.9&371.1)	42.7 (10.9&273.9)	P=0.962	7.53 (-178.79&80.61)	-15.71 (-531.82&80.98)	18.79 (-182.83&84.09)	**P=0.020**
	15s	34 (6.4&723.8)	31.05 (9.6&352.3)	38.1 (12.0&247.5)	P=0.854	8.08 (-170.18&72.63)	-7.4 (-407.58&94.16)	24.06 (-169.70&78.52)	P=0.096
	20s	28.35 (7.3&483.0)	25.6 (6.8&390.4)	32.8 (9.1&255.3)	P=0.697	21.20 (-118.35&77.47)	-0.97 (-289.39&94.32)	20.54 (-231.31&85.06)	P=0.070
	30s	22.1 (4.1&506.6)	22.45 (6.4&314.6)	36.2 (7.3&266.2)	P=0.784	29.74 (-118.97&93.91)	18.55 (-425.87&84.73)	30.09 (-158.59&80.75)	P=0.148
	90s	21.1 (4.3&377.2)	17.0 (3.2&310.5)	29.7 (6.5&276.2)	P=0.095	45.32 (-99.66&87.38)	35.05 (-135.90&86.11)	38.07 (-171.72&80.83)	P=0.126
Time to reach baseline (s)		7 (1&120)	15.5 (2&120)	11 (2&120)	**P<0.001**				
slope % drop in flux (5s-90s)						0 .60 (-0.30&2.62)	0 .86 (-1.14&7.92)	0.33 (-1.61&2.18)	**P=0.008**
slope % drop in flux (10s-90s)						0.42 (-0.43&2.01)	0.51 (-1.51&5.25)	0.12 (-1.69&1.89)	**P=0.007**

Table 5.13 Changes in cutaneous microcirculation during passive leg lowering in patients with CVI (with frank ulcers and without) as measured with laser Doppler flowmetery.



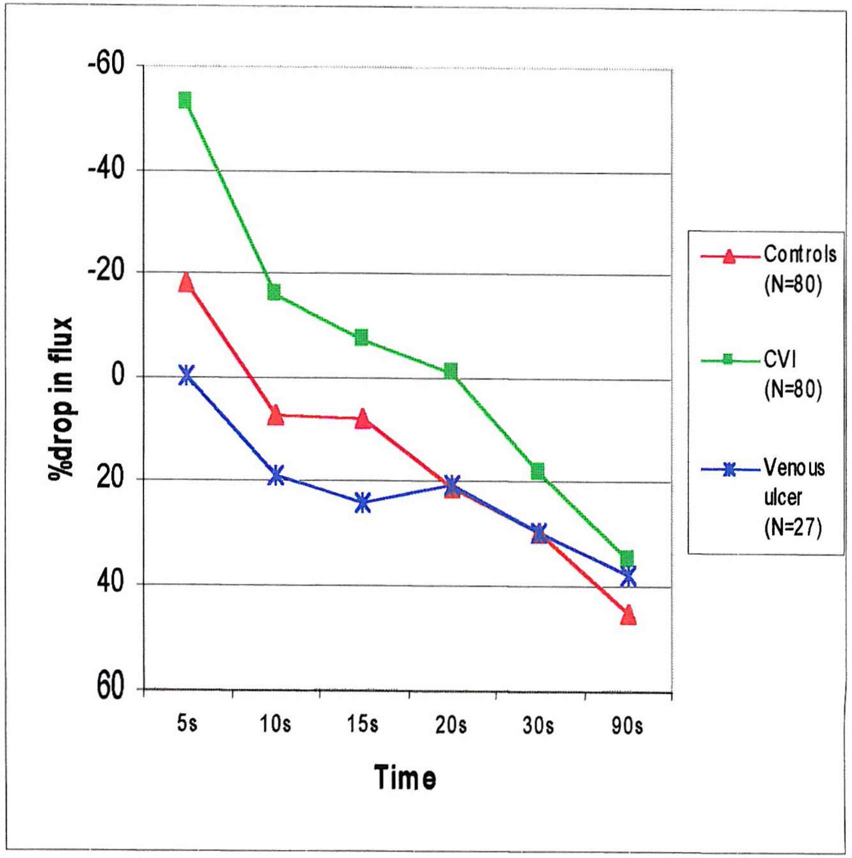


Figure 5.23 Changes in cutaneous microcirculation (flux & %drop in flux) during passive leg lowering in patients with CVI (with frank ulcers and without). A significant reduction in the %drop in flux (at 5s & 10s of dependency) in the CVI compared to both controls and venous ulcer groups and a significant increase in flux (A.U.) at 90s in the venous ulcer group compared to CVI.

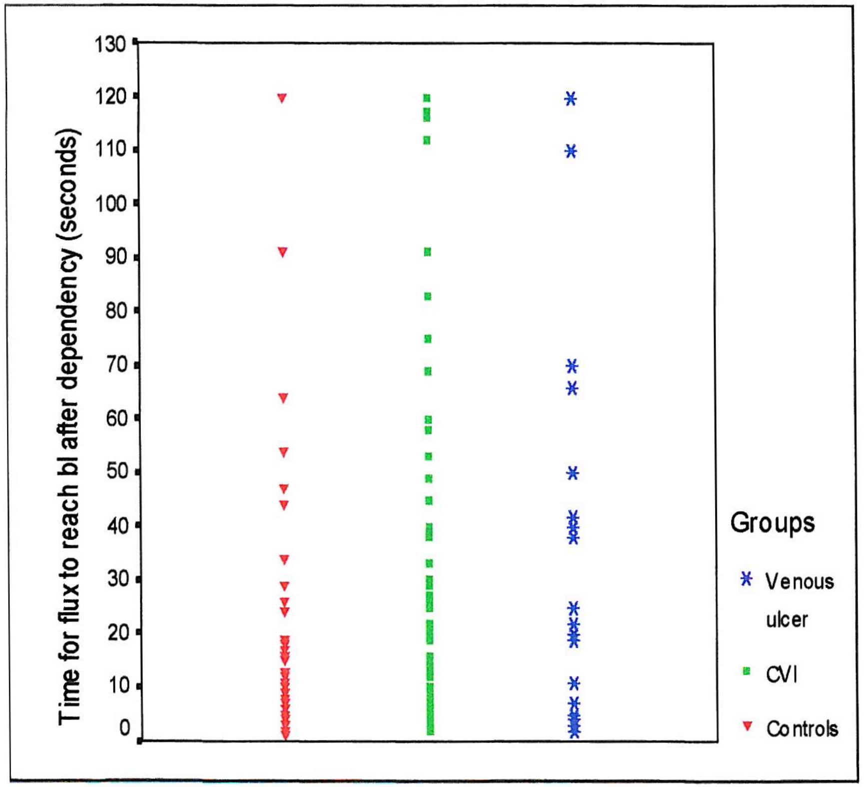


Figure 5.24 Changes in cutaneous microcirculation (the time required for the flux to return to baseline values after dependency) during passive leg lowering in patients with CVI. A significant delay in the time was found in the CVI compared to controls.

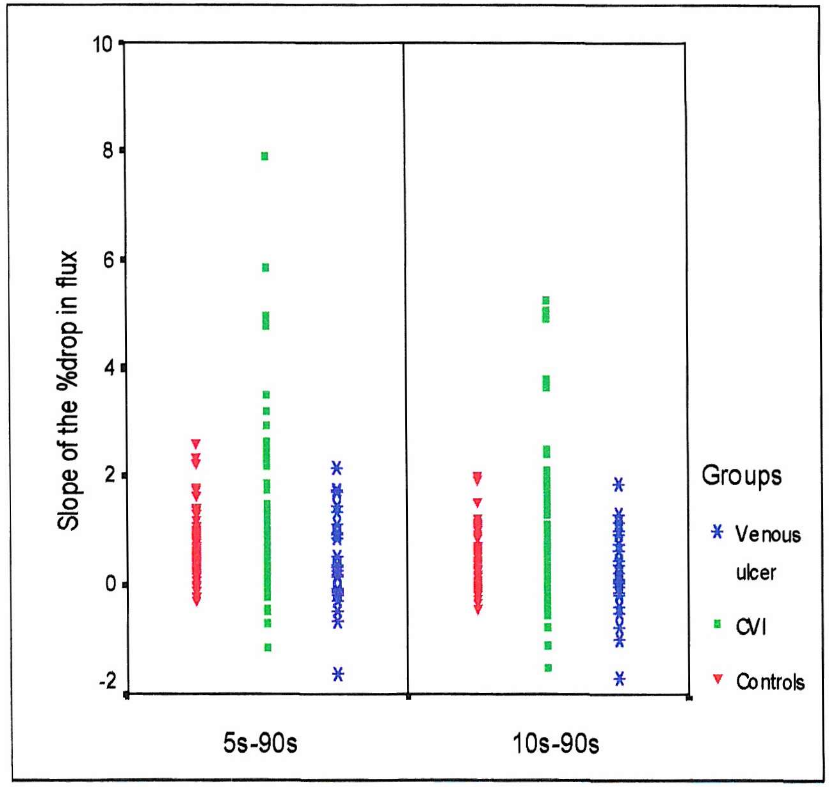
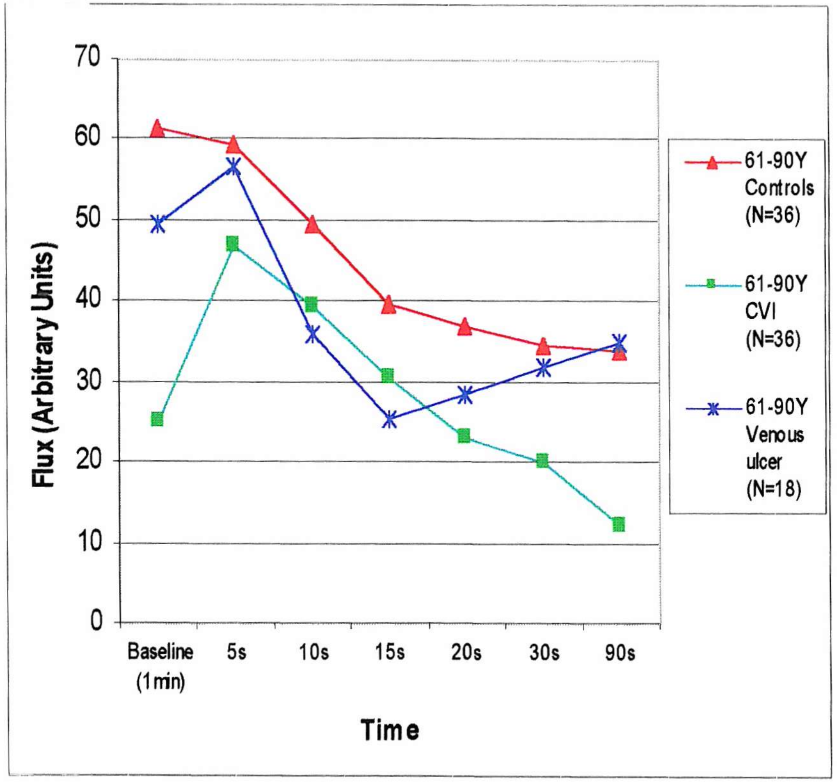


Figure 5.25 Changes in cutaneous microcirculation (slopes of %drop in flux) during passive leg lowering, in patients with CVI. Significantly higher slopes were present in the CVI group compared to both controls and venous ulcer groups, and a significant reduction in the slope (10s-90s) in the venous ulcers compared to controls. The presence of higher slopes in the CVI resulted from lower %drop in flux at 5s & 10s.

		In the elderly (61-90Y)							
		Flux (A. U.)				% drop in Flux			
		Controls (N=36)	CVI (N=36)	Venous ulcer (N=18)	Significance	Controls (N=36)	CVI (N=36)	Venous ulcer (N=18)	Significance
Baseline		61.5 (5.8&542.6)	25.25 (6.0&138.5)	49.75 (7.8&202.1)	**P=0.002**				
Lowering	5s	59.4 (12.3&792.7)	46.75 (8.4&132.9)	56.6 (15.3&268.3)	P=0.168	-11.11 (-350.46&77.43)	-57.58 (-914.50&40.0)	-3.18 (-328.28&74.15)	**P=0.036**
	10s	49.75 (7.5&723.1)	39.25 (12.9&125.2)	36.05 (10.9&273.9)	P=0.290	18.8 (-156.19&80.61)	-40.81 (-531.82&57.27)	18.87 (-182.83&84.09)	**P=0.003**
	15s	39.65 (8.3&723.8)	30.55 (10.0&127.4)	25.55 (12.0&247.5)	P=0.091	11.94 (-133.18&72.63)	-12.55 (-407.58&59.34)	23.97 (-169.70&76.14)	**P=0.036**
	20s	36.95 (8.4&483.0)	22.95 (6.8&133.1)	28.45 (9.1&255.3)	P=0.057	16.39 (-118.35&77.47)	-6.72 (-239.39&62.05)	20.49 (-231.31&75.02)	P=0.090
	30s	34.75 (7.7&506.6)	19.9 (7.1&185.0)	31.95 (7.3&266.2)	**P=0.027**	30.64 (-118.97&93.91)	18.63 (-82.63&64.69)	32.49 (-158.59&74.91)	P=0.334
	90s	34.0 (4.8&377.2)	12.3 (3.2&122.2)	34.9 (6.5&276.2)	**P=0.001**	30.43 (-99.66&87.38)	42.14 (-45.03&83.33)	40.64 (-171.72&63.23)	P=0.574
Time to reach baseline (s)		5 (1&120)	17 (2&60)	15 (2&120)	**P=0.036**				
slope % drop in flux (5s-90s)						0.41 (-0.29&2.24)	0.95 (-0.48&7.92)	0.22 (-0.65&2.18)	**P=0.003**
slope % drop in flux (10s-90s)						0.35 (-0.31&1.12)	0.7 (-0.77&5.25)	0.11 (-1.01&1.18)	**P=0.001**

Table 5.14 Changes in cutaneous microcirculation during passive leg lowering in elderly patients with CVI (with frank ulcers and without) as measured with laser Doppler flowmetery at the pulp of the big toe.



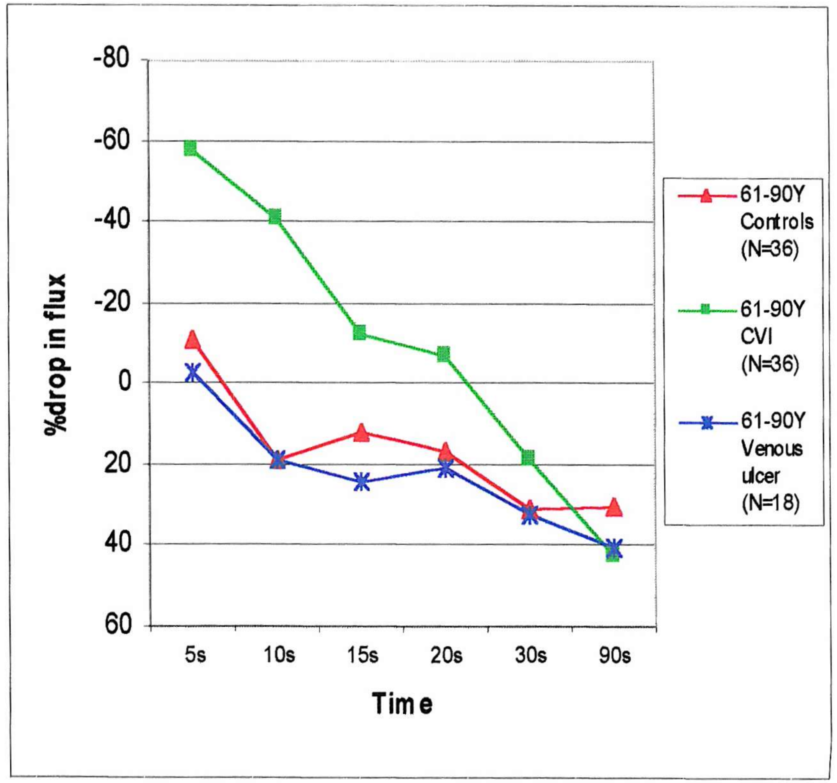


Figure 5.26 Changes in cutaneous microcirculation (flux & %drop in flux) during passive leg lowering in elderly patients with CVI. Significant lower flux (A.U.) at baseline, 15s, 20s, 30s & 90s and significant reduction in the %drop in flux at 5s, 10s, 15s & 20s were found in the elderly CVI compared to elderly controls. A significant lower flux (A.U.) at 90s was found in the elderly CVI compared to elderly venous ulcer.

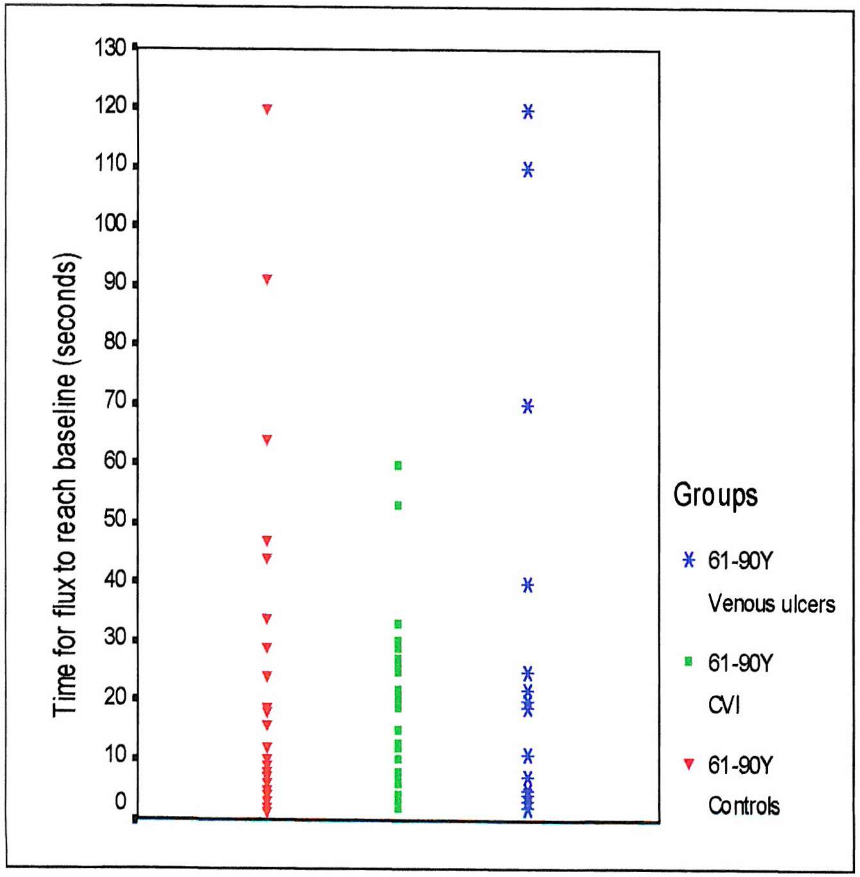


Figure 5.27 Changes in cutaneous microcirculation (the time required for the flux to return to baseline values after dependency) during passive leg lowering in elderly patients with CVI. A significant longer time was found in the elderly CVI when compared to elderly controls.

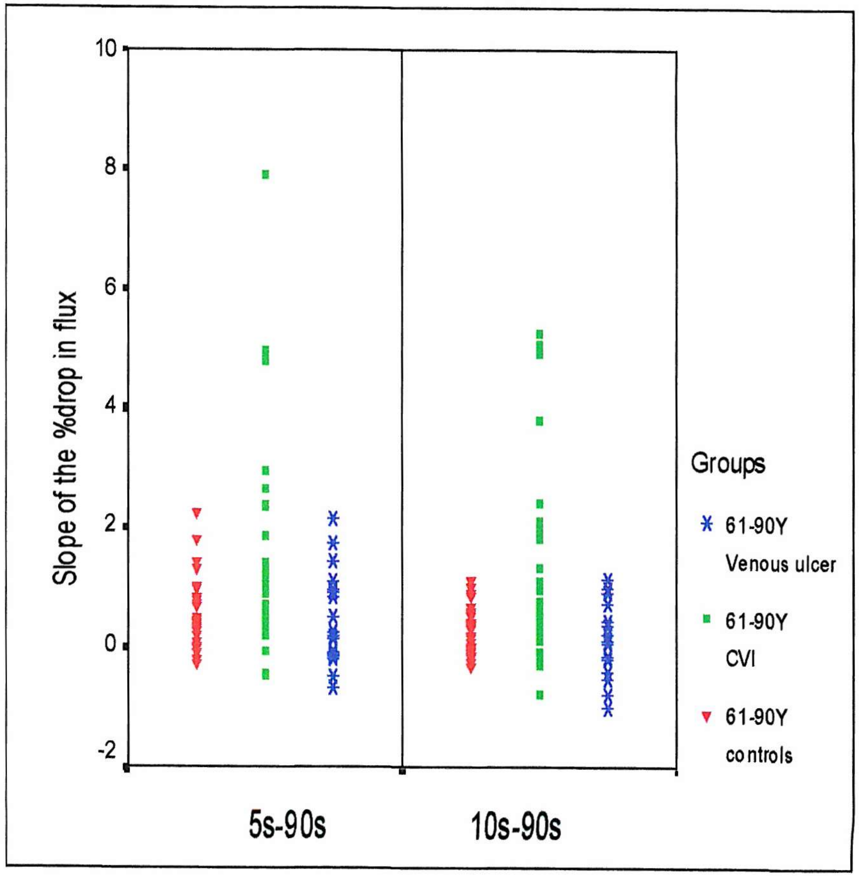


Figure 5.28 Changes in cutaneous microcirculation (slopes of %drop in flux) during passive leg lowering in elderly patients with CVI. Significant higher slopes were found in the elderly CVI group compared to elderly controls, as a result of the lower %drop in flux at the first 20s after dependency in the elderly CVI.

	In the elderly (61-90Y) male								In the elderly (61-90Y) female							
	Flux (A. U.)			Significance	%change in Flux			Significance	Flux (A. U.)			Significance	%change in Flux			Significance
	Controls (N=16)	CVI (N=10)	Venous ulcer (N=4)		Controls (N=16)	CVI (N=10)	Venous ulcer (N=4)		Controls (N=20)	CVI (N=26)	Venous ulcer (N=14)		Controls (N=20)	CVI (N=26)	Venous ulcer (N=14)	
Baseline	63.45 (10.9&218.6)	29.70 (18.3&118.7)	112.50 (12.6&181.7)	P=0.122					56.85 (5.8&542.6)	21.95 (6.0&138.5)	29.10 (7.8&202.1)	**P=0.015**				
Lowering 5s	56.00 (14.4&237.7)	48.00 (29.6&106.4)	55.95 (18.2&142.2)	P=0.731	1.67 (-350.46&69.68)	-42.58 (-282.73&16.68)	29.08 (-69.05&74.15)	P=0.088	61.05 (12.3&792.7)	44.05 (8.4&132.9)	56.60 (15.3&268.3)	P=0.190	-33.73 (-220.44&77.43)	-61.79 (-914.50&40.00)	-12.65 (-328.28&67.94)	P=0.240
Lowering 10s	55.50 (12.0&190.5)	33.85 (16.1&124.3)	53.45 (11.2&101.2)	P=0.646	19.42 (-156.19&80.61)	4.21 (-133.09&30.81)	45.89 (-131.75&84.09)	P=0.093	46.20 (7.5&723.1)	41.30 (12.9&125.2)	36.05 (10.9&273.9)	P=0.604	15.89 (-99.50&77.16)	-58.59 (-531.82&57.27)	1.83 (-182.83&68.73)	**P=0.014**
Lowering 15s	52.60 (15.9&146.2)	29.10 (16.7&89.8)	43.40 (16.8&65.4)	P=0.482	26.14 (-62.39&61.47)	18.48 (-85.57&38.28)	61.68 (-93.65&76.14)	P=0.202	36.90 (8.3&723.8)	30.55 (10.0&127.4)	25.05 (12.0&247.5)	P=0.273	6.82 (-133.18&72.63)	-30.77 (-407.58&59.34)	22.21 (-169.70&75.56)	P=0.059
Lowering 20s	49.60 (10.7&172.4)	28.20 (14.7&67.6)	43.85 (21.8&123.0)	P=0.228	16.17 (-118.35&77.47)	26.07 (-27.70&51.98)	42.72 (-73.02&65.77)	P=0.854	33.15 (8.4&483.0)	22.40 (6.8&133.1)	27.55 (9.1&255.3)	P=0.245	16.57 (-82.76&69.72)	-11.40 (-239.39&62.05)	20.41 (-231.31&75.02)	P=0.060
Lowering 30s	59.45 (11.1&223.6)	22.10 (12.0&63.7)	55.65 (7.6&7.6)	P=0.181	22.16 (-50.13&77.34)	38.08 (-15.85&55.56)	40.79 (-24.84&61.25)	P=0.779	29.00 (7.7&506.6)	17.35 (7.1&185.0)	21.00 (7.3&266.2)	P=0.160	33.18 (-118.97&93.91)	-3.15 (-82.63&64.69)	24.48 (-158.59&74.91)	P=0.144
Lowering 90s	46.70 (9.1&176.1)	12.80 (4.3&66.9)	65.45 (6.9&189.4)	**P=0.017**	26.04 (-16.49&81.87)	66.20 (22.57&83.33)	41.65 (-22.51&51.95)	**P=0.007**	29.95 (4.8&377.2)	11.90 (3.2&122.2)	21.20 (6.5&276.2)	P=0.065	46.44 (-99.66&87.38)	25.86 (-45.03&75.57)	40.25 (-171.72&63.23)	P=0.361
Time to reach baseline (s)	4 (2&64)	9 (4&25)	15 (3&70)	P=0.236					5.5 (1&120)	23.50 (2.0&60.0)	15 (2&120)	P=0.208				
Slope % drop in flux (5s-90s)					0.30 (-0.20&2.24)	0.81 (0.27&2.96)	-0.28 (-0.65&1.77)	**P=0.012**	Slope % drop in flux (5s-90s)				0.49 (-0.29&1.82)	1.11 (-.48&7.92)	0.39 (-0.16&2.18)	P=0.093
Slope % drop in flux (10s-90s)					0.11 (-0.31&1.03)	0.60 (0.14&2.00)	-0.63 (-1.01&-0.13)	**P=0.001**	Slope % drop in flux (10s-90s)				0.37 (-0.25&1.12)	0.77 (-0.77&5.25)	0.17 (-0.38&1.18)	P=0.060

Table 5.15 Changes in cutaneous microcirculation during passive leg lowering in elderly male and female patients with CVI (with frank ulcers and without) as measured with laser Doppler flowmetery at the pulp of the big toe.

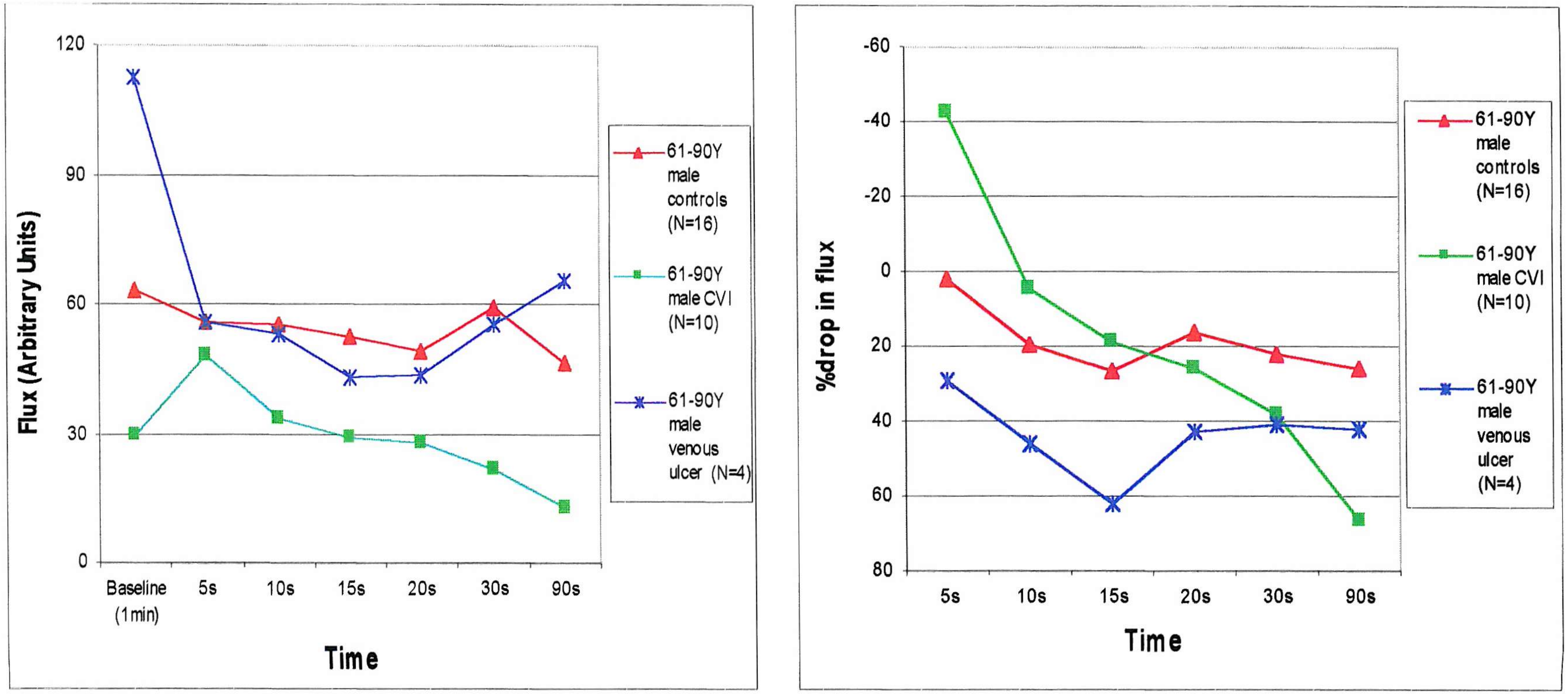


Figure 5.29 In the elderly males, a significant lower flux (A.U.) at 90s was found in the CVI compared to controls. The %drop in flux at 90s was significantly higher in the elderly CVI compared to elderly male controls and elderly male patients with venous ulcers.

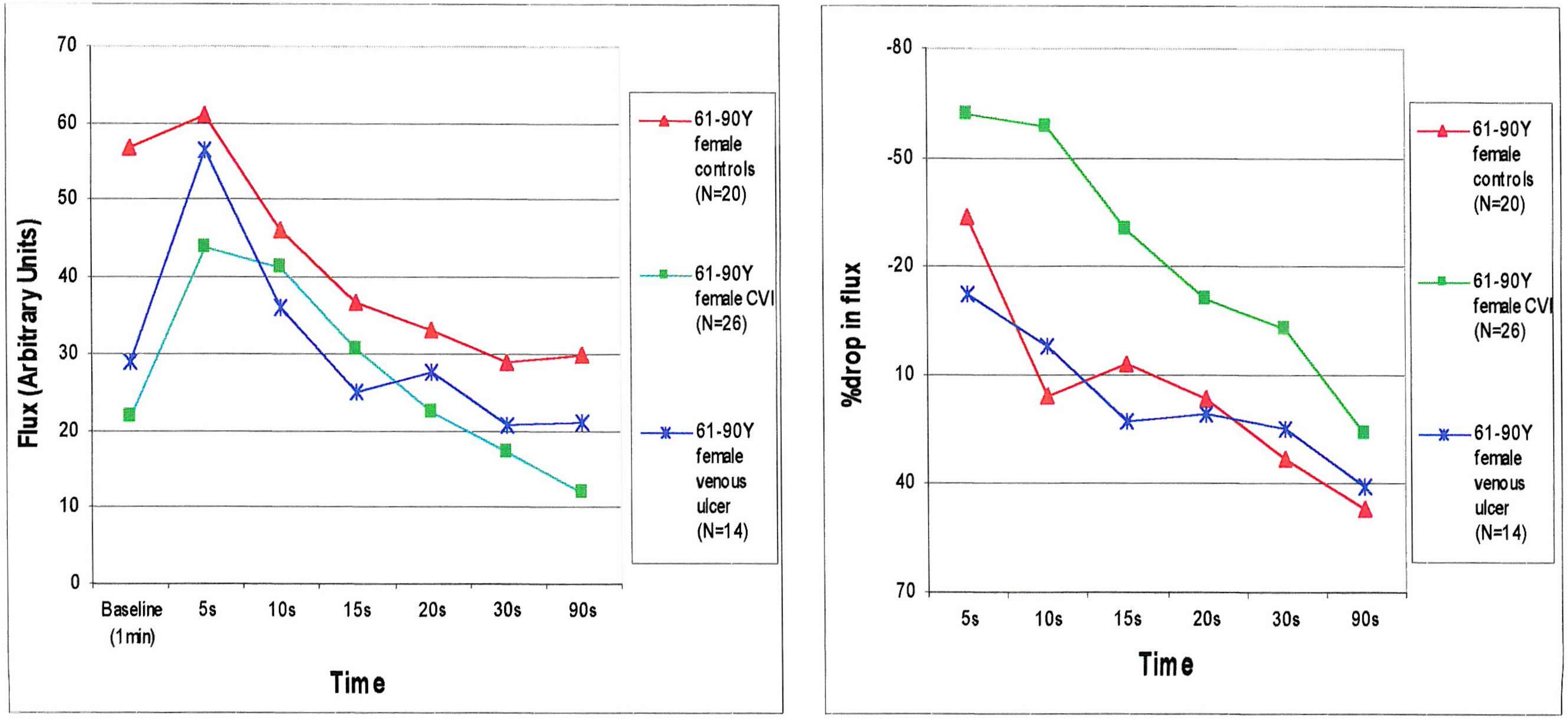


Figure 5.30 In the elderly females, a significant decrease in baseline flux was found in the CVI only group compared to controls. After dropping the leg 50cm passively, the %drop in flux at 10s was significantly lower in the elderly females with CVI compared to elderly female controls.

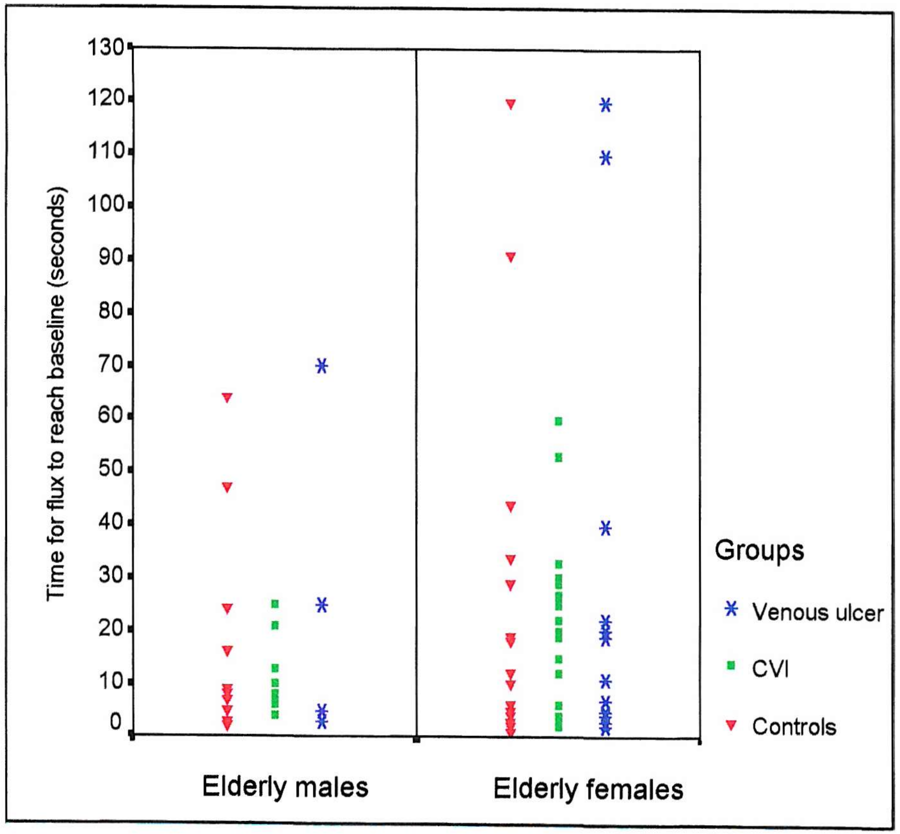


Figure 5.31 Changes in the time required for the flux to return to baseline values after dependency after passive leg lowering were statistically non-significant in both elderly male and female patients with CVI.

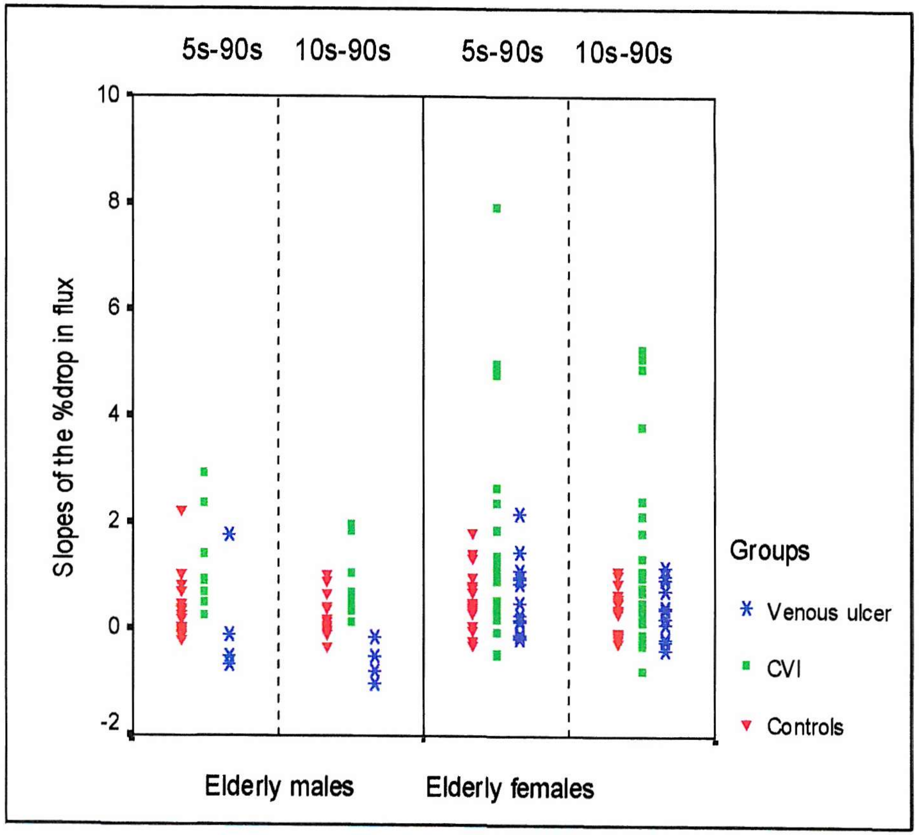


Figure 5.32 Changes in the slopes of %drop in flux after passive leg lowering. Significant higher slopes were found in the elderly male CVI compared to elderly male controls, a significant higher (10s-90s) slop in the elderly male CVI compared to elderly venous ulcer group. A significant lower slope (10s-90s) was found in the elderly male venous ulcers compared to elderly male controls. The differences in the elderly females were statistically non-significant.

5.6 Discussion

The aim of this chapter was to test the mechanical and microcirculatory properties of skin prone to ulceration using the techniques described in earlier chapters.

5.6.1 Durometer findings

Hardness index 1 was significantly increased in the ulcer group compared with controls and the CVI group (P=0.003 & 0.03 Mann-Whitney test), table 5.1. A significant increase in hardness index 2 in patients with venous ulcers was found compared to controls (P=0.03, Mann-Whitney test).

Hardness index 1 was significantly increased in elderly patients with venous ulcers (P=0.006, Mann-Whitney test) and elderly patients with CVI (P=0.038, Mann-Whitney test), compared to controls. When the effect of CVI and venous ulceration were examined in the elderly females and males, a significant difference in hardness index 1 was found within the elderly females (P=0.027, Kruskal Wallis test), no differences were found between the elderly male groups (table 5.3). The difference between the elderly female groups is attributed to a significant increase in hardness index 1 in elderly females with CVI (P=0.044, Mann-Whitney test) and elderly females with venous ulcers (P=0.023, Mann-Whitney test) compared to elderly female controls. The absence of significant differences in the elderly male groups may result from the insufficient number of elderly male patients (CVI= 4 & venous ulcers = 3) included in the study.

The increase in hardness index 1 in patients with venous ulcers and elderly patients with CVI (with and without venous ulcers) are attributed to the likely changes in tissue structure and composition – the latter includes oedema. Le Blanc et al. (1997) reported no significant changes in patients with CVI after testing the middle of the leg in the region between the medial malleolus and the Achilles tendon. No interpretations were offered in respect to age effects; the site studied was also dissimilar to the ones tested in this thesis.

5.6.2 Extensometer findings

Relaxation index was different among groups (P=0.005, Kruskal-Wallis test), it was reduced in the venous ulcer group compared to controls (P=0.001, Mann-Whitney test), table 5.4. The difference in relaxation index between patients with venous ulcers and patients with CVI was on the margin of significance (P= 0.074, Mann-Whitney test).

The relaxation index was significantly reduced in elderly patients with venous ulcers compared to both elderly controls and elderly CVI (P=0.006 & 0.01 respectively, Mann-Whitney test), table 5.5. Extensibility index was reduced in elderly patients with CVI as well as those with venous ulcers (P=0.02 & 0.011 respectively, Independent T-test).

When the effect of CVI with and without ulceration was examined in the elderly males and females, differences between elderly male patients with CVI (with and without venous ulcers) and elderly male controls were statistically non-significant. A significant reduction in extensibility index were found in the elderly females with CVI and elderly females with venous ulcers (P=0.022 & 0.018 respectively, independent sample test) compared to elderly female controls. Relaxation index was significantly reduced in the elderly females with venous ulcers compared to the elderly female controls and the elderly female patients with CVI (P=0.009 & 0.013 respectively, Mann-Whitney test). The insignificant differences between the elderly male groups may arise from the small number of elderly male patients included in the study (CVI =6 and venous ulcer =4), although the lack of true differences in extensibility and relaxation in the elderly male groups can not be excluded.

These reductions suggest a decrease in viscoelasticity associated with the presence of CVI and venous ulceration. The reduction in relaxation index is in accord with Mourad et al. (1988), where a degree of reduction in a parameter extracted from the relaxation phase was found in patients with the gravitational syndrome. The reduction in extensibility index in the elderly CVI (with and without ulcers) in general and the elderly female patients was surprising since skin changes with CVI i.e. skin thickening, oedema etc were expected to increase the force required to stretch the skin. This would have the effect of increasing the extensibility index. One explanation for this is that the force used to extend was dissipated more in oedematous tissues.

5.6.3 Cutaneous microcirculation during skin extension/relaxation

On the forearm skin, changes in the microcirculation during extension/relaxation were not statistically different among the three groups as shown in table 5.7. In the leg, high flux (A.U.) was found in the ulcerated group compared to controls, this increase in flux is similar to the reported by Sindrup et al. (1987), none the less, it did not promote healing. The recovery of the LDF flux during relaxation phase was lowest in magnitude and slowest in the venous ulcer group followed by CVI followed by controls, table 5.8. This inability to respond to a minor challenge in the groups with oedema was considered to be analogous to response on diabetic skin (Rayman et al. 1986). An explanation of this analogy is outside the scope of this thesis.

In the elderly legs, results were similar to the above findings, table 5.10. In the forearms, differences between the three elderly groups were not statistically significant except during the extension phase, where a higher %change in flux was found in the elderly CVI compared to elderly controls, table 5.9.

In the forearms of elderly males and females, differences in the LDF parameters between the three groups within each sex were statistically non-significant, table 5.11. In the elderly female legs and during the relaxation phase, the recovery of the flux (%change in flux) was lower in both patient groups compared to controls, table 5.12. The effect of CVI with and without venous ulcers in elderly male legs was statistically non-significant, probably due to the insufficient number of elderly male patients included in the study. The reduced ability of the flux to recover during relaxation phase in the legs of elderly female patients could be related to changes introduced by the presence of CVI (with and without ulcers) in the microcirculation. The mechanism behind these changes could not be explained results obtained in this study.

5.6.4 The postural vasoconstrictor response

Previous workers measured the change in LDF flux with passive leg lowering and expressed this change about the baseline. A fall in flux would be a positive value accepted as an expression of an intact vasoconstrictor response. In analyzing the data presented in this work, changes on lowering were measured at several time points about baseline values. The slopes of the %drop in flux and the time to reach baseline values after leg lowering were also calculated.

The time course of change in LDF flux with leg lowering was different in the three groups. LDF flux values decreased in all groups. Percentage drop in flux was significantly lower, during the early stages of leg lowering, in patients with CVI compared to controls and resulted in the rate of drop of the flux (slopes) being significantly higher in the CVI, table 5.13. Further analysis of data showed a significant increase in the time needed for the flux to return to baseline in the CVI group compared to controls. In patients with venous ulcers, the rate of the flux drop (slope of %drop in flux between 10-90 seconds) was significantly lower than controls.

The flux (A.U.) was significantly lower (at baseline and during 30-90 seconds of leg lowering) and the time for the flux to reach baseline after leg lowering continued to be significantly long in elderly CVI compared to elderly controls. The %drop in flux continued to be significantly low in the elderly CVI compared to elderly controls and resulted in the presence of significant higher slopes in elderly CVI, table 5.14. Differences between elderly patients with venous ulcers and elderly controls were statistically non-significant.

In the elderly male with CVI, a significant reduction in the flux (A.U.) was found at 90s of dependency compared to elderly male controls and resulted in the %drop in flux at 90s being significantly higher in the elderly male CVI compared to the other two groups. The increase in the %drop in flux at 90s resulted in the presence of significant increase in the slopes of the %drop in the elderly male CVI compared to controls and venous ulcers. The difference between elderly male controls and elderly male patients with venous ulcers was restricted to the presence of a significant lower slope (10s-90s) in the venous ulcer group. The effects of CVI (with and without venous ulcers) on the postural vasoconstrictive response in the elderly female legs were statistically non-significant, table 5.15.

With CVI and in the venous ulcer group, the %drop in flux at 90seconds, was similar to controls (table 5.13 & 5.14), except in elderly male CVI, where the %drop was higher than in elderly male controls and elderly male patient with venous ulcers (table 5.15). This implies an intact response in patients with CVI, those with venous ulcers and controls. An intact postural vasoconstrictive response is associated with oedema protection. This finding is in discord with Allen et al. (1988) and Gniadecka et al. (1991).

Allen et al. (1988) studied 8 patients (2 with frank venous ulcers), and reported an impaired response at 5 minutes. Gniadecka et al. (1991) studied the postural vasoconstrictive response in the region of the medial malleolus on 5 patients, initially there were no changes on dependency. After “oedema removal” a reduction in blood flow was detected (Gniadecka et al. 1991).

In the work reported in this thesis, the response was measured for 2 minutes on the pulp of the big toe. In the elderly controls there was an impaired response, as reported in chapter 4, but not in patients with CVI. The differences with the above mentioned reports may be due to site differences or duration of measurements.

Allen et al. (1988) worked on the pulp of the big toe, and it might be permissible to compare his reports with findings in this thesis. Findings in this chapter demonstrate a fall in blood flow i.e. an intact response in both patients group. If the postural vasoconstrictive response protects from oedema formation, the two groups were protected, in fact all had oedema. This begs the question whether this mechanism protects against vasogenic oedema formation?

The Postural vasoconstrictive response was discussed in the literature through the 1990's. The inference that this mechanism offered protection from oedema formation was based on studies on pre-menopausal oedema. The reduction in blood flow measured in CVI was to accommodate changes in posture but unlikely to protect against oedema.

Chapter Six: Discussion

The aim of this study was to examine changes in some mechanical and microcirculatory properties of skin in chronic venous disease, a condition often characterised by unrelieved oedema, induration, eczema, fibrosis and lipodermatosclerosis. When some or all these changes are present, the skin is prone to ulceration. The relative contribution of each of these factors is unclear; this may be of significance to wound management. Oedema was suggested to be associated with impaired ulcer healing (Prasad et al. 1990) though the author did not propose any causative mechanism.

For the work presented in this thesis, two techniques were chosen to address mechanical properties of tissues at risk of ulceration and one to measure changes in the microcirculation. The durometer and extensometer were chosen to examine cutaneous hardness, extensibility and relaxation respectively. Laser Doppler flowmetry, was used to examine the responses of the cutaneous microcirculation to a simple challenge and postural changes.

6.1 Technical findings from this work

Durometry and extensometry enabled the measurement of significant differences in hardness and extensibility between subjects, variations between subjects were significantly higher than within subjects. Reliability and coefficient of variation (CV) were determined for both techniques. The durometer had a CV ranging from (5.3%-8.6%) and Reliability of (51.9%-91.6%). The CV for the extensometer ranged from (5.5%-15.4%) whilst the Reliability ranged between (3.2%-72.2%).

CV is commonly used to express the figure of merit of a technique, is better known and accepted than Reliability. Reliability, on the other hand, accounts for random variations in a technique. Both are useful, the choice between these statistical comparators should be determined by experimental objectives after due consideration of the measured parameters and protocols.

The durometer is simple and may be used in a clinical setting. The technique measures the resistance to indentation of a specific volume of tissues. It was used to examine changes in hardness with location and differences in cutaneous hardness were found on legs and hands. On legs, cutaneous hardness was significantly higher nearer the medial malleolus (where ulcers occur) compared to other sites nearer the knee joint. These findings are attributed to the differences in volume as well as the nature of the tissues at different sites. The device may have value in assessing benefits of therapy in skin and soft tissue disorders.

Hardness values measured with durometry were better expressed as indices, which makes control measurements on forearms essential. The protocol derived for this study is recommended for use. It was used to examine differences between sexes, and the effect of age. Cutaneous hardness increases with age and is higher in females. These findings may serve to explain the preponderance of elderly females suffering with chronic venous ulcers. Factors that might contribute to changes in hardness index with age include loss of elasticity, fragility and cutaneous atrophy.

Patients with frank venous ulcers had higher hardness indices. Elderly patients with CVI had higher hardness index values than controls (significant increase in hardness index 1 in elderly female patients). The change in hardness index in patients with CVI is speculatively related to induration. The likely significance of induration in the pathophysiology of venous ulcers is not clear.

As demonstrated, the extensometer may be used to measure cutaneous extensibility and relaxation reliably. Cutaneous extensibility is related to the resistance of the skin to stretching, and relaxation is related to the change in the cutaneous resistance at the end of the stretching phase with time. Findings with this technique demonstrate its promise to examine the anisotropy of skin as well as its memory. Results showed that Langer's lines to be lines of minimum extensibility and the importance of recovery after strain.

As with durometry both extensibility and relaxation varied with locations, data from legs being significantly higher compared to measurements obtained from the forearms. This confirmed the site dependency of these properties. These variations are attributed to the differences in skin thickness as well as the composition of the tissues underneath it. In the absence of a method for examining variations in skin thickness with location and its effects on the mechanical properties, expressing these values as indices was more meaningful.

Differences between sexes were non-significant, a reduction in extensibility was found with age. This observation is thought to be related to changes in viscoelasticity (the loss of elasticity described previously by Gilchrest 1982), in addition to skin atrophy, both associated with cutaneous ageing.

An increase in extensibility and a reduction in relaxation indices were found in patients with frank ulcers, in elderly patients with CVI, and in elderly female patients with CVI. These changes are suggested to result from a decrease in viscoelasticity related to oedema, where the increase in extensibility is thought to arise from the force required stretching the skin being dissipated on oedema removal. The reduction in relaxation index was suggested to result from the presence of extra fluid in the tissues. These changes would effect skin tension, but findings in the thesis do not permit comments in depth on the role of skin tension as a cause for ulceration as proposed by Chant (1990).

The LDF for measuring cutaneous microcirculation was a simple and well-tolerated technique. When the cutaneous circulation was challenged by skin extension/relaxation, blood flow increased at the end of relaxation phase compared to baseline. This demonstrated the ability of the cutaneous microcirculation to respond to a minor challenge. Changes in the microcirculation during extension/relaxation were measured in the leg as well as in the forearms, the latter a control site not affected by the presence of CVI or venous ulceration.

Although changes in the cutaneous microcirculation with age were found in the forearms and differences between sexes were detected in the leg, the overall effect of age and sex on the microcirculation measured during extension and relaxation in both extremities were not significant. The lack of statistical significance suggests that further experiments are needed to examine the effect of ageing and sex on the microcirculation.
Impairment in the cutaneous microcirculation of the lower leg was found in patients with frank ulcers and to a lesser degree, in CVI. Similar results were found in the elderly patients with CVI and elderly female patients with CVI. This impairment is analogous to finding of skin microangiopathy in diabetics (Rayman et al. 1986).

A recent study reported that patients with CVI had a degree of peripheral neuropathy manifest as disturbances in the A-α fibers, A-β fibers, A-δ fibers and thermoafferent-C fibers (Reinhardt et al. 2000). The authors suggest that this neuropathy resulted from increased endoneural pressures, and ischemia. **Does unrelieved oedema lead to microangiopathy and ischemia?** The results presented in this work permit the observation that oedema and microangiopathy in CVI are associated. The results do not permit observations about ischemia though it is reasonable to state that the impairment of the microcirculation might affect nutritional state of the tissues; this in turn could affect venous ulcer healing.

The LDF was used to examine the postural vasoconstrictive response, after determining the effects of age and sex. In controls, the response was found to be impaired with age, which is in accord with previous studies (Gniadecka et al 1994a). A significant reduction in the microcirculation after passive leg lowering was found in the female compared to male controls, this finding which suggest that the response is better in the female controls. A better response in women is inconsistent with women being prone to peripheral oedema.

An intact postural vasoconstrictive response was detected in patients with CVI as well as these with venous ulcers. Results from the elderly patients and elderly male and female patients were similar to the above findings. These findings are in discord with previous studies, where impairment in the response was associated with increase prevalence of oedema in CVI (Allen et al. 1988 & Gniadecka et al. 1991). It would appear from the results presented in this thesis, that this test is unable to discriminate between patients with chronic venous disease. The results also suggest that the postural vasoconstrictor response may not be an oedema protective mechanism as hitherto proposed.

From the different techniques used, changes in some mechanical properties were found with age. These changes seem to result from the ageing process and may contribute to the elderly being prone to ulceration. A change in the cutaneous hardness, extensibility, relaxation and the microcirculation were found in patients with CVI, these changes are attributed to the effects of oedema on cutaneous tissues. Although impaired postural vasoconstrictive response was found in the elderly, its role in oedema prevention is open to speculation.

6.2 How does this work contribute to the understanding of the pathophysiology of venous ulcers?

The state of knowledge obtained at the time of this work began was summarised in figure 1.2. A physiological flow chart presented in figure 6.1, sums up the findings of the work presented in this thesis. The essential difference between these figures is centred around the role of unrelieved oedema in venous ulceration. The results presented in this work permit the observations that hardness, extension/relaxation (expressed as indices), and mircovascular reactivity are altered when there is unrelieved oedema. This situation could lead to a decrease in metabolic activity, skin thickening and fibrosis all acting to make healing more difficult; in other words the chronicity of the ulcer is perpetuated.

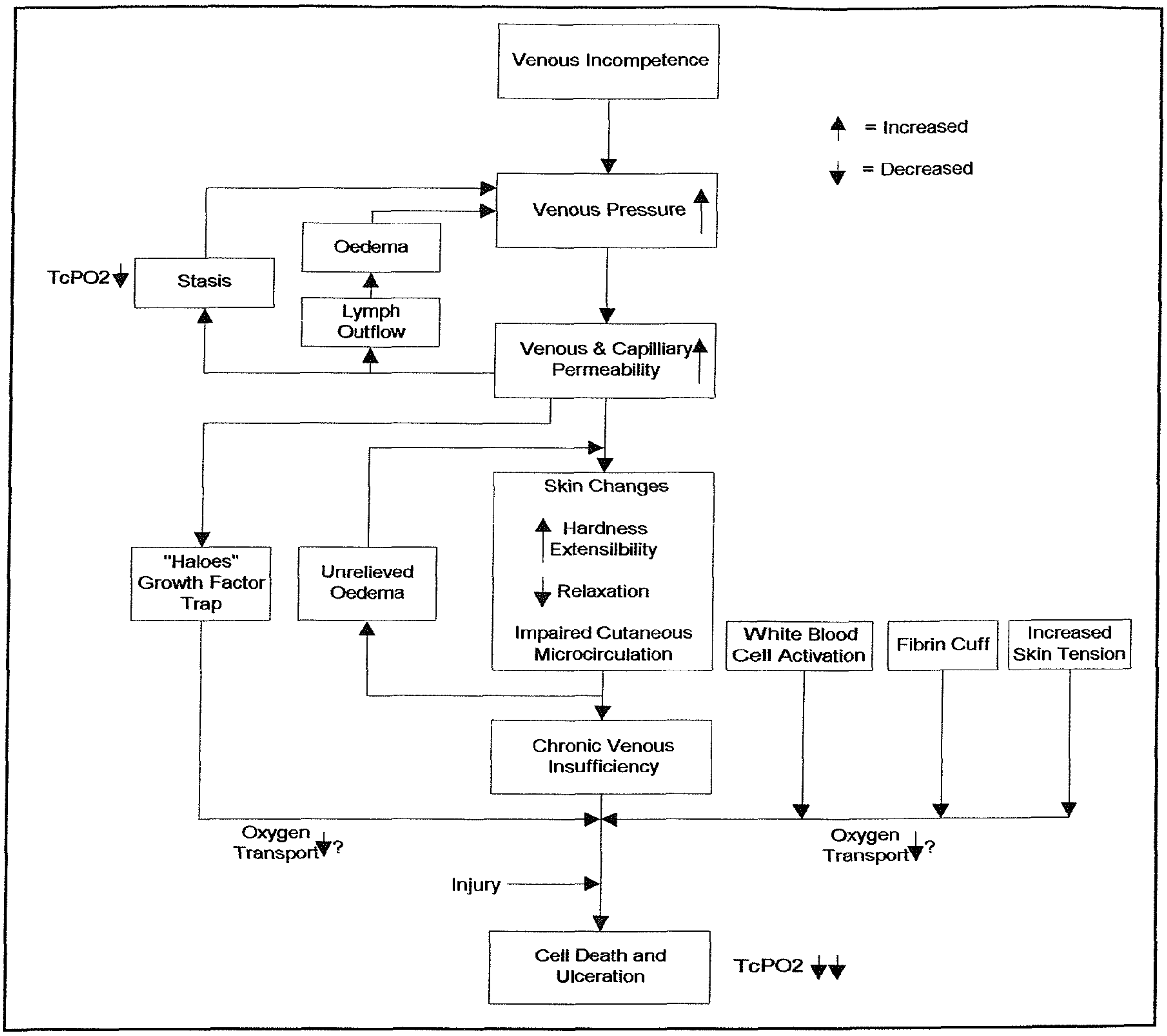


Figure 6.1 A flow chart describing proposed changes that lead to ulceration based on findings described in this submission.

Relieving tissue oedema (and consequently after load) has been shown to improve tissue nutrition (Kolari et al. 1988 and Barnes et al. 1992a) and would be associated with decreasing hardness indices. The key to improving the cycle of events linking tissue changes with oedema, is in relieving it (oedema). These results do not render any clearer the reason for ulceration; they do provide techniques and a database, which may be used to identify hard-to-heal ulcers.

Does increased skin tension cause ulcers? The concept of increased skin tension as a cause of venous ulcers was proposed by Chant (1990). This is an attractive though incomplete proposition for two main reasons. Firstly, venous ulcers occur in the lower third of the leg and are clinically recognised by the oval presentation with sloping edges. Patients often give a history of trauma. These factors contradict the skin tension concept that would require skin to pull apart resulting in ulcers anywhere on the leg. In addition, venous ulcers are not always seen on patients with lymphoedema which could be anticipated were the skin tension concept sound.

Without doubt, unrelieved oedema has far reaching effects either to increase the propensity for ulceration or to perpetuate its chronic nature. The test procedures determined in this work should be used to identify sub-sets of chronic wounds all currently classified as venous ulcers.

A limitation of this work is that oedema was not classified or quantified. As stated at the outset, the techniques achieving this aim were unavailable. The work described in this thesis offers quantification of some effects of oedema previously unreported, and offers the scope for expanding these studies to include techniques to locate oedema

Chapter Seven: Recommendations for further work

Oedema characterisation is essential, both high frequency ultrasound and MRI possess the ability to examine oedema location and hence the ability to quantify it. Ultrasound has the advantage of being cost and time effective. High frequency ultrasonography will have a major role in chronic wounds assessment through image characterisation, where signal analysis and processing are tools to examine the physical parameters of the wound that would provide information about the healing process in-vivo.

The effect of oedema removal (bandaging and/or elevation) on the cutaneous mechanical properties and its microcirculation is an aspect that requires investigation.

Sonographic imaging during uniaxial extensometry is suggested to yield a method to measure a two-dimensional map of the strain in response to application of surface stress and may provide the possibility to calculate cutaneous bulk modulus.

With extensometry, the ability to differentiate between the elastic and the viscous components of the extension/relaxation curve may result in the ability to examine their role in different skin pathology and could result in suggesting a model for skin behaviour under different conditions.

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Appendix 1
Transforming durometry reading of hardness (durometer units) into hardness (Newtons)

REX GAUGE COMPANY, INC.

1250 BUSCH PARKWAY
BUFFALO GROVE, IL 60089
TEL: 847/465-9009
FAX: 847/465-9229
http//www.rexgauge.com

A Division of Schultes Precision Manufacturing

Dear Lina,

Here is the information you requested. I'm also faxing off some information on our OO durometer with the removable lower barrel. It is used in the medical industry and can be cleaned in a steam autoclave. Is there any way would could get a copy of your paper?

Best Regards,

Al Blum

Spring Force Combinations

Force, N = 0.203 + 0.00908 *Hoo*
where *Hoo* = hardness reading on Type OO durometers.

Calibration Loads

DURO READING	OO
0	21g.
10	30g.
20	39g.
30	48g.
40	58g.
50	67g.
60	76g.
70	86g.
80	95g.
90	104g.
100	113g.
	+/- 2.6g.

Appendix 2

Reproducibility of the durometer for measuring cutaneous hardness

I.D.	Sex	Age	**Forearm cutaneous hardness (Newtons) measured at** 5cm inferior to antecubital fossa	10cm inferior to antecubital fossa	middle of the forearm	**Leg cutaneous hardness (Newtons) measured at** 5cm superior to medial malleolus	10cm superior to medial malleolus	middle of the leg
1	male	50	0.27	0.47	0.58	0.44	0.38	0.27
			0.26	0.37	0.58	0.40	0.35	0.31
			0.29	0.38	0.58	0.33	0.30	0.27
			0.28	0.46	0.42	0.38	0.35	0.31
			0.28	0.41	0.49	0.33	0.32	0.30
2	male	40	0.24	0.34	0.36	0.39	0.38	0.40
			0.27	0.31	0.43	0.39	0.38	0.37
			0.31	0.31	0.39	0.38	0.38	0.34
			0.31	0.30	0.39	0.39	0.37	0.33
			0.29	0.29	0.38	0.39	0.39	0.32
3	male	37	0.28	0.38	0.38	0.42	0.40	0.27
			0.30	0.38	0.38	0.44	0.37	0.26
			0.28	0.34	0.41	0.45	0.40	0.29
			0.25	0.32	0.38	0.39	0.38	0.30
			0.27	0.34	0.38	0.40	0.38	0.32
4	female	30	0.25	0.29	0.32	0.38	0.41	0.45
			0.23	0.30	0.31	0.40	0.44	0.42
			0.24	0.28	0.30	0.40	0.45	0.41
			0.24	0.28	0.31	0.42	0.40	0.40
			0.22	0.29	0.30	0.43	0.40	0.42
5	female	40	0.20	0.31	0.31	0.48	0.49	0.46
			0.20	0.30	0.32	0.42	0.48	0.46
			0.23	0.29	0.31	0.48	0.46	0.48
			0.20	0.29	0.31	0.43	0.40	0.46
			0.20	0.31	0.32	0.39	0.46	0.46
6	female	46	0.21	0.26	0.28	0.34	0.39	0.41
			0.20	0.25	0.29	0.34	0.40	0.39
			0.20	0.27	0.29	0.33	0.43	0.43
			0.22	0.25	0.28	0.36	0.40	0.38
			0.22	0.24	0.27	0.38	0.43	0.40
7	female	27	0.21	0.30	0.34	0.40	0.48	0.44
			0.22	0.29	0.31	0.44	0.48	0.46
			0.22	0.31	0.31	0.42	0.48	0.44
			0.21	0.29	0.34	0.44	0.48	0.42
			0.22	0.30	0.35	0.42	0.48	0.43

Appendix 3

The effect of repetition on Fpeak & relaxation time measured in asymptomatic controls

			Force at maximum extension (natural log Fpeak measured at)					
			Forearm (5cm inferior to antecubital fossa)			Leg (5cm superior to medial malleolus)		
I.D.	Sex	Age	1st extension	2nd extension	3rd extension	1st extension	2nd extension	3rd extension
1	male	44	1.18	1.04	1.01	3.16	3.03	2.9
2	male	40	2.47	2.44	2.36	3.01	2.72	2.88
3	female	43	2	1.9	1.55	Artifact in one of the measurements		
4	female	53	1.48	1.46	1.58	2.06	2.01	1.98
5	male	40	2.27	1.85	1.69	2.33	2.11	2.12
6	female	31	2.4	1.97	1.74	Artifact in one of the measurements		
7	female	27	1.34	1.23	0.9	2.82	2.61	2.51
8	male	31	0.67	0.51	0.51	2.67	2.2	2.29
9	female	39	1.37	1.42	1.46	Artifact in one of the measurements		
10	male	63	1.11	1.21	1.14	2.46	2.3	2.28
11	male	23	1.42	1.34	1.23	2.53	2.32	2.22
12	male	37	1.59	1.32	1.26	3.14	2.88	2.72
13	male	35	1.21	0.77	0.97	Artifact in one of the measurements		

No of cases	**13**	**13**	**13**	**9**	**9**	**9**
Mean	**1.58**	**1.42**	**1.34**	**2.69**	**2.46**	**2.43**
Standard deviation	**0.55**	**0.52**	**0.47**	**0.38**	**0.36**	**0.34**
Median	**1.42**	**1.34**	**1.26**	**2.67**	**2.32**	**2.29**

Appendix 3 continued/...

I.D.	Sex	Age	Relaxation time (natural log of the time to rerach 0.696Fpeak in the relaxation phase, measured at) Forearm (5cm inferior to antecubital fossa) 1st extension	2nd extension	3rd extension	Leg (5cm superior to medial malleolus) 1st extension	2nd extension	3rd extension
1	male	44	2.44	2.67	3.09	4.49	5.03	4.83
2	male	40	3.37	3.71	3.22	3.22	4.73	4.57
3	female	43	3.22	4.49	5.56	Artifact in one of the measurements		
4	female	53	2.56	2.83	3.61	2.56	3.61	3.37
5	male	40	2.88	3.34	3.56	2.3	3.5	3.81
6	female	31	3.17	3.68	3.97	Artifact in one of the measurements		
7	female	27	2.74	5.33	3.23	2.92	4.26	5.11
8	male	31	3.57	4.7	3.11	3.42	4.57	4.28
9	female	39	3.31	4.23	5.58	Artifact in one of the measurements		
10	male	63	2.6	3.62	3.54	3.96	6.34	6.35
11	male	23	3.16	5	4.24	3.8	4.51	5.93
12	male	37	2.97	3.28	2.6	4.79	4.88	5.41
13	male	35	3.65	5.58	2.92	Artifact in one of the measurements		

No of cases	**13**	**13**	**13**	**9**	**9**	**9**
Mean	**3.05**	**4.04**	**3.71**	**3.50**	**4.60**	**4.85**
Standard deviation	**0.39**	**0.93**	**0.93**	**0.84**	**0.84**	**0.97**
Median	**3.16**	**3.71**	**3.54**	**3.42**	**4.57**	**4.83**

Appendix 4
The effect of Langer's line on Fpeak and relaxation time measured in asymptomatic controls

			Force at maximum extension (natural log) measured at			
			Forearm		Leg	
			Extension plane with respect to Langer's lines			
I.D.	Sex	Age	Parallel	Perpendicular	Parallel	Perpendicular
1	male	49.00	2.07	-0.02	3.05	1.32
2	female	39.00	1.26	1.14	2.88	2.23
3	male	64.00	1.11	1.26	2.94	2.02
4	female	44.00	1.79	0.08	2.47	1.53
5	female	44.00	0.45	0.08	2.49	1.69
6	female	35.00	1.61	0.45	2.41	1.72
7	male	18.00	1.55	0.77	2.87	1.87
8	female	53.00	1.23	0.39	2.55	1.69
9	female	24.00	1.01	-0.02	2.88	2.27
10	female	29.00	1.29	-0.13	2.37	1.93
11	female	26.00	0.94	-0.37	3.10	1.93
12	female	33.00	Artifact in one of the measurements		2.73	1.72
13	female	24.00	Artifact in one of the measurements		2.47	2.30
Number of cases			**11.00**	**11.00**	**13.00**	**13.00**
Mean			**1.30**	**0.33**	**2.71**	**1.86**
Standard deviation			**0.44**	**0.53**	**0.26**	**0.30**
Median			**1.26**	**0.08**	**2.73**	**1.87**

			Relaxation time (natural log) measured at			
			Forearm		Leg	
			extension plane with respect to Langer's line			
I.D.	Sex	Age	Parallel	Perpendicular	Parallel	Perpendicular
1	male	49.00	2.51	3.49	2.46	2.48
2	female	39.00	2.38	2.55	2.26	2.32
3	male	64.00	2.37	2.45	2.95	2.80
4	female	44.00	2.89	5.05	2.91	2.35
5	female	44.00	2.96	3.05	3.27	2.82
6	female	35.00	3.42	3.86	2.55	2.64
7	male	18.00	2.58	2.58	2.61	2.58
8	female	53.00	2.72	4.02	2.56	2.47
9	female	24.00	Artifact in one of the measurements		3.90	2.64
10	female	29.00	2.58	4.53	Artifact in one of the measurements	
11	female	26.00	2.45	4.55	2.90	2.68
12	female	33.00	Artifact in one of the measurements		2.22	2.51
13	female	24.00	Artifact in one of the measurements		2.16	3.04
Number of cases			**10.00**	**10.00**	**12.00**	**12.00**
Mean			**2.69**	**3.61**	**2.73**	**2.61**
Standard deviation			**0.33**	**0.94**	**0.50**	**0.21**
Median			**2.58**	**3.68**	**2.58**	**2.61**

Appendix 5

Reproducibility of the extensometer for measuring Fpeak and relaxation time

			Fpeak (natural log) measured at		Relaxation time (natural log) measured at	
I.D.	Sex	Age	Forearm	Leg	Forearm	Leg
1	female	39	1.21	2.40	2.41	2.75
			1.42	2.60	2.53	2.94
			1.34	2.07	2.61	2.90
			1.21	2.01	2.68	3.10
			1.57	2.32	2.78	2.76
2	male	40	1.46	2.71	2.71	2.64
			1.37	2.62	4.53	3.43
			1.93	2.74	2.83	3.53
			1.72	2.86	3.04	3.48
			1.77	2.75	2.68	3.79
3	male	23	1.44	2.86	3.22	2.94
			1.26	2.75	3.37	3.37
			1.83	2.69	3.22	3.28
			1.08	2.62	2.78	2.69
			1.21	2.68	2.81	3.31
4	male	63	1.69	2.91	2.71	2.83
			1.39	2.79	3.63	2.38
			1.37	2.83	2.92	3.04
			1.01	2.97	2.90	3.62
			1.44	2.94	2.46	2.61
5	male	49	1.93	2.49	3.30	3.26
			1.76	2.41	2.61	4.09
			1.63	2.72	2.81	3.46
			1.69	2.30	3.17	2.51
			2.20	2.40	2.77	3.40

Appendix 6

The relationship between cutaneous hardness and both Fpeak and relaxation time in both extremities

			Forearm, 5cm inferior to antecubital fossa			Mid-leg		
I.D.	Age	sex	Fpeak (nat.log)	Hardness (Newtons)	Relaxation time (nat.log)	Fpeak (nat.log)	Hardness (Newtons)	Relaxation time (nat.log)
1	78	female	(-0.15)*	0.22	2.40	2.42	0.39	2.59
2	61	male	1.24	0.27	2.38	3.02	0.37	2.61
3	73	female	(-0.11)*	0.24	(2.87)*	2.78	0.38	2.68
4	83	female	(-0.58)*	0.22	artifact	2.59	0.33	2.37
5	51	male	(1.67)*	0.29	(2.84)*	2.55	0.41	2.29
6	68	female	(-0.32)*	0.25	2.66	2.35	0.43	2.98
7	55	female	(1.88)*	(0.32)*	2.49	2.94	0.43	2.61
8	69	female	0.74	0.20	2.43	3.22	0.43	3.17
9	68	female	0.62	0.20	2.51	2.84	0.34	2.97
10	52	female	1.13	0.25	2.34	3.37	0.48	2.66
11	53	female	0.88	0.22	2.73	2.38	0.31	2.60
12	65	male	0.99	0.25	2.42	2.13	0.40	2.68
13	68	male	0.72	0.24	2.34	3.02	0.40	2.53
14	61	male	0.52	0.23	2.44	2.89	0.43	2.58
15	80	female	0.69	0.20	2.29	2.63	0.29	3.17
16	77	female	(-0.07)*	0.20	2.37			
17	71	female	0.88	0.25	2.33	2.11	0.43	2.68
18	73	male	0.88	0.21	2.54	2.96	0.36	2.55
19	65	female	0.89	0.22	2.45	3.13	0.43	2.89
20	75	female	0.77	0.21	2.36	2.85	0.43	2.71
21	70	female	0.77	0.24	2.49	2.50	0.40	2.41
22	66	female	1.07	0.20	2.38	2.30	0.35	2.28
23	70	female	0.23	0.21	artifact	2.00	0.30	2.29
24	70	female	0.62	0.22	2.51	2.89	0.39	2.96
25	68	male	1.14	0.27	2.61	2.89	0.37	2.59
26	70	female		0.20		2.87	0.48	3.12

()* =outliers

Appendix 7

Regional variations in cutaneous hardness, hardness (Newtons) was measured at three locations within each extremity in asymptomatic controls

I.D.	Age	Sex	Cutaneous hardness (Newtons) measured at: Forearm, 5cm inferior to antecubital fossa	Forearm, 10cm inferior to antecubital fossa	Mid-forearm	Leg, 5cm superior to medial malleolus	Leg, 10cm superior to medial malleolus	Mid-leg
1	22	female	0.33	0.33	0.28	0.46	0.40	0.37
2	21	female	0.20	0.26	0.36	0.38	0.36	0.29
3	27	female	0.31	0.33	0.36	0.41	0.40	0.31
4	35	female	0.27	0.32	0.35	0.31	0.38	0.29
5	31	female	0.21	0.28	0.30	0.48	0.43	0.29
6	37	female	0.20	0.31	0.35	0.48	0.41	0.31
7	26	female		unavailable		0.47	0.46	0.37
8	50	male	0.27	0.47	0.58	0.44	0.38	0.27
9	34	male	0.31	0.31	0.52	0.31	0.29	0.29
10	34	male	0.29	0.33	0.58	0.43	0.40	0.32
11	33	female	0.28	0.35	0.31	0.37	0.37	0.27
12	34	female	0.31	0.37	0.38	0.48	0.46	0.31
13	32	female	0.24	0.30	0.35	0.42	0.31	0.28
14	39	female	0.25	0.28	0.30	0.34	0.31	0.27
15	40	male	0.24	0.34	0.36	0.39	0.38	0.40
16	48	male	0.29	0.28	0.24	0.33	0.38	0.27
17	38	male	0.22	0.40	0.33	0.46	0.38	0.36
18	37	male	0.28	0.38	0.38	0.42	0.40	0.27
19	33	male	0.25	0.31	0.34	0.38	0.30	0.28
20	31	female	0.28	0.31	0.31	0.47	0.46	0.33
21	58	male	0.38	0.43	0.43	0.46	0.38	0.31
22	45	female	0.27	0.31	0.33	0.48	0.38	0.33
23	30	female	0.25	0.29	0.32	0.38	0.41	0.45
24	65	male	0.29	0.30	0.34	0.45	0.45	0.37
25	78	female	0.22	0.23	0.28	0.43	0.47	0.39
26	40	female	0.20	0.31	0.31	0.48	0.49	0.46
27	61	male	0.27	0.31	0.26	0.48	0.44	0.37
28	46	female	0.21	0.26	0.28	0.34	0.39	0.41
29	51	male	0.20	0.29	0.33	0.48	0.39	0.20
30	73	female	0.24	0.24	0.28	0.41	0.41	0.38

Appendix 7 continued/...

I.D.	Age	Sex	Cutaneous hardness (Newtons) measured at: Forearm, 5cm inferior to antecubital fossa	Forearm, 10cm inferior to antecubital fossa	Mid-forearm	Leg, 5cm superior to medial malleolus	Leg, 10cm superior to medial malleolus	Mid-leg
31	83	female	0.22	0.20	0.24	0.39	0.40	0.33
32	51	male	0.29	0.31	0.36	0.49	0.46	0.41
33	68	female	0.25	0.27	0.28	0.43	0.45	0.43
34	27	female	0.21	0.30	0.34	0.40	0.48	0.44
35	55	female	0.32	0.30	0.29	0.47	0.49	0.43
36	69	female	0.20	0.27	0.27	0.43	0.43	0.43
37	68	female	0.20	0.25	0.27	0.46	0.40	0.34
38	52	female	0.25	0.29	0.38	0.48	0.51	0.49
39	53	female	0.22	0.31	0.31	0.31	0.38	0.38
40	65	male	0.25	0.31	0.35	0.38	0.43	0.40
41	68	male	0.24	0.26	0.30	0.49	0.54	0.40
42	61	male	0.23	0.28	0.29	0.43	0.40	0.43
43	80	female	0.20	0.20	0.20	0.32	0.36	0.29
44	77	female	0.20	0.20	0.22	0.40	0.42	0.29
45	71	female	0.25	0.28	0.31	0.40	0.48	0.43
46	73	male	0.21	0.29	0.28	0.45	0.43	0.36
47	65	female	0.22	0.27	0.28	0.46	0.48	0.43
48	75	female	0.21	0.22	0.22	0.38	0.38	0.43
49	70	female	0.24	0.27	0.27	0.31	0.40	0.40
50	66	female	0.20	0.26	0.28	0.31	0.38	0.35
51	70	female	0.21	0.21	0.22	0.31	0.40	0.30
52	70	female	0.22	0.28	0.31	0.37	0.43	0.39
53	68	male	0.27	0.28	0.31	0.52	0.43	0.37
54	70	female	0.20	0.20	0.27	0.43	0.49	0.48

	Forearm, 5cm inferior to antecubital fossa	Forearm, 10cm inferior to antecubital fossa	Mid-forearm	Leg, 5cm superior to medial malleolus	Leg, 10cm superior to medial malleolus	Mid-leg
Number of cases	**53**	**53**	**53**	**54**	**54**	**54**
Median	**0.24**	**0.29**	**0.31**	**0.43**	**0.40**	**0.36**
Minimum	**0.20**	**0.20**	**0.20**	**0.31**	**0.29**	**0.20**
Maximum	**0.38**	**0.47**	**0.58**	**0.52**	**0.54**	**0.49**

Appendix 8

Hardness indices measured in both males and females asymptomatic controls

		Hardness indices measured in males		
I.D.	Age	Index 1	Index 2	Index 3
8	50	1.65	0.82	0.46
9	34	1.00	0.94	0.56
10	34	1.46	1.22	0.56
15	40	1.64	1.13	1.13
16	48	1.12	1.32	1.11
17	38	2.07	0.95	1.10
18	37	1.48	1.05	0.70
19	33	1.51	0.97	0.84
21	58	1.19	0.89	0.73
24	65	1.55	1.48	1.08
27	61	1.78	1.41	1.42
29	51	2.34	1.34	0.61
32	51	1.68	1.47	1.15
40	65	1.51	1.38	1.16
41	68	2.06	2.09	1.33
42	61	1.91	1.46	1.46
46	73	2.11	1.46	1.30
53	68	1.95	1.51	1.17

Number of cases	**18**	**18**	**18**
Median	**1.65**	**1.33**	**1.11**
Minimum	**1.00**	**0.82**	**0.46**
Maximum	**2.34**	**2.09**	**1.46**

Appendix 8 continued/...

		Hardness indices measured in females		
I.D.	Age	Index 1	Index 2	Index 3
1	22	1.39	1.22	1.29
2	21	1.89	1.39	0.82
3	27	1.31	1.22	0.87
4	35	1.17	1.17	0.84
5	31	2.29	1.56	0.97
6	37	2.34	1.34	0.90
7	26			
11	33	1.33	1.05	0.85
12	34	1.52	1.25	0.83
13	32	1.76	1.03	0.82
14	39	1.34	1.10	0.88
20	31	1.64	1.47	1.07
22	45	1.78	1.23	0.99
23	30	1.55	1.40	1.40
25	78	1.94	2.03	1.43
26	40	2.39	1.58	1.47
28	46	1.60	1.50	1.49
30	73	1.72	1.72	1.40
31	83	1.78	1.98	1.38
33	68	1.73	1.68	1.56
34	27	1.90	1.60	1.29
35	55	1.45	1.63	1.46
36	69	2.12	1.61	1.61
37	68	2.25	1.62	1.27
38	52	1.91	1.74	1.28
39	53	1.41	1.23	1.23
43	80	1.58	1.76	1.45
44	77	1.98	2.07	1.33
45	71	1.62	1.67	1.38
47	65	2.07	1.82	1.56
48	75	1.77	1.74	1.94
49	70	1.30	1.51	1.51
50	66	1.54	1.49	1.22
51	70	1.47	1.90	1.37
52	70	1.66	1.51	1.26
54	70	2.12	2.43	1.78

Number of cases	**35**	**35**	**35**
Median	**1.72**	**1.56**	**1.29**
Minimum	**1.17**	**1.03**	**0.82**
Maximum	**2.39**	**2.43**	**1.94**

Appendix 9

The effect of age on cutaneous hardness indices

I.D.	Age	Sex	Hardness indices measured in 21-40Y asymptomatic controls Index 1	Index 2	Index 3
1	22	female	1.39	1.22	1.29
2	21	female	1.89	1.39	0.82
3	27	female	1.31	1.22	0.87
4	35	female	1.17	1.17	0.84
5	31	female	2.29	1.56	0.97
6	37	female	2.34	1.34	0.90
7	26	female			
9	34	male	1.00	0.94	0.56
10	34	male	1.46	1.22	0.56
11	33	female	1.33	1.05	0.85
12	34	female	1.52	1.25	0.83
13	32	female	1.76	1.03	0.82
14	39	female	1.34	1.10	0.88
15	40	male	1.64	1.13	1.13
17	38	male	2.07	0.95	1.10
18	37	male	1.48	1.05	0.70
19	33	male	1.51	0.97	0.84
20	31	female	1.64	1.47	1.07
23	30	female	1.55	1.40	1.40
26	40	female	2.39	1.58	1.47
34	27	female	1.90	1.60	1.29
Number of cases			**20**	**20**	**20**
Median			**1.54**	**1.22**	**0.88**
Minimum			**1.00**	**0.94**	**0.56**
Maximum			**2.39**	**1.60**	**1.47**

I.D.	Age	Sex	Hardness indices measured in 41-60Y asymptomatic controls Index 1	Index 2	Index 3
8	50	male	1.65	0.82	0.46
16	48	male	1.12	1.32	1.11
21	58	male	1.19	0.89	0.73
22	45	female	1.78	1.23	0.99
28	46	female	1.60	1.50	1.49
29	51	male	2.34	1.34	0.61
32	51	male	1.68	1.47	1.15
35	55	female	1.45	1.63	1.46
38	52	female	1.91	1.74	1.28
39	53	female	1.41	1.23	1.23
Number of cases			**10.00**	**10.00**	**10.00**
Median			**1.62**	**1.33**	**1.13**
Minimum			**1.12**	**0.82**	**0.46**
Maximum			**2.34**	**1.74**	**1.49**

Appendix 9 continued/…

I.D.	Age	Sex	Hardness indices measured in 61-90Y asymptomatic controls Index 1	Index 2	Index 3
24	65	male	1.55	1.48	1.08
25	78	female	1.94	2.03	1.43
27	61	male	1.78	1.41	1.42
30	73	female	1.72	1.72	1.40
31	83	female	1.78	1.98	1.38
33	68	female	1.73	1.68	1.56
36	69	female	2.12	1.61	1.61
37	68	female	2.25	1.62	1.27
40	65	male	1.51	1.38	1.16
41	68	male	2.06	2.09	1.33
42	61	male	1.91	1.46	1.46
43	80	female	1.58	1.76	1.45
44	77	female	1.98	2.07	1.33
45	71	female	1.62	1.67	1.38
46	73	male	2.11	1.46	1.30
47	65	female	2.07	1.82	1.56
48	75	female	1.77	1.74	1.94
49	70	female	1.30	1.51	1.51
50	66	female	1.54	1.49	1.22
51	70	female	1.47	1.90	1.37
52	70	female	1.66	1.51	1.26
53	68	male	1.95	1.51	1.17
54	70	female	2.12	2.43	1.78
Number of cases			**23**	**23**	**23**
Median			**1.78**	**1.67**	**1.38**
Minimum			**1.30**	**1.38**	**1.08**
Maximum			**2.25**	**2.43**	**1.94**

Appendix 10

The effect of both age and sex on cutaneous hardness indices

I.D.	Age	Sex	Hardness indices measured in 21-40Y male asymptomatic controls Index 1	Index 2	Index 3
9	34	male	1.00	0.94	0.56
10	34	male	1.46	1.22	0.56
15	40	male	1.64	1.13	1.13
17	38	male	2.07	0.95	1.10
18	37	male	1.48	1.05	0.70
19	33	male	1.51	0.97	0.84

Number of cases	**6**	**6**	**6**
Median	**1.50**	**1.01**	**0.77**
Minimum	**1.00**	**0.94**	**0.56**
Maximum	**2.07**	**1.22**	**1.13**

I.D.	Age	Sex	Hardness indices measured in 21-40Y female asymptomatic controls Index 1	Index 2	Index 3
1	22	female	1.39	1.22	1.29
2	21	female	1.89	1.39	0.82
3	27	female	1.31	1.22	0.87
4	35	female	1.17	1.17	0.84
5	31	female	2.29	1.56	0.97
6	37	female	2.34	1.34	0.90
7	26	female			
11	33	female	1.33	1.05	0.85
12	34	female	1.52	1.25	0.83
13	32	female	1.76	1.03	0.82
14	39	female	1.34	1.10	0.88
20	31	female		1.47	1.07
23	30	female	1.55	1.40	1.40
26	40	female	2.39	1.58	1.47
34	27	female	1.90	1.60	1.29

Number of cases	**14**	**14**	**14**
Median	**1.55**	**1.29**	**0.89**
Minimum	**1.17**	**1.03**	**0.82**
Maximum	**2.39**	**1.60**	**1.47**

Appendix 10 continued/...

I.D.	Age	Sex	Hardness indices measured in 41-60Y male asymptomatic controls		
			Index 1	Index 2	Index 3
8	50	male	1.65	0.82	0.46
16	48	male	1.12	1.32	1.11
21	58	male	1.19	0.89	0.73
29	51	male	2.34	1.34	0.61
32	51	male	1.68	1.47	1.15
Number of cases			**5**	**5**	**5**
Median			**1.65**	**1.32**	**0.73**
Minimum			**1.12**	**0.82**	**0.46**
Maximum			**2.34**	**1.47**	**1.15**

I.D.	Age	Sex	Hardness indices measured in 41-60Y female asymptomatic controls		
			Index 1	Index 2	Index 3
22	45	female	1.78	1.23	0.99
28	46	female	1.60	1.50	1.49
35	55	female	1.45	1.63	1.46
38	52	female	1.91	1.74	1.28
39	53	female	1.41	1.23	1.23
Number of cases			**5**	**5**	**5**
Median			**1.60**	**1.50**	**1.28**
Minimum			**1.41**	**1.23**	**0.99**
Maximum			**1.91**	**1.74**	**1.49**

Appendix 10 continued/...

I.D.	Age	Sex	Hardness indices measured in 61-90Y male asymptomatic controls Index 1	Index 2	Index 3
24	65	male	1.55	1.48	1.08
27	61	male	1.78	1.41	1.42
40	65	male	1.51	1.38	1.16
41	68	male	2.06	2.09	1.33
42	61	male	1.91	1.46	1.46
46	73	male	2.11	1.46	1.30
53	68	male	1.95	1.51	1.17

Number of cases	**7**	**7**	**7**
Median	**1.91**	**1.46**	**1.30**
Minimum	**1.51**	**1.38**	**1.08**
Maximum	**2.11**	**2.09**	**1.46**

I.D.	Age	Sex	Hardness indices measured in 61-90Y female asymptomatic controls Index 1	Index 2	Index 3
25	78	female	1.94	2.03	1.43
30	73	female	1.72	1.72	1.40
31	83	female	1.78	1.98	1.38
33	68	female	1.73	1.68	1.56
36	69	female	2.12	1.61	1.61
37	68	female	2.25	1.62	1.27
43	80	female	1.58	1.76	1.45
44	77	female	1.98	2.07	1.33
45	71	female	1.62	1.67	1.38
47	65	female	2.07	1.82	1.56
48	75	female	1.77	1.74	1.94
49	70	female	1.30	1.51	1.51
50	66	female	1.54	1.49	1.22
51	70	female	1.47	1.90	1.37
52	70	female	1.66	1.51	1.26
54	70	female	2.12	2.43	1.78

Number of cases	**16**	**16**	**16**
Median	**1.75**	**1.73**	**1.41**
Minimum	**1.30**	**1.49**	**1.22**
Maximum	**2.25**	**2.43**	**1.94**

Appendix 11

Regional variations in force at maximum extension (Fpeak) and relaxation time

			Natural log Fpeak measured at		Natural log relaxation time measured at	
I.D.	Age	Sex	Forearm	Leg	Forearm	Leg
1	44	male	1.57	2.42	2.35	3.71
2	40	male	2.47	3.29	3.37	3.42
3	43	female	""2	unavailable	""3.22	unavailable
4	53	female	1.48	2.06	2.56	2.56
5	40	male	2.27	2.33	2.88	2.30
6	31	female	2.40	3.14	3.17	4.79
7	27	female	1.34	2.34	2.81	3.60
8	31	male	0.67	2.46	3.57	3.96
9	39	female	1.21	2.40	2.41	2.75
10	63	male	1.11	2.67	2.60	3.42
11	23	male	1.42	2.82	3.16	2.92
12	37	male	1.59	3.01	2.97	3.22
13	35	male	""1.21	robe did not stic	""3.65	probe did not stick
14	49	male	1.93	2.49	3.30	3.26
15	49	female	1.48	1.88	2.41	2.98
16	49	male	1.57	3.03	3.14	3.68
17	47	female	1.53	3.15	2.45	4.32
18	48	female	1.51	2.94	2.42	2.57
19	45	female	1.46	3.00	3.39	3.06
20	25	female	1.91	2.95	2.33	3.25
21	33	male	2.05	3.11	2.24	3.29
22	33	male	1.61	2.20	2.41	2.55
23	22	female	1.85	2.91	2.66	3.01
24	22	female	1.81	3.10	2.58	3.34
25	22	female	0.94	2.68	2.91	3.65
26	23	male	""1.98	skin erythema	""3.87	skin erythema
27	58	male	1.63	2.53	3.16	6.40
28	69	female	2.25	3.12	2.57	2.74
29	44	female	1.79	2.94	2.89	2.95
30	28	male	1.77	3.12	2.53	2.73
31	30	female	""1.69	unavailable	""2.40	unavailable
32	56	male	""1.67	unavailable	""2.39	unavailable
33	35	female	""1.91	unavailable	""2.46	unavailable
34	38	female	1.51	3.10	2.58	2.35
35	47	female	""2.12	robe did not stic	""2.23	probe did not stick
36	42	female	1.32	3.19	2.37	2.78
37	27	male	1.98	3.12	2.68	2.44
38	44	female	0.45	2.47	2.96	2.91
39	35	female	1.61	2.49	3.42	3.27
40	18	male	1.55	2.41	2.58	2.55
41	26	female	1.11	2.55	2.60	2.56
42	53	female	1.23	2.88	2.72	3.90
43	24	female	""1.01	unavailable	""2.61	unavailable
44	29	female	1.29	3.10	2.58	2.90
45	26	female	0.94	2.73	2.45	2.22
46	24	female	1.08	2.47	2.15	2.16
47	45	male	0.82	2.88	2.77	2.78
48	58	female	1.98	2.36	2.90	2.82

Appendix 11 continued/...

I.D.	Age	Sex	Natural log Fpeak measured at Forearm	Leg	Natural log relaxation time measured at Forearm	Leg
49	25	male	0.39	2.53	3.11	3.80
50	21	female	0.69	2.62	2.52	2.61
51	44	female	1.43	2.81	2.54	2.72
52	65	female	unavailable	""2.38	unavailable	""4.53
53	51	male	unavailable	""2.97	unavailable	""3.46
54	72	male	unavailable	""2.88	unavailable	""3.26
55	78	female	-0.15	2.42	2.40	2.59
56	61	male	1.24	3.02	2.38	2.61
57	73	female	-0.11	2.78	2.87	2.68
58	83	female	-0.58	2.59	4.35	2.37
59	51	male	1.67	2.55	2.84	2.29
60	68	female	-0.31	2.35	2.66	2.98
61	55	female	1.88	2.94	2.49	2.61
62	69	female	0.74	3.22	2.43	3.17
63	68	female	0.62	2.84	2.51	2.97
64	52	female	1.13	3.37	2.34	2.66
65	53	female	0.88	2.38	2.73	2.60
66	65	male	0.99	2.13	2.42	2.68
67	68	male	0.72	3.02	2.34	2.53
68	61	male	0.52	2.89	2.44	2.58
69	80	female	0.69	2.63	2.29	3.17
70	77	female	""-0.07	robe did not stic	""2.38	probe did not stick
71	71	female	0.88	2.11	2.33	2.68
72	73	male	0.88	2.96	2.54	2.55
73	65	female	0.89	3.13	2.45	2.89
74	75	female	0.77	2.85	2.36	2.71
75	70	female	0.77	2.50	2.49	2.41
76	66	female	1.07	2.30	2.38	2.28
77	70	female	0.23	2.00	tifact (probe detache	""2.29
78	70	female	0.62	2.89	2.51	2.96
79	68	male	1.14	2.89	2.61	2.59
80	70	female	artifact (unvoluntry	""2.87	tifact (unvoluntry movemer	""3.12

"" Paired data were not available and was not included in statistical analysis

Number of cases	**67**	**67**	**66**	**66**
Mean	**1.21**	**2.73**	**2.69**	**2.98**
Standard deviation	**0.64**	**0.35**	**0.38**	**0.67**
Median	**1.24**	**2.81**	**2.58**	**2.78**
Minimum	**-0.58**	**1.88**	**2.15**	**2.16**
Maximum	**2.47**	**3.37**	**4.35**	**6.40**

Appendix 12
Extensibility and relaxation indices measured in both males and females asymptomatic controls

In the male group			
I.D.	Age	Extensibility index	Relaxation index
1	44	0.85	1.36
2	40	0.83	0.05
5	40	0.06	-0.57
8	31	1.78	0.39
10	63	1.56	0.82
11	23	1.40	-0.24
12	37	1.42	0.25
13	35	""	""
14	49	0.56	-0.04
16	49	1.46	0.54
21	33	1.06	1.05
22	33	0.59	0.14
26	23	""	""
27	58	0.90	3.24
30	28	1.34	0.20
32	56	""	""
37	27	1.14	-0.24
40	18	0.86	-0.04
47	45	2.07	0.01
49	25	2.15	0.69
53	51	""	""
54	72	""	""
56	61	1.78	0.22
59	51	0.89	-0.55
66	65	1.14	0.26
67	68	2.30	0.19
68	61	2.37	0.15
72	73	2.08	0.02
79	68	1.75	-0.01

"" The index value was not calculated due to the unavailability of data from both extremities

Number of cases	**24**	**24**
Mean	**1.35**	**0.33**
Standard deviatio	**0.61**	**0.77**
Median	**1.37**	**0.17**
Minimum	**0.06**	**-0.57**
Maximum	**2.37**	**3.24**

Appendix 12 continued/...

In the female group			
I.D.	Age	Extensibility index	Relaxation index
3	43	""	""
4	53	0.58	0.00
6	31	0.75	1.62
7	27	1.00	0.78
9	39	1.19	0.34
15	49	0.40	0.57
17	47	1.62	1.87
18	48	1.43	0.15
19	45	1.53	-0.33
20	25	1.03	0.92
23	22	1.06	0.36
24	22	1.30	0.76
25	22	1.75	0.74
28	69	0.87	0.17
29	44	1.15	0.06
31	30	""	""
33	35	""	""
34	38	1.60	-0.24
35	47	""	""
36	42	1.87	0.41
38	44	2.01	-0.05
39	35	0.88	-0.14
41	26	1.43	-0.04
42	53	1.65	1.17
43	24	""	""
44	29	1.81	0.32
45	26	1.80	-0.22
46	24	1.40	0.01
48	58	0.38	-0.07
50	21	1.94	0.09
51	44	1.38	0.18
52	65	""	""
55	78	2.57	0.19
57	73	2.88	-0.18
58	83	3.17	-1.98
60	68	2.67	0.33
61	55	1.06	0.12
62	69	2.48	0.74
63	68	2.23	0.46
64	52	2.24	0.33
65	53	1.50	-0.13
69	80	1.95	0.88
70	77	""	""
71	71	1.23	0.35

Appendix 12 continued/...

In the female group			
I.D.	Age	Extensibility index	Relaxation index
73	65	2.24	0.44
74	75	2.09	0.36
75	70	1.74	-0.08
76	66	1.24	-0.11
77	70	1.77	Artifact
78	70	2.27	0.44
80	70	""	""

"" The index value was not calculated due to the unavailability of data from both extremities

Number of cases	**43**	**42**
Mean	**1.61**	**0.28**
Standard deviatio	**0.64**	**0.59**
Median	**1.60**	**0.25**
Minimum	**0.38**	**-1.98**
Maximum	**3.17**	**1.87**

Appendix 13

The effect of age on extensibility and relaxation indices measured in asymptomatic controls

I.D.	Age	Sex	In 21-40Y asymptomatic controls Extensibility index	Relaxation index
2	40	male	0.83	0.05
5	40	male	0.06	-0.57
6	31	female	0.75	1.62
7	27	female	1.00	0.78
8	31	male	1.78	0.39
9	39	female	1.19	0.34
11	23	male	1.40	-0.24
12	37	male	1.42	0.25
13	35	male	""	""
20	25	female	1.03	0.92
21	33	male	1.06	1.05
22	33	male	0.59	0.14
23	22	female	1.06	0.36
24	22	female	1.30	0.76
25	22	female	1.75	0.74
26	23	male	""	""
30	28	male	1.34	0.20
31	30	female	""	""
33	35	female	""	""
34	38	female	1.60	-0.24
37	27	male	1.14	-0.24
39	35	female	0.88	-0.14
40	18	male	0.86	-0.04
41	26	female	1.43	-0.04
43	24	female	""	""
44	29	female	1.81	0.32
45	26	female	1.80	-0.22
46	24	female	1.40	0.01
49	25	male	2.15	0.69
50	21	female	1.94	0.09

"" The index value was not calculated due to the unavailability of data from both extremities

Number of cases	**25**	**25**
Mean	**1.26**	**0.28**
Standard deviation	**0.48**	**0.50**
Median	**1.30**	**0.20**
Minimum	**0.06**	**-0.57**
Maximum	**2.15**	**1.62**

Appendix 13 continued/...

I.D.	Age	Sex	In 41-60Y asymptomatic controls Extensibility index	Relaxation index
1	44	male	0.85	1.36
3	43	female	""	""
4	53	female	0.58	0.00
14	49	male	0.56	-0.04
15	49	female	0.40	0.57
16	49	male	1.46	0.54
17	47	female	1.62	1.87
18	48	female	1.43	0.15
19	45	female	1.53	-0.33
27	58	male	0.90	3.24
29	44	female	1.15	0.06
32	56	male	""	""
35	47	female	""	""
36	42	female	1.87	0.41
38	44	female	2.01	-0.05
42	53	female	1.65	1.17
47	45	male	2.07	0.01
48	58	female	0.38	-0.07
51	44	female	1.38	0.18
53	51	male	""	""
59	51	male	0.89	-0.55
61	55	female	1.06	0.12
64	52	female	2.24	0.33
65	53	female	1.50	-0.13

"" The index value was not calculated due to the unavailability of data from both extremities

Number of cases	**20**	**20**
Mean	**1.28**	**0.44**
Standard deviation	**0.56**	**0.88**
Median	**1.41**	**0.13**
Minimum	**0.38**	**-0.55**
Maximum	**2.24**	**3.24**

Appendix 13 continued/...

I.D.	Age	Sex	In 61-90Y asymptomatic controls Extensibility index	Relaxation index
10	63	male	1.56	0.82
28	69	female	0.87	0.17
52	65	female	""	""
54	72	male	""	""
55	78	female	2.57	0.19
56	61	male	1.78	0.22
57	73	female	2.88	-0.18
58	83	female	3.17	-1.98
60	68	female	2.67	0.33
62	69	female	2.48	0.74
63	68	female	2.23	0.46
66	65	male	1.14	0.26
67	68	male	2.30	0.19
68	61	male	2.37	0.15
69	80	female	1.95	0.88
70	77	female	""	""
71	71	female	1.23	0.35
72	73	male	2.08	0.02
73	65	female	2.24	0.44
74	75	female	2.09	0.36
75	70	female	1.74	-0.08
76	66	female	1.24	-0.11
77	70	female	1.77	artifact
78	70	female	2.27	0.44
79	68	male	1.75	-0.01
80	70	female	""	""

"" The index value was not calculated due to the unavailability of data from both extremities

Number of cases	**22**	**21**
Mean	**2.02**	**0.17**
Standard deviation	**0.58**	**0.57**
Median	**2.08**	**0.22**
Minimum	**0.87**	**-1.98**
Maximum	**3.17**	**0.88**

Appendix 14

The effect of both age and sex on extensibility and relaxation indices

I.D.	Age	Sex	Indices measured at 21-40Y control males: Extensibility index	Relaxation index
2	40	male	0.83	0.05
5	40	male	0.06	-0.57
8	31	male	1.78	0.39
11	23	male	1.40	-0.24
12	37	male	1.42	0.25
13	35	male	""	""
21	33	male	1.06	1.05
22	33	male	0.59	0.14
26	23	male	""	""
30	28	male	1.34	0.20
37	27	male	1.14	-0.24
40	18	male	0.86	-0.04
49	25	male	2.15	0.69

	Extensibility index	Relaxation index
Number of cases	**11**	**11**
Mean	**1.15**	**0.15**
Standard deviation	**0.57**	**0.45**
Median	**1.14**	**0.14**
Minimum	**0.06**	**-0.57**
Maximum	**2.15**	**1.05**

I.D.	Age	Sex	Indices measured at 21-40Y control females: Extensibility index	Relaxation index
6	31	female	0.75	1.62
7	27	female	1.00	0.78
9	39	female	1.19	0.34
20	25	female	1.03	0.92
23	22	female	1.06	0.36
24	22	female	1.30	0.76
25	22	female	1.75	0.74
31	30	female	""	""
33	35	female	""	""
34	38	female	1.60	-0.24
39	35	female	0.88	-0.14
41	26	female	1.43	-0.04
43	24	female	""	""
44	29	female	1.81	0.32
45	26	female	1.80	-0.22
46	24	female	1.40	0.01
50	21	female	1.94	0.09

	Extensibility index	Relaxation index
Number of cases	**14**	**14**
Mean	**1.35**	**0.38**
Standard deviation	**0.38**	**0.53**
Median	**1.35**	**0.33**
Minimum	**0.75**	**-0.24**
Maximum	**1.94**	**1.62**

"" The index was not calculated due to the unavailability of data from both extremities

Appendix 14 continued/...

I.D.	Age	Sex	Indices measured at 41-60Y control males Extensibility index	Relaxation index
1	44	male	0.85	1.36
14	49	male	0.56	-0.04
16	49	male	1.46	0.54
27	58	male	0.90	3.24
32	56	male	""	""
47	45	male	2.07	0.01
53	51	male	""	""
59	51	male	0.89	-0.55

	Extensibility index	Relaxation index
Number of cases	**6**	**6**
Mean	**1.12**	**0.76**
Standard deviation	**0.55**	**1.38**
Median	**0.89**	**0.27**
Minimum	**0.56**	**-0.55**
Maximum	**2.07**	**3.24**

I.D.	Age	Sex	Indices measured at 41-60Y control females Extensibility index	Relaxation index
3	43	female	""	""
4	53	female	0.58	0.00
17	47	female	1.62	1.87
18	48	female	1.43	0.15
19	45	female	1.53	-0.33
15	49	female	0.40	0.57
29	44	female	1.15	0.06
35	47	female	""	""
36	42	female	1.87	0.41
38	44	female	2.01	-0.05
42	53	female	1.65	1.17
48	58	female	0.38	-0.07
51	44	female	1.38	0.18
61	55	female	1.06	0.12
64	52	female	2.24	0.33
65	53	female	1.50	-0.13

	Extensibility index	Relaxation index
Number of cases	**14**	**14**
Mean	**1.34**	**0.30**
Standard deviation	**0.58**	**0.58**
Median	**1.46**	**0.13**
Minimum	**0.38**	**-0.33**
Maximum	**2.24**	**1.87**

"" The index was not calculated due to the unavailability of data from both extremities

Appendix 14 continued/...

I.D.	Age	Sex	Indices measured at 61-90Y control males Extensibility index	Relaxation index
10	63	male	1.56	0.82
54	72	male	""	""
56	61	male	1.78	0.22
66	65	male	1.14	0.26
67	68	male	2.30	0.19
68	61	male	2.37	0.15
72	73	male	2.08	0.02
79	68	male	1.75	-0.01

Number of cases	**7**	**7**
Mean	**1.85**	**0.23**
Standard deviation	**0.43**	**0.28**
Median	**1.78**	**0.19**
Minimum	**1.14**	**-0.01**
Maximum	**2.37**	**0.82**

I.D.	Age	Sex	Indices measured at 61-90yY control females Extensibility index	Relaxation index
28	69	female	0.87	0.17
52	65	female	""	""
55	78	female	2.57	0.19
57	73	female	2.88	-0.18
58	83	female	3.17	-1.98
60	68	female	2.67	0.33
62	69	female	2.48	0.74
63	68	female	2.23	0.46
69	80	female	1.95	0.88
70	77	female	""	""
71	71	female	1.23	0.35
73	65	female	2.24	0.44
74	75	female	2.09	0.36
75	70	female	1.74	-0.08
76	66	female	1.24	-0.11
77	70	female	1.77	artifact
78	70	female	2.27	0.44
80	70	female	""	""

Number of cases	**15**	**14**
Mean	**2.09**	**0.14**
Standard deviation	**0.64**	**0.68**
Median	**2.23**	**0.34**
Minimum	**0.87**	**-1.98**
Maximum	**3.17**	**0.88**

"" The index was not calculated due to the unavailability of data from both extremities

Appendix 15

In the forearm of asymptomatic controls, the change in the flux and %change in flux before and during the application of cutaneous extension/relaxation

				The flux (arbitrary units) was measured during						The %chnge in flux was measured during				
			Measurement	Before extensior	During	-----Relaxation phase-----				During	-----Relaxation phase-----			
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	extension	1min	2min	3min	4min
301	40	male	4	39.00	33.10	30.40	42.50	54.90	60.70	-15.13	-22.05	8.97	40.77	55.64
302	37	male	4	30.60	35.70	43.90	54.50	61.50	69.40	16.67	43.46	78.10	100.98	126.80
303	43	female	4	50.60	41.60	16.80	22.50	26.30	27.80	-17.79	-66.80	-55.53	-48.02	-45.06
304	65	female	4	63.50	67.30	68.90	87.80	91.00	91.60	5.98	8.50	38.27	43.31	44.25
305	53	female	4	19.00	40.90	43.00	49.20	59.70	55.70	115.26	126.32	158.95	214.21	193.16
306	40	male	4	40.60	64.60	27.40	34.10	37.90	39.60	59.11	-32.51	-16.01	-6.65	-2.46
307	31	female	4	47.90	49.20	35.70	54.90	69.20	77.50	2.71	-25.47	14.61	44.47	61.80
308	28	female	4	42.00	60.20	71.30	89.80	107.50	122.70	43.33	69.76	113.81	155.95	192.14
309	44	female	4	33.10	36.00	33.10	32.70	39.10	43.00	8.76	.00	-1.21	18.13	29.91
310	72	male	4	34.00	38.40	41.70	37.50	37.30	37.90	12.94	22.65	10.29	9.71	11.47
311	44	female	4	54.60	60.00	58.30	58.20	57.70	56.80	9.89	6.78	6.59	5.68	4.03
312	58	male	4	22.70	37.10	50.00	51.70	55.30	56.00	63.44	120.26	127.75	143.61	146.70
313	69	female	4	34.60	51.90	37.80	40.20	42.10	45.40	50.00	9.25	16.18	21.68	31.21
314	22	female	4	19.20	37.10	35.40	36.00	39.00	39.70	93.23	84.38	87.50	103.13	106.77
315	22	female	4	28.20	41.40	32.00	41.10	41.70	38.70	46.81	13.48	45.74	47.87	37.23
316	51	male	4	35.40	54.00	32.20	29.50	28.90	30.90	52.54	-9.04	-16.67	-18.36	-12.71
317	33	male	4	188.50	188.40	138.60	163.90	181.70	194.10	-.05	-26.47	-13.05	-3.61	2.97
318	33	male	4	33.00	41.90	70.50	99.30	110.30	87.10	26.97	113.64	200.91	234.24	163.94
319	25	female	4	24.70	30.70	40.80	63.80	77.20	88.30	24.29	65.18	158.30	212.55	257.49
320	45	female	4	9.50	17.30	22.00	28.50	26.90	27.70	82.11	131.58	200.00	183.16	191.58
321	47	female	4	21.20	53.20	16.40	23.20	28.30	31.80	150.94	-22.64	9.43	33.49	50.00
322	49	male	4	32.10	56.40	53.70	70.40	71.30	77.10	75.70	67.29	119.31	122.12	140.19
323	48	female	4	13.50	31.10	31.20	37.40	38.00	36.40	130.37	131.11	177.04	181.48	169.63

Appendix 15 continued/...

I.D.	Age	Sex	Measurement duration (min)	The flux (arbitrary units) was measured during: Before extension baseline	During extension	Relaxation phase: 1min	2min	3min	4min	The %chnge in flux was measured during: During extension	Relaxation phase: 1min	2min	3min	4min
324	49	female	4	13.30	20.10	23.30	32.80	44.60	38.60	51.13	75.19	146.62	235.34	190.23
325	39	female	4	33.00	35.10	41.00	52.60	46.10	44.50	6.36	24.24	59.39	39.70	34.85
326	23	male	4	15.30	19.90	23.20	25.40	25.10	25.40	30.07	51.63	66.01	64.05	66.01
327	28	female	4	52.90	69.80	71.40	90.30	108.60	121.70	31.95	34.97	70.70	105.29	130.06
328	32	male	4	61.10	69.80	78.10	93.90	93.90	90.70	14.24	27.82	53.68	53.68	48.45
329	49	male	4	65.70	88.70	59.90	74.40	93.80	97.10	35.01	-8.83	13.24	42.77	47.79
330	63	male	4	38.00	49.50	37.00	46.30	41.40	44.40	30.26	-2.63	21.84	8.95	16.84
331	36	male	4	13.30	20.90	15.10	18.90	20.60	21.50	57.14	13.53	42.11	54.89	61.65
332	45	male	3	""58.6	""71.7	""69.2	""59.4	""46.3		""22.36	""18.09	""1.37	""-20.99	
333	35	female	4	32.10	38.70	35.00	66.10	68.80	81.30	20.56	9.03	105.92	114.33	153.27
334	44	female	4	22.90	28.80	31.70	38.90	41.40	42.90	25.76	38.43	69.87	80.79	87.34
335	44	male	0			unavailable						unavailable		
336	26	male	0			unavailable						unavailable		
337	47	female	0			unavailable						unavailable		
338	65	female	4	40.20	55.30	38.30	35.60	34.80	33.40	37.56	-4.73	-11.44	-13.43	-16.92
339	69	male	4	31.70	45.70	26.50	31.50	41.70	44.90	44.16	-16.40	-.63	31.55	41.64
340	70	female	4	24.60	30.70	22.10	28.30	31.70	29.80	24.80	-10.16	15.04	28.86	21.14
341	71	female	4	60.40	73.70	52.90	51.30	59.60	62.40	22.02	-12.42	-15.07	-1.32	3.31
342	62	male	4	44.40	46.00	45.30	59.10	57.00	72.20	3.60	2.03	33.11	28.38	62.61
343	69	female	4	20.50	24.40	26.90	28.10	34.20	36.20	19.02	31.22	37.07	66.83	76.59
344	69	female	4	20.20	21.90	19.40	21.10	17.20	22.00	8.42	-3.96	4.46	-14.85	8.91
345	69	male	4	87.90	100.50	88.50	76.00	65.00	76.30	14.33	.68	-13.54	-26.05	-13.20
346	74	female	4	23.20	32.30	34.40	42.80	52.40	75.30	39.22	48.28	84.48	125.86	224.57
347	69	male	4	39.60	47.50	45.60	41.50	39.80	41.80	19.95	15.15	4.80	.51	5.56

Appendix 15 continued/...

				The flux (arbitrary units) was measured during						The %chnge in flux was measured during				
			Measurement	Before extension	During	----------Relaxation phase----------				During	----------Relaxation phase----------			
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	extension	1min	2min	3min	4min
348	71	female	4	68.00	67.50	100.20	114.80	107.90	108.40	-.74	47.35	68.82	58.68	59.41
349	71	female	4	156.50	146.50	118.40	135.30	154.00	174.10	-6.39	-24.35	-13.55	-1.60	11.25
350	68	female	4	68.60	72.30	85.10	94.00	98.70	101.20	5.39	24.05	37.03	43.88	47.52
351	62	male	4	29.70	33.50	38.00	43.80	56.60	45.30	12.79	27.95	47.47	90.57	52.53
352	62	male	4	29.10	37.30	32.50	41.70	51.40	44.60	28.18	11.68	43.30	76.63	53.26
353	62	male	4	26.30	33.60	39.90	44.60	44.00	45.80	1.92	3.58	4.81	4.66	5.13

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**49**	**49**	**49**	**49**	**49**	**49**	**49**	**49**	**49**	**49**	**49**
Mean	**41.55**	**50.56**	**46.14**	**54.65**	**59.45**	**62.40**	**32.96**	**24.73**	**49.90**	**64.06**	**70.13**
Standard deviation	**32.32**	**30.63**	**26.19**	**30.59**	**33.76**	**36.66**	**35.28**	**45.77**	**61.59**	**71.83**	**72.25**
Median	**33.00**	**41.60**	**38.00**	**43.80**	**51.40**	**45.40**	**24.80**	**13.48**	**37.07**	**43.88**	**50.00**
Minimum	**9.50**	**17.30**	**15.10**	**18.90**	**17.20**	**21.50**	**-17.79**	**-66.80**	**-55.53**	**-48.02**	**-45.06**
Maximum	**188.50**	**188.40**	**138.60**	**163.90**	**181.70**	**194.10**	**150.94**	**131.58**	**200.91**	**235.34**	**257.49**

Appendix 16

In the leg of asymptomatic controls, the change in the flux and %change in flux before and during the application of cutaneous extension/relaxation

					The flux (arbitrary units)								
			Measurement	Before extension	extension	----------Relaxation phase----------							
I.D.	Age	Sex	duration (min)	baseline	phase	1min	2min	3min	4min	5min	6min	7min	8min
301	40	male						unavailable					
302	37	male	5	""14.6	""15.4	""6.2	""8.2	""9.5	""10.9	""10.9			
303	43	female						unavailable					
304	65	female						unavailable					
305	53	female						unavailable					
306	40	male	8	41.00	58.90	44.10	48.90	52.00	53.40	41.40	47.70	47.30	61.10
307	31	female	8	25.50	40.60	24.50	34.10	27.90	25.40	32.10	38.20	38.50	43.50
308	28	female	8	53.20	51.70	39.30	52.30	64.80	72.20	78.90	82.90	87.70	83.30
309	44	female	8	55.80	46.70	38.20	55.80	78.60	96.10	111.00	108.00	122.10	127.40
310	72	male	8	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00
311	44	female	8	34.10	40.90	28.30	38.80	45.90	50.10	47.50	53.70	55.20	58.30
312	58	male	8	47.40	42.00	28.80	37.80	38.40	37.10	33.40	35.10	36.30	41.60
313	69	female	8	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10
314	22	female	8	38.80	38.60	26.30	31.90	35.50	38.00	39.70	40.10	42.80	42.90
315	22	female	8	18.30	30.00	15.40	17.40	19.00	26.80	24.70	21.90	22.00	29.20
316	51	male	8	22.60	23.10	13.20	17.50	16.80	23.60	24.60	23.90	26.10	25.60
317	33	male	8	30.10	35.00	38.50	51.60	60.70	60.20	66.40	64.90	64.50	65.00
318	33	male	8	49.40	52.90	20.70	27.80	35.50	38.70	47.20	57.90	64.00	73.90
319	25	female	8	12.00	15.80	10.50	13.40	17.20	19.80	23.20	24.30	25.20	27.80
320	45	female	8	13.50	18.70	11.40	15.60	20.70	24.90	31.70	37.00	39.50	35.60
321	47	female						unavailable					
322	49	male	8	20.10	28.10	19.40	23.70	26.00	28.30	25.70	27.80	26.70	26.20
323	48	female	8	13.70	28.20	11.10	12.70	14.20	17.00	18.60	19.10	21.00	23.50
324	49	female	8	19.60	27.10	16.60	19.80	26.10	23.50	21.40	22.10	23.90	22.00

Appendix 16 continued/…

				The flux (arbitrary units)									
			Measurement	Before extension	extension	Relaxation phase							
I.D.	Age	Sex	duration (min)	baseline	phase	1min	2min	3min	4min	5min	6min	7min	8min
325	39	female	8	60.40	70.70	31.60	42.60	40.90	45.50	47.90	50.10	44.40	50.40
326	23	male	8	40.60	54.40	13.90	18.00	20.20	19.00	23.90	21.60	19.00	17.90
327	28	female						unavailable					
328	32	male	8	19.60	25.70	17.20	20.40	22.40	22.50	23.00	24.50	23.30	24.30
329	49	male	8	47.40	67.40	58.00	80.00	80.50	110.20	131.90	147.70	165.20	176.40
330	63	male						unavailable					
331	36	male						unavailable					
332	45	male	5	""43.6	""38.7	""26.5	""29	""31.3	""31.5	""32.7			
333	35	female	8	26.40	32.00	17.30	20.10	22.30	22.90	23.50	23.00	26.90	27.90
334	44	female	8	25.40	36.00	24.80	34.00	40.80	47.90	53.70	57.90	62.20	66.50
335	44	male	6	""42.6	""38.8	""30.4	""46.3	""56.6	""60.2	""59.7	""63.9		
336	26	male	8	18.00	17.20	7.00	12.00	12.50	14.10	16.10	18.50	18.90	17.40
337	47	female	8	27.10	21.80	8.70	11.40	15.50	16.20	17.00	17.50	19.90	19.70
338	65	female	8	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50
339	69	male	8	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00
340	70	female	8	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60
341	71	female	8	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40
342	62	male	8	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60
343	69	female	8	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20
344	69	female	8	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80
345	69	male	8	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20
346	74	female	8	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60

Appendix 16 continued/...

				The flux (arbitrary units)									
			Measurement	Before extension	extension	-----------------------------------Relaxation phase							--
I.D.	Age	Sex	duration (min)	baseline	phase	1min	2min	3min	4min	5min	6min	7min	8min
347	69	male	8	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50
348	71	female	8	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30
349	71	female	8	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30
350	68	female	8	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20
351	62	male	8	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40
352	62	male	8	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20
353	62	male	8	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**
Mean	**28.04**	**35.48**	**21.86**	**28.48**	**33.73**	**38.06**	**40.27**	**43.42**	**45.57**	**47.68**
Standard deviation	**12.81**	**15.02**	**11.32**	**15.66**	**18.92**	**22.62**	**25.95**	**28.48**	**31.15**	**33.59**
Median	**25.45**	**29.90**	**17.75**	**24.20**	**26.05**	**28.70**	**31.05**	**33.70**	**36.05**	**35.90**
Minimum	**12.00**	**15.80**	**7.00**	**10.90**	**12.50**	**13.10**	**13.10**	**13.90**	**13.90**	**12.60**
Maximum	**60.40**	**70.70**	**58.00**	**80.00**	**80.50**	**110.20**	**131.90**	**147.70**	**165.20**	**176.40**

Appendix 16 continued/...

I.D.	Age	Sex	Measurement duration (min)	%change in flux [(flux extension or relaxation - flux bl)/flux bl]* 100 extension phase	Relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min
301	40	male						unavailable				
302	37	male	5	""5.48	""-57.53	""-43.84	""-34.93	""-25.34	""-25.34			
303	43	female						unavailable				
304	65	female						unavailable				
305	53	female						unavailable				
306	40	male	8	43.66	7.56	19.27	26.83	30.24	0.98	16.34	15.37	49.02
307	31	female	8	59.22	-3.92	33.73	9.41	-0.39	25.88	49.80	50.98	70.59
308	28	female	8	-2.82	-26.13	-1.69	21.80	35.71	48.31	55.83	64.85	56.58
309	44	female	8	-16.31	-31.54	0.00	40.86	72.22	98.92	93.55	118.82	128.32
310	72	male	8	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85
311	44	female	8	19.94	-17.01	13.78	34.60	46.92	39.30	57.48	61.88	70.97
312	58	male	8	-11.39	-39.24	-20.25	-18.99	-21.73	-29.54	-25.95	-23.42	-12.24
313	69	female	8	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74
314	22	female	8	-0.52	-32.22	-17.78	-8.51	-2.06	2.32	3.35	10.31	10.57
315	22	female	8	63.93	-15.85	-4.92	3.83	46.45	34.97	19.67	20.22	59.56
316	51	male	8	2.21	-41.59	-22.57	-25.66	4.42	8.85	5.75	15.49	13.27
317	33	male	8	16.28	27.91	71.43	101.66	100.00	120.60	115.61	114.29	115.95
318	33	male	8	7.09	-58.10	-43.72	-28.14	-21.66	-4.45	17.21	29.55	49.60
319	25	female	8	31.67	-12.50	11.67	43.33	65.00	93.33	102.50	110.00	131.67
320	45	female	8	38.52	-15.56	15.56	53.33	84.44	134.81	174.07	192.59	163.70
321	47	female						unavailable				
322	49	male	8	39.80	-3.48	17.91	29.35	40.80	27.86	38.31	32.84	30.35
323	48	female	8	105.84	-18.98	-7.30	3.65	24.09	35.77	39.42	53.28	71.53
324	49	female	8	38.27	-15.31	1.02	33.16	19.90	9.18	12.76	21.94	12.24
325	39	female	8	17.05	-47.68	-29.47	-32.28	-24.67	-20.70	-17.05	-26.49	-16.56
326	23	male	8	33.99	-65.76	-55.67	-50.25	-53.20	-41.13	-46.80	-53.20	-55.91
327	28	female						unavailable				

Appendix 16 continued/…

				%change in flux [(flux$_{extension\ or\ relaxation}$- flux$_{bl}$)/flux$_{bl}$]* 100								
			Measurement	extension	----------Relaxation phase----------							
I.D.	Age	Sex	duration (min)	phase	1min	2min	3min	4min	5min	6min	7min	8min
328	32	male	8	31.12	-12.24	4.08	14.29	14.80	17.35	25.00	18.88	23.98
								unavailable				
329	49	male	8	42.19	22.36	68.78	69.83	132.49	178.27	211.60	248.52	272.15
330	63	male						unavailable				
331	36	male						unavailable				
332	45	male	5	""-11.24	""-39.22	""-33.49	""-28.21	""-27.75	""-25			
333	35	female	8	21.21	-34.47	-23.86	-15.53	-13.26	-10.98	-12.88	1.89	5.68
334	44	female	8	41.73	-2.36	33.86	60.63	88.58	111.42	127.95	144.88	161.81
335	44	male	6	""-8.92	""-28.64	""8.69	""32.86	""41.32	""40.14	""50		
336	26	male	8	-4.44	-61.11	-33.33	-30.56	-21.67	-10.56	2.78	5.00	-3.33
337	47	female	8	-19.56	-67.90	-57.93	-42.80	-40.22	-37.27	-35.42	-26.57	-27.31
338	65	female	8	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59
339	69	male	8	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36
340	70	female	8	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48
341	71	female	8	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88
342	62	male	8	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62
343	69	female	8	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13
344	69	female	8	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-0.70	10.49
345	69	male	8	52.17	-36.02	-32.30	-8.70	4.97	0.00	8.07	25.47	25.47
346	74	female	8	19.72	18.31	15.96	.20.66	24.88	37.09	32.86	67.61	67.14
347	69	male	8	26.90	-13.71	-6.09	-4.57	13.20	-0.51	8.12	-1.02	-1.02
348	71	female	8	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54

Appendix 16 continued/...

				%change in flux [(flux$_{extension\ or\ relaxation}$- flux$_{bl}$)/flux$_{bl}$]* 100								
			Measurement	extension	---Relaxation phase---							
I.D.	Age	Sex	duration (min)	phase	1min	2min	3min	4min	5min	6min	7min	8min
349	71	female	8	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80
350	68	female	8	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46
351	62	male	8	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63
352	62	male	8	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15
353	62	male	8	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**
Mean	**34.49**	**-18.90**	**3.49**	**23.68**	**40.28**	**47.06**	**59.09**	**67.06**	**73.44**
Standard deviation	**48.13**	**27.78**	**35.03**	**48.56**	**58.94**	**65.32**	**77.55**	**84.56**	**88.15**
Median	**27.45**	**-19.49**	**-0.85**	**19.21**	**27.56**	**26.87**	**35.59**	**34.58**	**53.09**
Minimum	**-19.56**	**-67.90**	**-57.93**	**-50.25**	**-53.20**	**-41.13**	**-46.80**	**-53.20**	**-55.91**
Maximum	**247.06**	**36.18**	**82.13**	**156.18**	**177.66**	**178.27**	**291.57**	**335.39**	**313.48**

Appendix 17

In the forearms of both male and female asymptomatic coontrols, the change in the cutaneous microcirculation with the application of cutaneous extension/relaxation measured with LDF

			Changes in the cutaneous microcirculation were measured in the forearms of control males													
			The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
		Measurement		During	----------------Relaxation phase------------				time to reach	During	-----------Relaxation phase----------------				Slope of %change in flux	
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
301	40	4	39.00	33.10	30.40	42.50	54.90	60.70	1.0	-15.13	-22.05	8.97	40.77	55.64	20.44	26.49
302	37	4	30.60	35.70	43.90	54.50	61.50	69.40	8.0	16.67	43.46	78.10	100.98	126.80	27.78	27.29
306	40	4	40.60	64.60	27.40	34.10	37.90	39.60	6.5	59.11	-32.51	-16.01	-6.65	-2.46	-9.73	9.95
310	72	4	34.00	38.40	41.70	37.50	37.30	37.90	7.0	12.94	22.65	10.29	9.71	11.47	-1.59	-3.41
312	58	4	22.70	37.10	50.00	51.70	55.30	56.00	6.0	63.44	120.26	127.75	143.61	146.70	18.99	9.52
316	51	4	35.40	54.00	32.20	29.50	28.90	30.90	3.0	52.54	-9.04	-16.67	-18.36	-12.71	-13.98	-1.27
317	33	4	188.50	188.40	138.60	163.90	181.70	194.10	4.0	-0.05	-26.47	-13.05	-3.61	2.97	2.89	9.78
318	33	4	33.00	41.90	70.50	99.30	110.30	87.10	8.0	26.97	113.64	200.91	234.24	163.94	39.45	18.42
322	49	4	32.10	56.40	53.70	70.40	71.30	77.10	3.0	75.70	67.29	119.31	122.12	140.19	18.38	22.15
326	23	4	15.30	19.90	23.20	25.40	25.10	25.40	7.0	30.07	51.63	66.01	64.05	66.01	8.43	4.12
328	32	4	61.10	69.80	78.10	93.90	93.90	90.70	5.0	14.24	27.82	53.68	53.68	48.45	9.43	6.19
329	49	4	65.70	88.70	59.90	74.40	93.80	97.10	1.0	35.01	-8.83	13.24	42.77	47.79	7.72	19.94
330	63	4	38.00	49.50	37.00	46.30	41.40	44.40	5.0	30.26	-2.63	21.84	8.95	16.84	-1.53	4.55
331	36	4	13.30	20.90	15.10	18.90	20.60	21.50	5.0	57.14	13.53	42.11	54.89	61.65	5.04	15.71
332	45	3	""58.6	""71.7	""69.2	""59.4	""46.3		""7	""22.36	""18.09	""1.37	""-20.99		""-14.674	""-19.54
335	44															
336	26															

Appendix 17 continued/…

			Changes in the cutaneous microcirculation were measured in the forearms of control males (continued)													
			The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
		Measurement		During	----Relaxation phase----				time to reach	During	----Relaxation phase----				Slope of %change in flux	
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
339	69	4	31.70	45.70	26.50	31.50	41.70	44.90	6.0	44.16	-16.40	-0.63	31.55	41.64	4.29	20.63
342	62	4	44.40	46.00	45.30	59.10	57.00	72.20	8.0	3.60	2.03	33.11	28.38	62.61	14.44	17.70
345	69	4	87.90	100.50	88.50	76.00	65.00	76.30	6.0	14.33	0.68	-13.54	-26.05	-13.20	-8.18	-5.42
347	69	4	39.60	47.50	45.60	41.50	39.80	41.80	3.0	19.95	15.15	4.80	0.51	5.56	-4.34	-3.31
351	62	4	29.70	33.50	38.00	43.80	56.60	45.30	4.0	12.79	27.95	47.47	90.57	52.53	14.21	11.68
352	62	4	29.10	37.30	32.50	41.70	51.40	44.60	3.0	28.18	11.68	43.30	76.63	53.26	11.51	15.81
353	62	4	26.30	33.60	39.90	44.60	44.00	45.80	2.0	1.92	3.58	4.81	4.66	5.13	0.75	0.45

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**
Mean	**44.67**	**54.40**	**48.48**	**56.21**	**60.45**	**62.04**	**4.83**	**27.80**	**19.21**	**38.85**	**50.16**	**51.47**	**7.83**	**10.81**
Standard deviation	**37.00**	**36.61**	**27.54**	**32.66**	**36.06**	**37.18**	**2.22**	**23.69**	**41.25**	**55.38**	**62.61**	**53.13**	**12.95**	**10.02**
Median	**34.00**	**45.70**	**41.70**	**44.60**	**54.90**	**45.80**	**5.00**	**26.97**	**11.68**	**21.84**	**40.77**	**48.45**	**7.72**	**9.95**
Minimum	**13.30**	**19.90**	**15.10**	**18.90**	**20.60**	**21.50**	**1.00**	**-15.13**	**-32.51**	**-16.67**	**-26.05**	**-13.20**	**-13.98**	**-5.42**
Maximum	**188.50**	**188.40**	**138.60**	**163.90**	**181.70**	**194.10**	**8.00**	**75.70**	**120.26**	**200.91**	**234.24**	**163.94**	**39.45**	**27.29**

Appendix 17 continued/…

Changes in the cutaneous microcirculation were measured in the forearms of control females

			The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
		Measurement		During	----Relaxation phase----				time to reach	During	----Relaxation phase----				Slope of %change in flux	
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
303	43	4	50.60	41.60	16.80	22.50	26.30	27.80	0.5	-17.79	-66.80	-55.53	-48.02	-45.06	-3.58	7.27
304	65	4	63.50	67.30	68.90	87.80	91.00	91.60	8.0	5.98	8.50	38.27	43.31	44.25	11.14	11.23
305	53	4	19.00	40.90	43.00	49.20	59.70	55.70	8.0	115.26	126.32	158.95	214.21	193.16	24.37	25.58
307	31	4	47.90	49.20	35.70	54.90	69.20	77.50	4.5	2.71	-25.47	14.61	44.47	61.80	18.81	29.17
308	28	4	42.00	60.20	71.30	89.80	107.50	122.70	1.0	43.33	69.76	113.81	155.95	192.14	38.38	40.93
309	44	4	33.10	36.00	33.10	32.70	39.10	43.00	7.0	8.76	0.00	-1.21	18.13	29.91	6.04	10.91
311	44	4	54.60	60.00	58.30	58.20	57.70	56.80	5.0	9.89	6.78	6.59	5.68	4.03	-1.28	-0.92
313	69	4	34.60	51.90	37.80	40.20	42.10	45.40	7.0	50.00	9.25	16.18	21.68	31.21	-2.52	7.14
314	22	4	19.20	37.10	35.40	36.00	39.00	39.70	7.0	93.23	84.38	87.50	103.13	106.77	4.58	8.28
315	22	4	28.20	41.40	32.00	41.10	41.70	38.70	1.5	46.81	13.48	45.74	47.87	37.23	1.52	7.34
319	25	4	24.70	30.70	40.80	63.80	77.20	88.30	6.0	24.29	65.18	158.30	212.55	257.49	61.38	63.12
320	45	4	9.50	17.30	22.00	28.50	26.90	27.70	1.0	82.11	131.58	200.00	183.16	191.58	27.05	16.32
321	47	4	21.20	53.20	16.40	23.20	28.30	31.80	5.0	150.94	-22.64	9.43	33.49	50.00	-14.58	24.20
323	48	4	13.50	31.10	31.20	37.40	38.00	36.40	4.0	130.37	131.11	177.04	181.48	169.63	12.89	12.00
324	49	4	13.30	20.10	23.30	32.80	44.60	38.60	3.0	51.13	75.19	146.62	235.34	190.23	43.84	43.38
325	39	4	33.00	35.10	41.00	52.60	46.10	44.50	2.0	6.36	24.24	59.39	39.70	34.85	7.24	1.21
327	28	4	52.90	69.80	71.40	90.30	108.60	121.70	1.0	31.95	34.97	70.70	105.29	130.06	26.65	31.99
333	35	4	32.10	38.70	35.00	66.10	68.80	81.30	7.0	20.56	9.03	105.92	114.33	153.27	37.07	44.11
334	44	4	22.90	28.80	31.70	38.90	41.40	42.90	7.0	25.76	38.43	69.87	80.79	87.34	16.55	15.77
337	47															

Appendix 17 continued/...

			Changes in the cutaneous microcirculation were measured in the forearms of control females (continued)													
			The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
		Measurement		During	----------Relaxation phase----------				time to reach	During	----------Relaxation phase----------				Slope of %change in flux	
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
338	65	4	40.20	55.30	38.30	35.60	34.80	33.40	1.0	37.56	-4.73	-11.44	-13.43	-16.92	-11.77	-3.86
340	70	4	24.60	30.70	22.10	28.30	31.70	29.80	4.0	24.80	-10.16	15.04	28.86	21.14	3.17	10.77
341	71	4	60.40	73.70	52.90	51.30	59.60	62.40	4.0	22.02	-12.42	-15.07	-1.32	3.31	-2.63	6.09
343	69	4	20.50	24.40	26.90	28.10	34.20	36.20	4.0	19.02	31.22	37.07	66.83	76.59	15.08	16.59
344	69	4	20.20	21.90	19.40	21.10	17.20	22.00	1.0	8.42	-3.96	4.46	-14.85	8.91	-0.99	1.93
346	74	4	23.20	32.30	34.40	42.80	52.40	75.30	2.0	39.22	48.28	84.48	125.86	224.57	44.83	57.03
348	71	4	68.00	67.50	100.20	114.80	107.90	108.40	8.0	-0.74	47.35	68.82	58.68	59.41	13.16	2.60
349	71	4	156.50	146.50	118.40	135.30	154.00	174.10	3.0	-6.39	-24.35	-13.55	-1.60	11.25	5.80	11.88
350	68	4	68.60	72.30	85.10	94.00	98.70	101.20	7.0	5.39	24.05	37.03	43.88	47.52	10.41	7.73

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**
Mean	**39.21**	**47.68**	**44.39**	**53.48**	**58.70**	**62.68**	**4.27**	**36.82**	**28.88**	**58.18**	**74.48**	**84.13**	**14.02**	**18.21**
Standard deviation	**28.80**	**25.59**	**25.50**	**29.50**	**32.57**	**36.94**	**2.58**	**41.96**	**49.21**	**65.62**	**77.49**	**81.94**	**18.30**	**17.59**
Median	**32.55**	**41.15**	**35.55**	**41.95**	**45.35**	**44.95**	**4.00**	**24.54**	**18.76**	**42.01**	**46.17**	**54.71**	**10.77**	**11.55**
Minimum	**9.50**	**17.30**	**16.40**	**21.10**	**17.20**	**22.00**	**0.50**	**-17.79**	**-66.80**	**-55.53**	**-48.02**	**-45.06**	**-14.58**	**-3.86**
Maximum	**156.50**	**146.50**	**118.40**	**135.30**	**154.00**	**174.10**	**8.00**	**150.94**	**131.58**	**200.00**	**235.34**	**257.49**	**61.38**	**63.12**

Appendix 18

In the legs of both male and female asymptomatic controls, the change in the cutaneous microcirculation with the application of cutaneous extension/relaxation measured with LDF

In the legs of control males			The flux (arbitrary units) was measured during										
		Measurement		During	----Relaxation phase----								time to reach
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
301	40												
302	37	5	""14.6	""15.4	""6.2	""8.2	""9.5	""10.9	""10.9				""2.5
306	40	8	41.00	58.90	44.10	48.90	52.00	53.40	41.40	47.70	47.30	61.10	
310	72	8	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00	1.0
312	58	8	47.40	42.00	28.80	37.80	38.40	37.10	33.40	35.10	36.30	41.60	4.0
316	51	8	22.60	23.10	13.20	17.50	16.80	23.60	24.60	23.90	26.10	25.60	1.0
317	33	8	30.10	35.00	38.50	51.60	60.70	60.20	66.40	64.90	64.50	65.00	6.0
318	33	8	49.40	52.90	20.70	27.80	35.50	38.70	47.20	57.90	64.00	73.90	2.0
322	49	8	20.10	28.10	19.40	23.70	26.00	28.30	25.70	27.80	26.70	26.20	6.0
326	23	8	40.60	54.40	13.90	18.00	20.20	19.00	23.90	21.60	19.00	17.90	3.0
328	32	8	19.60	25.70	17.20	20.40	22.40	22.50	23.00	24.50	23.30	24.30	3.0
329	49	8	47.40	67.40	58.00	80.00	80.50	110.20	131.90	147.70	165.20	176.40	4.0
330	63												
331	36												
332	45	5	""43.6	""38.7	""26.5	""29	""31.3	""31.5	""32.7				""2
335	44	6	""42.6	""38.8	""30.4	""46.3	""56.6	""60.2	""59.7	""63.9			""5.5
336	26	8	18.00	17.20	7.00	12.00	12.50	14.10	16.10	18.50	18.90	17.40	2.0
339	69	8	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00	6.0

Appendix 18 continued/...

In the legs of control males			The flux (arbitrary units) was measured during										
		Measurement		During	---Relaxation phase---								time to reach
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
342	62	8	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60	4.0
345	69	8	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20	4.0
347	69	8	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50	5.0
351	62	8	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40	5.0
352	62	8	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20	5.0
353	62	8	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40	6.0

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean	**29.01**	**37.17**	**22.53**	**28.71**	**32.29**	**35.42**	**37.01**	**40.09**	**41.70**	**43.82**	**3.94**
Standard deviation	**12.41**	**16.51**	**14.13**	**18.86**	**20.78**	**24.24**	**29.13**	**32.36**	**36.26**	**39.56**	**1.71**
Median	**26.00**	**33.25**	**17.10**	**21.55**	**24.05**	**25.90**	**25.95**	**28.05**	**29.45**	**27.60**	**4.00**
Minimum	**13.50**	**16.80**	**7.00**	**10.90**	**12.50**	**14.10**	**13.10**	**14.00**	**13.90**	**12.60**	**1.00**
Maximum	**49.40**	**67.40**	**58.00**	**80.00**	**80.50**	**110.20**	**131.90**	**147.70**	**165.20**	**176.40**	**6.00**

Appendix 18 continued/...

In the legs of control males			The %change in flux was measured during										
		Measurement	During	---Relaxation phase---								Slope of %change in flux	
I.D.	Age	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
301	40												
302	37	5	""5.48	""-57.53	""-43.84	""-34.93	""-25.34	""-25.34					
306	40	8	43.66	7.56	19.27	26.83	30.24	0.98	16.34	15.37	49.02	0.22	2.50
310	72	8	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85	2.34	4.69
312	58	8	-11.39	-39.24	-20.25	-18.99	-21.73	-29.54	-25.95	-23.42	-12.24	0.37	1.72
316	51	8	2.21	-41.59	-22.57	-25.66	4.42	8.85	5.75	15.49	13.27	5.11	8.01
317	33	8	16.28	27.91	71.43	101.66	100.00	120.60	115.61	114.29	115.95	12.75	10.63
318	33	8	7.09	-58.10	-43.72	-28.14	-21.66	-4.45	17.21	29.55	49.60	9.64	15.16
322	49	8	39.80	-3.48	17.91	29.35	40.80	27.86	38.31	32.84	30.35	1.84	3.87
326	23	8	33.99	-65.76	-55.67	-50.25	-53.20	-41.13	-46.80	-53.20	-55.91	-4.92	1.23
328	32	8	31.12	-12.24	4.08	14.29	14.80	17.35	25.00	18.88	23.98	1.83	4.31
329	49	8	42.19	22.36	68.78	69.83	132.49	178.27	211.60	248.52	272.15	33.21	37.12
330	63												
331	36												
332	45	5	""-11.24	""-39.22	""-33.49	""-28.21	""-27.75	""-25					
335	44	6	""-8.92	""-28.64	""8.69	""32.86	""41.32	""40.14	""50				
336	26	8	-4.44	-61.11	-33.33	-30.56	-21.67	-10.56	2.78	5.00	-3.33	4.92	8.42
339	69	8	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36	3.48	6.76

Appendix 18 continued/...

In the legs of control males			The %change in flux was measured during										
		Measurement	During	---------Relaxation phase---------								Slope of %change in flux	
I.D.	Age	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
342	62	8	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62	-18.83	-1.15
345	69	8	52.17	-36.02	-32.30	-8.70	4.97	0.00	8.07	25.47	25.47	2.79	9.10
347	69	8	26.90	-13.71	-6.09	-4.57	13.20	-0.51	8.12	-1.02	-1.02	-0.69	1.65
351	62	8	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63	4.13	7.37
352	62	8	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15	21.79	24.77
353	62	8	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71	16.58	16.54

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean	**34.19**	**-22.48**	**-1.99**	**11.64**	**23.36**	**26.21**	**35.80**	**40.35**	**45.00**	**5.36**	**9.04**
Standard deviation	**56.32**	**29.05**	**38.61**	**47.33**	**52.42**	**63.07**	**65.83**	**75.42**	**81.94**	**11.03**	**9.47**
Median	**27.45**	**-21.16**	**-14.73**	**-6.63**	**9.08**	**0.49**	**13.27**	**17.18**	**24.72**	**3.13**	**7.06**
Minimum	**-11.39**	**-65.76**	**-55.67**	**-50.25**	**-53.20**	**-41.13**	**-46.80**	**-53.20**	**-55.91**	**-18.83**	**-1.15**
Maximum	**247.06**	**27.91**	**71.43**	**110.00**	**132.49**	**178.27**	**211.60**	**248.52**	**272.15**	**33.21**	**37.12**

Appendix 18 continued/...

In the legs of control females			The flux (arbitrary units) was measured during										
		Measurement		During	----------Relaxation phase----------								time to reach
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
303	43												
304	65												
305	53												
307	31	8	25.50	40.60	24.50	34.10	27.90	25.40	32.10	38.20	38.50	43.50	2.0
308	28	8	53.20	51.70	39.30	52.30	64.80	72.20	78.90	82.90	87.70	83.30	5.0
309	44	8	55.80	46.70	38.20	55.80	78.60	96.10	111.00	108.00	122.10	127.40	1.0
311	44	8	34.10	40.90	28.30	38.80	45.90	50.10	47.50	53.70	55.20	58.30	4.0
313	69	8	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10	3.0
314	22	8	38.80	38.60	26.30	31.90	35.50	38.00	39.70	40.10	42.80	42.90	4.0
315	22	8	18.30	30.00	15.40	17.40	19.00	26.80	24.70	21.90	22.00	29.20	3.0
319	25	8	12.00	15.80	10.50	13.40	17.20	19.80	23.20	24.30	25.20	27.80	2.0
320	45	8	13.50	18.70	11.40	15.60	20.70	24.90	31.70	37.00	39.50	35.60	2.0
321	47												
323	48	8	13.70	28.20	11.10	12.70	14.20	17.00	18.60	19.10	21.00	23.50	5.0
324	49	8	19.60	27.10	16.60	19.80	26.10	23.50	21.40	22.10	23.90	22.00	8.0
325	39	8	60.40	70.70	31.60	42.60	40.90	45.50	47.90	50.10	44.40	50.40	6.0
327	28												
333	35	8	26.40	32.00	17.30	20.10	22.30	22.90	23.50	23.00	26.90	27.90	3.0
334	44	8	25.40	36.00	24.80	34.00	40.80	47.90	53.70	57.90	62.20	66.50	6.0
337	47	8	27.10	21.80	8.70	11.40	15.50	16.20	17.00	17.50	19.90	19.70	3.0
338	65	8	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50	7.0
340	70	8	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60	3.0
341	71	8	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40	4.0

Appendix 18 continued/...

In the legs of control females			The flux (arbitrary units) was measured during										
		Measurement		During	----------Relaxation phase----------								time to reach
I.D.	Age	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
343	69	8	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20	7.0
344	69	8	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80	4.0
346	74	8	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60	2.0
348	71	8	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30	1.0
349	71	8	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30	3.0
350	68	8	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20	6.0

Number of cases	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**
Mean	**27.31**	**34.22**	**21.35**	**28.30**	**34.80**	**40.05**	**42.72**	**45.93**	**48.47**	**50.58**	**3.92**
Standard deviation	**13.32**	**14.02**	**8.97**	**13.20**	**17.78**	**21.64**	**23.65**	**25.63**	**27.15**	**28.89**	**1.95**
Median	**25.45**	**29.70**	**19.20**	**28.40**	**31.20**	**33.60**	**35.90**	**39.15**	**41.15**	**43.20**	**3.50**
Minimum	**12.00**	**15.80**	**8.70**	**11.40**	**13.50**	**13.10**	**13.70**	**13.90**	**14.20**	**15.80**	**1.00**
Maximum	**60.40**	**70.70**	**39.30**	**55.80**	**78.60**	**96.10**	**111.00**	**108.00**	**122.10**	**127.40**	**8.00**

Appendix 18 continued/...

In the legs of control females			The %change in flux was measured during									Slope of %change in flux	
		Measurement	During	---------Relaxation phase---------									
I.D.	Age	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
303	43												
304	65												
305	53												
307	31	8	59.22	-3.92	33.73	9.41	-0.39	25.88	49.80	50.98	70.59	4.31	8.99
308	28	8	-2.82	-26.13	-1.69	21.80	35.71	48.31	55.83	64.85	56.58	10.87	12.22
309	44	8	-16.31	-31.54	0.00	40.86	72.22	98.92	93.55	118.82	128.32	21.25	22.59
311	44	8	19.94	-17.01	13.78	34.60	46.92	39.30	57.48	61.88	70.97	8.88	10.92
313	69	8	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74	7.81	12.03
314	22	8	-0.52	-32.22	-17.78	-8.51	-2.06	2.32	3.35	10.31	10.57	3.75	5.71
315	22	8	63.93	-15.85	-4.92	3.83	46.45	34.97	19.67	20.22	59.56	2.85	8.21
319	25	8	31.67	-12.50	11.67	43.33	65.00	93.33	102.50	110.00	131.67	16.65	20.32
320	45	8	38.52	-15.56	15.56	53.33	84.44	134.81	174.07	192.59	163.70	25.39	30.39
321	47												
323	48	8	105.84	-18.98	-7.30	3.65	24.09	35.77	39.42	53.28	71.53	3.42	12.57
324	49	8	38.27	-15.31	1.02	33.16	19.90	9.18	12.76	21.94	12.24	0.12	2.68
325	39	8	17.05	-47.68	-29.47	-32.28	-24.67	-20.70	-17.05	-26.49	-16.56	-0.57	3.36
327	28												
333	35	8	21.21	-34.47	-23.86	-15.53	-13.26	-10.98	-12.88	1.89	5.68	1.22	5.00
334	44	8	41.73	-2.36	33.86	60.63	88.58	111.42	127.95	144.88	161.81	19.35	22.97
337	47	8	-19.56	-67.90	-57.93	-42.80	-40.22	-37.27	-35.42	-26.57	-27.31	2.39	5.55
338	65	8	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59	7.10	11.28
340	70	8	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48	40.15	45.31

Appendix 18 continued/...

In the legs of control females			The %change in flux was measured during										
		Measurement	During	--Relaxation phase-------------------------------------								Slope of %change in flux	
I.D.	Age	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
341	71	8	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88	10.82	13.22
343	69	8	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13	21.52	28.51
344	69	8	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-0.70	10.49	-5.15	-0.80
346	74	8	19.72	18.31	15.96	20.66	24.88	37.09	32.86	67.61	67.14	6.46	7.72
348	71	8	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54	16.82	19.60
349	71	8	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80	33.22	35.90
350	68	8	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46	28.58	31.65
Number of cases			**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**
Mean			**34.72**	**-16.21**	**7.60**	**32.72**	**52.97**	**62.69**	**76.56**	**87.10**	**94.78**	**11.97**	**15.66**
Standard deviation			**42.24**	**27.09**	**32.31**	**48.47**	**61.40**	**63.81**	**82.30**	**86.97**	**88.21**	**11.69**	**11.82**
Median			**26.44**	**-16.43**	**3.33**	**23.72**	**46.68**	**42.21**	**56.65**	**66.23**	**70.78**	**8.35**	**12.12**
Minimum			**-19.56**	**-67.90**	**-57.93**	**-42.80**	**-40.22**	**-37.27**	**-35.42**	**-26.57**	**-27.31**	**-5.15**	**-0.80**
Maximum			**131.62**	**36.18**	**82.13**	**156.18**	**177.66**	**169.10**	**291.57**	**335.39**	**313.48**	**40.15**	**45.31**

Appendix 19

The effects of age on the cutaneous microcirculation during extension/relaxation, measured in the forearms of asymptomatic controls

Changes in the cutaneous microcirculation measured in the forearms of young (21-40Y)controls

				The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
			Measurement		During	----------------Relaxation phase------------				time to reach	During	-----------Relaxation phase----------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
301	40	male	4	39.00	33.10	30.40	42.50	54.90	60.70	1.0	-15.13	-22.05	8.97	40.77	55.64	20.44	26.49
302	37	male	4	30.60	35.70	43.90	54.50	61.50	69.40	8.0	16.67	43.46	78.10	100.98	126.80	27.78	27.29
306	40	male	4	40.60	64.60	27.40	34.10	37.90	39.60	6.5	59.11	-32.51	-16.01	-6.65	-2.46	-9.73	9.95
307	31	female	4	47.90	49.20	35.70	54.90	69.20	77.50	4.5	2.71	-25.47	14.61	44.47	61.80	18.81	29.17
308	28	female	4	42.00	60.20	71.30	89.80	107.50	122.70	1.0	43.33	69.76	113.81	155.95	192.14	38.38	40.93
314	22	female	4	19.20	37.10	35.40	36.00	39.00	39.70	7.0	93.23	84.38	87.50	103.13	106.77	4.58	8.28
315	22	female	4	28.20	41.40	32.00	41.10	41.70	38.70	1.5	46.81	13.48	45.74	47.87	37.23	1.52	7.34
317	33	male	4	188.50	188.40	138.60	163.90	181.70	194.10	4.0	-0.05	-26.47	-13.05	-3.61	2.97	2.89	9.78
318	33	male	4	33.00	41.90	70.50	99.30	110.30	87.10	8.0	26.97	113.64	200.91	234.24	163.94	39.45	18.42
319	25	female	4	24.70	30.70	40.80	63.80	77.20	88.30	6.0	24.29	65.18	158.30	212.55	257.49	61.38	63.12
325	39	female	4	33.00	35.10	41.00	52.60	46.10	44.50	2.0	6.36	24.24	59.39	39.70	34.85	7.24	1.21
326	23	male	4	15.30	19.90	23.20	25.40	25.10	25.40	7.0	30.07	51.63	66.01	64.05	66.01	8.43	4.12
327	28	female	4	52.90	69.80	71.40	90.30	108.60	121.70	1.0	31.95	34.97	70.70	105.29	130.06	26.65	31.99
328	32	male	4	61.10	69.80	78.10	93.90	93.90	90.70	5.0	14.24	27.82	53.68	53.68	48.45	9.43	6.19
331	36	male	4	13.30	20.90	15.10	18.90	20.60	21.50	5.0	57.14	13.53	42.11	54.89	61.65	5.04	15.71
333	35	female	4	32.10	38.70	35.00	66.10	68.80	81.30	7.0	20.56	9.03	105.92	114.33	153.27	37.07	44.11
336	26	male															
Number of cases				**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean				**43.84**	**52.28**	**49.36**	**64.19**	**71.50**	**75.18**	**4.66**	**28.64**	**27.79**	**67.29**	**85.10**	**93.54**	**18.71**	**21.51**
Standard deviation				**40.72**	**39.53**	**30.51**	**36.49**	**41.40**	**44.39**	**2.61**	**26.85**	**42.64**	**58.45**	**68.82**	**72.12**	**18.60**	**17.29**
Median				**33.00**	**40.05**	**38.25**	**54.70**	**65.15**	**73.45**	**5.00**	**25.63**	**26.03**	**62.70**	**59.47**	**63.90**	**14.12**	**17.07**
Minimum				**13.30**	**19.90**	**15.10**	**18.90**	**20.60**	**21.50**	**1.00**	**-15.13**	**-32.51**	**-16.01**	**-6.65**	**-2.46**	**-9.73**	**1.21**
Maximum				**188.50**	**188.40**	**138.60**	**163.90**	**181.70**	**194.10**	**8.00**	**93.23**	**113.64**	**200.91**	**234.24**	**257.49**	**61.38**	**63.12**

Appendix 19 continued/...

Changes in the cutaneous microcirculation measured in the forearms of middle-aged (41-60Y)controls																	
				The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
			Measurement		During	---------------Relaxation phase------------				time to reach	During	-----------Relaxation phase---------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
303	43	female	4	50.60	41.60	16.80	22.50	26.30	27.80	0.5	-17.79	-66.80	-55.53	-48.02	-45.06	-3.58	7.27
305	53	female	4	19.00	40.90	43.00	49.20	59.70	55.70	8.0	115.26	126.32	158.95	214.21	193.16	24.37	25.58
309	44	female	4	33.10	36.00	33.10	32.70	39.10	43.00	7.0	8.76	0.00	-1.21	18.13	29.91	6.04	10.91
311	44	female	4	54.60	60.00	58.30	58.20	57.70	56.80	5.0	9.89	6.78	6.59	5.68	4.03	-1.28	-0.92
312	58	male	4	22.70	37.10	50.00	51.70	55.30	56.00	6.0	63.44	120.26	127.75	143.61	146.70	18.99	9.52
316	51	male	4	35.40	54.00	32.20	29.50	28.90	30.90	3.0	52.54	-9.04	-16.67	-18.36	-12.71	-13.98	-1.27
320	45	female	4	9.50	17.30	22.00	28.50	26.90	27.70	1.0	82.11	131.58	200.00	183.16	191.58	27.05	16.32
321	47	female	4	21.20	53.20	16.40	23.20	28.30	31.80	5.0	150.94	-22.64	9.43	33.49	50.00	-14.58	24.20
322	49	male	4	32.10	56.40	53.70	70.40	71.30	77.10	3.0	75.70	67.29	119.31	122.12	140.19	18.38	22.15
323	48	female	4	13.50	31.10	31.20	37.40	38.00	36.40	4.0	130.37	131.11	177.04	181.48	169.63	12.89	12.00
324	49	female	4	13.30	20.10	23.30	32.80	44.60	38.60	3.0	51.13	75.19	146.62	235.34	190.23	43.84	43.38
329	49	male	4	65.70	88.70	59.90	74.40	93.80	97.10	1.0	35.01	-8.83	13.24	42.77	47.79	7.72	19.94
332	45	male	3	""58.6	""71.7	""69.2	""59.4	""46.3		""7	""22.36	""18.09	""1.37	""-20.99			
334	44	female	4	22.90	28.80	31.70	38.90	41.40	42.90	7.0	25.76	38.43	69.87	80.79	87.34	16.55	15.77
335	44	male															
337	47	female															

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**
Mean	**30.28**	**43.48**	**36.28**	**42.26**	**47.02**	**47.83**	**4.12**	**60.24**	**45.36**	**73.49**	**91.88**	**91.75**	**10.95**	**15.76**
Standard deviation	**17.37**	**19.14**	**15.28**	**17.17**	**20.03**	**20.63**	**2.47**	**50.12**	**67.71**	**85.15**	**94.00**	**84.76**	**16.69**	**11.92**
Median	**22.90**	**40.90**	**32.20**	**37.40**	**41.40**	**42.90**	**4.00**	**52.54**	**38.43**	**69.87**	**80.79**	**87.34**	**12.89**	**15.77**
Minimum	**9.50**	**17.30**	**16.40**	**22.50**	**26.30**	**27.70**	**0.50**	**-17.79**	**-66.80**	**-55.53**	**-48.02**	**-45.06**	**-14.58**	**-1.27**
Maximum	**65.70**	**88.70**	**59.90**	**74.40**	**93.80**	**97.10**	**8.00**	**150.94**	**131.58**	**200.00**	**235.34**	**193.16**	**43.84**	**43.38**

Appendix 19 continued/...

Changes in the cutaneous microcirculation measured in the forearms of elderly (61-90Y)controls

				The flux (arbitrary units) was measured during							The %chnge in flux was measured during						
			Measurement		During	----------------Relaxation phase-------------				time to reach	During	------------Relaxation phase----------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
304	65	female	4	63.50	67.30	68.90	87.80	91.00	91.60	8.0	5.98	8.50	38.27	43.31	44.25	11.14	11.23
310	72	male	4	34.00	38.40	41.70	37.50	37.30	37.90	7.0	12.94	22.65	10.29	9.71	11.47	-1.59	-3.41
313	69	female	4	34.60	51.90	37.80	40.20	42.10	45.40	7.0	50.00	9.25	16.18	21.68	31.21	-2.52	7.14
330	63	male	4	38.00	49.50	37.00	46.30	41.40	44.40	5.0	30.26	-2.63	21.84	8.95	16.84	-1.53	4.55
338	65	female	4	40.20	55.30	38.30	35.60	34.80	33.40	1.0	37.56	-4.73	-11.44	-13.43	-16.92	-11.77	-3.86
339	69	male	4	31.70	45.70	26.50	31.50	41.70	44.90	6.0	44.16	-16.40	-0.63	31.55	41.64	4.29	20.63
340	70	female	4	24.60	30.70	22.10	28.30	31.70	29.80	4.0	24.80	-10.16	15.04	28.86	21.14	3.17	10.77
341	71	female	4	60.40	73.70	52.90	51.30	59.60	62.40	4.0	22.02	-12.42	-15.07	-1.32	3.31	-2.63	6.09
342	62	male	4	44.40	46.00	45.30	59.10	57.00	72.20	8.0	3.60	2.03	33.11	28.38	62.61	14.44	17.70
343	69	female	4	20.50	24.40	26.90	28.10	34.20	36.20	4.0	19.02	31.22	37.07	66.83	76.59	15.08	16.59
344	69	female	4	20.20	21.90	19.40	21.10	17.20	22.00	1.0	8.42	-3.96	4.46	-14.85	8.91	-0.99	1.93
345	69	male	4	87.90	100.50	88.50	76.00	65.00	76.30	6.0	14.33	0.68	-13.54	-26.05	-13.20	-8.18	-5.42
346	74	female	4	23.20	32.30	34.40	42.80	52.40	75.30	2.0	39.22	48.28	84.48	125.86	224.57	44.83	57.03
347	69	male	4	39.60	47.50	45.60	41.50	39.80	41.80	3.0	19.95	15.15	4.80	0.51	5.56	-4.34	-3.31
348	71	female	4	68.00	67.50	100.20	114.80	107.90	108.40	8.0	-0.74	47.35	68.82	58.68	59.41	13.16	2.60
349	71	female	4	156.50	146.50	118.40	135.30	154.00	174.10	3.0	-6.39	-24.35	-13.55	-1.60	11.25	5.80	11.88
350	68	female	4	68.60	72.30	85.10	94.00	98.70	101.20	7.0	5.39	24.05	37.03	43.88	47.52	10.41	7.73
351	62	male	4	29.70	33.50	38.00	43.80	56.60	45.30	4.0	12.79	27.95	47.47	90.57	52.53	14.21	11.68
352	62	male	4	29.10	37.30	32.50	41.70	51.40	44.60	3.0	28.18	11.68	43.30	76.63	53.26	11.51	15.81
353	62	male	4	26.30	33.60	39.90	44.60	44.00	45.80	2.0	1.92	3.58	4.81	4.66	5.13	0.75	0.45
Number of cases				**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Mean				**47.05**	**53.79**	**49.97**	**55.07**	**57.89**	**61.65**	**4.65**	**18.67**	**8.89**	**20.64**	**29.14**	**37.35**	**5.76**	**9.39**
Standard deviation				**31.88**	**29.27**	**27.57**	**30.74**	**32.27**	**35.87**	**2.35**	**15.77**	**19.93**	**27.77**	**39.09**	**51.28**	**12.20**	**13.61**
Median				**36.30**	**46.75**	**39.10**	**43.30**	**47.70**	**45.35**	**4.00**	**16.68**	**6.04**	**15.61**	**25.03**	**26.18**	**3.73**	**7.43**
Minimum				**20.20**	**21.90**	**19.40**	**21.10**	**17.20**	**22.00**	**1.00**	**-6.39**	**-24.35**	**-15.07**	**-26.05**	**-16.92**	**-11.77**	**-5.42**
Maximum				**156.50**	**146.50**	**118.40**	**135.30**	**154.00**	**174.10**	**8.00**	**50.00**	**48.28**	**84.48**	**125.86**	**224.57**	**44.83**	**57.03**

Appendix 20

The effects of age on the cutaneous microcirculation during extension/relaxation, measured at the legs of asymptomatic controls

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) controls

The flux (arbitrary units) was measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
301	40	male												
302	37	male	5	""14.6	""15.4	""6.2	""8.2	""9.5	""10.9	""10.9				""2.5
306	40	male	8	41.00	58.90	44.10	48.90	52.00	53.40	41.40	47.70	47.30	61.10	
307	31	female	8	25.50	40.60	24.50	34.10	27.90	25.40	32.10	38.20	38.50	43.50	2.00
308	28	female	8	53.20	51.70	39.30	52.30	64.80	72.20	78.90	82.90	87.70	83.30	5.00
314	22	female	8	38.80	38.60	26.30	31.90	35.50	38.00	39.70	40.10	42.80	42.90	4.00
315	22	female	8	18.30	30.00	15.40	17.40	19.00	26.80	24.70	21.90	22.00	29.20	3.00
317	33	male	8	30.10	35.00	38.50	51.60	60.70	60.20	66.40	64.90	64.50	65.00	6.00
318	33	male	8	49.40	52.90	20.70	27.80	35.50	38.70	47.20	57.90	64.00	73.90	2.00
319	25	female	8	12.00	15.80	10.50	13.40	17.20	19.80	23.20	24.30	25.20	27.80	2.00
325	39	female	8	60.40	70.70	31.60	42.60	40.90	45.50	47.90	50.10	44.40	50.40	6.00
326	23	male	8	40.60	54.40	13.90	18.00	20.20	19.00	23.90	21.60	19.00	17.90	3.00
327	28	female												
328	32	male	8	19.60	25.70	17.20	20.40	22.40	22.50	23.00	24.50	23.30	24.30	3.00
331	36	male												
333	35	female	8	26.40	32.00	17.30	20.10	22.30	22.90	23.50	23.00	26.90	27.90	3.00
336	26	male	8	18.00	17.20	7.00	12.00	12.50	14.10	16.10	18.50	18.90	17.40	2.00

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**
Mean	**33.33**	**40.27**	**23.56**	**30.04**	**33.15**	**35.27**	**37.54**	**39.66**	**40.35**	**43.43**	**3.42**
Standard deviation	**15.14**	**16.61**	**11.76**	**14.71**	**17.07**	**17.97**	**18.75**	**20.10**	**21.24**	**21.85**	**1.51**
Median	**30.10**	**38.60**	**20.70**	**27.80**	**27.90**	**26.80**	**32.10**	**38.20**	**38.50**	**42.90**	**3.00**
Minimum	**12.00**	**15.80**	**7.00**	**12.00**	**12.50**	**14.10**	**16.10**	**18.50**	**18.90**	**17.40**	**2.00**
Maximum	**60.40**	**70.70**	**44.10**	**52.30**	**64.80**	**72.20**	**78.90**	**82.90**	**87.70**	**83.30**	**6.00**

Appendix 20 continued/...

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) controls

The %chnge in flux was measured

I.D.	Age	Sex	Measurement duration (min)	During extension	----during relaxation phase---- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
301	40	male												
302	37	male	5	""5.48	""-57.53	""-43.84	""-34.93	""-25.34	""-25.34					
306	40	male	8	43.66	7.56	19.27	26.83	30.24	0.98	16.34	15.37	49.02	0.22	2.50
307	31	female	8	59.22	-3.92	33.73	9.41	-0.39	25.88	49.80	50.98	70.59	4.31	8.99
308	28	female	8	-2.82	-26.13	-1.69	21.80	35.71	48.31	55.83	64.85	56.58	10.87	12.22
314	22	female	8	-0.52	-32.22	-17.78	-8.51	-2.06	2.32	3.35	10.31	10.57	3.75	5.71
315	22	female	8	63.93	-15.85	-4.92	3.83	46.45	34.97	19.67	20.22	59.56	2.85	8.21
317	33	male	8	16.28	27.91	71.43	101.66	100.00	120.60	115.61	114.29	115.95	12.75	10.63
318	33	male	8	7.09	-58.10	-43.72	-28.14	-21.66	-4.45	17.21	29.55	49.60	9.64	15.16
319	25	female	8	31.67	-12.50	11.67	43.33	65.00	93.33	102.50	110.00	131.67	16.65	20.32
325	39	female	8	17.05	-47.68	-29.47	-32.28	-24.67	-20.70	-17.05	-26.49	-16.56	-0.57	3.36
326	23	male	8	33.99	-65.76	-55.67	-50.25	-53.20	-41.13	-46.80	-53.20	-55.91	-4.92	1.23
327	28	female												
328	32	male	8	31.12	-12.24	4.08	14.29	14.80	17.35	25.00	18.88	23.98	1.83	4.31
331	36	male												
333	35	female	8	21.21	-34.47	-23.86	-15.53	-13.26	-10.98	-12.88	1.89	5.68	1.22	5.00
336	26	male	8	-4.44	-61.11	-33.33	-30.56	-21.67	-10.56	2.78	5.00	-3.33	4.92	8.42

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	During extension	1min	2min	3min	4min	5min	6min	7min	8min	Slope (ext-8min)	Slope (1min-8min)
Number of cases	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**
Mean	**24.42**	**-25.73**	**-5.41**	**4.30**	**11.95**	**19.69**	**25.49**	**27.82**	**38.26**	**4.89**	**8.16**
Standard deviation	**22.29**	**28.01**	**34.50**	**39.88**	**42.32**	**45.76**	**45.88**	**47.83**	**52.02**	**6.02**	**5.43**
Median	**21.21**	**-26.13**	**-4.92**	**3.83**	**-0.39**	**2.32**	**17.21**	**18.88**	**49.02**	**3.75**	**8.21**
Minimum	**-4.44**	**-65.76**	**-55.67**	**-50.25**	**-53.20**	**-41.13**	**-46.80**	**-53.20**	**-55.91**	**-4.92**	**1.23**
Maximum	**63.93**	**27.91**	**71.43**	**101.66**	**100.00**	**120.60**	**115.61**	**114.29**	**131.67**	**16.65**	**20.32**

Appendix 20 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) controls

The flux (arbitrary units) was measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
303	43	female												
305	53	female												
309	44	female	8	55.80	46.70	38.20	55.80	78.60	96.10	111.00	108.00	122.10	127.40	1.00
311	44	female	8	34.10	40.90	28.30	38.80	45.90	50.10	47.50	53.70	55.20	58.30	4.00
312	58	male	8	47.40	42.00	28.80	37.80	38.40	37.10	33.40	35.10	36.30	41.60	4.00
316	51	male	8	22.60	23.10	13.20	17.50	16.80	23.60	24.60	23.90	26.10	25.60	1.00
320	45	female	8	13.50	18.70	11.40	15.60	20.70	24.90	31.70	37.00	39.50	35.60	2.00
321	47	female												
322	49	male	8	20.10	28.10	19.40	23.70	26.00	28.30	25.70	27.80	26.70	26.20	6.00
323	48	female	8	13.70	28.20	11.10	12.70	14.20	17.00	18.60	19.10	21.00	23.50	5.00
324	49	female	8	19.60	27.10	16.60	19.80	26.10	23.50	21.40	22.10	23.90	22.00	8.00
329	49	male	8	47.40	67.40	58.00	80.00	80.50	110.20	131.90	147.70	165.20	176.40	4.00
332	45	male	5	""43.6	""38.7	""26.5	""29	""31.3	""31.5	""32.7				""2
334	44	female	8	25.40	36.00	24.80	34.00	40.80	47.90	53.70	57.90	62.20	66.50	6.00
335	44	male	6	""42.6	""38.8	""30.4	""46.3	""56.6	""60.2	""59.7	""63.9			""5.5
337	47	female	8	27.10	21.80	8.70	11.40	15.50	16.20	17.00	17.50	19.90	19.70	3.00

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
Mean	**29.70**	**34.55**	**23.50**	**31.55**	**36.68**	**43.17**	**46.95**	**49.98**	**54.37**	**56.62**	**4.00**
Standard deviation	**14.54**	**14.17**	**14.66**	**21.09**	**23.69**	**31.84**	**38.84**	**41.64**	**47.20**	**50.67**	**2.19**
Median	**25.40**	**28.20**	**19.40**	**23.70**	**26.10**	**28.30**	**31.70**	**35.10**	**36.30**	**35.60**	**4.00**
Minimum	**13.50**	**18.70**	**8.70**	**11.40**	**14.20**	**16.20**	**17.00**	**17.50**	**19.90**	**19.70**	**1.00**
Maximum	**55.80**	**67.40**	**58.00**	**80.00**	**80.50**	**110.20**	**131.90**	**147.70**	**165.20**	**176.40**	**8.00**

Appendix 20 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) controls

The %chnge in flux was measured during

I.D.	Age	Sex	Measurement duration (min)	During extension	--during relaxation phase-- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
303	43	female												
305	53	female												
309	44	female	8	-16.31	-31.54	0.00	40.86	72.22	98.92	93.55	118.82	128.32	21.25	22.59
311	44	female	8	19.94	-17.01	13.78	34.60	46.92	39.30	57.48	61.88	70.97	8.88	10.92
312	58	male	8	-11.39	-39.24	-20.25	-18.99	-21.73	-29.54	-25.95	-23.42	-12.24	0.37	1.72
316	51	male	8	2.21	-41.59	-22.57	-25.66	4.42	8.85	5.75	15.49	13.27	5.11	8.01
320	45	female	8	38.52	-15.56	15.56	53.33	84.44	134.81	174.07	192.59	163.70	25.39	30.39
321	47	female												
322	49	male	8	39.80	-3.48	17.91	29.35	40.80	27.86	38.31	32.84	30.35	1.84	3.87
323	48	female	8	105.84	-18.98	-7.30	3.65	24.09	35.77	39.42	53.28	71.53	3.42	12.57
324	49	female	8	38.27	-15.31	1.02	33.16	19.90	9.18	12.76	21.94	12.24	0.12	2.68
329	49	male	8	42.19	22.36	68.78	69.83	132.49	178.27	211.60	248.52	272.15	33.21	37.12
332	45	male	5	""-11.24	""-39.22	""-33.49	""-28.21	""-27.75	""-25					
334	44	female	8	41.73	-2.36	33.86	60.63	88.58	111.42	127.95	144.88	161.81	19.35	22.97
335	44	male	6	""-8.92	""-28.64	""8.69	""32.86	""41.32	""40.14	""50				
337	47	female	8	-19.56	-67.90	-57.93	-42.80	-40.22	-37.27	-35.42	-26.57	-27.31	2.39	5.55

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
Mean	**25.57**	**-20.96**	**3.90**	**21.63**	**41.08**	**52.51**	**63.59**	**76.39**	**80.44**	**11.03**	**14.40**
Standard deviation	**36.39**	**23.84**	**32.85**	**37.34**	**51.12**	**69.18**	**80.10**	**89.16**	**92.00**	**11.67**	**12.07**
Median	**38.27**	**-17.01**	**1.02**	**33.16**	**40.80**	**35.77**	**39.42**	**53.28**	**70.97**	**5.11**	**10.92**
Minimum	**-19.56**	**-67.90**	**-57.93**	**-42.80**	**-40.22**	**-37.27**	**-35.42**	**-26.57**	**-27.31**	**0.12**	**1.72**
Maximum	**105.84**	**22.36**	**68.78**	**69.83**	**132.49**	**178.27**	**211.60**	**248.52**	**272.15**	**33.21**	**37.12**

Appendix 20 continued/…

Changes in the cutaneous microcirculation were measured in the legs of elderly (61-90Y) controls

The flux (arbitrary units) was measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
304	65	female												
310	72	male	8	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00	1.00
313	69	female	8	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10	3.00
330	63	male												
338	65	female	8	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50	7.00
339	69	male	8	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00	6.00
340	70	female	8	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60	3.00
341	71	female	8	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40	4.00
342	62	male	8	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60	4.00
343	69	female	8	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20	7.00
344	69	female	8	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80	4.00
345	69	male	8	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20	4.00
346	74	female	8	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60	2.00
347	69	male	8	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50	5.00
348	71	female	8	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30	1.00
349	71	female	8	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30	3.00
350	68	female	8	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20	6.00
351	62	male	8	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40	5.00
352	62	male	8	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20	5.00
353	62	male	8	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40	6.00
Number of cases				**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean				**23.21**	**32.60**	**19.63**	**25.47**	**32.34**	**36.96**	**38.16**	**42.13**	**43.96**	**45.29**	**4.22**
Standard deviation				**7.85**	**14.29**	**8.72**	**12.63**	**17.89**	**19.63**	**21.20**	**24.71**	**25.26**	**28.34**	**1.83**
Median				**19.80**	**29.25**	**17.25**	**23.70**	**25.65**	**29.15**	**30.20**	**32.70**	**35.75**	**35.90**	**4.00**
Minimum				**13.50**	**16.80**	**10.30**	**10.90**	**13.50**	**13.10**	**13.10**	**13.90**	**13.90**	**12.60**	**1.00**
Maximum				**38.40**	**67.40**	**42.20**	**55.80**	**73.50**	**80.80**	**75.50**	**83.00**	**84.70**	**111.20**	**7.00**

Appendix 20 continued/...

Changes in the cutaneous microcirculation were measured in the legs of elderly (61-90Y) controls

I.D.	Age	Sex	Measurement duration (min)	The %chnge in flux was measured during: During extension	---during relaxation phase--- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
304	65	female												
310	72	male	8	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85	2.34	4.69
313	69	female	8	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74	7.81	12.03
330	63	male												
338	65	female	8	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59	7.10	11.28
339	69	male	8	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36	3.48	6.76
340	70	female	8	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48	40.15	45.31
341	71	female	8	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88	10.82	13.22
342	62	male	8	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62	-18.83	-1.15
343	69	female	8	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13	21.52	28.51
344	69	female	8	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-0.70	10.49	-5.15	-0.80
345	69	male	8	52.17	-36.02	-32.30	-8.70	4.97	0.00	8.07	25.47	25.47	2.79	9.10
346	74	female	8	19.72	18.31	15.96	20.66	24.88	37.09	32.86	67.61	67.14	6.46	7.72
347	69	male	8	26.90	-13.71	-6.09	-4.57	13.20	-0.51	8.12	-1.02	-1.02	-0.69	1.65
348	71	female	8	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54	16.82	19.60
349	71	female	8	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80	33.22	35.90
350	68	female	8	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46	28.58	31.65
351	62	male	8	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63	4.13	7.37
352	62	male	8	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15	21.79	24.77
353	62	male	8	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71	16.58	16.54
Number of cases				**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean				**47.22**	**-12.70**	**9.67**	**38.93**	**60.26**	**63.49**	**80.61**	**89.71**	**94.58**	**11.05**	**15.23**
Standard deviation				**64.47**	**29.88**	**37.18**	**56.64**	**67.38**	**71.56**	**88.75**	**95.79**	**101.98**	**14.40**	**13.21**
Median				**27.45**	**-20.20**	**-0.23**	**20.84**	**41.72**	**41.11**	**55.80**	**70.98**	**68.44**	**7.46**	**11.65**
Minimum				**-19.24**	**-62.06**	**-32.30**	**-25.78**	**-18.23**	**-29.95**	**-25.13**	**-25.67**	**-32.62**	**-18.83**	**-1.15**
Maximum				**247.06**	**36.18**	**82.13**	**156.18**	**177.66**	**169.10**	**291.57**	**335.39**	**313.48**	**40.15**	**45.31**

Appendix 21

The effects of age and sex on the cutaneous microcirculation during extension/relaxation, measured at the forearms of asymptomatic controls

Changes in the cutaneous microcirculation measured in the forearms of young (21-40Y) male controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
			Measurement	at	During	------------during relaxation phase--------				time to reach	During	-------during relaxation phase-------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
301	40	male	4	39.00	33.10	30.40	42.50	54.90	60.70	1.0	-15.13	-22.05	8.97	40.77	55.64	20.44	26.49
302	37	male	4	30.60	35.70	43.90	54.50	61.50	69.40	8.0	16.67	43.46	78.10	100.98	126.80	27.78	27.29
306	40	male	4	40.60	64.60	27.40	34.10	37.90	39.60	6.5	59.11	-32.51	-16.01	-6.65	-2.46	-9.73	9.95
317	33	male	4	188.50	188.40	138.60	163.90	181.70	194.10	4.0	-0.05	-26.47	-13.05	-3.61	2.97	2.89	9.78
318	33	male	4	33.00	41.90	70.50	99.30	110.30	87.10	8.0	26.97	113.64.	200.91	234.24	163.94	39.45	18.42
326	23	male	4	15.30	19.90	23.20	25.40	25.10	25.40	7.0	30.07	51.63	66.01	64.05	66.01	8.43	4.12
328	32	male	4	61.10	69.80	78.10	93.90	93.90	90.70	5.0	14.24	27.82	53.68	53.68	48.45	9.43	6.19
331	36	male	4	13.30	20.90	15.10	18.90	20.60	21.50	5.0	57.14	13.53	42.11	54.89	61.65	5.04	15.71
336	26	male															
Number of cases				**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean				**52.68**	**59.29**	**53.40**	**66.56**	**73.24**	**73.56**	**5.56**	**23.63**	**21.13**	**52.59**	**67.29**	**65.37**	**12.97**	**14.74**
Standard deviation				**56.91**	**55.26**	**41.12**	**49.34**	**53.95**	**55.26**	**2.35**	**25.73**	**49.42**	**69.55**	**76.12**	**56.54**	**15.53**	**8.81**
Median				**36.00**	**38.80**	**37.15**	**48.50**	**58.20**	**65.05**	**5.75**	**21.82**	**20.68**	**47.89**	**54.28**	**58.65**	**8.93**	**12.83**
Minimum				**13.30**	**19.90**	**15.10**	**18.90**	**20.60**	**21.50**	**1.00**	**-15.13**	**-32.51**	**-16.01**	**-6.65**	**-2.46**	**-9.73**	**4.12**
Maximum				**188.50**	**188.40**	**138.60**	**163.90**	**181.70**	**194.10**	**8.00**	**59.11**	**113.64**	**200.91**	**234.24**	**163.94**	**39.45**	**27.29**

Appendix 21 continued/...

Changes in the cutaneous microcirculation measured in the forearms of young (21-40Y) female controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
			Measurement	at	During	------------during relaxation phase--------				time to reach	During	--------during relaxation phase-------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
307	31	female	4	47.90	49.20	35.70	54.90	69.20	77.50	4.5	2.71	-25.47	14.61	44.47	61.80	18.81	29.17
308	28	female	4	42.00	60.20	71.30	89.80	107.50	122.70	1.0	43.33	69.76	113.81	155.95	192.14	38.38	40.93
314	22	female	4	19.20	37.10	35.40	36.00	39.00	39.70	7.0	93.23	84.38	87.50	103.13	106.77	4.58	8.28
315	22	female	4	28.20	41.40	32.00	41.10	41.70	38.70	1.5	46.81	13.48	45.74	47.87	37.23	1.52	7.34
319	25	female	4	24.70	30.70	40.80	63.80	77.20	88.30	6.0	24.29	65.18	158.30	212.55	257.49	61.38	63.12
325	39	female	4	33.00	35.10	41.00	52.60	46.10	44.50	2.0	6.36	24.24	59.39	39.70	34.85	7.24	1.21
327	28	female	4	52.90	69.80	71.40	90.30	108.60	121.70	1.0	31.95	34.97	70.70	105.29	130.06	26.65	31.99
333	35	female	4	32.10	38.70	35.00	66.10	68.80	81.30	7.0	20.56	9.03	105.92	114.33	153.27	37.07	44.11
Number of cases				**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean				**35.00**	**45.28**	**45.33**	**61.83**	**69.76**	**76.80**	**3.75**	**33.66**	**34.45**	**82.00**	**102.91**	**121.70**	**24.46**	**28.27**
Standard deviation				**11.65**	**13.53**	**16.34**	**20.16**	**27.47**	**34.12**	**2.67**	**28.74**	**36.77**	**44.61**	**60.25**	**78.34**	**20.60**	**21.41**
Median				**32.55**	**40.05**	**38.25**	**59.35**	**69.00**	**79.40**	**3.25**	**28.12**	**29.61**	**79.10**	**104.21**	**118.41**	**22.73**	**30.58**
Minimum				**19.20**	**30.70**	**32.00**	**36.00**	**39.00**	**38.70**	**1.00**	**2.71**	**-25.47**	**14.61**	**39.70**	**34.85**	**1.52**	**1.21**
Maximum				**52.90**	**69.80**	**71.40**	**90.30**	**108.60**	**122.70**	**7.00**	**93.23**	**84.38**	**158.30**	**212.55**	**257.49**	**61.38**	**63.12**

Appendix 21 continued/...

Changes in the cutaneous microcirculation measured in the forearms of middle-aged (41-60Y) male controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
			Measurement	at	During	------------during relaxation phase---------				time to reach	During	--------during relaxation phase-------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
312	58	male	4	22.70	37.10	50.00	51.70	55.30	56.00	6.0	63.44	120.26	127.75	143.61	146.70	18.99	9.52
316	51	male	4	35.40	54.00	32.20	29.50	28.90	30.90	3.0	52.54	-9.04	-16.67	-18.36	-12.71	-13.98	-1.27
322	49	male	4	32.10	56.40	53.70	70.40	71.30	77.10	3.0	75.70	67.29	119.31	122.12	140.19	18.38	22.15
329	49	male	4	65.70	88.70	59.90	74.40	93.80	97.10	1.0	35.01	-8.83	13.24	42.77	47.79	7.72	19.94
332	45	male	3	""58.6	""71.7	""69.2	""59.4	""46.3		""7	""22.36	""18.09	""1.37	""-20.99			
335	44	male															

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases				**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Mean				**38.98**	**59.05**	**48.95**	**56.50**	**62.33**	**65.28**	**3.25**	**56.67**	**42.42**	**60.91**	**72.53**	**80.49**	**7.78**	**12.58**
Standard deviation				**18.61**	**21.55**	**11.89**	**20.54**	**27.31**	**28.40**	**2.06**	**17.27**	**63.12**	**73.42**	**74.52**	**76.82**	**15.40**	**10.75**
Median				**33.75**	**55.20**	**51.85**	**61.05**	**63.30**	**66.55**	**3.00**	**57.99**	**29.23**	**66.28**	**82.44**	**93.99**	**13.05**	**14.73**
Minimum				**22.70**	**37.10**	**32.20**	**29.50**	**28.90**	**30.90**	**1.00**	**35.01**	**-9.04**	**-16.67**	**-18.36**	**-12.71**	**-13.98**	**-1.27**
Maximum				**65.70**	**88.70**	**59.90**	**74.40**	**93.80**	**97.10**	**6.00**	**75.70**	**120.26**	**127.75**	**143.61**	**146.70**	**18.99**	**22.15**

Appendix 21 continued/...

Changes in the cutaneous microcirculation measured in the forearms of middle-aged (41-60Y) female controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
			Measurement	at	During	------------during relaxation phase---------				time to reach	During	--------during relaxation phase-------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
303	43	female	4	50.60	41.60	16.80	22.50	26.30	27.80	0.5	-17.79	-66.80	-55.53	-48.02	-45.06	-3.58	7.27
305	53	female	4	19.00	40.90	43.00	49.20	59.70	55.70	8.0	115.26	126.32	158.95	214.21	193.16	24.37	25.58
309	44	female	4	33.10	36.00	33.10	32.70	39.10	43.00	7.0	8.76	0.00	-1.21	18.13	29.91	6.04	10.91
311	44	female	4	54.60	60.00	58.30	58.20	57.70	56.80	5.0	9.89	6.78	6.59	5.68	4.03	-1.28	-0.92
320	45	female	4	9.50	17.30	22.00	28.50	26.90	27.70	1.0	82.11	131.58	200.00	183.16	191.58	27.05	16.32
321	47	female	4	21.20	53.20	16.40	23.20	28.30	31.80	5.0	150.94	-22.64	9.43	33.49	50.00	-14.58	24.20
323	48	female	4	13.50	31.10	31.20	37.40	38.00	36.40	4.0	130.37	131.11	177.04	181.48	169.63	12.89	12.00
324	49	female	4	13.30	20.10	23.30	32.80	44.60	38.60	3.0	51.13	75.19	146.62	235.34	190.23	43.84	43.38
334	44	female	4	22.90	28.80	31.70	38.90	41.40	42.90	7.0	25.76	38.43	69.87	80.79	87.34	16.55	15.77
337	47	female															
Number of cases				**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**
Mean				**26.41**	**36.56**	**30.64**	**35.93**	**40.22**	**40.08**	**4.50**	**61.83**	**46.66**	**79.08**	**100.47**	**96.76**	**12.37**	**17.17**
Standard deviation				**16.37**	**14.15**	**13.45**	**11.73**	**12.37**	**10.77**	**2.65**	**60.39**	**73.33**	**93.48**	**104.41**	**92.05**	**17.94**	**12.75**
Median				**21.20**	**36.00**	**31.20**	**32.80**	**39.10**	**38.60**	**5.00**	**51.13**	**38.43**	**69.87**	**80.79**	**87.34**	**12.89**	**15.77**
Minimum				**9.50**	**17.30**	**16.40**	**22.50**	**26.30**	**27.70**	**0.50**	**-17.79**	**-66.80**	**-55.53**	**-48.02**	**-45.06**	**-14.58**	**-0.92**
Maximum				**54.60**	**60.00**	**58.30**	**58.20**	**59.70**	**56.80**	**8.00**	**150.94**	**131.58**	**200.00**	**235.34**	**193.16**	**43.84**	**43.38**

Appendix 21 continued/...

Changes in the cutaneous microcirculation measured in the forearms of elderly (61-90Y) male controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
			Measurement	at	During	----during relaxation phase----				time to reach	During	----during relaxation phase----				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
310	72	male	4	34.00	38.40	41.70	37.50	37.30	37.90	7.0	12.94	22.65	10.29	9.71	11.47	-1.59	-3.41
330	63	male	4	38.00	49.50	37.00	46.30	41.40	44.40	5.0	30.26	-2.63	21.84	8.95	16.84	-1.53	4.55
339	69	male	4	31.70	45.70	26.50	31.50	41.70	44.90	6.0	44.16	-16.40	-0.63	31.55	41.64	4.29	20.63
342	62	male	4	44.40	46.00	45.30	59.10	57.00	72.20	8.0	3.60	2.03	33.11	28.38	62.61	14.44	17.70
345	69	male	4	87.90	100.50	88.50	76.00	65.00	76.30	6.0	14.33	0.68	-13.54	-26.05	-13.20	-8.18	-5.42
347	69	male	4	39.60	47.50	45.60	41.50	39.80	41.80	3.0	19.95	15.15	4.80	0.51	5.56	-4.34	-3.31
351	62	male	4	29.70	33.50	38.00	43.80	56.60	45.30	4.0	12.79	27.95	47.47	90.57	52.53	14.21	11.68
352	62	male	4	29.10	37.30	32.50	41.70	51.40	44.60	3.0	28.18	11.68	43.30	76.63	53.26	11.51	15.81
353	62	male	4	26.30	33.60	39.90	44.60	44.00	45.80	2.0	1.92	3.58	4.81	4.66	5.13	0.75	0.45

Number of cases	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**
Mean	**40.08**	**48.00**	**43.89**	**46.89**	**48.24**	**50.36**	**4.89**	**18.68**	**7.19**	**16.83**	**24.99**	**26.20**	**3.28**	**6.52**
Standard deviation	**18.83**	**20.59**	**17.78**	**13.19**	**9.59**	**13.80**	**2.03**	**13.56**	**13.64**	**20.88**	**37.30**	**26.73**	**8.33**	**10.10**
Median	**34.00**	**45.70**	**39.90**	**43.80**	**44.00**	**44.90**	**5.00**	**14.33**	**3.58**	**10.29**	**9.71**	**16.84**	**0.75**	**4.55**
Minimum	**26.30**	**33.50**	**26.50**	**31.50**	**37.30**	**37.90**	**2.00**	**1.92**	**-16.40**	**-13.54**	**-26.05**	**-13.20**	**-8.18**	**-5.42**
Maximum	**87.90**	**100.50**	**88.50**	**76.00**	**65.00**	**76.30**	**8.00**	**44.16**	**27.95**	**47.47**	**90.57**	**62.61**	**14.44**	**20.63**

Appendix 21 continued/...

Changes in the cutaneous microcirculation measured in the forearms of elderly (61-90Y) female controls

				The flux (arbitrary units) was measured							The %chnge in flux was measured						
I.D.	Age	Sex	Measurement duration (min	at baseline	During extension	------------during relaxation phase-------- 1min	2min	3min	4min	time to reach peak (s)	During extension	--------during relaxation phase------------ 1min	2min	3min	4min	Slope of %change in flux (ext-4min)	(1min-4min)
304	65	female	4	63.50	67.30	68.90	87.80	91.00	91.60	8.0	5.98	8.50	38.27	43.31	44.25	11.14	11.23
313	69	female	4	34.60	51.90	37.80	40.20	42.10	45.40	7.0	50.00	9.25	16.18	21.68	31.21	-2.52	7.14
338	65	female	4	40.20	55.30	38.30	35.60	34.80	33.40	1.0	37.56	-4.73	-11.44	-13.43	-16.92	-11.77	-3.86
340	70	female	4	24.60	30.70	22.10	28.30	31.70	29.80	4.0	24.80	-10.16	15.04	28.86	21.14	3.17	10.77
341	71	female	4	60.40	73.70	52.90	51.30	59.60	62.40	4.0	22.02	-12.42	-15.07	-1.32	3.31	-2.63	6.09
343	69	female	4	20.50	24.40	26.90	28.10	34.20	36.20	4.0	19.02	31.22	37.07	66.83	76.59	15.08	16.59
344	69	female	4	20.20	21.90	19.40	21.10	17.20	22.00	1.0	8.42	-3.96	4.46	-14.85	8.91	-0.99	1.93
346	74	female	4	23.20	32.30	34.40	42.80	52.40	75.30	2.0	39.22	48.28	84.48	125.86	224.57	44.83	57.03
348	71	female	4	68.00	67.50	100.20	114.80	107.90	108.40	8.0	-0.74	47.35	68.82	58.68	59.41	13.16	2.60
349	71	female	4	156.50	146.50	118.40	135.30	154.00	174.10	3.0	-6.39	-24.35	-13.55	-1.60	11.25	5.80	11.88
350	68	female	4	68.60	72.30	85.10	94.00	98.70	101.20	7.0	5.39	24.05	37.03	43.88	47.52	10.41	7.73
Number of cases				**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
Mean				**52.75**	**58.53**	**54.95**	**61.75**	**65.78**	**70.89**	**4.45**	**18.66**	**10.28**	**23.75**	**32.53**	**46.48**	**7.79**	**11.74**
Standard deviation				**39.59**	**35.13**	**33.62**	**39.32**	**41.87**	**45.65**	**2.66**	**18.05**	**24.52**	**33.05**	**41.97**	**64.97**	**14.74**	**16.02**
Median				**40.20**	**55.30**	**38.30**	**42.80**	**52.40**	**62.40**	**4.00**	**19.02**	**8.50**	**16.18**	**28.86**	**31.21**	**5.80**	**7.73**
Minimum				**20.20**	**21.90**	**19.40**	**21.10**	**17.20**	**22.00**	**1.00**	**-6.39**	**-24.35**	**-15.07**	**-14.85**	**-16.92**	**-11.77**	**-3.86**
Maximum				**156.50**	**146.50**	**118.40**	**135.30**	**154.00**	**174.10**	**8.00**	**50.00**	**48.28**	**84.48**	**125.86**	**224.57**	**44.83**	**57.03**

Appendix 22

The effects of age and sex on the cutaneous microcirculation during skin extension/relaxation, measured at the legs of asymptomatic controls

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) male controls

				The flux (arbitrary units) was measured										
			Measurement	at	During	during relaxation phase								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
301	40	male												
302	37	male	5.00	""14.6	""15.4	""6.2	""8.2	""9.5	""10.9	""10.9				""2.5
306	40	male	8.00	41.00	58.90	44.10	48.90	52.00	53.40	41.40	47.70	47.30	61.10	
317	33	male	8.00	30.10	35.00	38.50	51.60	60.70	60.20	66.40	64.90	64.50	65.00	6.0
318	33	male	8.00	49.40	52.90	20.70	27.80	35.50	38.70	47.20	57.90	64.00	73.90	2.0
326	23	male	8.00	40.60	54.40	13.90	18.00	20.20	19.00	23.90	21.60	19.00	17.90	3.0
328	32	male	8.00	19.60	25.70	17.20	20.40	22.40	22.50	23.00	24.50	23.30	24.30	3.0
331	36	male												
336	26	male	8.00	18.00	17.20	7.00	12.00	12.50	14.10	16.10	18.50	18.90	17.40	2.0

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Mean	**33.12**	**40.68**	**23.57**	**29.78**	**33.88**	**34.65**	**36.33**	**39.18**	**39.50**	**43.27**	**3.20**
Standard deviation	**12.68**	**17.19**	**14.57**	**16.66**	**19.11**	**19.16**	**18.92**	**20.18**	**21.88**	**26.08**	**1.64**
Median	**35.35**	**43.95**	**18.95**	**24.10**	**28.95**	**30.60**	**32.65**	**36.10**	**35.30**	**42.70**	**3.00**
Minimum	**18.00**	**17.20**	**7.00**	**12.00**	**12.50**	**14.10**	**16.10**	**18.50**	**18.90**	**17.40**	**2.00**
Maximum	**49.40**	**58.90**	**44.10**	**51.60**	**60.70**	**60.20**	**66.40**	**64.90**	**64.50**	**73.90**	**6.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) male controls

The %chnge in flux was measured

I.D.	Age	Sex	Measurement duration (min)	During extension	---during relaxation phase--- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
301	40	male												
302	37	male	5.00	""5.48	""-57.53	""-43.84	""-34.93	""-25.34	""-25.34					
306	40	male	8.00	43.66	7.56	19.27	26.83	30.24	.98	16.34	15.37	49.02	.22	2.50
317	33	male	8.00	16.28	27.91	71.43	101.66	100.00	120.60	115.61	114.29	115.95	12.75	10.63
318	33	male	8.00	7.09	-58.10	-43.72	-28.14	-21.66	-4.45	17.21	29.55	49.60	9.64	15.16
326	23	male	8.00	33.99	-65.76	-55.67	-50.25	-53.20	-41.13	-46.80	-53.20	-55.91	-4.92	1.23
328	32	male	8.00	31.12	-12.24	4.08	14.29	14.80	17.35	25.00	18.88	23.98	1.83	4.31
331	36	male												
336	26	male	8.00	-4.44	-61.11	-33.33	-30.56	-21.67	-10.56	2.78	5.00	-3.33	4.92	8.42

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Mean	**21.28**	**-26.96**	**-6.32**	**5.64**	**8.09**	**13.80**	**21.69**	**21.65**	**29.88**	**4.07**	**7.04**
Standard deviation	**18.15**	**40.15**	**47.69**	**55.35**	**53.87**	**55.73**	**52.78**	**53.98**	**57.72**	**6.45**	**5.34**
Median	**23.70**	**-35.17**	**-14.63**	**-6.93**	**-3.43**	**-1.74**	**16.77**	**17.12**	**36.50**	**3.38**	**6.37**
Minimum	**-4.44**	**-65.76**	**-55.67**	**-50.25**	**-53.20**	**-41.13**	**-46.80**	**-53.20**	**-55.91**	**-4.92**	**1.23**
Maximum	**43.66**	**27.91**	**71.43**	**101.66**	**100.00**	**120.60**	**115.61**	**114.29**	**115.95**	**12.75**	**15.16**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) female controls

				The flux (arbitrary units) was measured										
			Measurement	at	During	during relaxation phase								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
307	31	female	8.00	25.50	40.60	24.50	34.10	27.90	25.40	32.10	38.20	38.50	43.50	2.0
308	28	female	8.00	53.20	51.70	39.30	52.30	64.80	72.20	78.90	82.90	87.70	83.30	5.0
314	22	female	8.00	38.80	38.60	26.30	31.90	35.50	38.00	39.70	40.10	42.80	42.90	4.0
315	22	female	8.00	18.30	30.00	15.40	17.40	19.00	26.80	24.70	21.90	22.00	29.20	3.0
319	25	female	8.00	12.00	15.80	10.50	13.40	17.20	19.80	23.20	24.30	25.20	27.80	2.0
325	39	female	8.00	60.40	70.70	31.60	42.60	40.90	45.50	47.90	50.10	44.40	50.40	6.0
327	28	female												
333	35	female	8.00	26.40	32.00	17.30	20.10	22.30	22.90	23.50	23.00	26.90	27.90	3.0
Number of cases				**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Mean				**33.51**	**39.91**	**23.56**	**30.26**	**32.51**	**35.80**	**38.57**	**40.07**	**41.07**	**43.57**	**3.57**
Standard deviation				**18.02**	**17.47**	**9.98**	**14.19**	**16.66**	**18.42**	**20.05**	**21.64**	**22.40**	**19.69**	**1.51**
Median				**26.40**	**38.60**	**24.50**	**31.90**	**27.90**	**26.80**	**32.10**	**38.20**	**38.50**	**42.90**	**3.00**
Minimum				**12.00**	**15.80**	**10.50**	**13.40**	**17.20**	**19.80**	**23.20**	**21.90**	**22.00**	**27.80**	**2.00**
Maximum				**60.40**	**70.70**	**39.30**	**52.30**	**64.80**	**72.20**	**78.90**	**82.90**	**87.70**	**83.30**	**6.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of young (21-40Y) female controls

I.D.	Age	Sex	Measurement duration (min)	During extension	The %chnge in flux was measured during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
307	31	female	8.00	59.22	-3.92	33.73	9.41	-.39	25.88	49.80	50.98	70.59	4.31	8.99
308	28	female	8.00	-2.82	-26.13	-1.69	21.80	35.71	48.31	55.83	64.85	56.58	10.87	12.22
314	22	female	8.00	-.52	-32.22	-17.78	-8.51	-2.06	2.32	3.35	10.31	10.57	3.75	5.71
315	22	female	8.00	63.93	-15.85	-4.92	3.83	46.45	34.97	19.67	20.22	59.56	2.85	8.21
319	25	female	8.00	31.67	-12.50	11.67	43.33	65.00	93.33	102.50	110.00	131.67	16.65	20.32
325	39	female	8.00	17.05	-47.68	-29.47	-32.28	-24.67	-20.70	-17.05	-26.49	-16.56	-0.57	3.36
327	28	female												
333	35	female	8.00	21.21	-34.47	-23.86	-15.53	-13.26	-10.98	-12.88	1.89	5.68	1.22	5.00

Number of cases	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Mean	**27.11**	**-24.68**	**-4.62**	**3.15**	**15.25**	**24.73**	**28.75**	**33.11**	**45.44**	**5.58**	**9.12**
Standard deviation	**26.47**	**14.95**	**22.01**	**24.98**	**33.71**	**39.18**	**43.15**	**45.55**	**50.05**	**6.05**	**5.74**
Median	**21.21**	**-26.13**	**-4.92**	**3.83**	**-0.39**	**25.88**	**19.67**	**20.22**	**56.58**	**3.75**	**8.21**
Minimum	**-2.82**	**-47.68**	**-29.47**	**-32.28**	**-24.67**	**-20.70**	**-17.05**	**-26.49**	**-16.56**	**-0.57**	**3.36**
Maximum	**63.93**	**-3.92**	**33.73**	**43.33**	**65.00**	**93.33**	**102.50**	**110.00**	**131.67**	**16.65**	**20.32**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) male controls

				The flux (arbitrary units) was measured										
			Measurement	at	During	----during relaxation phase----								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
312	58	male	8.00	47.40	42.00	28.80	37.80	38.40	37.10	33.40	35.10	36.30	41.60	4.0
316	51	male	8.00	22.60	23.10	13.20	17.50	16.80	23.60	24.60	23.90	26.10	25.60	1.0
322	49	male	8.00	20.10	28.10	19.40	23.70	26.00	28.30	25.70	27.80	26.70	26.20	6.0
329	49	male	8.00	47.40	67.40	58.00	80.00	80.50	110.20	131.90	147.70	165.20	176.40	4.0
332	45	male	5.00	""43.6	""38.7	""26.5	""29	""31.3	""31.5	""32.7				""2
335	44	male	6.00	""42.6	""38.8	""30.4	""46.3	""56.6	""60.2	""59.7	""63.9			""5.5

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Mean	**34.38**	**40.15**	**29.85**	**39.75**	**40.43**	**49.80**	**53.90**	**58.63**	**63.58**	**67.45**	**3.75**
Standard deviation	**15.07**	**19.85**	**19.83**	**28.15**	**28.14**	**40.65**	**52.15**	**59.56**	**67.91**	**73.01**	**2.06**
Median	**35.00**	**35.05**	**24.10**	**30.75**	**32.20**	**32.70**	**29.55**	**31.45**	**31.50**	**33.90**	**4.00**
Minimum	**20.10**	**23.10**	**13.20**	**17.50**	**16.80**	**23.60**	**24.60**	**23.90**	**26.10**	**25.60**	**1.00**
Maximum	**47.40**	**67.40**	**58.00**	**80.00**	**80.50**	**110.20**	**131.90**	**147.70**	**165.20**	**176.40**	**6.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) male controls														
				The %chnge in flux was measured										
			Measurement	During	----------during relaxation phase----------								Slope of %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
312	58	male	8.00	-11.39	-39.24	-20.25	-18.99	-21.73	-29.54	-25.95	-23.42	-12.24	0.37	1.72
316	51	male	8.00	2.21	-41.59	-22.57	-25.66	4.42	8.85	5.75	15.49	13.27	5.11	8.01
322	49	male	8.00	39.80	-3.48	17.91	29.35	40.80	27.86	38.31	32.84	30.35	1.84	3.87
329	49	male	8.00	42.19	22.36	68.78	69.83	132.49	178.27	211.60	248.52	272.15	33.21	37.12
332	45	male	5.00	""-11.24	""-39.22	""-33.49	""-28.21	""-27.75	""-25					
335	44	male	6.00	""-8.92	""-28.64	""8.69	""32.86	""41.32	""40.14	""50				

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	During extension	1min	2min	3min	4min	5min	6min	7min	8min	Slope (ext-8min)	Slope (1min-8min)
Number of cases	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Mean	**18.20**	**-15.49**	**10.97**	**13.63**	**39.00**	**46.36**	**57.43**	**68.36**	**75.88**	**10.13**	**12.68**
Standard deviation	**26.92**	**30.67**	**42.78**	**44.77**	**67.40**	**91.12**	**106.08**	**122.39**	**132.01**	**15.51**	**16.50**
Median	**21.01**	**-21.36**	**-1.17**	**5.18**	**22.61**	**18.36**	**22.03**	**24.16**	**21.81**	**3.48**	**5.94**
Minimum	**-11.39**	**-41.59**	**-22.57**	**-25.66**	**-21.73**	**-29.54**	**-25.95**	**-23.42**	**-12.24**	**0.37**	**1.72**
Maximum	**42.19**	**22.36**	**68.78**	**69.83**	**132.49**	**178.27**	**211.60**	**248.52**	**272.15**	**33.21**	**37.12**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) female controls

I.D.	Age	Sex	Measurement duration (min)	The flux (arbitrary units) was measured: at baseline	During extension	during relaxation phase: 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
303	43	female												
305	53	female												
309	44	female	8.00	55.80	46.70	38.20	55.80	78.60	96.10	111.00	108.00	122.10	127.40	1.0
311	44	female	8.00	34.10	40.90	28.30	38.80	45.90	50.10	47.50	53.70	55.20	58.30	4.0
320	45	female	8.00	13.50	18.70	11.40	15.60	20.70	24.90	31.70	37.00	39.50	35.60	2.0
321	47	female												
323	48	female	8.00	13.70	28.20	11.10	12.70	14.20	17.00	18.60	19.10	21.00	23.50	5.0
324	49	female	8.00	19.60	27.10	16.60	19.80	26.10	23.50	21.40	22.10	23.90	22.00	8.0
334	44	female	8.00	25.40	36.00	24.80	34.00	40.80	47.90	53.70	57.90	62.20	66.50	6.0
337	47	female	8.00	27.10	21.80	8.70	11.40	15.50	16.20	17.00	17.50	19.90	19.70	3.0

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Mean	**27.03**	**31.34**	**19.87**	**26.87**	**34.54**	**39.39**	**42.99**	**45.04**	**49.11**	**50.43**	**4.14**
Standard deviation	**14.70**	**10.23**	**10.92**	**16.57**	**22.91**	**28.59**	**33.23**	**32.21**	**36.30**	**38.61**	**2.41**
Median	**25.40**	**28.20**	**16.60**	**19.80**	**26.10**	**24.90**	**31.70**	**37.00**	**39.50**	**35.60**	**4.00**
Minimum	**13.50**	**18.70**	**8.70**	**11.40**	**14.20**	**16.20**	**17.00**	**17.50**	**19.90**	**19.70**	**1.00**
Maximum	**55.80**	**46.70**	**38.20**	**55.80**	**78.60**	**96.10**	**111.00**	**108.00**	**122.10**	**127.40**	**8.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of middle-aged (41-60Y) female controls

The %chnge in flux was measured

I.D.	Age	Sex	Measurement duration (min)	During extension	---during relaxation phase--- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
303	43	female												
305	53	female												
309	44	female	8.00	-16.31	-31.54	.00	40.86	72.22	98.92	93.55	118.82	128.32	21.25	22.59
311	44	female	8.00	19.94	-17.01	13.78	34.60	46.92	39.30	57.48	61.88	70.97	8.88	10.92
320	45	female	8.00	38.52	-15.56	15.56	53.33	84.44	134.81	174.07	192.59	163.70	25.39	30.39
321	47	female												
323	48	female	8.00	105.84	-18.98	-7.30	3.65	24.09	35.77	39.42	53.28	71.53	3.42	12.57
324	49	female	8.00	38.27	-15.31	1.02	33.16	19.90	9.18	12.76	21.94	12.24	0.12	2.68
334	44	female	8.00	41.73	-2.36	33.86	60.63	88.58	111.42	127.95	144.88	161.81	19.35	22.97
337	47	female	8.00	-19.56	-67.90	-57.93	-42.80	-40.22	-37.27	-35.42	-26.57	-27.31	2.39	5.55

Number of cases	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Mean	**29.78**	**-24.09**	**-0.15**	**26.21**	**42.28**	**56.02**	**67.11**	**80.97**	**83.04**	**11.54**	**15.38**
Standard deviation	**42.29**	**21.11**	**28.84**	**35.42**	**45.60**	**61.52**	**70.91**	**75.45**	**73.29**	**10.28**	**10.17**
Median	**38.27**	**-17.01**	**1.02**	**34.60**	**46.92**	**39.30**	**57.48**	**61.88**	**71.53**	**8.88**	**12.57**
Minimum	**-19.56**	**-67.90**	**-57.93**	**-42.80**	**-40.22**	**-37.27**	**-35.42**	**-26.57**	**-27.31**	**0.12**	**2.68**
Maximum	**105.84**	**-2.36**	**33.86**	**60.63**	**88.58**	**134.81**	**174.07**	**192.59**	**163.70**	**25.39**	**30.39**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of elderly (61-90Y) male controls

The flux (arbitrary units) was measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
310	72	male	8.00	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00	1.0
330	63	male												
339	69	male	8.00	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00	6.0
342	62	male	8.00	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60	4.0
345	69	male	8.00	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20	4.0
347	69	male	8.00	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50	5.0
351	62	male	8.00	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40	5.0
352	62	male	8.00	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20	5.0
353	62	male	8.00	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40	6.0
Number of cases				**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean				**23.25**	**33.05**	**18.10**	**22.39**	**27.03**	**28.80**	**29.06**	**31.50**	**32.41**	**32.41**	**4.50**
Standard deviation				**9.63**	**15.72**	**10.52**	**14.47**	**19.42**	**16.95**	**20.09**	**21.21**	**22.35**	**23.71**	**1.60**
Median				**19.20**	**28.25**	**14.85**	**17.95**	**20.65**	**23.40**	**22.90**	**25.75**	**26.20**	**24.60**	**5.00**
Minimum				**13.50**	**16.80**	**10.30**	**10.90**	**14.70**	**16.90**	**13.10**	**14.00**	**13.90**	**12.60**	**1.00**
Maximum				**38.40**	**64.90**	**42.20**	**55.80**	**73.50**	**69.10**	**75.50**	**81.00**	**84.00**	**87.40**	**6.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of elderly (61-90Y) male controls

The %chnge in flux was measured

I.D.	Age	Sex	Measurement duration (min)	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
310	72	male	8.00	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85	2.34	4.69
330	63	male												
339	69	male	8.00	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36	3.48	6.76
342	62	male	8.00	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62	-18.83	-1.15
345	69	male	8.00	52.17	-36.02	-32.30	-8.70	4.97	.00	8.07	25.47	25.47	2.79	9.10
347	69	male	8.00	26.90	-13.71	-6.09	-4.57	13.20	-.51	8.12	-1.02	-1.02	-0.69	1.65
351	62	male	8.00	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63	4.13	7.37
352	62	male	8.00	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15	21.79	24.77
353	62	male	8.00	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71	16.58	16.54
Number of cases				**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean				**51.87**	**-22.63**	**-5.21**	**15.13**	**27.01**	**25.45**	**35.57**	**40.37**	**40.89**	**3.95**	**8.72**
Standard deviation				**80.70**	**21.21**	**32.97**	**48.42**	**47.94**	**59.32**	**57.22**	**67.55**	**75.47**	**12.09**	**8.35**
Median				**27.45**	**-21.16**	**-16.00**	**-6.63**	**9.08**	**-0.25**	**9.16**	**17.49**	**12.23**	**3.14**	**7.07**
Minimum				**-4.95**	**-48.64**	**-32.30**	**-25.78**	**-18.23**	**-29.95**	**-25.13**	**-25.67**	**-32.62**	**-18.83**	**-1.15**
Maximum				**247.06**	**20.57**	**59.43**	**110.00**	**102.22**	**122.22**	**131.43**	**151.85**	**168.15**	**21.79**	**24.77**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of elderly (61-90Y) female controls														
				The flux (arbitrary units) was measured										
			Measurement	at	During	during relaxation phase								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
304	65	female												
313	69	female	8.00	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10	3.0
338	65	female	8.00	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50	7.0
340	70	female	8.00	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60	3.0
341	71	female	8.00	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40	4.0
343	69	female	8.00	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20	7.0
344	69	female	8.00	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80	4.0
346	74	female	8.00	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60	2.0
348	71	female	8.00	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30	1.0
349	71	female	8.00	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30	3.0
350	68	female	8.00	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20	6.0

Number of cases	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mean	**23.17**	**32.24**	**20.85**	**27.93**	**36.59**	**43.49**	**45.43**	**50.64**	**53.19**	**55.60**	**4.00**
Standard deviation	**6.65**	**13.90**	**7.34**	**11.10**	**16.30**	**19.94**	**20.08**	**24.95**	**24.57**	**28.53**	**2.05**
Median	**20.60**	**29.25**	**19.20**	**28.40**	**35.55**	**43.70**	**46.65**	**45.15**	**46.85**	**46.45**	**3.50**
Minimum	**14.30**	**18.10**	**12.20**	**13.40**	**13.50**	**13.10**	**13.70**	**13.90**	**14.20**	**15.80**	**1.00**
Maximum	**36.90**	**67.40**	**37.10**	**53.00**	**70.90**	**80.80**	**75.20**	**83.00**	**84.70**	**111.20**	**7.00**

Appendix 22 continued/...

Changes in the cutaneous microcirculation measured in the legs of elderly (61-90Y) female controls

The %chnge in flux was measured

I.D.	Age	Sex	Measurement duration (min)	During extension	----during relaxation phase---- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
304	65	female												
313	69	female	8.00	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74	7.81	12.03
338	65	female	8.00	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59	7.10	11.28
340	70	female	8.00	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48	40.15	45.31
341	71	female	8.00	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88	10.82	13.22
343	69	female	8.00	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13	21.52	28.51
344	69	female	8.00	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-.70	10.49	-5.15	-0.80
346	74	female	8.00	19.72	18.31	15.96	20.66	24.88	37.09	32.86	67.61	67.14	6.46	7.72
348	71	female	8.00	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54	16.82	19.60
349	71	female	8.00	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80	33.22	35.90
350	68	female	8.00	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46	28.58	31.65
Number of cases				**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mean				**43.50**	**-4.75**	**21.57**	**57.97**	**86.87**	**93.93**	**116.65**	**129.18**	**137.53**	**16.73**	**20.44**
Standard deviation				**52.45**	**34.34**	**37.57**	**57.71**	**70.85**	**67.97**	**95.31**	**99.43**	**102.97**	**14.04**	**14.41**
Median				**34.99**	**3.30**	**14.49**	**47.11**	**83.88**	**100.17**	**90.90**	**102.12**	**110.07**	**13.82**	**16.41**
Minimum				**-19.24**	**-62.06**	**-26.02**	**-6.50**	**-8.39**	**-4.20**	**-2.80**	**-0.70**	**10.49**	**-5.15**	**-0.80**
Maximum				**131.62**	**36.18**	**82.13**	**156.18**	**177.66**	**169.10**	**291.57**	**335.39**	**313.48**	**40.15**	**45.31**

Appendix 23

The postural vasoconstrictive response: the effect of passive leg lowering on the cutaneous microcirculation in asymptomatic controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	The %drop in flux measured after passive leg lowering at 5s	10s	15s	20s	30s	90s
100	25	male	right	24.30	43.90	34.50	31.80	28.40	17.40	6.20	-80.66	-41.98	-30.86	-16.87	28.40	74.49
101	23	female	right	16.60	25.70	25.20	16.20	14.50	10.70	6.40	-54.82	-51.81	2.41	12.65	35.54	61.45
102	40	male	right	125.90	97.40	91.20	36.30	48.60	62.00	98.20	22.64	27.56	71.17	61.40	50.75	22.00
103	28	female	right	21.60	63.30	48.70	38.50	45.90	21.90	11.80	-193.06	-125.46	-78.24	-112.50	-1.39	45.37
104	22	female	right	12.50	13.20	11.80	9.60	8.70	7.70	5.50	-5.60	5.60	23.20	30.40	38.40	56.00
105	34	male	right	42.90	55.40	57.30	37.20	44.80	36.20	33.70	-29.14	-33.57	13.29	-4.43	15.62	21.45
106	25	female	right	215.50	145.40	94.80	227.10	161.50	61.90	43.20	32.53	56.01	-5.38	25.06	71.28	79.95
107	27	male	right	82.50	63.50	29.10	34.50	26.90	22.20	43.80	23.03	64.73	58.18	67.39	73.09	46.91
108	26	female	right	177.30	138.80	92.20	76.80	68.30	50.70	82.70	21.71	48.00	56.68	61.48	71.40	53.36
109	34	male	right	15.90	29.00	20.60	20.00	15.10	15.30	9.60	-82.39	-29.56	-25.79	5.03	3.77	39.62
110	22	female	right	20.10	21.10	17.20	21.70	16.70	17.40	10.20	-4.98	14.43	-7.96	16.92	13.43	49.25
111	38	male	right	179.80	108.90	96.80	155.50	141.90	182.20	114.00	39.43	46.16	13.52	21.08	-1.33	36.60
112	29	female	right	43.20	54.80	41.80	32.50	31.60	27.20	20.70	-26.85	3.24	24.77	26.85	37.04	52.08
113	26	female	right	17.60	23.90	17.50	16.60	13.70	13.50	11.50	-35.80	0.57	5.68	22.16	23.30	34.66
114	22	female	right	19.30	53.20	44.90	46.40	23.70	20.80	9.10	-175.65	-132.64	-140.41	-22.80	-7.77	52.85
115	21	female	right	191.80	178.90	85.40	162.80	133.10	80.60	90.40	6.73	55.47	15.12	30.60	57.98	52.87
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	-50.27	-12.10	-29.57	9.14	7.80	30.38
117	42	female	right	214.80	236.00	204.60	180.60	139.40	109.70	88.30	-9.87	4.75	15.92	35.10	48.93	58.89
118	58	male	right	67.10	115.20	84.30	88.70	93.40	97.70	89.20	-71.68	-25.63	-32.19	-39.20	-45.60	-32.94
119	44	female	right	26.80	27.80	29.80	23.00	21.10	18.00	17.70	-3.73	-11.19	14.18	21.27	32.84	33.96

Appendix 23 continued/...

I.D.	Age	Sex	Leg	The flux (arbitrary units) measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	The %drop in flux measured after passive leg lowering at 5s	10s	15s	20s	30s	90s
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	68.66	80.61	42.16	51.37	53.80	56.70
121	41	female	right	37.40	33.20	29.00	29.50	23.20	16.30	14.40	11.23	22.46	21.12	37.97	56.42	61.50
122	32	male	right	42.80	41.90	27.90	21.50	19.20	11.70	10.30	2.10	34.81	49.77	55.14	72.66	75.93
123	25	male	right	10.00	9.60	9.30	9.40	5.00	3.90	4.10	4.00	7.00	6.00	50.00	61.00	59.00
124	44	female	right	23.00	40.70	33.60	26.90	21.70	17.80	7.90	-76.96	-46.09	-16.96	5.65	22.61	65.65
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	-21.37	-2.82	7.90	21.51	33.43	59.31
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	-20.17	15.32	26.09	52.73	35.09	29.83
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	25.22	53.67	-0.29	41.94	48.39	60.12
128	52	male	right	37.20	47.80	41.80	37.90	38.80	36.90	21.50	-28.49	-12.37	-1.88	-4.30	0.81	42.20
129	41	male	right	144.60	101.00	71.20	81.50	90.50	98.70	83.30	30.15	50.76	43.64	37.41	31.74	42.39
130	51	female	right	39.40	24.70	20.10	11.40	13.70	11.30	14.00	37.31	48.98	71.07	65.23	71.32	64.47
131	42	male	right	144.70	85.80	78.80	78.00	82.80	34.20	60.60	40.70	45.54	46.10	42.78	76.36	58.12
132	43	female	right	247.40	255.30	224.60	269.90	272.00	216.00	38.50	-3.19	9.22	-9.09	-9.94	12.69	84.44
133	42	female	right	8.00	11.00	9.60	7.50	7.70	6.80	5.10	-37.50	-20.00	6.25	3.75	15.00	36.25
134	44	male	right	11.00	14.10	9.80	20.40	8.20	12.40	5.70	-28.18	10.91	-85.45	25.45	-12.73	48.18
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	-220.44	-91.97	-47.45	-31.39	-62.77	21.90
136	53	male	right	13.70	22.80	12.40	7.70	7.30	6.90	5.80	-66.42	9.49	43.80	46.72	49.64	57.66
137	46	female	right	10.10	12.20	13.80	9.50	10.10	9.70	6.00	-20.79	-36.63	5.94	0.00	3.96	40.59
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	6.84	33.41	53.53	45.72	48.92	20.01
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	14.30	18.94	4.26	31.47	27.07	44.43
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	52.92	77.16	72.63	51.60	32.94	48.47
141	48	female	right	32.70	30.20	12.80	18.10	11.30	13.40	7.00	7.65	60.86	44.65	65.44	59.02	78.59
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	-46.09	-33.27	-33.39	10.98	6.63	30.48
143	53	female	right	97.50	107.20	91.80	64.90	50.70	45.12	40.00	-9.95	5.85	33.44	48.00	53.72	58.97

Appendix 23 continued/...

I.D.	Age	Sex	Leg	The flux (arbitrary units) measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	The %drop in flux measured after passive leg lowering at 5s	10s	15s	20s	30s	90s
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	0.83	14.97	8.25	11.20	28.34	23.74
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	-81.76	12.84	-55.41	-4.05	34.46	66.22
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	18.10	20.18	15.10	21.61	-50.13	20.44
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	64.88	55.06	8.78	11.64	35.79	20.58
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	-81.78	-50.58	50.00	-17.83	-14.73	29.26
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	69.68	62.53	61.47	77.47	76.63	68.21
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	-7.83	29.86	53.91	-1.16	48.99	47.25
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	26.69	47.21	57.17	58.76	62.35	81.87
100	25	male	left	18.00	38.10	41.70	17.60	22.10	11.90	7.60	-111.67	-131.67	2.22	-22.78	33.89	57.78
101	23	female	left	9.10	12.80	12.80	12.50	9.90	10.20	5.80	-40.66	-40.66	-37.36	-8.79	-12.09	36.26
102	40	male	left	161.90	108.40	111.70	101.30	117.20	139.70	32.70	33.05	31.01	37.43	27.61	13.71	79.80
103	28	female	left	20.80	20.50	25.20	29.00	20.20	20.90	8.80	1.44	-21.15	-39.42	2.88	-0.48	57.69
104	22	female	left	11.10	26.30	25.00	19.90	22.20	15.00	6.20	-136.94	-125.23	-79.28	-100.00	-35.14	44.14
105	34	male	left	7.10	16.10	18.00	11.00	8.20	4.10	4.70	-126.76	-153.52	-54.93	-15.49	42.25	33.80
106	25	female	left	80.70	67.50	66.40	51.90	22.40	6.70	27.70	16.36	17.72	35.69	72.24	91.70	65.68
107	27	male	left	64.70	30.80	22.00	32.70	53.90	20.30	9.50	52.40	66.00	49.46	16.69	68.62	85.32
108	26	female	left	98.30	126.10	103.90	100.90	127.00	82.00	138.60	-28.28	-5.70	-2.64	-29.20	16.58	-41.00
109	34	male	left	21.60	49.10	38.40	57.40	42.20	29.00	11.00	-127.31	-77.78	-165.74	-95.37	-34.26	49.07
110	22	female	left	45.20	62.80	80.80	65.30	62.90	37.50	36.20	-38.94	-78.76	-44.47	-39.16	17.04	19.91
111	38	male	left	149.10	116.30	98.80	147.60	213.30	70.90	109.40	22.00	33.74	1.01	-43.06	52.45	26.63
112	29	female	left	29.70	87.90	82.80	42.70	28.00	35.30	30.40	-195.96	-178.79	-43.77	5.72	-18.86	-2.36
113	26	female	left	17.50	19.80	20.10	18.10	17.40	18.90	9.80	-13.14	-14.86	-3.43	0.57	-8.00	44.00
114	22	female	left	13.30	68.40	47.40	37.30	20.80	16.80	8.00	-414.29	-256.39	-180.45	-56.39	-26.32	39.85

Appendix 23 continued/...

I.D.	Age	Sex	Leg	The flux (arbitrary units) measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	The %drop in flux measured after passive leg lowering at 5s	10s	15s	20s	30s	90s
115	21	female	left	133.00	146.90	36.90	21.50	17.00	12.80	30.10	-10.45	72.26	83.83	87.22	90.38	77.37
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	-153.64	-91.95	5.75	-9.96	9.20	28.35
117	42	female	left	80.10	75.80	57.50	41.90	34.80	25.00	17.50	5.37	28.21	47.69	56.55	68.79	78.15
118	58	male	left	50.60	50.00	25.10	23.90	24.00	22.80	22.70	1.19	50.40	52.77	52.57	54.94	55.14
119	44	female	left	106.50	149.30	155.40	160.60	136.20	102.10	79.80	-40.19	-45.92	-50.80	-27.89	4.13	25.07
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	49.54	32.62	48.00	-21.85	-24.77	20.31
121	41	female	left	28.60	41.20	40.10	34.20	21.70	15.40	6.00	-44.06	-40.21	-19.58	24.13	46.15	79.02
122	32	male	left	38.90	94.90	90.20	41.30	29.90	25.80	86.30	-143.96	-131.88	-6.17	23.14	33.68	-121.85
123	25	male	left	9.60	27.20	33.90	23.20	24.10	17.00	9.20	-183.33	-253.13	-141.67	-151.04	-77.08	4.17
124	44	female	left	16.70	52.40	40.50	27.50	22.70	11.50	5.60	-213.77	-142.51	-64.67	-35.93	31.14	66.47
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	-14.40	30.28	60.88	69.72	64.48	48.45
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	-27.46	38.24	26.20	73.72	77.34	44.85
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00
128	52	male	left	14.40	21.20	10.20	15.80	8.60	14.00	8.30	-47.22	29.17	-9.72	40.28	2.78	42.36
129	41	male	left	147.80	179.40	96.10	117.30	98.60	80.50	77.20	-21.38	34.98	20.64	33.29	45.53	47.77
130	51	female	left	9.50	11.10	6.00	6.40	7.50	7.80	5.20	-16.84	36.84	32.63	21.05	17.89	45.26
131	42	male	left	110.70	68.90	118.60	96.80	101.90	94.90	71.40	37.76	-7.14	12.56	7.95	14.27	35.50
132	43	female	left	22.60	14.00	13.30	13.90	10.60	8.60	7.60	38.05	41.15	38.50	53.10	61.95	66.37
133	42	female	left	9.30	15.00	15.60	13.00	8.00	5.20	4.30	-61.29	-67.74	-39.78	13.98	44.09	53.76
134	44	male	left	5.70	17.20	9.60	15.40	8.50	10.40	10.80	-201.75	-68.42	-170.18	-49.12	-82.46	-89.47
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59
136	53	male	left	17.80	16.70	26.20	13.40	13.80	15.20	6.50	6.18	-47.19	24.72	22.47	14.61	63.48
137	46	female	left	11.10	14.20	18.50	13.60	7.60	8.40	6.20	-27.93	-66.67	-22.52	31.53	24.32	44.14
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	13.45	12.85	49.22	21.13	-2.29	19.44

Appendix 23 continued/...

				The flux (arbitrary units) measured							The %drop in flux measured					
				at	--------after passive leg lowering at--------						--------after passive leg lowering at--------					
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	5s	10s	15s	20s	30s	90s
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	34.73	34.73	54.78	65.40	78.11	78.77
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66
141	48	female	left	20.20	18.80	16.80	13.00	8.70	7.90	6.20	6.93	16.83	35.64	56.93	60.89	69.31
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	16.36	41.41	60.99	44.22	60.69	74.74
143	53	female	left	132.50	100.50	93.80	89.80	81.40	59.90	29.70	24.15	29.21	32.23	38.57	54.79	77.58
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	2.51	18.66	-11.42	-8.64	-42.62	31.48
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	10.84	34.41	47.72	68.25	65.40	71.10
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	-75.82	-68.32	-26.92	-30.59	-23.99	23.81
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	77.43	25.14	66.99	28.83	93.91	87.38
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	-85.79	49.73	30.05	54.10	57.92	73.77
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	-28.56	-22.42	-32.84	-17.95	11.81	28.28
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	-84.02	-156.19	-21.65	5.15	15.98	-16.49

Number of cases	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**	**104**
Mean	**77.42**	**79.65**	**67.44**	**65.91**	**60.72**	**52.11**	**45.08**	**-37.52**	**-13.01**	**-0.92**	**11.34**	**23.17**	**40.21**
Standard deviation	**87.84**	**95.53**	**87.06**	**94.07**	**78.29**	**73.72**	**66.29**	**82.95**	**68.10**	**55.19**	**45.62**	**42.42**	**37.74**
Median	**41.10**	**49.90**	**41.10**	**34.20**	**28.20**	**21.80**	**19.70**	**-15.62**	**8.11**	**7.07**	**21.11**	**31.44**	**47.08**
Minimum	**5.70**	**9.60**	**6.00**	**6.40**	**5.00**	**3.90**	**4.10**	**-414.29**	**-256.39**	**-180.45**	**-151.04**	**-118.97**	**-121.85**
Maximum	**542.60**	**792.70**	**723.10**	**723.80**	**483.00**	**506.60**	**377.20**	**77.43**	**80.61**	**83.83**	**87.22**	**93.91**	**87.38**

Appendix 24

The postural vasoconstrictive response measured at the pulp of the big toe in male and female controls

In control males

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	_---------after passive leg lowering at----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
100	25	male	right	24.30	43.90	34.50	31.80	28.40	17.40	6.20	16.0	-80.66	-41.98	-30.86	-16.87	28.40	74.49	1.59	1.38
102	40	male	right	125.90	97.40	91.20	36.30	48.60	62.00	98.20	5.0	22.64	27.56	71.17	61.40	50.75	22.00	-0.21	-0.38
105	34	male	right	42.90	55.40	57.30	37.20	44.80	36.20	33.70	7.0	-29.14	-33.57	13.29	-4.43	15.62	21.45	0.51	0.41
107	27	male	right	82.50	63.50	29.10	34.50	26.90	22.20	43.80	4.0	23.03	64.73	58.18	67.39	73.09	46.91	-0.01	-0.22
109	34	male	right	15.90	29.00	20.60	20.00	15.10	15.30	9.60	19.0	-82.39	-29.56	-25.79	5.03	3.77	39.62	1.06	0.78
111	38	male	right	179.80	108.90	96.80	155.50	141.90	182.20	114.00	1.0	39.43	46.16	13.52	21.08	-1.33	36.60	0.03	0.12
118	58	male	right	67.10	115.20	84.30	88.70	93.40	97.70	89.20	54.0	-71.68	-25.63	-32.19	-39.20	-45.60	-32.94	0.16	-0.01
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	2.0	68.66	80.61	42.16	51.37	53.80	56.70	-0.10	-0.05
122	32	male	right	42.80	41.90	27.90	21.50	19.20	11.70	10.30	5.0	2.10	34.81	49.77	55.14	72.66	75.93	0.61	0.40
123	25	male	right	10.00	9.60	9.30	9.40	5.00	3.90	4.10	5.0	4.00	7.00	6.00	50.00	61.00	59.00	0.61	0.53
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	9.0	-20.17	15.32	26.09	52.73	35.09	29.83	0.26	0.02
128	52	male	right	37.20	47.80	41.80	37.90	38.80	36.90	21.50	9.0	-28.49	-12.37	-1.88	-4.30	0.81	42.20	0.72	0.65
129	41	male	right	144.60	101.00	71.20	81.50	90.50	98.70	83.30	4.0	30.15	50.76	43.64	37.41	31.74	42.39	0.03	-0.03
131	42	male	right	144.70	85.80	78.80	78.00	82.80	34.20	60.60	3.0	40.70	45.54	46.10	42.78	76.36	58.12	0.19	0.15
134	44	male	right	11.00	14.10	9.80	20.40	8.20	12.40	5.70	7.0	-28.18	10.91	-85.45	25.45	-12.73	48.18	0.88	0.87
136	53	male	right	13.70	22.80	12.40	7.70	7.30	6.90	5.80	8.0	-66.42	9.49	43.80	46.72	49.64	57.66	0.82	0.36
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	2.0	6.84	33.41	53.53	45.72	48.92	20.01	-0.11	-0.31
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	3.0	0.83	14.97	8.25	11.20	28.34	23.74	0.21	0.15
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	3.0	18.10	20.18	15.10	21.61	-50.13	20.44	0.00	0.07
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	2.0	69.68	62.53	61.47	77.47	76.63	68.21	0.02	0.02
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	7.0	-7.83	29.86	53.91	-1.16	48.99	47.25	0.39	0.21
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	2.0	26.69	47.21	57.17	58.76	62.35	81.87	0.49	0.37
100	25	male	left	18.00	38.10	41.70	17.60	22.10	11.90	7.60	15.0	-111.67	-131.67	2.22	-22.78	33.89	57.78	1.78	1.51
102	40	male	left	161.90	108.40	111.70	101.30	117.20	139.70	32.70	4.0	33.05	31.01	37.43	27.61	13.71	79.80	0.58	0.65
105	34	male	left	7.10	16.10	18.00	11.00	8.20	4.10	4.70	17.0	-126.76	-153.52	-54.93	-15.49	42.25	33.80	1.78	1.52

Appendix 24 continued/...

In control males				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	_---------after passive leg lowering at----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
107	27	male	left	64.70	30.80	22.00	32.70	53.90	20.30	9.50	3.0	52.40	66.00	49.46	16.69	68.62	85.32	0.43	0.47
109	34	male	left	21.60	49.10	38.40	57.40	42.20	29.00	11.00	41.0	-127.31	-77.78	-165.74	-95.37	-34.26	49.07	2.10	2.08
111	38	male	left	149.10	116.30	98.80	147.60	213.30	70.90	109.40	2.0	22.00	33.74	1.01	-43.06	52.45	26.63	0.19	0.26
118	58	male	left	50.60	50.00	25.10	23.90	24.00	22.80	22.70	5.0	1.19	50.40	52.77	52.57	54.94	55.14	0.28	0.04
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	3.0	49.54	32.62	48.00	-21.85	-24.77	20.31	-0.20	-0.02
122	32	male	left	38.90	94.90	90.20	41.30	29.90	25.80	86.30	16.0	-143.96	-131.88	-6.17	23.14	33.68	-121.85	-0.36	-0.98
123	25	male	left	9.60	27.20	33.90	23.20	24.10	17.00	9.20	38.0	-183.33	-253.13	-141.67	-151.04	-77.08	4.17	2.47	2.52
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	8.0	-27.46	38.24	26.20	73.72	77.34	44.85	0.38	0.00
128	52	male	left	14.40	21.20	10.20	15.80	8.60	14.00	8.30	7.0	-47.22	29.17	-9.72	40.28	2.78	42.36	0.60	0.32
129	41	male	left	147.80	179.40	96.10	117.30	98.60	80.50	77.20	7.0	-21.38	34.98	20.64	33.29	45.53	47.77	0.47	0.23
131	42	male	left	110.70	68.90	118.60	96.80	101.90	94.90	71.40	4.0	37.76	-7.14	12.56	7.95	14.27	35.50	0.25	0.42
134	44	male	left	5.70	17.20	9.60	15.40	8.50	10.40	10.80	120.0	-201.75	-68.42	-170.18	-49.12	-82.46	-89.47	0.61	0.10
136	53	male	left	17.80	16.70	26.20	13.40	13.80	15.20	6.50	2.0	6.18	-47.19	24.72	22.47	14.61	63.48	0.84	0.92
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	3.0	13.45	12.85	49.22	21.13	-2.29	19.44	-0.04	-0.08
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	5.0	2.51	18.66	-11.42	-8.64	-42.62	31.48	0.34	0.42
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	64.0	-75.82	-68.32	-26.92	-30.59	-23.99	23.81	1.03	0.91
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	24.0	-28.56	-22.42	-32.84	-17.95	11.81	28.28	0.69	0.68
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	47.0	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26	2.24	1.03
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	16.0	-84.02	-156.19	-21.65	5.15	15.98	-16.49	0.83	0.68
Number of cases				**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**
Mean				**72.72**	**71.26**	**59.10**	**55.34**	**56.04**	**52.16**	**46.76**	**14.27**	**-31.22**	**-9.13**	**2.44**	**9.43**	**19.47**	**33.01**	**0.58**	**0.44**
Standard deviation				**61.33**	**56.00**	**45.78**	**44.81**	**49.40**	**50.89**	**45.05**	**22.00**	**81.67**	**71.00**	**57.41**	**48.75**	**42.45**	**39.67**	**0.67**	**0.64**
Median				**50.40**	**49.10**	**41.75**	**36.05**	**36.85**	**28.70**	**25.70**	**6.00**	**-3.50**	**15.14**	**13.40**	**21.11**	**28.37**	**40.91**	**0.45**	**0.34**
Minimum				**5.70**	**9.60**	**9.30**	**7.70**	**5.00**	**3.90**	**4.10**	**1.00**	**-350.5**	**-253.1**	**-170.2**	**-151.0**	**-82.5**	**-121.9**	**-0.36**	**-0.98**
Maximum				**218.60**	**237.7**	**190.5**	**155.5**	**213.3**	**223.6**	**176.1**	**120.00**	**69.68**	**80.61**	**71.17**	**77.47**	**77.34**	**85.32**	**2.47**	**2.52**

Appendix 24 continued/...

In control females				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at--------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
101	23	female	right	16.60	25.70	25.20	16.20	14.50	10.70	6.40	15.0	-54.82	-51.81	2.41	12.65	35.54	61.45	1.20	1.02
103	28	female	right	21.60	63.30	48.70	38.50	45.90	21.90	11.80	19.0	-193.06	-125.46	-78.24	-112.50	-1.39	45.37	2.35	1.95
104	22	female	right	12.50	13.20	11.80	9.60	8.70	7.70	5.50	11.0	-5.60	5.60	23.20	30.40	38.40	56.00	0.60	0.50
106	25	female	right	215.50	145.40	94.80	227.10	161.50	61.90	43.20	3.0	32.53	56.01	-5.38	25.06	71.28	79.95	0.63	0.66
108	26	female	right	177.30	138.80	92.20	76.80	68.30	50.70	82.70	4.0	21.71	48.00	56.68	61.48	71.40	53.36	0.15	-0.02
110	22	female	right	20.10	21.10	17.20	21.70	16.70	17.40	10.20	7.0	-4.98	14.43	-7.96	16.92	13.43	49.25	0.58	0.55
112	29	female	right	43.20	54.80	41.80	32.50	31.60	27.20	20.70	7.0	-26.85	3.24	24.77	26.85	37.04	52.08	0.67	0.46
113	26	female	right	17.60	23.90	17.50	16.60	13.70	13.50	11.50	10.0	-35.80	0.57	5.68	22.16	23.30	34.66	0.56	0.35
114	22	female	right	19.30	53.20	44.90	46.40	23.70	20.80	9.10	28.0	-175.65	-132.64	-140.41	-22.80	-7.77	52.85	2.40	2.08
115	21	female	right	191.80	178.90	85.40	162.80	133.10	80.60	90.40	2.0	6.73	55.47	15.12	30.60	57.98	52.87	0.35	0.21
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	18.0	-50.27	-12.10	-29.57	9.14	7.80	30.38	0.73	0.56
117	42	female	right	214.80	236.00	204.60	180.60	139.40	109.70	88.30	9.0	-9.87	4.75	15.92	35.10	48.93	58.89	0.68	0.55
119	44	female	right	26.80	27.80	29.80	23.00	21.10	18.00	17.70	3.0	-3.73	-11.19	14.18	21.27	32.84	33.96	0.42	0.37
121	41	female	right	37.40	33.20	29.00	29.50	23.20	16.30	14.40	4.0	11.23	22.46	21.12	37.97	56.42	61.50	0.53	0.45
124	44	female	right	23.00	40.70	33.60	26.90	21.70	17.80	7.90	17.0	-76.96	-46.09	-16.96	5.65	22.61	65.65	1.40	1.16
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	12.0	-21.37	-2.82	7.90	21.51	33.43	59.31	0.81	0.68
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	4.0	25.22	53.67	-0.29	41.94	48.39	60.12	0.38	0.35
130	51	female	right	39.40	24.70	20.10	11.40	13.70	11.30	14.00	1.0	37.31	48.98	71.07	65.23	71.32	64.47	0.17	0.05
132	43	female	right	247.40	255.30	224.60	269.90	272.00	216.00	38.50	6.0	-3.19	9.22	-9.09	-9.94	12.69	84.44	1.08	1.13
133	42	female	right	8.00	11.00	9.60	7.50	7.70	6.80	5.10	13.0	-37.50	-20.00	6.25	3.75	15.00	36.25	0.69	0.54
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	44.0	-220.44	-91.97	-47.45	-31.39	-62.77	21.90	1.82	1.12
137	46	female	right	10.10	12.20	13.80	9.50	10.10	9.70	6.00	16.0	-20.79	-36.63	5.94	0.00	3.96	40.59	0.73	0.71

In control females

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	----------after passive leg lowering at----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	4.0	14.30	18.94	4.26	31.47	27.07	44.43	0.36	0.36
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	2.0	52.92	77.16	72.63	51.60	32.94	48.47	-0.20	-0.25
141	48	female	right	32.70	30.20	12.80	18.10	11.30	13.40	7.00	5.0	7.65	60.86	44.65	65.44	59.02	78.59	0.51	0.29
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	19.0	-46.09	-33.27	-33.39	10.98	6.63	30.48	0.80	0.69
143	53	female	right	97.50	107.20	91.80	64.90	50.70	45.12	40.00	8.0	-9.95	5.85	33.44	48.00	53.72	58.97	0.61	0.43
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	10.0	-81.76	12.84	-55.41	-4.05	34.46	66.22	1.33	1.03
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	2.0	64.88	55.06	8.78	11.64	35.79	20.58	-0.29	-0.12
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	1.0	-81.78	-50.58	50.00	-17.83	-14.73	29.26	0.83	0.52
101	23	female	left	9.10	12.80	12.80	12.50	9.90	10.20	5.80	17.0	-40.66	-40.66	-37.36	-8.79	-12.09	36.26	0.91	0.89
103	28	female	left	20.80	20.50	25.20	29.00	20.20	20.90	8.80	7.0	1.44	-21.15	-39.42	2.88	-0.48	57.69	0.89	1.04
104	22	female	left	11.10	26.30	25.00	19.90	22.20	15.00	6.20	42.0	-136.94	-125.23	-79.28	-100.00	-35.14	44.14	2.04	1.92
106	25	female	left	80.70	67.50	66.40	51.90	22.40	6.70	27.70	1.0	16.36	17.72	35.69	72.24	91.70	65.68	0.49	0.35
108	26	female	left	98.30	126.10	103.90	100.90	127.00	82.00	138.60	11.0	-28.28	-5.70	-2.64	-29.20	16.58	-41.00	-0.30	-0.43
110	22	female	left	45.20	62.80	80.80	65.30	62.90	37.50	36.20	29.0	-38.94	-78.76	-44.47	-39.16	17.04	19.91	0.92	0.98
112	29	female	left	29.70	87.90	82.80	42.70	28.00	35.30	30.40	17.0	-195.96	-178.79	-43.77	5.72	-18.86	-2.36	1.66	1.11
113	26	female	left	17.50	19.80	20.10	18.10	17.40	18.90	9.80	13.0	-13.14	-14.86	-3.43	0.57	-8.00	44.00	0.67	0.68
114	22	female	left	13.30	68.40	47.40	37.30	20.80	16.80	8.00	18.0	-414.29	-256.39	-180.45	-56.39	-26.32	39.85	3.98	2.86
115	21	female	left	133.00	146.90	36.90	21.50	17.00	12.80	30.10	6.0	-10.45	72.26	83.83	87.22	90.38	77.37	0.40	-0.04
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	29.0	-153.64	-91.95	5.75	-9.96	9.20	28.35	1.43	0.87
117	42	female	left	80.10	75.80	57.50	41.90	34.80	25.00	17.50	5.0	5.37	28.21	47.69	56.55	68.79	78.15	0.65	0.47
119	44	female	left	106.50	149.30	155.40	160.60	136.20	102.10	79.80	24.0	-40.19	-45.92	-50.80	-27.89	4.13	25.07	0.86	0.88
121	41	female	left	28.60	41.20	40.10	34.20	21.70	15.40	6.00	18.0	-44.06	-40.21	-19.58	24.13	46.15	79.02	1.37	1.25

Appendix 24 continued/...

In control females

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured after passive leg lowering at 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
124	44	female	left	16.70	52.40	40.50	27.50	22.70	11.50	5.60	26.0	-213.77	-142.51	-64.67	-35.93	31.14	66.47	2.62	2.01
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	6.0	-14.40	30.28	60.88	69.72	64.48	48.45	0.30	-0.03
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	34.0	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00	0.08	-0.16
130	51	female	left	9.50	11.10	6.00	6.40	7.50	7.80	5.20	4.0	-16.84	36.84	32.63	21.05	17.89	45.26	0.39	0.19
132	43	female	left	22.60	14.00	13.30	13.90	10.60	8.60	7.60	4.0	38.05	41.15	38.50	53.10	61.95	66.37	0.32	0.30
133	42	female	left	9.30	15.00	15.60	13.00	8.00	5.20	4.30	19.0	-61.29	-67.74	-39.78	13.98	44.09	53.76	1.31	1.17
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	91.0	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59	0.51	0.31
137	46	female	left	11.10	14.20	18.50	13.60	7.60	8.40	6.20	16.0	-27.93	-66.67	-22.52	31.53	24.32	44.14	0.95	0.93
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	3.0	34.73	34.73	54.78	65.40	78.11	78.77	0.46	0.38
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	120.0	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66	-0.02	-0.09
141	48	female	left	20.20	18.80	16.80	13.00	8.70	7.90	6.20	5.0	6.93	16.83	35.64	56.93	60.89	69.31	0.60	0.47
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	4.0	16.36	41.41	60.99	44.22	60.69	74.74	0.48	0.34
143	53	female	left	132.50	100.50	93.80	89.80	81.40	59.90	29.70	2.0	24.15	29.21	32.23	38.57	54.79	77.58	0.61	0.59
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	5.0	10.84	34.41	47.72	68.25	65.40	71.10	0.49	0.31
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	2.0	77.43	25.14	66.99	28.83	93.91	87.38	0.43	0.59
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	3.0	-85.79	49.73	30.05	54.10	57.92	73.77	0.99	0.38

	baseline	5s	10s	15s	20s	30s	90s	Time to baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
Number of cases	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Mean	**80.87**	**85.80**	**73.55**	**73.67**	**64.15**	**52.08**	**43.84**	**14.75**	**-42.13**	**-15.85**	**-3.39**	**12.73**	**25.88**	**45.49**	**0.82**	**0.65**
Standard deviation	**103.45**	**116.42**	**107.77**	**117.65**	**94.31**	**87.18**	**78.67**	**19.94**	**84.26**	**66.35**	**53.87**	**43.55**	**42.54**	**35.67**	**0.73**	**0.61**
Median	**33.40**	**51.60**	**40.30**	**31.00**	**22.55**	**18.55**	**15.70**	**8.50**	**-18.82**	**1.90**	**5.71**	**21.16**	**32.89**	**52.86**	**0.64**	**0.53**
Minimum	**5.80**	**11.00**	**6.00**	**6.40**	**7.50**	**5.20**	**4.30**	**1.00**	**-414.3**	**-256.4**	**-180.5**	**-112.5**	**-119.0**	**-99.66**	**-0.30**	**-0.43**
Maximum	**542.60**	**792.7**	**723.1**	**723.8**	**483.0**	**506.6**	**377.2**	**120.00**	**77.43**	**77.16**	**83.83**	**87.22**	**93.91**	**87.38**	**3.98**	**2.86**

Appendix 25

The effect of age on the postural vasoconstrictive response, measured at the pulp of the big toe in asymptomatic controls

In young (21-40Y) asymptomatic controls																			
				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
100	25	male	right	24.30	43.90	34.50	31.80	28.40	17.40	6.20	16.0	-80.66	-41.98	-30.86	-16.87	28.40	74.49	1.59	1.38
101	23	female	right	16.60	25.70	25.20	16.20	14.50	10.70	6.40	15.0	-54.82	-51.81	2.41	12.65	35.54	61.45	1.20	1.02
102	40	male	right	125.90	97.40	91.20	36.30	48.60	62.00	98.20	5.0	22.64	27.56	71.17	61.40	50.75	22.00	-0.21	-0.38
103	28	female	right	21.60	63.30	48.70	38.50	45.90	21.90	11.80	19.0	-193.06	-125.46	-78.24	-112.50	-1.39	45.37	2.35	1.95
104	22	female	right	12.50	13.20	11.80	9.60	8.70	7.70	5.50	11.0	-5.60	5.60	23.20	30.40	38.40	56.00	0.60	0.50
105	34	male	right	42.90	55.40	57.30	37.20	44.80	36.20	33.70	7.0	-29.14	-33.57	13.29	-4.43	15.62	21.45	0.51	0.41
106	25	female	right	215.50	145.40	94.80	227.10	161.50	61.90	43.20	3.0	32.53	56.01	-5.38	25.06	71.28	79.95	0.63	0.66
107	27	male	right	82.50	63.50	29.10	34.50	26.90	22.20	43.80	4.0	23.03	64.73	58.18	67.39	73.09	46.91	-0.01	-0.22
108	26	female	right	177.30	138.80	92.20	76.80	68.30	50.70	82.70	4.0	21.71	48.00	56.68	61.48	71.40	53.36	0.15	-0.02
109	34	male	right	15.90	29.00	20.60	20.00	15.10	15.30	9.60	19.0	-82.39	-29.56	-25.79	5.03	3.77	39.62	1.06	0.78
110	22	female	right	20.10	21.10	17.20	21.70	16.70	17.40	10.20	7.0	-4.98	14.43	-7.96	16.92	13.43	49.25	0.58	0.55
111	38	male	right	179.80	108.90	96.80	155.50	141.90	182.20	114.00	1.0	39.43	46.16	13.52	21.08	-1.33	36.60	0.03	0.12
112	29	female	right	43.20	54.80	41.80	32.50	31.60	27.20	20.70	7.0	-26.85	3.24	24.77	26.85	37.04	52.08	0.67	0.46
113	26	female	right	17.60	23.90	17.50	16.60	13.70	13.50	11.50	10.0	-35.80	0.57	5.68	22.16	23.30	34.66	0.56	0.35
114	22	female	right	19.30	53.20	44.90	46.40	23.70	20.80	9.10	28.0	-175.65	-132.64	-140.41	-22.80	-7.77	52.85	2.40	2.08
115	21	female	right	191.80	178.90	85.40	162.80	133.10	80.60	90.40	2.0	6.73	55.47	15.12	30.60	57.98	52.87	0.35	0.21
122	32	male	right	42.80	41.90	27.90	21.50	19.20	11.70	10.30	5.0	2.10	34.81	49.77	55.14	72.66	75.93	0.61	0.40
123	25	male	right	10.00	9.60	9.30	9.40	5.00	3.90	4.10	5.0	4.00	7.00	6.00	50.00	61.00	59.00	0.61	0.53
100	25	male	left	18.00	38.10	41.70	17.60	22.10	11.90	7.60	15.0	-111.67	-131.67	2.22	-22.78	33.89	57.78	1.78	1.51
101	23	female	left	9.10	12.80	12.80	12.50	9.90	10.20	5.80	17.0	-40.66	-40.66	-37.36	-8.79	-12.09	36.26	0.91	0.89
102	40	male	left	161.90	108.40	111.70	101.30	117.20	139.70	32.70	4.0	33.05	31.01	37.43	27.61	13.71	79.80	0.58	0.65
103	28	female	left	20.80	20.50	25.20	29.00	20.20	20.90	8.80	7.0	1.44	-21.15	-39.42	2.88	-0.48	57.69	0.89	1.04

Appendix 25 continued/...

In young (21-40Y) asymptomatic controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured after passive leg lowering at 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
104	22	female	left	11.10	26.30	25.00	19.90	22.20	15.00	6.20	42.0	-136.94	-125.23	-79.28	-100.00	-35.14	44.14	2.04	1.92
105	34	male	left	7.10	16.10	18.00	11.00	8.20	4.10	4.70	17.0	-126.76	-153.52	-54.93	-15.49	42.25	33.80	1.78	1.52
106	25	female	left	80.70	67.50	66.40	51.90	22.40	6.70	27.70	1.0	16.36	17.72	35.69	72.24	91.70	65.68	0.49	0.35
107	27	male	left	64.70	30.80	22.00	32.70	53.90	20.30	9.50	3.0	52.40	66.00	49.46	16.69	68.62	85.32	0.43	0.47
108	26	female	left	98.30	126.10	103.90	100.90	127.00	82.00	138.60	11.0	-28.28	-5.70	-2.64	-29.20	16.58	-41.00	-0.30	-0.43
109	34	male	left	21.60	49.10	38.40	57.40	42.20	29.00	11.00	41.0	-127.31	-77.78	-165.74	-95.37	-34.26	49.07	2.10	2.08
110	22	female	left	45.20	62.80	80.80	65.30	62.90	37.50	36.20	29.0	-38.94	-78.76	-44.47	-39.16	17.04	19.91	0.92	0.98
111	38	male	left	149.10	116.30	98.80	147.60	213.30	70.90	109.40	2.0	22.00	33.74	1.01	-43.06	52.45	26.63	0.19	0.26
112	29	female	left	29.70	87.90	82.80	42.70	28.00	35.30	30.40	17.0	-195.96	-178.79	-43.77	5.72	-18.86	-2.36	1.66	1.11
113	26	female	left	17.50	19.80	20.10	18.10	17.40	18.90	9.80	13.0	-13.14	-14.86	-3.43	0.57	-8.00	44.00	0.67	0.68
114	22	female	left	13.30	68.40	47.40	37.30	20.80	16.80	8.00	18.0	-414.29	-256.39	-180.45	-56.39	-26.32	39.85	3.98	2.86
115	21	female	left	133.00	146.90	36.90	21.50	17.00	12.80	30.10	6.0	-10.45	72.26	83.83	87.22	90.38	77.37	0.40	-0.04
122	32	male	left	38.90	94.90	90.20	41.30	29.90	25.80	86.30	16.0	-143.96	-131.88	-6.17	23.14	33.68	-121.85	-0.36	-0.98
123	25	male	left	9.60	27.20	33.90	23.20	24.10	17.00	9.20	38.0	-183.33	-253.13	-141.67	-151.04	-77.08	4.17	2.47	2.52
Number of cases				**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**
Mean				**60.81**	**63.55**	**50.06**	**50.71**	**47.40**	**34.39**	**32.87**	**12.92**	**-55.09**	**-36.12**	**-14.96**	**0.12**	**24.76**	**40.84**	**0.95**	**0.78**
Standard deviation				**62.79**	**45.33**	**32.04**	**50.38**	**50.15**	**37.82**	**37.48**	**11.05**	**95.47**	**88.20**	**64.12**	**53.54**	**38.85**	**37.63**	**0.93**	**0.85**
Median				**27.00**	**54.00**	**40.05**	**33.60**	**25.50**	**20.55**	**11.25**	**10.50**	**-27.57**	**-10.28**	**-0.82**	**9.19**	**25.85**	**47.99**	**0.62**	**0.60**
Minimum				**7.10**	**9.60**	**9.30**	**9.40**	**5.00**	**3.90**	**4.10**	**1.00**	**-414.29**	**-256.39**	**-180.45**	**-151.04**	**-77.08**	**-121.85**	**-0.36**	**-0.98**
Maximum				**215.5**	**178.9**	**111.7**	**227.1**	**213.3**	**182.2**	**138.6**	**42.00**	**52.40**	**72.26**	**83.83**	**87.22**	**91.70**	**85.32**	**3.98**	**2.86**

In middle-aged (41-60Y) asymptomatic controls				The flux (arbitrary units) was measured							Time for flux to reach baseline (s)	The %drop in flux was measured						Slopes of %drop in flux between	
				at	----------after passive leg lowering at------------							----------after passive leg lowering at-----------							
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s		5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
117	42	female	right	214.80	236.00	204.60	180.60	139.40	109.70	88.30	9.0	-9.87	4.75	15.92	35.10	48.93	58.89	0.68	0.55
118	58	male	right	67.10	115.20	84.30	88.70	93.40	97.70	89.20	54.0	-71.68	-25.63	-32.19	-39.20	-45.60	-32.94	0.16	-0.01
119	44	female	right	26.80	27.80	29.80	23.00	21.10	18.00	17.70	3.0	-3.73	-11.19	14.18	21.27	32.84	33.96	0.42	0.37
121	41	female	right	37.40	33.20	29.00	29.50	23.20	16.30	14.40	4.0	11.23	22.46	21.12	37.97	56.42	61.50	0.53	0.45
124	44	female	right	23.00	40.70	33.60	26.90	21.70	17.80	7.90	17.0	-76.96	-46.09	-16.96	5.65	22.61	65.65	1.40	1.16
128	52	male	right	37.20	47.80	41.80	37.90	38.80	36.90	21.50	9.0	-28.49	-12.37	-1.88	-4.30	0.81	42.20	0.72	0.65
129	41	male	right	144.60	101.00	71.20	81.50	90.50	98.70	83.30	4.0	30.15	50.76	43.64	37.41	31.74	42.39	0.03	-0.03
130	51	female	right	39.40	24.70	20.10	11.40	13.70	11.30	14.00	1.0	37.31	48.98	71.07	65.23	71.32	64.47	0.17	0.05
131	42	male	right	144.70	85.80	78.80	78.00	82.80	34.20	60.60	3.0	40.70	45.54	46.10	42.78	76.36	58.12	0.19	0.15
132	43	female	right	247.40	255.30	224.60	269.90	272.00	216.00	38.50	6.0	-3.19	9.22	-9.09	-9.94	12.69	84.44	1.08	1.13
133	42	female	right	8.00	11.00	9.60	7.50	7.70	6.80	5.10	13.0	-37.50	-20.00	6.25	3.75	15.00	36.25	0.69	0.54
134	44	male	right	11.00	14.10	9.80	20.40	8.20	12.40	5.70	7.0	-28.18	10.91	-85.45	25.45	-12.73	48.18	0.88	0.87
136	53	male	right	13.70	22.80	12.40	7.70	7.30	6.90	5.80	8.0	-66.42	9.49	43.80	46.72	49.64	57.66	0.82	0.36
137	46	female	right	10.10	12.20	13.80	9.50	10.10	9.70	6.00	16.0	-20.79	-36.63	5.94	0.00	3.96	40.59	0.73	0.71
141	48	female	right	32.70	30.20	12.80	18.10	11.30	13.40	7.00	5.0	7.65	60.86	44.65	65.44	59.02	78.59	0.51	0.29
143	53	female	right	97.50	107.20	91.80	64.90	50.70	45.12	40.00	8.0	-9.95	5.85	33.44	48.00	53.72	58.97	0.61	0.43
117	42	female	left	80.10	75.80	57.50	41.90	34.80	25.00	17.50	5.0	5.37	28.21	47.69	56.55	68.79	78.15	0.65	0.47
118	58	male	left	50.60	50.00	25.10	23.90	24.00	22.80	22.70	5.0	1.19	50.40	52.77	52.57	54.94	55.14	0.28	0.04
119	44	female	left	106.50	149.30	155.40	160.60	136.20	102.10	79.80	24.0	-40.19	-45.92	-50.80	-27.89	4.13	25.07	0.86	0.88
121	41	female	left	28.60	41.20	40.10	34.20	21.70	15.40	6.00	18.0	-44.06	-40.21	-19.58	24.13	46.15	79.02	1.37	1.25

Appendix 25 continued/...

In middle-aged (41-60Y) asymptomatic controls

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
124	44	female	left	16.70	52.40	40.50	27.50	22.70	11.50	5.60	26.0	-213.77	-142.51	-64.67	-35.93	31.14	66.47	2.62	2.01
128	52	male	left	14.40	21.20	10.20	15.80	8.60	14.00	8.30	7.0	-47.22	29.17	-9.72	40.28	2.78	42.36	0.60	0.32
129	41	male	left	147.80	179.40	96.10	117.30	98.60	80.50	77.20	7.0	-21.38	34.98	20.64	33.29	45.53	47.77	0.47	0.23
130	51	female	left	9.50	11.10	6.00	6.40	7.50	7.80	5.20	4.0	-16.84	36.84	32.63	21.05	17.89	45.26	0.39	0.19
131	42	male	left	110.70	68.90	118.60	96.80	101.90	94.90	71.40	4.0	37.76	-7.14	12.56	7.95	14.27	35.50	0.25	0.42
132	43	female	left	22.60	14.00	13.30	13.90	10.60	8.60	7.60	4.0	38.05	41.15	38.50	53.10	61.95	66.37	0.32	0.30
133	42	female	left	9.30	15.00	15.60	13.00	8.00	5.20	4.30	19.0	-61.29	-67.74	-39.78	13.98	44.09	53.76	1.31	1.17
134	44	male	left	5.70	17.20	9.60	15.40	8.50	10.40	10.80	120.0	-201.75	-68.42	-170.18	-49.12	-82.46	-89.47	0.61	0.10
136	53	male	left	17.80	16.70	26.20	13.40	13.80	15.20	6.50	2.0	6.18	-47.19	24.72	22.47	14.61	63.48	0.84	0.92
137	46	female	left	11.10	14.20	18.50	13.60	7.60	8.40	6.20	16.0	-27.93	-66.67	-22.52	31.53	24.32	44.14	0.95	0.93
141	48	female	left	20.20	18.80	16.80	13.00	8.70	7.90	6.20	5.0	6.93	16.83	35.64	56.93	60.89	69.31	0.60	0.47
143	53	female	left	132.50	100.50	93.80	89.80	81.40	59.90	29.70	2.0	24.15	29.21	32.23	38.57	54.79	77.58	0.61	0.59
Number of cases				**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**
Mean				**60.61**	**62.83**	**53.48**	**51.63**	**46.45**	**38.77**	**27.19**	**13.59**	**-24.52**	**-3.19**	**3.77**	**22.52**	**29.39**	**48.71**	**0.70**	**0.56**
Standard deviation				**64.16**	**64.59**	**56.43**	**60.18**	**57.65**	**46.78**	**29.41**	**21.99**	**58.22**	**46.04**	**48.44**	**30.58**	**34.31**	**33.26**	**0.49**	**0.45**
Median				**30.65**	**36.95**	**29.40**	**25.40**	**21.70**	**15.85**	**12.40**	**7.00**	**-13.40**	**7.53**	**15.05**	**28.49**	**32.29**	**56.40**	**0.61**	**0.46**
Minimum				**5.70**	**11.00**	**6.00**	**6.40**	**7.30**	**5.20**	**4.30**	**1.00**	**-213.77**	**-142.51**	**-170.18**	**-49.12**	**-82.46**	**-89.47**	**0.03**	**-0.03**
Maximum				**247.4**	**255.3**	**224.6**	**269.9**	**272.0**	**216.0**	**89.2**	**120.0**	**40.7**	**60.9**	**71.1**	**65.4**	**76.4**	**84.4**	**2.6**	**2.0**

Appendix 25 continued/...

In elderly (61-90Y) asymptomatic controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	----------after passive leg lowering at------------- 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured ----------after passive leg lowering at----------- 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	18.0	-50.27	-12.10	-29.57	9.14	7.80	30.38	0.73	0.56
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	2.0	68.66	80.61	42.16	51.37	53.80	56.70	-0.10	-0.05
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	12.0	-21.37	-2.82	7.90	21.51	33.43	59.31	0.81	0.68
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	9.0	-20.17	15.32	26.09	52.73	35.09	29.83	0.26	0.02
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	4.0	25.22	53.67	-0.29	41.94	48.39	60.12	0.38	0.35
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	44.0	-220.44	-91.97	-47.45	-31.39	-62.77	21.90	1.82	1.12
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	2.0	6.84	33.41	53.53	45.72	48.92	20.01	-0.11	-0.31
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	4.0	14.30	18.94	4.26	31.47	27.07	44.43	0.36	0.36
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	2.0	52.92	77.16	72.63	51.60	32.94	48.47	-0.20	-0.25
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	19.0	-46.09	-33.27	-33.39	10.98	6.63	30.48	0.80	0.69
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	3.0	0.83	14.97	8.25	11.20	28.34	23.74	0.21	0.15
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	10.0	-81.76	12.84	-55.41	-4.05	34.46	66.22	1.33	1.03
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	3.0	18.10	20.18	15.10	21.61	-50.13	20.44	0.00	0.07
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	2.0	64.88	55.06	8.78	11.64	35.79	20.58	-0.29	-0.12
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	1.0	-81.78	-50.58	50.00	-17.83	-14.73	29.26	0.83	0.52
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	2.0	69.68	62.53	61.47	77.47	76.63	68.21	0.02	0.02
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	7.0	-7.83	29.86	53.91	-1.16	48.99	47.25	0.39	0.21
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	2.0	26.69	47.21	57.17	58.76	62.35	81.87	0.49	0.37
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	29.0	-153.64	-91.95	5.75	-9.96	9.20	28.35	1.43	0.87
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	3.0	49.54	32.62	48.00	-21.85	-24.77	20.31	-0.20	-0.02
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	6.0	-14.40	30.28	60.88	69.72	64.48	48.45	0.30	-0.03
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	8.0	-27.46	38.24	26.20	73.72	77.34	44.85	0.38	0.00

Appendix 25 continued/...

In elderly (61-90Y) asymptomatic controls

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	34.0	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00	0.08	-0.16
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	91.0	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59	0.51	0.31
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	3.0	13.45	12.85	49.22	21.13	-2.29	19.44	-0.04	-0.08
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	3.0	34.73	34.73	54.78	65.40	78.11	78.77	0.46	0.38
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	120.0	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66	-0.02	-0.09
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	4.0	16.36	41.41	60.99	44.22	60.69	74.74	0.48	0.34
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	5.0	2.51	18.66	-11.42	-8.64	-42.62	31.48	0.34	0.42
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	5.0	10.84	34.41	47.72	68.25	65.40	71.10	0.49	0.31
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	64.0	-75.82	-68.32	-26.92	-30.59	-23.99	23.81	1.03	0.91
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	2.0	77.43	25.14	66.99	28.83	93.91	87.38	0.43	0.59
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	3.0	-85.79	49.73	30.05	54.10	57.92	73.77	0.99	0.38
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	24.0	-28.56	-22.42	-32.84	-17.95	11.81	28.28	0.69	0.68
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	47.0	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26	2.24	1.03
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	16.0	-84.02	-156.19	-21.65	5.15	15.98	-16.49	0.83	0.68
Number of cases				**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**
Mean				**108.98**	**110.69**	**97.22**	**93.81**	**86.72**	**81.69**	**73.18**	**17.03**	**-31.50**	**1.37**	**8.95**	**12.61**	**16.05**	**32.03**	**0.50**	**0.33**
Standard deviation				**116.42**	**139.96**	**130.60**	**138.10**	**107.32**	**106.01**	**97.49**	**26.54**	**87.32**	**56.04**	**49.52**	**46.74**	**51.50**	**40.74**	**0.56**	**0.39**
Median				**61.50**	**59.40**	**49.75**	**39.65**	**36.95**	**34.75**	**34.00**	**5.00**	**-11.11**	**18.80**	**11.94**	**16.39**	**30.64**	**30.43**	**0.41**	**0.35**
Minimum				**5.80**	**12.30**	**7.50**	**8.30**	**8.40**	**7.70**	**4.80**	**1.00**	**-350.46**	**-156.19**	**-133.18**	**-118.35**	**-118.97**	**-99.66**	**-0.29**	**-0.31**
Maximum				**542.6**	**792.7**	**723.1**	**723.8**	**483.0**	**506.6**	**377.2**	**120.0**	**77.4**	**80.6**	**72.6**	**77.5**	**93.9**	**87.4**	**2.2**	**1.1**

Appendix 26

The effect of both age & sex on the postural vasoconstrictive response, measured at the pulp of the big toe in asymptomatic controls

In young (21-40Y) male controls

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	-----------after passive leg lowering at--------------						flux to reach	-----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
100	25	male	right	24.30	43.90	34.50	31.80	28.40	17.40	6.20	16.0	-80.66	-41.98	-30.86	-16.87	28.40	74.49	1.59	1.38
102	40	male	right	125.90	97.40	91.20	36.30	48.60	62.00	98.20	5.0	22.64	27.56	71.17	61.40	50.75	22.00	-0.21	-0.38
105	34	male	right	42.90	55.40	57.30	37.20	44.80	36.20	33.70	7.0	-29.14	-33.57	13.29	-4.43	15.62	21.45	0.51	0.41
107	27	male	right	82.50	63.50	29.10	34.50	26.90	22.20	43.80	4.0	23.03	64.73	58.18	67.39	73.09	46.91	-0.01	-0.22
109	34	male	right	15.90	29.00	20.60	20.00	15.10	15.30	9.60	19.0	-82.39	-29.56	-25.79	5.03	3.77	39.62	1.06	0.78
111	38	male	right	179.80	108.90	96.80	155.50	141.90	182.20	114.00	1.0	39.43	46.16	13.52	21.08	-1.33	36.60	0.03	0.12
122	32	male	right	42.80	41.90	27.90	21.50	19.20	11.70	10.30	5.0	2.10	34.81	49.77	55.14	72.66	75.93	0.61	0.40
123	25	male	right	10.00	9.60	9.30	9.40	5.00	3.90	4.10	5.0	4.00	7.00	6.00	50.00	61.00	59.00	0.61	0.53
100	25	male	left	18.00	38.10	41.70	17.60	22.10	11.90	7.60	15.0	-111.67	-131.67	2.22	-22.78	33.89	57.78	1.78	1.51
102	40	male	left	161.90	108.40	111.70	101.30	117.20	139.70	32.70	4.0	33.05	31.01	37.43	27.61	13.71	79.80	0.58	0.65
105	34	male	left	7.10	16.10	18.00	11.00	8.20	4.10	4.70	17.0	-126.76	-153.52	-54.93	-15.49	42.25	33.80	1.78	1.52
107	27	male	left	64.70	30.80	22.00	32.70	53.90	20.30	9.50	3.0	52.40	66.00	49.46	16.69	68.62	85.32	0.43	0.47
109	34	male	left	21.60	49.10	38.40	57.40	42.20	29.00	11.00	41.0	-127.31	-77.78	-165.74	-95.37	-34.26	49.07	2.10	2.08
111	38	male	left	149.10	116.30	98.80	147.60	213.30	70.90	109.40	2.0	22.00	33.74	1.01	-43.06	52.45	26.63	0.19	0.26
122	32	male	left	38.90	94.90	90.20	41.30	29.90	25.80	86.30	16.0	-143.96	-131.88	-6.17	23.14	33.68	-121.85	-0.36	-0.98
123	25	male	left	9.60	27.20	33.90	23.20	24.10	17.00	9.20	38.0	-183.33	-253.13	-141.67	-151.04	-77.08	4.17	2.47	2.52

Number of cases	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean	**62.19**	**58.16**	**51.34**	**48.64**	**52.55**	**41.85**	**36.89**	**12.38**	**-42.91**	**-33.88**	**-7.70**	**-1.35**	**27.33**	**36.92**	**0.82**	**0.69**
Standard deviation	**59.33**	**35.63**	**34.33**	**45.65**	**56.82**	**50.61**	**40.85**	**12.20**	**77.76**	**92.60**	**66.55**	**58.13**	**40.72**	**48.41**	**0.87**	**0.92**
Median	**40.85**	**46.50**	**36.45**	**33.60**	**29.15**	**21.25**	**10.65**	**6.00**	**-13.52**	**-11.28**	**4.11**	**10.86**	**33.78**	**43.27**	**0.59**	**0.50**
Minimum	**7.1**	**9.6**	**9.3**	**9.4**	**5.0**	**3.9**	**4.1**	**1.00**	**-183.3**	**-253.1**	**-165.7**	**-151.0**	**-77.1**	**-121.9**	**-0.36**	**-0.98**
Maximum	**179.8**	**116.3**	**111.7**	**155.5**	**213.3**	**182.2**	**114.0**	**41.0**	**52.4**	**66.0**	**71.2**	**67.4**	**73.1**	**85.3**	**2.5**	**2.5**

Appendix 26 continued/...

In young (21-40Y) female controls

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	----------after passive leg lowering at----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
101	23	female	right	16.60	25.70	25.20	16.20	14.50	10.70	6.40	15.0	-54.82	-51.81	2.41	12.65	35.54	61.45	1.20	1.02
103	28	female	right	21.60	63.30	48.70	38.50	45.90	21.90	11.80	19.0	-193.06	-125.46	-78.24	-112.50	-1.39	45.37	2.35	1.95
104	22	female	right	12.50	13.20	11.80	9.60	8.70	7.70	5.50	11.0	-5.60	5.60	23.20	30.40	38.40	56.00	0.60	0.50
106	25	female	right	215.50	145.40	94.80	227.10	161.50	61.90	43.20	3.0	32.53	56.01	-5.38	25.06	71.28	79.95	0.63	0.66
108	26	female	right	177.30	138.80	92.20	76.80	68.30	50.70	82.70	4.0	21.71	48.00	56.68	61.48	71.40	53.36	0.15	-0.02
110	22	female	right	20.10	21.10	17.20	21.70	16.70	17.40	10.20	7.0	-4.98	14.43	-7.96	16.92	13.43	49.25	0.58	0.55
112	29	female	right	43.20	54.80	41.80	32.50	31.60	27.20	20.70	7.0	-26.85	3.24	24.77	26.85	37.04	52.08	0.67	0.46
113	26	female	right	17.60	23.90	17.50	16.60	13.70	13.50	11.50	10.0	-35.80	0.57	5.68	22.16	23.30	34.66	0.56	0.35
114	22	female	right	19.30	53.20	44.90	46.40	23.70	20.80	9.10	28.0	-175.65	-132.64	-140.41	-22.80	-7.77	52.85	2.40	2.08
115	21	female	right	191.80	178.90	85.40	162.80	133.10	80.60	90.40	2.0	6.73	55.47	15.12	30.60	57.98	52.87	0.35	0.21
101	23	female	left	9.10	12.80	12.80	12.50	9.90	10.20	5.80	17.0	-40.66	-40.66	-37.36	-8.79	-12.09	36.26	0.91	0.89
103	28	female	left	20.80	20.50	25.20	29.00	20.20	20.90	8.80	7.0	1.44	-21.15	-39.42	2.88	-0.48	57.69	0.89	1.04
104	22	female	left	11.10	26.30	25.00	19.90	22.20	15.00	6.20	42.0	-136.94	-125.23	-79.28	-100.00	-35.14	44.14	2.04	1.92
106	25	female	left	80.70	67.50	66.40	51.90	22.40	6.70	27.70	1.0	16.36	17.72	35.69	72.24	91.70	65.68	0.49	0.35
108	26	female	left	98.30	126.10	103.90	100.90	127.00	82.00	138.60	11.0	-28.28	-5.70	-2.64	-29.20	16.58	-41.00	-0.30	-0.43
110	22	female	left	45.20	62.80	80.80	65.30	62.90	37.50	36.20	29.0	-38.94	-78.76	-44.47	-39.16	17.04	19.91	0.92	0.98
112	29	female	left	29.70	87.90	82.80	42.70	28.00	35.30	30.40	17.0	-195.96	-178.79	-43.77	5.72	-18.86	-2.36	1.66	1.11
113	26	female	left	17.50	19.80	20.10	18.10	17.40	18.90	9.80	13.0	-13.14	-14.86	-3.43	0.57	-8.00	44.00	0.67	0.68
114	22	female	left	13.30	68.40	47.40	37.30	20.80	16.80	8.00	18.0	-414.29	-256.39	-180.45	-56.39	-26.32	39.85	3.98	2.86
115	21	female	left	133.00	146.90	36.90	21.50	17.00	12.80	30.10	6.0	-10.45	72.26	83.83	87.22	90.38	77.37	0.40	-0.04
Number of cases				**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Mean				**59.71**	**67.87**	**49.04**	**52.37**	**43.28**	**28.43**	**29.66**	**13.35**	**-64.83**	**-37.91**	**-20.77**	**1.30**	**22.70**	**43.97**	**1.06**	**0.86**
Standard deviation				**66.93**	**52.34**	**30.97**	**54.99**	**45.20**	**22.99**	**35.30**	**10.35**	**108.58**	**86.91**	**63.22**	**51.08**	**38.23**	**27.11**	**0.99**	**0.81**
Median				**21.20**	**58.80**	**43.35**	**34.90**	**22.30**	**19.85**	**11.65**	**11.00**	**-27.57**	**-10.28**	**-4.41**	**9.19**	**16.81**	**50.67**	**0.67**	**0.67**
Minimum				**9.1**	**12.8**	**11.8**	**9.6**	**8.7**	**6.7**	**5.5**	**1.0**	**-414.3**	**-256.4**	**-180.5**	**-112.5**	**-35.1**	**-41.0**	**-0.3**	**-0.4**
Maximum				**215.5**	**178.9**	**103.9**	**227.1**	**161.5**	**82.0**	**138.6**	**42.0**	**32.5**	**72.3**	**83.8**	**87.2**	**91.7**	**80.0**	**4.0**	**2.9**

Appendix 26 continued/...

In middle-aged (41-60Y) male controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured after passive leg lowering at 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
118	58	male	right	67.10	115.20	84.30	88.70	93.40	97.70	89.20	54.0	-71.68	-25.63	-32.19	-39.20	-45.60	-32.94	0.16	-0.01
128	52	male	right	37.20	47.80	41.80	37.90	38.80	36.90	21.50	9.0	-28.49	-12.37	-1.88	-4.30	0.81	42.20	0.72	0.65
129	41	male	right	144.60	101.00	71.20	81.50	90.50	98.70	83.30	4.0	30.15	50.76	43.64	37.41	31.74	42.39	0.03	-0.03
131	42	male	right	144.70	85.80	78.80	78.00	82.80	34.20	60.60	3.0	40.70	45.54	46.10	42.78	76.36	58.12	0.19	0.15
134	44	male	right	11.00	14.10	9.80	20.40	8.20	12.40	5.70	7.0	-28.18	10.91	-85.45	25.45	-12.73	48.18	0.88	0.87
136	53	male	right	13.70	22.80	12.40	7.70	7.30	6.90	5.80	8.0	-66.42	9.49	43.80	46.72	49.64	57.66	0.82	0.36
118	58	male	left	50.60	50.00	25.10	23.90	24.00	22.80	22.70	5.0	1.19	50.40	52.77	52.57	54.94	55.14	0.28	0.04
128	52	male	left	14.40	21.20	10.20	15.80	8.60	14.00	8.30	7.0	-47.22	29.17	-9.72	40.28	2.78	42.36	0.60	0.32
129	41	male	left	147.80	179.40	96.10	117.30	98.60	80.50	77.20	7.0	-21.38	34.98	20.64	33.29	45.53	47.77	0.47	0.23
131	42	male	left	110.70	68.90	118.60	96.80	101.90	94.90	71.40	4.0	37.76	-7.14	12.56	7.95	14.27	35.50	0.25	0.42
134	44	male	left	5.70	17.20	9.60	15.40	8.50	10.40	10.80	120.0	-201.75	-68.42	-170.18	-49.12	-82.46	-89.47	0.61	0.10
136	53	male	left	17.80	16.70	26.20	13.40	13.80	15.20	6.50	2.0	6.18	-47.19	24.72	22.47	14.61	63.48	0.84	0.92
Number of cases				**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Mean				**63.78**	**61.68**	**48.68**	**49.73**	**48.03**	**43.72**	**38.58**	**19.17**	**-29.10**	**5.87**	**-4.60**	**18.02**	**12.49**	**30.87**	**0.49**	**0.34**
Standard deviation				**57.57**	**51.03**	**39.04**	**39.53**	**41.26**	**37.69**	**34.42**	**34.73**	**66.35**	**39.11**	**65.41**	**33.29**	**44.71**	**45.39**	**0.30**	**0.33**
Median				**43.90**	**48.90**	**34.00**	**30.90**	**31.40**	**28.50**	**22.10**	**7.00**	**-24.78**	**10.20**	**16.60**	**29.37**	**14.44**	**45.08**	**0.54**	**0.28**
Minimum				**5.7**	**14.1**	**9.6**	**7.7**	**7.3**	**6.9**	**5.7**	**2.0**	**-201.8**	**-68.4**	**-170.2**	**-49.1**	**-82.5**	**-89.5**	**0.03**	**-0.03**
Maximum				**147.8**	**179.4**	**118.6**	**117.3**	**101.9**	**98.7**	**89.2**	**120.0**	**40.7**	**50.8**	**52.8**	**52.6**	**76.4**	**63.5**	**0.88**	**0.92**

Appendix 26 continued/...

In middle-aged (41-60Y) female controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured after passive leg lowering at 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
117	42	female	right	214.80	236.00	204.60	180.60	139.40	109.70	88.30	9.0	-9.87	4.75	15.92	35.10	48.93	58.89	0.68	0.55
119	44	female	right	26.80	27.80	29.80	23.00	21.10	18.00	17.70	3.0	-3.73	-11.19	14.18	21.27	32.84	33.96	0.42	0.37
121	41	female	right	37.40	33.20	29.00	29.50	23.20	16.30	14.40	4.0	11.23	22.46	21.12	37.97	56.42	61.50	0.53	0.45
124	44	female	right	23.00	40.70	33.60	26.90	21.70	17.80	7.90	17.0	-76.96	-46.09	-16.96	5.65	22.61	65.65	1.40	1.16
130	51	female	right	39.40	24.70	20.10	11.40	13.70	11.30	14.00	1.0	37.31	48.98	71.07	65.23	71.32	64.47	0.17	0.05
132	43	female	right	247.40	255.30	224.60	269.90	272.00	216.00	38.50	6.0	-3.19	9.22	-9.09	-9.94	12.69	84.44	1.08	1.13
133	42	female	right	8.00	11.00	9.60	7.50	7.70	6.80	5.10	13.0	-37.50	-20.00	6.25	3.75	15.00	36.25	0.69	0.54
137	46	female	right	10.10	12.20	13.80	9.50	10.10	9.70	6.00	16.0	-20.79	-36.63	5.94	0.00	3.96	40.59	0.73	0.71
141	48	female	right	32.70	30.20	12.80	18.10	11.30	13.40	7.00	5.0	7.65	60.86	44.65	65.44	59.02	78.59	0.51	0.29
143	53	female	right	97.50	107.20	91.80	64.90	50.70	45.12	40.00	8.0	-9.95	5.85	33.44	48.00	53.72	58.97	0.61	0.43
117	42	female	left	80.10	75.80	57.50	41.90	34.80	25.00	17.50	5.0	5.37	28.21	47.69	56.55	68.79	78.15	0.65	0.47
119	44	female	left	106.50	149.30	155.40	160.60	136.20	102.10	79.80	24.0	-40.19	-45.92	-50.80	-27.89	4.13	25.07	0.86	0.88
121	41	female	left	28.60	41.20	40.10	34.20	21.70	15.40	6.00	18.0	-44.06	-40.21	-19.58	24.13	46.15	79.02	1.37	1.25
124	44	female	left	16.70	52.40	40.50	27.50	22.70	11.50	5.60	26.0	-213.77	-142.51	-64.67	-35.93	31.14	66.47	2.62	2.01
130	51	female	left	9.50	11.10	6.00	6.40	7.50	7.80	5.20	4.0	-16.84	36.84	32.63	21.05	17.89	45.26	0.39	0.19
132	43	female	left	22.60	14.00	13.30	13.90	10.60	8.60	7.60	4.0	38.05	41.15	38.50	53.10	61.95	66.37	0.32	0.30
133	42	female	left	9.30	15.00	15.60	13.00	8.00	5.20	4.30	19.0	-61.29	-67.74	-39.78	13.98	44.09	53.76	1.31	1.17
137	46	female	left	11.10	14.20	18.50	13.60	7.60	8.40	6.20	16.0	-27.93	-66.67	-22.52	31.53	24.32	44.14	0.95	0.93
141	48	female	left	20.20	18.80	16.80	13.00	8.70	7.90	6.20	5.0	6.93	16.83	35.64	56.93	60.89	69.31	0.60	0.47
143	53	female	left	132.50	100.50	93.80	89.80	81.40	59.90	29.70	2.0	24.15	29.21	32.23	38.57	54.79	77.58	0.61	0.59
Number of cases				**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Mean				**58.71**	**63.53**	**56.36**	**52.76**	**45.51**	**35.80**	**20.35**	**10.25**	**-21.77**	**-8.63**	**8.79**	**25.22**	**39.53**	**59.42**	**0.82**	**0.70**
Standard deviation				**69.20**	**72.78**	**65.49**	**70.72**	**66.59**	**52.19**	**24.38**	**7.69**	**54.42**	**49.90**	**35.78**	**29.39**	**21.79**	**17.03**	**0.54**	**0.47**
Median				**27.70**	**31.70**	**29.40**	**24.95**	**21.40**	**14.40**	**7.75**	**7.00**	**-9.91**	**5.30**	**15.05**	**27.83**	**45.12**	**62.98**	**0.66**	**0.55**
Minimum				**8.0**	**11.0**	**6.0**	**6.4**	**7.5**	**5.2**	**4.3**	**1.0**	**-213.8**	**-142.5**	**-64.7**	**-35.9**	**4.0**	**25.07**	**0.17**	**0.05**
Maximum				**247.4**	**255.3**	**224.6**	**269.9**	**272.0**	**216.0**	**88.3**	**26.0**	**38.1**	**60.9**	**71.1**	**65.4**	**71.3**	**84.44**	**2.62**	**2.01**

Appendix 26 continued/…

In elderly 61-90Y) male controls

I.D.	Age	Sex	Leg	The flux (arbitrary units) was measured at baseline	after passive leg lowering at 5s	10s	15s	20s	30s	90s	Time for flux to reach baseline (s)	The %drop in flux was measured after passive leg lowering at 5s	10s	15s	20s	30s	90s	Slopes of %drop in flux between 5s-90s	10s-90s
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	2.0	68.66	80.61	42.16	51.37	53.80	56.70	-0.10	-0.05
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	9.0	-20.17	15.32	26.09	52.73	35.09	29.83	0.26	0.02
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	2.0	6.84	33.41	53.53	45.72	48.92	20.01	-0.11	-0.31
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	3.0	0.83	14.97	8.25	11.20	28.34	23.74	0.21	0.15
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	3.0	18.10	20.18	15.10	21.61	-50.13	20.44	0.00	0.07
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	2.0	69.68	62.53	61.47	77.47	76.63	68.21	0.02	0.02
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	7.0	-7.83	29.86	53.91	-1.16	48.99	47.25	0.39	0.21
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	2.0	26.69	47.21	57.17	58.76	62.35	81.87	0.49	0.37
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	3.0	49.54	32.62	48.00	-21.85	-24.77	20.31	-0.20	-0.02
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	8.0	-27.46	38.24	26.20	73.72	77.34	44.85	0.38	0.00
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	3.0	13.45	12.85	49.22	21.13	-2.29	19.44	-0.04	-0.08
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	5.0	2.51	18.66	-11.42	-8.64	-42.62	31.48	0.34	0.42
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	64.0	-75.82	-68.32	-26.92	-30.59	-23.99	23.81	1.03	0.91
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	24.0	-28.56	-22.42	-32.84	-17.95	11.81	28.28	0.69	0.63
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	47.0	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26	2.24	1.03
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	16.0	-84.02	-156.19	-21.65	5.15	15.98	-16.49	0.83	0.68
Number of cases				**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean				**89.96**	**91.55**	**74.68**	**66.24**	**65.53**	**68.81**	**62.77**	**12.50**	**-21.13**	**4.35**	**17.87**	**13.77**	**16.85**	**30.72**	**0.40**	**0.26**
Standard deviation				**65.83**	**71.53**	**57.46**	**48.23**	**48.55**	**57.92**	**53.39**	**18.09**	**97.92**	**61.04**	**38.45**	**49.16**	**43.93**	**25.14**	**0.60**	**0.39**
Median				**63.45**	**56.00**	**55.50**	**52.60**	**49.60**	**59.45**	**46.70**	**4.00**	**1.67**	**19.42**	**26.14**	**16.17**	**22.16**	**26.04**	**0.30**	**0.11**
Minimum				**10.9**	**14.4**	**12.0**	**15.9**	**10.7**	**11.1**	**9.1**	**2.0**	**-350.5**	**-156.2**	**-62.4**	**-118.3**	**-50.1**	**-16.5**	**-0.20**	**-0.31**
Maximum				**218.6**	**237.7**	**190.5**	**146.2**	**172.4**	**223.6**	**176.1**	**64.0**	**69.7**	**80.6**	**61.5**	**77.5**	**77.3**	**81.9**	**2.24**	**1.03**

Appendix 26 continued/…

In elderly 61-90Y) female controls

				The flux (arbitrary units) was measured							Time for	The %drop in flux was measured						Slopes of %drop	
				at	-----------after passive leg lowering at--------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	18.0	-50.27	-12.10	-29.57	9.14	7.80	30.38	0.73	0.56
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	12.0	-21.37	-2.82	7.90	21.51	33.43	59.31	0.81	0.68
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	4.0	25.22	53.67	-0.29	41.94	48.39	60.12	0.38	0.35
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	44.0	-220.44	-91.97	-47.45	-31.39	-62.77	21.90	1.82	1.12
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	4.0	14.30	18.94	4.26	31.47	27.07	44.43	0.36	0.36
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	2.0	52.92	77.16	72.63	51.60	32.94	48.47	-0.20	-0.25
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	19.0	-46.09	-33.27	-33.39	10.98	6.63	30.48	0.80	0.69
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	10.0	-81.76	12.84	-55.41	-4.05	34.46	66.22	1.33	1.03
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	2.0	64.88	55.06	8.78	11.64	35.79	20.58	-0.29	-0.12
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	1.0	-81.78	-50.58	50.00	-17.83	-14.73	29.26	0.83	0.52
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	29.0	-153.64	-91.95	5.75	-9.96	9.20	28.35	1.43	0.87
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	6.0	-14.40	30.28	60.88	69.72	64.48	48.45	0.30	-0.03
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	34.0	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00	0.08	-0.16
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	91.0	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59	0.51	0.31
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	3.0	34.73	34.73	54.78	65.40	78.11	78.77	0.46	0.38
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	120.0	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66	-0.02	-0.09
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	4.0	16.36	41.41	60.99	44.22	60.69	74.74	0.48	0.34
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	5.0	10.84	34.41	47.72	68.25	65.40	71.10	0.49	0.31
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	2.0	77.43	25.14	66.99	28.83	93.91	87.38	0.43	0.59
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	3.0	-85.79	49.73	30.05	54.10	57.92	73.77	0.99	0.38
Number of cases				**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Mean				**124.20**	**126.01**	**115.25**	**115.88**	**103.67**	**92.01**	**81.52**	**20.65**	**-39.80**	**-1.02**	**1.82**	**11.68**	**15.41**	**33.07**	**0.59**	**0.39**
Standard deviation				**144.90**	**177.46**	**167.46**	**179.28**	**136.65**	**133.42**	**122.85**	**31.75**	**79.46**	**53.20**	**56.83**	**45.98**	**57.98**	**50.56**	**0.53**	**0.39**
Median				**56.85**	**61.05**	**46.20**	**36.90**	**33.15**	**29.00**	**29.95**	**5.50**	**-33.73**	**15.89**	**6.82**	**16.57**	**33.18**	**46.44**	**0.49**	**0.37**
Minimum				**5.8**	**12.3**	**7.5**	**8.3**	**8.4**	**7.7**	**4.8**	**1.0**	**-220.4**	**-99.5**	**-133.2**	**-82.8**	**-119.0**	**-99.7**	**-0.29**	**-0.25**
Maximum				**542.6**	**792.7**	**723.1**	**723.8**	**483.0**	**506.6**	**377.2**	**120.0**	**77.4**	**77.2**	**72.6**	**69.7**	**93.9**	**87.4**	**1.82**	**1.12**

Appendix 27

Changes in hardness indices in patients with CVI (with frank venous ulcers and without)

Hardness indices measured in asymptomatic controls					
I.D.	Age	Sex	Index 1	Index 2	Index 3
6	37	female	2.34	1.34	0.90
14	39	female	1.34	1.10	0.88
16	48	male	1.12	1.32	1.11
22	45	female	1.78	1.23	0.99
25	78	female	1.94	2.03	1.43
26	40	female	2.39	1.58	1.47
28	46	female	1.60	1.50	1.49
29	51	male	2.34	1.34	0.61
30	73	female	1.72	1.72	1.40
31	83	female	1.78	1.98	1.38
33	68	female	1.73	1.68	1.56
35	55	female	1.45	1.63	1.46
36	69	female	2.12	1.61	1.61
37	68	female	2.25	1.62	1.27
38	52	female	1.91	1.74	1.28
39	53	female	1.41	1.23	1.23
40	65	male	1.51	1.38	1.16
41	68	male	2.06	2.09	1.33
43	80	female	1.58	1.76	1.45
44	77	female	1.98	2.07	1.33
45	71	female	1.62	1.67	1.38
46	73	male	2.11	1.46	1.30
47	65	female	2.07	1.82	1.56
48	75	female	1.77	1.74	1.94
49	70	female	1.30	1.51	1.51
50	66	female	1.54	1.49	1.22
51	70	female	1.47	1.90	1.37
52	70	female	1.66	1.51	1.26
53	68	male	1.95	1.51	1.17
54	70	female	2.12	2.43	1.78

	Index 1	Index 2	Index 3
Number of cases	**30**	**30**	**30**
Mean	**1.80**	**1.63**	**1.33**
Standard deviation	**0.34**	**0.30**	**0.27**
Median	**1.78**	**1.62**	**1.35**
Minimum	**1.12**	**1.10**	**0.61**
Maximum	**2.39**	**2.43**	**1.94**

Appendix 27 continued/...

Hardness indices measured in patients with CVI					
I.D.	Age	Sex	Index 1	Index 2	Index 3
102	43	male	1.45	1.26	1.18
103	61	female	1.48	1.38	1.09
104	53	female	1.56	1.05	1.03
106	56	female	1.85	1.49	1.28
107	72	female	1.99	1.83	1.35
108	40	female	1.60	1.28	0.90
109	42	female	1.80	1.23	1.21
110	69	female	1.63	2.11	2.17
111	35	female	1.98	1.25	1.08
113	76	female	3.37	2.17	2.55
114	47	female	1.95	1.49	1.43
115	56	female	1.27	1.35	1.68
116	61	female	2.81	2.15	1.71
117	69	male	2.93	2.48	1.44
118	86	female	1.91	1.92	1.87
119	71	male	2.56	2.41	1.64
120	78	female	2.16	1.58	1.30
121	74	female	2.10	1.47	1.43
122	69	female	2.09	2.40	1.66
123	65	female	1.46	1.36	1.15
124	71	female	2.19	2.15	1.76
125	65	female	2.34	1.55	1.65
126	79	male	1.59	1.19	1.35
127	70	female	1.94	2.03	1.73
128	80	male	1.89	1.68	1.29
129	55	male	1.74	1.31	1.06
130	68	female	2.35	2.33	1.26
131	38	female	2.06	1.56	1.29
132	84	female	1.74	1.51	1.30
138	73	female	2.11	1.89	1.48

Number of cases	**30**	**30**	**30**
Mean	**2.00**	**1.70**	**1.44**
Standard deviation	**0.47**	**0.42**	**0.35**
Median	**1.95**	**1.55**	**1.35**
Minimum	**1.27**	**1.05**	**0.90**
Maximum	**3.37**	**2.48**	**2.55**

Appendix 27 continued/...

Hardness indices measured in patients with venous ulcers					
I.D.	Age	Sex	Index 1	Index 2	Index 3
201	73	female	1.69	1.63	#
202	75	male	2.35	2.11	#
203	75	female	2.48	//	#
204	85	female	1.07	1.68	#
205	58	male	//	1.63	1.55
206	46	male	2.22	1.52	0.81
207	83	female	//	2.51	1.51
208	82	female	3.12	2.40	1.61
209	69	male	1.92	1.23	1.10
210	80	female	2.29	2.26	1.74
211	79	female	2.19	1.57	0.92
212	80	male	3.46	2.79	1.68
213	78	female	2.51	//	1.41
214	73	female	2.97	3.19	2.07

// data were not available due to the presence of ulcer
= data were not measured

Number of cases	**12**	**12**	**10**
Mean	**2.36**	**2.04**	**1.44**
Standard deviation	**0.64**	**0.60**	**0.39**
Median	**2.32**	**1.89**	**1.53**
Minimum	**1.07**	**1.23**	**0.81**
Maximum	**3.46**	**3.19**	**2.07**

Appendix 28

Changes in the hardness indices in elderly (61-90Y) patients with CVI (with frank venous ulcers and without)

Hardness indices measured in elderly (61-90Y) asymptomatic controls					
I.D.	Age	Sex	Index 1	Index 2	Index 3
25	78	female	1.94	2.03	1.43
30	73	female	1.72	1.72	1.40
31	83	female	1.78	1.98	1.38
33	68	female	1.73	1.68	1.56
36	69	female	2.12	1.61	1.61
37	68	female	2.25	1.62	1.27
40	65	male	1.51	1.38	1.16
41	68	male	2.06	2.09	1.33
43	80	female	1.58	1.76	1.45
44	77	female	1.98	2.07	1.33
45	71	female	1.62	1.67	1.38
46	73	male	2.11	1.46	1.30
47	65	female	2.07	1.82	1.56
48	75	female	1.77	1.74	1.94
49	70	female	1.30	1.51	1.51
50	66	female	1.54	1.49	1.22
51	70	female	1.47	1.90	1.37
52	70	female	1.66	1.51	1.26
53	68	male	1.95	1.51	1.17
54	70	female	2.12	2.43	1.78

Number of cases	**30**	**30**	**30**
Mean	**1.81**	**1.75**	**1.42**
Standard deviation	**0.27**	**0.27**	**0.20**
Median	**1.78**	**1.70**	**1.38**
Minimum	**1.30**	**1.38**	**1.16**
Maximum	**2.25**	**2.43**	**1.94**

Appendix 28 continued/...

Hardness indices measured in elderly (61-90Y) patients with CVI					
I.D.	Age	Sex	Index 1	Index 2	Index 3
103	61	female	1.48	1.38	1.09
107	72	female	1.99	1.83	1.35
110	69	female	1.63	2.11	2.17
113	76	female	3.37	2.17	2.55
116	61	female	2.81	2.15	1.71
117	69	male	2.93	2.48	1.44
118	86	female	1.91	1.92	1.87
119	71	male	2.56	2.41	1.64
120	78	female	2.16	1.58	1.30
121	74	female	2.10	1.47	1.43
122	69	female	2.09	2.40	1.66
123	65	female	1.46	1.36	1.15
124	71	female	2.19	2.15	1.76
125	65	female	2.34	1.55	1.65
126	79	male	1.59	1.19	1.35
127	70	female	1.94	2.03	1.73
128	80	male	1.89	1.68	1.29
130	68	female	2.35	2.33	1.26
132	84	female	1.74	1.51	1.30
138	73	female	2.11	1.89	1.48

	Index 1	Index 2	Index 3
Number of cases	**30**	**30**	**30**
Mean	**2.13**	**1.88**	**1.56**
Standard deviation	**0.50**	**0.40**	**0.35**
Median	**2.09**	**1.91**	**1.46**
Minimum	**1.46**	**1.19**	**1.09**
Maximum	**3.37**	**2.48**	**2.55**

Appendix 28 continued/…

Hardness indices measured in elderly (61-90Y) patients with venous ulcers					
I.D.	Age	Sex	Index 1	Index 2	Index 3
201	73	female	1.69	1.63	#
202	75	male	2.35	2.11	#
203	75	female	2.48	//	#
204	85	female	1.07	1.68	#
207	83	female	//	2.51	1.51
208	82	female	3.12	2.40	1.61
209	69	male	1.92	1.23	1.10
210	80	female	2.29	2.26	1.74
211	79	female	2.19	1.57	0.92
212	80	male	3.46	2.79	1.68
213	78	female	2.51	//	1.41
214	73	female	2.97	3.19	2.07

// data were not available due to the presence of ulcer
= data were not measured

Number of cases	**11**	**10**	**8**
Mean	**2.37**	**2.14**	**1.50**
Standard deviation	**0.67**	**0.61**	**0.37**
Median	**2.35**	**2.18**	**1.56**
Minimum	**1.07**	**1.23**	**0.92**
Maximum	**3.46**	**3.19**	**2.07**

Appendix 29

Changes in extensibility and relaxation indices in patients with CVI (with frank venous ulcers and without)

Extensibility and relaxation indices measured in asymptomatic controls

I.D.	Age	Sex	Extensibility index	Relaxation index
1	44	male	0.85	1.36
3	43	female	""	""
4	53	female	0.58	0.00
6	31	female	0.75	1.62
7	27	female	1.00	0.78
9	39	female	1.19	0.34
10	63	male	1.56	0.82
12	37	male	1.42	0.25
14	49	male	0.56	-0.04
15	49	female	0.40	0.57
16	49	male	1.46	0.54
17	47	female	1.62	1.87
18	48	female	1.43	0.15
19	45	female	1.53	-0.33
21	33	male	1.06	1.05
27	58	male	0.90	3.24
28	69	female	0.87	0.17
29	44	female	1.15	0.06
32	56	male	""	""
34	38	female	1.60	-0.24
35	47	female	""	""
36	42	female	1.87	0.41
38	44	female	2.01	-0.05
39	35	female	0.88	-0.14
42	53	female	1.65	1.17
44	29	female	1.81	0.32
47	45	male	2.07	0.01
48	58	female	0.38	-0.07
51	44	female	1.38	0.18
52	65	female	""	""
53	51	male	""	""
54	72	male	""	""
55	78	female	2.57	0.19
56	61	male	1.78	0.22
57	73	female	2.88	-0.18
58	83	female	3.17	-1.98
59	51	male	0.89	-0.55
60	68	female	2.67	0.33
61	55	female	1.06	0.12

Appendix 29 continued/...

Extensibility and relaxation indices measured in asymptomatic controls

I.D.	Age	Sex	Extensibility index	Relaxation index
62	69	female	2.48	0.74
63	68	female	2.23	0.46
64	52	female	2.24	0.33
65	53	female	1.50	-0.13
66	65	male	1.14	0.26
67	68	male	2.30	0.19
68	61	male	2.37	0.15
69	80	female	1.95	0.88
70	77	female	""	""
71	71	female	1.23	0.35
72	73	male	2.08	0.02
73	65	female	2.24	0.44
74	75	female	2.09	0.36
75	70	female	1.74	-0.08
76	66	female	1.24	-0.11
77	70	female	1.77	Artifact
78	70	female	2.27	0.44
79	68	male	1.75	-0.01
80	70	female	""	""

"" index was not calculated due to the unavailability of data from both extremities

Number of cases	**50**	**49**
Mean	**1.59**	**0.34**
Standard deviation	**0.66**	**0.72**
Median	**1.58**	**0.22**
Minimum	**0.38**	**-1.98**
Maximum	**3.17**	**3.24**

Appendix 29 continued/…

Extensibility and relaxation indices measured in Patients with CVI

I.D.	Age	Sex	Extensibility index	Relaxation index
101	67	female	1.78	-0.15
102	68	male	1.46	0.10
103	39	female	1.20	-1.37
104	51	male	1.87	-0.24
105	55	female	1.42	-2.88
106	74	female	1.64	0.58
107	45	female	1.41	0.70
108	51	female	1.87	-0.68
109	63	male	1.39	0.90
110	35	female	""	""
111	53	male	1.01	-1.01
112	66	female	""	""
113	51	female	1.21	-2.10
114	78	female	1.44	0.87
115	33	male	1.02	-0.53
116	55	female	1.24	-0.27
117	59	female	0.82	-0.23
118	73	female	1.46	0.51
119	50	male	1.53	-0.55
120	35	male	1.26	0.36
121	71	female	""	""
122	59	male	0.69	0.64
123	40	female	1.01	0.20
124	50	female	""	""
125	50	female	1.01	0.30
126	79	female	0.54	0.66
127	32	female	""	""
128	56	female	""	""
129	25	female	1.40	1.03
130	73	female	1.31	0.43
131	72	female	""	""
132	81	male	2.32	0.16
133	53	male	""	""
134	70	female	1.18	-2.50
135	67	female	1.66	0.16
136	70	female	1.79	0.12
137	69	male	2.35	0.65
138	58	female	2.65	0.18
139	43	female	1.80	Artifact
140	76	female	1.35	-0.12
141	54	female	1.09	-0.46
142	59	male	""	""

Appendix 29 continued/...

Extensibility and relaxation indices measured in Patients with CVI

I.D.	Age	Sex	Extensibility index	Relaxation index
143	43	male	1.57	0.03
144	52	female	1.37	0.04
145	47	female	2.45	0.06
146	75	female	2.27	0.50
147	51	female	1.68	0.34
148	67	female	1.60	-1.92
149	67	female	1.59	-0.17
150	75	female	2.37	0.51
151	46	female	0.68	-0.10
152	73	male	""	""
153	70	female	2.21	0.24
154	54	female	1.79	0.70
155	74	female	""	""
156	46	female	2.32	0.86
157	47	female	1.84	0.50
158	67	male	""	""
159	66	male	""	""
160	65	female	0.53	-0.22
161	71	female	2.61	0.18
162	65	female	2.08	0.28
163	79	male	1.08	0.30
164	70	female	1.70	0.15
165	80	male	1.45	-0.38
166	55	male	2.03	-1.36
167	68	female	1.08	0.06
168	38	female	0.73	0.12

"" index was not calculated due to the unavailability of data from both extremities

	Extensibility index	Relaxation index
Number of cases	**55**	**54**
Mean	**1.53**	**-0.07**
Standard deviation	**0.53**	**0.83**
Median	**1.46**	**0.14**
Minimum	**0.53**	**-2.88**
Maximum	**2.65**	**1.03**

Appendix 29 continued/...

Extensibility and relaxation indices measured in Patients with frank venous ulcers				
I.D.	Age	Sex	Extensibility index	Relaxation index
301	70	female	2.27	-0.72
302	60	female	1.81	0.89
303	81	female	1.82	-0.39
304	49	female	1.34	0.00
305	75	male	2.10	-0.15
306	72	female	1.18	-0.70
307	62	female	0.92	-0.68
308	61	male	1.40	0.48
309	65	female	1.68	-0.29
310	73	male	1.44	-0.08
311	74	female	2.33	-2.58
312	57	male	0.65	-3.06
313	66	female	0.16	0.22
314	56	female	1.11	0.16
315	34	male	1.80	-0.44
316	72	female	1.24	0.15
317	75	female	1.26	-0.07
318	85	female	2.23	0.40
319	58	male	2.33	0.18
320	54	male	0.94	-0.03
321	83	female	0.19	-0.36
322	69	male	1.19	0.04

Number of cases	**22**	**22**
Mean	**1.43**	**-0.32**
Standard deviation	**0.63**	**0.90**
Median	**1.37**	**-0.08**
Minimum	**0.16**	**-3.06**
Maximum	**2.33**	**0.89**

Appendix 30

Changes in extensibility and relaxation indices in elderly (61-90Y) patients with CVI (with frank venous ulcers and without)

Extensibility and relaxation indices measured in the elderly asymptomatic controls

I.D.	Age	Sex	Extensibility index	Relaxation index
10	63	male	1.56	0.82
28	69	female	0.87	0.17
52	65	female	""	""
54	72	male	""	""
55	78	female	2.57	0.19
56	61	male	1.78	0.22
57	73	female	2.88	-0.18
58	83	female	3.17	-1.98
60	68	female	2.67	0.33
62	69	female	2.48	0.74
63	68	female	2.23	0.46
66	65	male	1.14	0.26
67	68	male	2.30	0.19
68	61	male	2.37	0.15
69	80	female	1.95	0.88
70	77	female	""	""
71	71	female	1.23	0.35
72	73	male	2.08	0.02
73	65	female	2.24	0.44
74	75	female	2.09	0.36
75	70	female	1.74	-0.08
76	66	female	1.24	-0.11
77	70	female	1.77	Artifact
78	70	female	2.27	0.44
79	68	male	1.75	-0.01
80	70	female	""	""

"" index was not calculated due to the unavailability of data from both extremities

Number of cases	**22**	**21**
Mean	**2.02**	**0.17**
Standard deviation	**0.58**	**0.57**
Median	**2.08**	**0.22**
Minimum	**0.87**	**-1.98**
Maximum	**3.17**	**0.88**

Appendix 30 continued/...

Extensibility and relaxation indices measured in elderly patients with CVI

I.D.	Age	Sex	Extensibility index	Relaxation index
101	67	female	1.78	-0.15
102	68	male	1.46	0.10
106	74	female	1.64	0.58
109	63	male	1.39	0.90
112	66	female	""	""
114	78	female	1.44	0.87
118	73	female	1.46	0.51
121	71	female	""	""
126	79	female	0.54	0.66
130	73	female	1.31	0.43
131	72	female	""	""
132	81	male	2.32	0.16
134	70	female	1.18	-2.50
135	67	female	1.66	0.16
136	70	female	1.79	0.12
137	69	male	2.35	0.65
140	76	female	1.35	-0.12
146	75	female	2.27	0.50
148	67	female	1.60	-1.92
149	67	female	1.59	-0.17
150	75	female	2.37	0.51
152	73	male	""	""
153	70	female	2.21	0.24
155	74	female	""	""
158	67	male	""	""
159	66	male	""	""
160	65	female	0.53	-0.22
161	71	female	2.61	0.18
162	65	female	2.08	0.28
163	79	male	1.08	0.30
164	70	female	1.70	0.15
165	80	male	1.45	-0.38
167	68	female	1.08	0.06

"" index was not calculated due to the unavailability of data from both extremities

	Extensibility index	Relaxation index
Number of cases	**26**	**26**
Mean	**1.63**	**0.07**
Standard deviation	**0.53**	**0.75**
Median	**1.59**	**0.17**
Minimum	**0.53**	**-2.50**
Maximum	**2.61**	**0.90**

Appendix 30 continued/...

Extensibility and relaxation indices measured in elderly patients with frank venous ulcers

I.D.	Age	Sex	Extensibility index	Relaxation index
301	70	female	2.27	-0.72
303	81	female	1.82	-0.39
305	75	male	2.10	-0.15
306	72	female	1.18	-0.70
307	62	female	0.92	-0.68
308	61	male	1.40	0.48
309	65	female	1.68	-0.29
310	73	male	1.44	-0.08
311	74	female	2.33	-2.58
313	66	female	0.16	0.22
316	72	female	1.24	0.15
317	75	female	1.26	-0.07
318	85	female	2.23	0.40
321	83	female	0.19	-0.36
322	69	male	1.19	0.04

Number of cases	**15**	**15**
Mean	**1.43**	**-0.32**
Standard deviation	**0.68**	**0.73**
Median	**1.40**	**-0.15**
Minimum	**0.16**	**-2.58**
Maximum	**2.33**	**0.48**

Appendix 31

The forearm cutaneous microcirculation during skin extension/relaxation, differences between controls and patients with CVI (with frank venous ulcers and without)

Forearms cutaneous microcirculation during skin extension/relaxation in asymptomatic controls

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	----------During relaxation phase-----				time to reach	During	------------During relaxation phase----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
302	37	male															
303	43	female	4	50.60	41.60	16.80	22.50	26.30	27.80	0.50	-17.79	-66.80	-55.53	-48.02	-45.06	-3.58	7.27
304	65	female	4	63.50	67.30	68.90	87.80	91.00	91.60	8.00	5.98	8.50	38.27	43.31	44.25	11.14	11.23
305	53	female	4	19.00	40.90	43.00	49.20	59.70	55.70	8.00	115.26	126.32	158.95	214.21	193.16	24.37	25.58
306	40	male															
307	31	female	4	47.90	49.20	35.70	54.90	69.20	77.50	4.50	2.71	-25.47	14.61	44.47	61.80	18.81	29.17
308	28	female															
309	44	female	4	33.10	36.00	33.10	32.70	39.10	43.00	7.00	8.76	0.00	-1.21	18.13	29.91	6.04	10.91
310	72	male	4	34.00	38.40	41.70	37.50	37.30	37.90	7.00	12.94	22.65	10.29	9.71	11.47	-1.59	-3.41
311	44	female	4	54.60	60.00	58.30	58.20	57.70	56.80	5.00	9.89	6.78	6.59	5.68	4.03	-1.28	-0.92
312	58	male	4	22.70	37.10	50.00	51.70	55.30	56.00	6.00	63.44	120.26	127.75	143.61	146.70	18.99	9.52
313	69	female	4	34.60	51.90	37.80	40.20	42.10	45.40	7.00	50.00	9.25	16.18	21.68	31.21	-2.52	7.14
316	51	male	4	35.40	54.00	32.20	29.50	28.90	30.90	3.00	52.54	-9.04	-16.67	-18.36	-12.71	-13.98	-1.27
317	33	male	4	188.50	188.40	138.60	163.90	181.70	194.10	4.00	-0.05	-26.47	-13.05	-3.61	2.97	2.89	9.78
320	45	female	4	9.50	17.30	22.00	28.50	26.90	27.70	1.00	82.11	131.58	200.00	183.16	191.58	27.05	16.32
321	47	female	4	21.20	53.20	16.40	23.20	28.30	31.80	5.00	150.94	-22.64	9.43	33.49	50.00	-14.58	24.20
322	49	male	4	32.10	56.40	53.70	70.40	71.30	77.10	3.00	75.70	67.29	119.31	122.12	140.19	18.38	22.15
323	48	female	4	13.50	31.10	31.20	37.40	38.00	36.40	4.00	130.37	131.11	177.04	181.48	169.63	12.89	12.00

Appendix 31 continued/...

Forearms cutaneous microcirculation during skin extension/relaxation in asymptomatic controls

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	----------During relaxation phase-----				time to reach	During	------------During relaxation phase----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
324	49	female	4	13.30	20.10	23.30	32.80	44.60	38.60	3.00	51.13	75.19	146.62	235.34	190.23	43.84	43.38
325	39	female	4	33.00	35.10	41.00	52.60	46.10	44.50	2.00	6.36	24.24	59.39	39.70	34.85	7.24	1.21
329	49	male	4	65.70	88.70	59.90	74.40	93.80	97.10	1.00	35.01	-8.83	13.24	42.77	47.79	7.72	19.94
330	63	male	4	38.00	49.50	37.00	46.30	41.40	44.40	5.00	30.26	-2.63	21.84	8.95	16.84	-1.53	4.55
331	36	male	4	13.30	20.90	15.10	18.90	20.60	21.50	5.00	57.14	13.53	42.11	54.89	61.65	5.04	15.71
332	45	male	3	""58.6	""71.7	""69.2	""59.4	""46.3		""7	""22.36	""18.09	""1.37	""-20.99			
333	35	female	4	32.10	38.70	35.00	66.10	68.80	81.30	7.00	20.56	9.03	105.92	114.33	153.27	37.07	44.11
334	44	female	4	22.90	28.80	31.70	38.90	41.40	42.90	7.00	25.76	38.43	69.87	80.79	87.34	16.55	15.77
335	44	male															
337	47	female															
338	65	female	4	40.20	55.30	38.30	35.60	34.80	33.40	1.00	37.56	-4.73	-11.44	-13.43	-16.92	-11.77	-3.86
339	69	male	4	31.70	45.70	26.50	31.50	41.70	44.90	6.00	44.16	-16.40	-0.63	31.55	41.64	4.29	20.63
340	70	female	4	24.60	30.70	22.10	28.30	31.70	29.80	4.00	24.80	-10.16	15.04	28.86	21.14	3.17	10.77
341	71	female	4	60.40	73.70	52.90	51.30	59.60	62.40	4.00	22.02	-12.42	-15.07	-1.32	3.31	-2.63	6.09
342	62	male															
343	69	female	4	20.50	24.40	26.90	28.10	34.20	36.20	4.00	19.02	31.22	37.07	66.83	76.59	15.08	16.59
344	69	female	4	20.20	21.90	19.40	21.10	17.20	22.00	1.00	8.42	-3.96	4.46	-14.85	8.91	-0.99	1.93
345	69	male	4	87.90	100.50	88.50	76.00	65.00	76.30	6.00	14.33	0.68	-13.54	-26.05	-13.20	-8.18	-5.42

Appendix 31 continued/...

Forearms cutaneous microcirculation during skin extension/relaxation in asymptomatic controls

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	----------During relaxation phase------				time to reach	During	-------------During relaxation phase-----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
346	74	female	4	23.20	32.30	34.40	42.80	52.40	75.30	2.00	39.22	48.28	84.48	125.86	224.57	44.83	57.03
347	69	male	4	39.60	47.50	45.60	41.50	39.80	41.80	3.00	19.95	15.15	4.80	0.51	5.56	-4.34	-3.31
348	71	female	4	68.00	67.50	100.20	114.80	107.90	108.40	8.00	-0.74	47.35	68.82	58.68	59.41	13.16	2.60
349	71	female	4	156.50	146.50	118.40	135.30	154.00	174.10	3.00	-6.39	-24.35	-13.55	-1.60	11.25	5.80	11.88
350	68	female	4	68.60	72.30	85.10	94.00	98.70	101.20	7.00	5.39	24.05	37.03	43.88	47.52	10.41	7.73
351	62	male															
352	62	male															
353	62	male															

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases				**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**
Mean				**44.70**	**53.61**	**46.49**	**53.47**	**57.25**	**60.76**	**4.47**	**35.20**	**21.09**	**42.60**	**53.73**	**61.20**	**8.46**	**13.15**
Standard deviation				**37.70**	**35.12**	**29.27**	**33.20**	**36.10**	**39.38**	**2.28**	**38.79**	**48.31**	**62.84**	**71.43**	**71.55**	**14.80**	**14.33**
Median				**33.55**	**46.60**	**37.40**	**42.15**	**43.35**	**44.70**	**4.25**	**23.41**	**8.77**	**15.61**	**36.59**	**42.95**	**5.92**	**10.84**
Minimum				**9.5**	**17.3**	**15.1**	**18.9**	**17.2**	**21.5**	**0.5**	**-17.79**	**-66.80**	**-55.53**	**-48.02**	**-45.06**	**-14.58**	**-5.42**
Maximum				**188.5**	**188.4**	**138.6**	**163.9**	**181.7**	**194.1**	**8.0**	**150.94**	**131.58**	**200.00**	**235.34**	**224.57**	**44.83**	**57.03**

Forearms cutaneous microcirculation during skin extension/relaxation in patients with CVI																	
				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	----------During relaxation phase-----				time to reach	During	------------During relaxation phase----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
100	67	female	4	12.10	22.20	17.20	15.00	16.80	15.50	5.00	83.47	42.15	23.97	38.84	28.10	-11.41	-2.73
101	68	male	4	17.00	42.70	22.70	22.90	26.10	29.90	7.00	151.18	33.53	34.71	53.53	75.88	-13.06	14.59
102	39	female	4	13.80	25.80	21.50	26.00	31.50	51.50	1.00	86.96	55.80	88.41	128.26	273.19	44.49	69.20
103	51	male	4	47.10	61.20	26.00	30.70	31.60	30.40	4.00	29.94	-44.80	-34.82	-32.91	-35.46	-11.89	2.99
104	55	female	4	24.10	49.80	33.10	27.80	24.80	24.80	3.00	106.64	37.34	15.35	2.90	2.90	-24.19	-11.58
105	74	female	4	26.60	42.50	48.20	47.80	56.20	58.00	5.00	59.77	81.20	79.70	111.28	118.05	14.66	14.21
106	45	female	4	19.20	41.10	31.30	38.00	45.50	44.30	7.00	114.06	63.02	97.92	136.98	130.73	10.73	24.22
107	51	female	4	20.90	26.80	24.70	24.40	20.60	20.50	5.00	28.23	18.18	16.75	-1.44	-1.91	-7.99	-7.85
108	63	male	1	""49.3	""76.3	""51.4				""5	""54.77	""4.26					
109	53	male	4	34.10	49.10	53.90	70.80	67.00	73.90	4.00	43.99	58.06	107.62	96.48	116.72	18.39	16.48
110	66	female	4	38.60	40.50	44.40	44.70	40.80	46.10	2.00	4.92	15.03	15.80	5.70	19.43	1.97	0.31
111	51	female	4	22.10	27.90	40.00	36.70	35.10	34.70	5.00	26.24	81.00	66.06	58.82	57.01	3.94	-7.92
112	78	female	4	46.60	75.80	79.00	111.40	99.80	100.80	1.00	62.66	69.53	139.06	114.16	116.31	15.19	11.54
113	33	male	4	41.80	68.90	105.90	142.90	135.50	122.40	7.00	64.83	153.35	241.87	224.16	192.82	32.68	10.07
114	55	female	4	16.00	38.90	29.20	26.80	27.50	27.60	3.00	143.13	82.50	67.50	71.88	72.50	-15.19	-2.56
115	58	female															
116	59	male	3	""30.60	""41.80	""28.20	""61	""61.60		""1	""36.60	""-7.84	""99.35	""101.31			
117	59	female															
118	73	female	4	22.10	31.30	23.20	27.80	28.80	30.90	2.00	41.63	4.98	25.79	30.32	39.82	2.17	10.91
119	35	male	4	20.40	39.30	28.40	39.50	39.50	32.70	5.00	92.65	39.22	93.63	93.63	60.29	-1.03	6.32
120	71	female	4	56.70	73.00	74.60	61.10	56.60	49.70	4.00	28.75	31.57	7.76	-0.18	-12.35	-11.40	-13.97
121	40	female	4	19.40	15.70	23.10	33.70	33.00	42.40	2.00	-19.07	19.07	73.71	70.10	118.56	32.63	29.49
122	50	female	4	29.30	37.20	32.90	71.50	90.20	91.10	1.00	26.96	12.29	144.03	207.85	210.92	56.35	65.97
123	69	female	3	""32.7	""41.5	""76.50	""96.70	""104.10		""7	""26.91	""133.95	""195.72	""218.35			
124	32	female	4	59.60	78.50	70.30	96.40	105.70	118.30	4.00	31.71	17.95	61.74	77.35	98.49	19.30	25.72

Appendix 31 continued/…

Forearms cutaneous microcirculation during skin extension/relaxation in patients with CVI

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	----------During relaxation phase-----				time to reach	During	------------During relaxation phase----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
125	73	female	4	21.70	29.80	18.80	28.20	22.40	21.90	7.00	37.33	-13.36	29.95	3.23	0.92	-5.62	1.61
126	72	female	4	71.60	94.40	85.40	81.40	67.10	61.70	7.00	31.84	19.27	13.69	-6.28	-13.83	-11.69	-11.93
127	81	male	2	""105	""140.10	""101.1(	""84.80			""1	""33.43	""-3.71	""-19.24				
128	53	male	2	""16.7	""20.60	""31.60	""37.80			""8	""23.35	""89.22	""126.35				
129	70	female	4	16.90	27.00	19.50	14.40	13.50	13.00	2.00	59.76	15.38	-14.79	-20.12	-23.08	-20.12	-12.07
130	51	female	4	21.90	21.70	17.30	14.50	13.70	13.00	6.00	-0.91	-21.00	-33.79	-37.44	-40.64	-9.59	-6.26
131	67	female	4	50.20	69.50	70.70	108.10	135.10	142.30	4.00	38.45	40.84	115.34	169.12	183.47	41.83	48.17
132	75	female	4	33.40	36.90	31.70	33.00	31.40	37.30	8.00	10.48	-5.09	-1.20	-5.99	11.68	0.15	4.55
133	73	male	4	44.60	61.70	22.90	24.70	22.80	28.90	4.00	38.34	-48.65	-44.62	-48.88	-35.20	-14.73	3.61
134	70	male	4	24.10	38.10	31.30	33.90	32.20	31.90	3.00	58.09	29.88	40.66	33.61	32.37	-4.77	0.04
135	54	male	4	17.70	27.00	24.90	41.40	43.70	51.90	3.00	52.54	40.68	133.90	146.89	193.22	38.76	47.06
136	74	female	4	121.40	130.30	115.10	113.70	120.90	119.50	6.00	7.33	-5.19	-6.34	-0.41	-1.57	-1.30	1.68
137	46	female	4	54.00	55.90	90.10	136.00	166.20	182.70	1.00	3.52	66.85	151.85	207.78	238.33	61.06	57.04
138	58	female	4	39.90	59.10	24.60	20.90	23.20	19.90	5.00	48.12	-38.35	-47.62	-41.85	-50.13	-20.00	-2.96
139	67	male	1	""34.70	""52.60	""33.10				""5	""51.59	""-4.61					
140	66	male	4	46.40	73.00	57.70	72.60	75.30	68.70	7.00	57.33	24.35	56.47	62.28	48.06	1.94	7.69
141	35	female															

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**	**33**
Mean	**34.89**	**48.87**	**43.62**	**52.08**	**53.94**	**55.70**	**4.24**	**50.03**	**29.59**	**53.33**	**59.08**	**67.44**	**6.43**	**11.93**
Standard deviation	**21.85**	**24.50**	**27.48**	**36.52**	**40.38**	**41.66**	**2.08**	**39.44**	**41.28**	**65.51**	**76.51**	**87.97**	**23.02**	**22.60**
Median	**26.60**	**41.10**	**31.30**	**36.70**	**35.10**	**42.40**	**4.00**	**41.63**	**29.88**	**40.66**	**53.53**	**48.06**	**0.15**	**4.55**
Minimum	**12.1**	**15.7**	**17.2**	**14.4**	**13.5**	**13.0**	**1.0**	**-19.07**	**-48.65**	**-47.62**	**-48.88**	**-50.13**	**-24.19**	**-13.97**
Maximum	**121.4**	**130.3**	**115.1**	**142.9**	**166.2**	**182.7**	**8.0**	**151.18**	**153.35**	**241.87**	**224.16**	**273.19**	**61.06**	**69.20**

Appendix 31 continued/...

Forearms cutaneous microcirculation during skin extension/relaxation in patients with frank venous ulcers

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	at	During	---------During relaxation phase-----				time to reach	During	------------During relaxation phase----------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
200	70	female	4	19.60	28.80	21.00	16.40	16.20	23.20	2.00	46.94	7.14	-16.33	-17.35	18.37	-8.16	3.27
201	81	female	4	20.10	36.10	29.10	23.40	29.40	28.50	7.00	79.60	44.78	16.42	46.27	41.79	-7.41	2.09
202	49	female	4	37.60	45.50	59.20	68.40	77.80	85.70	3.00	21.01	57.45	81.91	106.91	127.93	26.33	23.64
203	72	female	4	42.40	68.90	74.70	62.60	46.70	42.10	8.00	62.50	76.18	47.64	10.14	-0.71	-19.25	-26.82
204	62	female	3	""91.80	""102.70	""95.90	""121	""124.80		""1	""11.87	""4.47	""31.81	""35.95			
205	61	male	4	43.20	65.50	48.80	43.60	45.00	47.30	3.00	51.62	12.96	0.93	4.17	9.49	-9.31	-0.72
206	65	female	4	138.90	156.30	99.90	125.90	122.10	157.80	5.00	12.53	-28.08	-9.36	-12.10	13.61	1.81	12.23
207	73	male	4	55.30	48.80	35.80	37.80	42.70	41.20	3.00	-11.75	-35.26	-31.65	-22.78	-25.50	-1.50	3.82
208	74	female	4	71.60	86.60	61.80	62.70	61.70	49.70	8.00	20.95	-13.69	-12.43	-13.83	-30.59	-10.32	-5.21
209	57	male	4	28.90	34.00	26.90	24.30	24.40	23.60	5.00	17.65	-6.92	-15.92	-15.57	-18.34	-8.06	-3.39
210	66	female	4	31.60	44.40	30.20	38.70	50.80	51.60	5.00	40.51	-4.43	22.47	60.76	63.29	11.08	24.15
211	56	female	4	19.90	33.20	57.20	64.10	59.90	60.80	5.00	66.83	187.44	222.11	201.01	205.53	29.10	3.32
212	72	female	4	29.00	37.10	20.90	19.30	19.80	22.00	3.00	27.93	-27.93	-33.45	-31.72	-24.14	-10.79	1.31
213	34	male	1	""94.30	""85.30	""57.20				""5	""-9.54	""-39.34					
214	60	female	4	13.40	22.00	13.80	13.30	13.20	15.40	8.00	64.18	2.99	-0.75	-1.49	14.93	-10.30	3.51
215	73	male	4	28.10	45.30	23.70	28.60	34.90	39.10	3.00	61.21	-15.66	1.78	24.20	39.15	-0.43	18.69
216	75	female	4	51.00	76.00	80.00	95.30	107.00	95.80	3.00	49.02	56.86	86.86	109.80	87.84	13.06	11.59
217	85	female	4	167.80	134.90	72.50	96.70	142.60	150.50	3.00	-19.61	-56.79	-42.37	-15.02	-10.31	6.04	16.68
218	58	male	4	52.20	54.20	36.10	47.90	49.00	51.90	3.00	3.83	-30.84	-8.24	-6.13	-0.57	1.59	9.29
219	56	male	4	20.90	61.70	43.20	45.20	48.00	50.00	4.00	195.22	106.70	116.27	129.67	139.23	-8.90	11.10
220	73	female	4	39.90	51.30	46.80	47.70	58.10	60.60	4.00	28.57	17.29	19.55	45.61	51.88	7.49	12.98

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**
Mean	**47.97**	**59.51**	**46.40**	**50.63**	**55.23**	**57.73**	**4.47**	**43.09**	**18.43**	**23.45**	**31.71**	**36.99**	**0.11**	**6.40**
Standard deviation	**40.26**	**34.77**	**23.62**	**30.22**	**35.27**	**39.66**	**1.95**	**45.82**	**58.89**	**64.48**	**63.63**	**63.74**	**12.88**	**11.71**
Median	**37.60**	**48.80**	**43.20**	**45.20**	**48.00**	**49.70**	**4.00**	**40.51**	**2.99**	**0.93**	**4.17**	**14.93**	**-1.50**	**3.82**
Minimum	**13.4**	**22.0**	**13.8**	**13.3**	**13.2**	**15.4**	**2.0**	**-19.61**	**-56.79**	**-42.37**	**-31.72**	**-30.59**	**-19.25**	**-26.82**
Maximum	**167.8**	**156.3**	**99.9**	**125.9**	**142.6**	**157.8**	**8.0**	**195.22**	**187.44**	**222.11**	**201.01**	**205.53**	**29.10**	**24.15**

Appendix 32

Changes in the leg cutaneous microcirculation during skin extension/relaxation in patients with CVI (with frank venous ulcers and without)

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs

The flux (arbitrary units) measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
301	40	male												
302	37	male	5	""14.6	""15.4	""6.2	""8.2	""9.5	""10.9	""10.9				""2.5
303	43	female												
304	65	female												
305	53	female												
306	40	male	8	41.00	58.90	44.10	48.90	52.00	53.40	41.40	47.70	47.30	61.10	missing
307	31	female	8	25.50	40.60	24.50	34.10	27.90	25.40	32.10	38.20	38.50	43.50	2.00
308	28	female	8	53.20	51.70	39.30	52.30	64.80	72.20	78.90	82.90	87.70	83.30	5.00
309	44	female	8	55.80	46.70	38.20	55.80	78.60	96.10	111.00	108.00	122.10	127.40	1.00
310	72	male	8	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00	1.00
311	44	female	8	34.10	40.90	28.30	38.80	45.90	50.10	47.50	53.70	55.20	58.30	4.00
312	58	male	8	47.40	42.00	28.80	37.80	38.40	37.10	33.40	35.10	36.30	41.60	4.00
313	69	female	8	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10	3.00
314	22	female												
315	22	female												
316	51	male	8	22.60	23.10	13.20	17.50	16.80	23.60	24.60	23.90	26.10	25.60	1.00
317	33	male	8	30.10	35.00	38.50	51.60	60.70	60.20	66.40	64.90	64.50	65.00	6.00
318	33	male												
319	25	female												
320	45	female	8	13.50	18.70	11.40	15.60	20.70	24.90	31.70	37.00	39.50	35.60	2.00
321	47	female												

Appendix 32 continued/…

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs

I.D.	Age	Sex	Measurement duration (min)	The flux (arbitrary units) measured: at baseline	During extension	during relaxation phase: 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
322	49	male	8	20.10	28.10	19.40	23.70	26.00	28.30	25.70	27.80	26.70	26.20	6.00
323	48	female	8	13.70	28.20	11.10	12.70	14.20	17.00	18.60	19.10	21.00	23.50	5.00
324	49	female	8	19.60	27.10	16.60	19.80	26.10	23.50	21.40	22.10	23.90	22.00	8.00
325	39	female	8	60.40	70.70	31.60	42.60	40.90	45.50	47.90	50.10	44.40	50.40	6.00
326	23	male												
327	28	female												
328	32	male												
329	49	male	8	47.40	67.40	58.00	80.00	80.50	110.20	131.90	147.70	165.20	176.40	4.00
330	63	male												
331	36	male												
332	45	male	5	""43.6	""38.7	""26.5	""29	""31.3	""31.5	""32.7				""2
333	35	female	8	26.40	32.00	17.30	20.10	22.30	22.90	23.50	23.00	26.90	27.90	3.00
334	44	female	8	25.40	36.00	24.80	34.00	40.80	47.90	53.70	57.90	62.20	66.50	6.00
335	44	male	6	""42.6	""38.8	""30.4	""46.3	""56.6	""60.2	""59.7	""63.9			""5.5
336	26	male												
337	47	female	8	27.10	21.80	8.70	11.40	15.50	16.20	17.00	17.50	19.90	19.70	3.00
338	65	female	8	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50	7.00
339	69	male	8	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00	6.00
340	70	female	8	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60	3.00
341	71	female	8	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40	4.00
342	62	male	8	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60	4.00
343	69	female	8	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20	7.00
344	69	female	8	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80	4.00
345	69	male	8	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20	4.00

Appendix 32 continued/…

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs														
				The flux (arbitrary units) measured										
			Measurement	at	During	---during relaxation phase---								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
346	74	female	8	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60	2.00
347	69	male	8	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50	5.00
348	71	female	8	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30	1.00
349	71	female	8	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30	3.00
350	68	female	8	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20	6.00
351	62	male	8	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40	5.00
352	62	male	8	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20	5.00
353	62	male	8	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40	6.00

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**34**
Mean	**28.03**	**35.88**	**23.06**	**30.15**	**35.83**	**40.57**	**42.67**	**46.14**	**48.53**	**50.55**	**4.18**
Standard deviation	**12.69**	**15.07**	**11.77**	**16.40**	**19.76**	**23.71**	**27.48**	**29.95**	**32.65**	**35.22**	**1.90**
Median	**25.50**	**29.80**	**19.40**	**26.80**	**27.90**	**29.20**	**32.10**	**35.10**	**36.30**	**39.30**	**4.00**
Minimum	**13.50**	**16.80**	**8.70**	**10.90**	**13.50**	**13.10**	**13.10**	**13.90**	**13.90**	**12.60**	**1.00**
Maximum	**60.40**	**70.70**	**58.00**	**80.00**	**80.50**	**110.20**	**131.90**	**147.70**	**165.20**	**176.40**	**8.00**

Appendix 32 continued/...

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs														
				The %change in flux measured										
			Measurement	During	-----during relaxation phase-----								Slope of the %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
301	40	male												
302	37	male	5	""5.48	""-57.53	""-43.84	""-34.93	""-25.34	""-25.34					
303	43	female												
304	65	female												
305	53	female												
306	40	male	8	43.66	7.56	19.27	26.83	30.24	0.98	16.34	15.37	49.02	0.22	2.50
307	31	female	8	59.22	-3.92	33.73	9.41	-0.39	25.88	49.80	50.98	70.59	4.31	8.99
308	28	female	8	-2.82	-26.13	-1.69	21.80	35.71	48.31	55.83	64.85	56.58	10.87	12.22
309	44	female	8	-16.31	-31.54	0.00	40.86	72.22	98.92	93.55	118.82	128.32	21.25	22.59
310	72	male	8	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85	2.34	4.69
311	44	female	8	19.94	-17.01	13.78	34.60	46.92	39.30	57.48	61.88	70.97	8.88	10.92
312	58	male	8	-11.39	-39.24	-20.25	-18.99	-21.73	-29.54	-25.95	-23.42	-12.24	0.37	1.72
313	69	female	8	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74	7.81	12.03
314	22	female												
315	22	female												
316	51	male	8	2.21	-41.59	-22.57	-25.66	4.42	8.85	5.75	15.49	13.27	5.11	8.01
317	33	male	8	16.28	27.91	71.43	101.66	100.00	120.60	115.61	114.29	115.95	12.75	10.63
318	33	male												
319	25	female												
320	45	female	8	38.52	-15.56	15.56	53.33	84.44	134.81	174.07	192.59	163.70	25.39	30.39
321	47	female												

Appendix 32 continued/…

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs

				The %change in flux measured										
			Measurement	During	---------------during relaxation phase---------------								Slope of the %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
322	49	male	8	39.80	-3.48	17.91	29.35	40.80	27.86	38.31	32.84	30.35	1.84	3.87
323	48	female	8	105.84	-18.98	-7.30	3.65	24.09	35.77	39.42	53.28	71.53	3.42	12.57
324	49	female	8	38.27	-15.31	1.02	33.16	19.90	9.18	12.76	21.94	12.24	0.12	2.68
325	39	female	8	17.05	-47.68	-29.47	-32.28	-24.67	-20.70	-17.05	-26.49	-16.56	-0.57	3.36
326	23	male												
327	28	female												
328	32	male												
329	49	male	8	42.19	22.36	68.78	69.83	132.49	178.27	211.60	248.52	272.15	33.21	37.12
330	63	male												
331	36	male												
332	45	male	5	""-11.24	""-39.22	""-33.49	""-28.21	""-27.75	""-25					
333	35	female	8	21.21	-34.47	-23.86	-15.53	-13.26	-10.98	-12.88	1.89	5.68	1.22	5.00
334	44	female	8	41.73	-2.36	33.86	60.63	88.58	111.42	127.95	144.88	161.81	19.35	22.97
335	44	male	6	""-8.92	""-28.64	""8.69	""32.86	""41.32	""40.14	""50				
336	26	male												
337	47	female	8	-19.56	-67.90	-57.93	-42.80	-40.22	-37.27	-35.42	-26.57	-27.31	2.39	5.55
338	65	female	8	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59	7.10	11.28
339	69	male	8	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36	3.48	6.76
340	70	female	8	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48	40.15	45.31
341	71	female	8	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88	10.82	13.22
342	62	male	8	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62	-18.83	-1.15
343	69	female	8	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13	21.52	28.51
344	69	female	8	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-0.70	10.49	-5.15	-0.80
345	69	male	8	52.17	-36.02	-32.30	-8.70	4.97	0.00	8.07	25.47	25.47	2.79	9.10

Cutaneous microcirculation during skin extension/relaxation in asymptomatic controls legs

The %change in flux measured

I.D.	Age	Sex	Measurement duration (min)	During extension	1min	2min	3min	4min	5min	6min	7min	8min	Slope of the %change in flux (ext-8min)	(1min-8min)
					-during relaxation phase-									
346	74	female	8	19.72	18.31	15.96	20.66	24.88	37.09	32.86	67.61	67.14	6.46	7.72
347	69	male	8	26.90	-13.71	-6.09	-4.57	13.20	-0.51	8.12	-1.02	-1.02	-0.69	1.65
348	71	female	8	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54	16.82	19.60
349	71	female	8	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80	33.22	35.90
350	68	female	8	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46	28.58	31.65
351	62	male	8	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63	4.13	7.37
352	62	male	8	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15	21.79	24.77
353	62	male	8	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71	16.58	16.54

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**	**35**
Mean	**36.74**	**-15.31**	**8.18**	**30.02**	**47.55**	**53.84**	**67.38**	**76.46**	**81.96**	**9.97**	**13.58**
Standard deviation	**51.57**	**27.33**	**35.09**	**49.19**	**59.68**	**67.39**	**80.50**	**87.57**	**91.21**	**12.42**	**11.90**
Median	**26.90**	**-18.98**	**1.02**	**21.80**	**34.21**	**35.77**	**49.80**	**53.28**	**67.14**	**6.46**	**10.63**
Minimum	**-19.56**	**-67.90**	**-57.93**	**-42.80**	**-40.22**	**-37.27**	**-35.42**	**-26.57**	**-32.62**	**-18.83**	**-1.15**
Maximum	**247.06**	**36.18**	**82.13**	**156.18**	**177.66**	**178.27**	**291.57**	**335.39**	**313.48**	**40.15**	**45.31**

Appendix 32 continued/…

Legs cutaneous microcirculation during skin extension/relaxation in patients with CVI

The flux (arbitrary units) measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	----during relaxation phase---- 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
100	67	female	8	48.80	45.60	40.30	55.70	68.90	75.40	96.50	104.30	99.10	92.20	1.00
101	68	male	6	""14.7	""21.1	""13.7	""17.8	""24.8	""18.1	""18.1	""19.2			""2
102	39	female	8	35.30	38.20	24.70	30.40	32.20	29.40	29.60	32.50	35.40	35.60	1.00
103	51	male	8	81.00	63.60	26.60	44.70	55.70	60.00	63.40	66.30	74.00	76.70	2.00
104	55	female	8	21.00	34.40	15.30	17.90	24.40	33.70	38.70	45.20	48.70	57.10	3.00
105	74	female	8	49.80	41.60	25.40	30.80	38.30	37.90	44.60	39.50	41.50	37.00	2.00
106	45	female	8	30.60	50.50	29.20	37.20	56.30	67.20	61.50	65.70	74.40	81.10	3.00
107	51	female												
108	63	male	8	31.80	36.90	22.70	27.90	33.00	30.40	30.30	28.30	28.40	30.70	1.00
109	53	male	8	27.10	44.40	24.10	34.60	44.80	51.10	51.20	49.90	51.60	50.40	3.00
110	66	female	8	27.90	38.40	22.50	24.40	27.30	26.90	27.10	26.00	30.70	30.80	7.00
111	51	female	8	18.30	23.30	14.50	17.40	19.20	19.50	19.50	21.60	25.00	23.80	1.00
112	78	female	8	25.30	36.90	13.20	15.70	18.80	19.20	21.70	24.30	24.50	27.50	2.00
113	33	male	8	40.30	42.20	32.10	38.60	42.40	43.70	45.20	48.40	52.10	50.90	2.00
114	55	female	8	14.80	22.90	12.80	19.50	20.40	23.80	26.60	27.20	27.90	24.90	3.00
115	58	female	8	14.80	19.00	12.10	15.90	13.60	14.70	15.50	15.60	15.00	14.80	3.00
116	59	male	8	33.70	34.50	21.90	29.10	31.90	38.10	37.30	35.40	37.70	36.10	1.00
117	59	female	8	17.30	21.70	10.60	10.90	12.70	15.20	15.70	16.10	17.00	18.30	3.00
118	73	female	8	8.20	13.10	6.90	7.50	7.60	7.60	7.90	7.80	8.30	8.20	2.00
119	35	male	8	26.10	33.70	24.00	34.70	34.90	40.40	46.20	48.50	45.00	48.70	2.00
120	71	female	8	62.90	52.40	33.40	41.80	48.70	46.20	49.10	52.10	53.50	59.10	2.00
121	40	female	8	15.40	14.50	8.50	10.80	14.30	15.40	15.10	13.70	14.30	15.80	1.00
122	50	female	8	58.60	74.70	52.80	49.30	60.80	61.70	68.80	71.50	70.70	72.60	3.00
123	69	female	8	18.80	29.20	20.90	32.00	39.00	45.00	50.70	51.70	53.40	61.60	3.00
124	32	female	8	18.70	21.00	12.10	15.30	17.00	19.70	18.40	19.00	20.90	21.10	4.00

Appendix 32 continued/...

Legs cutaneous microcirculation during skin extension/relaxation in patients with CVI

The flux (arbitrary units) measured

I.D.	Age	Sex	Measurement duration (min)	at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
125	73	female	8	10.50	11.10	9.90	12.80	12.90	13.00	11.60	12.60	12.00	12.10	7.00
126	72	female	4	11.2""	14.8""	21.3""	25.4""	25.7""	26.5""					""1
127	81	male	5	""38.3	""44.4	""37.4	""38.2	""38.6	""35.7	""36.5				""4
128	53	male	3	""23.9	""28.6	""23.9	""40	""51.8						""1
129	70	female	8	17.10	19.70	10.70	16.70	19.50	20.30	20.20	20.30	21.00	20.30	1.00
130	51	female	8	17.00	29.80	20.20	18.50	22.30	19.10	20.50	25.50	26.90	26.30	2.00
131	67	female	7	""84.1	""51	""49.2	""76.7	""97.9	""131.1	""142.5	""153.3	""152.4		""2
132	75	female	8	175.90	134.80	58.30	119.70	152.20	176.10	169.20	196.00	192.10	201.10	1.00
133	73	male	8	91.90	78.70	52.00	91.90	88.90	86.30	88.70	79.90	70.70	75.90	1.00
134	70	male	8	15.80	28.40	8.90	10.70	15.20	21.00	34.50	41.10	43.80	31.70	1.00
135	54	male	8	33.50	35.00	20.20	31.00	36.10	44.40	51.40	57.30	62.60	71.00	1.00
136	74	female	8	121.90	115.20	79.30	108.70	116.70	133.10	127.10	1131.60	114.40	123.10	2.00
137	46	female	8	36.40	19.30	18.80	26.20	35.30	42.40	49.30	57.20	62.10	64.10	1.00
138	58	female	8	35.30	42.60	25.50	30.70	24.60	27.30	22.30	16.60	12.00	12.20	3.00
139	67	male	4	""77.6	""46.7	""21.6	""28.2	""36.3	""43.9					""1
140	66	male	6	""54.4	""48.6	""44.8	""50.3	""54.1	""57.6	""64.5	""57.9			""2
141	35	female	8	20.40	48.00	18.80	21.80	24.70	30.00	32.20	41.20	45.30	50.80	2.00

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**
Mean	**38.30**	**41.04**	**24.39**	**33.26**	**38.55**	**42.21**	**44.34**	**76.17**	**47.41**	**48.93**	**2.26**
Standard deviation	**34.62**	**26.70**	**15.96**	**26.20**	**30.56**	**34.51**	**34.05**	**189.66**	**35.87**	**37.92**	**1.48**
Median	**27.50**	**35.95**	**21.40**	**28.50**	**32.05**	**32.05**	**35.90**	**40.30**	**42.65**	**36.55**	**2.00**
Minimum	**8.20**	**11.10**	**6.90**	**7.50**	**7.60**	**7.60**	**7.90**	**7.80**	**8.30**	**8.20**	**1.00**
Maximum	**175.90**	**134.80**	**79.30**	**119.70**	**152.20**	**176.10**	**169.20**	**1131.60**	**192.10**	**201.10**	**7.00**

Appendix 32 continued/...

Legs cutaneous microcirculation during skin extension/relaxation in patients with CVI

				The %change in flux measured										
			Measurement	During	----------during relaxation phase----------								Slope of the %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
100	67	female	8	-6.56	-17.42	14.14	41.19	54.51	97.75	113.73	103.07	88.93	16.65	17.26
101	68	male	6	""43.54	""-6.80	""21.09	""68.71	""23.13	""23.13	""30.61				
102	39	female	8	8.22	-30.03	-13.88	-8.78	-16.71	-16.15	-7.93	0.28	0.85	1.10	3.45
103	51	male	8	-21.48	-67.16	-44.81	-31.23	-25.93	-21.73	-18.15	-8.64	-5.31	5.05	7.82
104	55	female	8	63.81	-27.14	-14.76	16.19	60.48	84.29	115.24	131.90	171.90	20.63	29.14
105	74	female	8	-16.47	-49.00	-38.15	-23.09	-23.90	-10.44	-20.68	-16.67	-25.70	1.79	3.47
106	45	female	8	65.03	-4.58	21.57	83.99	119.61	100.98	114.71	143.14	165.03	17.44	22.25
107	51	female												
108	63	male	8	16.04	-28.62	-12.26	3.77	-4.40	-4.72	-11.01	-10.69	-3.46	-0.50	1.66
109	53	male	8	63.84	-11.07	27.68	65.31	88.56	88.93	84.13	90.41	85.98	8.83	12.50
110	66	female	8	37.63	-19.35	-12.54	-2.15	-3.58	-2.87	-6.81	10.04	10.39	-0.17	3.66
111	51	female	8	27.32	-20.77	-4.92	4.92	6.56	6.56	18.03	36.61	30.05	3.84	7.18
112	78	female	8	45.85	-47.83	-37.94	-25.69	-24.11	-14.23	-3.95	-3.16	8.70	1.08	7.68
113	33	male	8	4.71	-20.35	-4.22	5.21	8.44	12.16	20.10	29.28	26.30	4.85	6.46
114	55	female	8	54.73	-13.51	31.76	37.84	60.81	79.73	83.78	88.51	68.24	8.43	12.06
115	58	female	8	28.38	-18.24	7.43	-8.11	-0.68	4.73	5.41	1.35	0.00	-0.77	1.71
116	59	male	8	2.37	-35.01	-13.65	-5.34	13.06	10.68	5.04	11.87	7.12	3.55	5.37
117	59	female	8	25.43	-38.73	-36.99	-26.59	-12.14	-9.25	-6.94	-1.73	5.78	1.83	6.54
118	73	female	8	59.76	-15.85	-8.54	-7.32	-7.32	-3.66	-4.88	1.22	0.00	-2.95	2.03
119	35	male	8	29.12	-8.05	32.95	33.72	54.79	77.01	85.82	72.41	86.59	10.34	12.36
120	71	female	8	-16.69	-46.90	-33.55	-22.58	-26.55	-21.94	-17.17	-14.94	-6.04	2.86	4.76
121	40	female	8	-5.84	-44.81	-29.87	-7.14	0.00	-1.95	-11.04	-7.14	2.60	3.16	5.14
122	50	female	8	27.47	-9.90	-15.87	3.75	5.29	17.41	22.01	20.65	23.89	2.78	5.79
123	69	female	8	55.32	11.17	70.21	107.45	139.36	169.68	175.00	184.04	227.66	24.66	27.59
124	32	female	8	12.30	-35.29	-18.18	-9.09	5.35	-1.60	1.60	11.76	12.83	3.17	6.09

Legs cutaneous microcirculation during skin extension/relaxation in patients with CVI

I.D.	Age	Sex	Measurement duration (min)	The %change in flux measured During extension	--------during relaxation phase-------- 1min	2min	3min	4min	5min	6min	7min	8min	Slope of the %change in flux (ext-8min)	(1min-8min)
125	73	female	8	5.71	-5.71	21.90	22.86	23.81	10.48	20.00	14.29	15.24	1.37	1.03
126	72	female	4	""32.14	""90.18	""126.79	""129.46	""136.61						
127	81	male	5	""15.93	""-2.35	""-0.26	""0.78	""-6.79						
128	53	male	3	""19.67	""0	""67.36	""116.74							
129	70	female	8	15.20	-37.43	-2.34	14.04	18.71	18.13	18.71	22.81	18.71	4.02	6.34
130	51	female	8	75.29	18.82	8.82	31.18	12.35	20.59	50.00	58.24	54.71	1.80	6.70
131	67	female	7	""-39.36	""-41.5	""-8.8	""16.41	""55.89	""69.44	""82.28	""81.21			
132	75	female	8	-23.37	-66.86	-31.95	-13.47	0.11	-3.81	11.43	9.21	14.33	7.92	10.06
133	73	male	8	-14.36	-43.42	0.00	-3.26	-6.09	-3.48	-13.06	-23.07	-17.41	0.38	0.48
134	70	male	8	79.75	-43.67	-32.28	-3.80	32.91	118.35	160.13	177.22	100.63	20.89	31.37
135	54	male	8	4.48	-39.70	-7.46	7.76	32.54	53.43	71.04	86.87	111.94	16.87	20.76
136	74	female	8	-5.50	-34.95	-10.83	-4.27	9.19	4.27	828.30	-6.15	0.98	29.99	32.95
137	46	female	8	-46.98	-48.35	-28.02	-3.02	16.48	35.44	57.14	70.60	76.10	17.63	18.62
138	58	female	8	20.68	-27.76	-13.03	-30.31	-22.66	-36.83	-52.97	-66.01	-65.44	-9.09	-7.27
139	67	male	4	""-39.82	""-72.17	""-63.66	""-53.22	""-43.43						
140	66	male	6	""-10.66	""-17.65	""-7.54	""-0.55	""5.88	""18.57	""6.43				
141	35	female	8	135.29	-7.84	6.86	21.08	47.06	57.84	101.96	122.06	149.02	11.19	22.95

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	During extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
Number of cases	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**	**34**
Mean	**23.72**	**-27.51**	**-6.55**	**7.79**	**18.70**	**26.93**	**58.49**	**39.40**	**42.39**	**7.08**	**10.47**
Standard deviation	**37.26**	**19.73**	**25.07**	**31.38**	**39.97**	**48.37**	**147.16**	**60.95**	**64.51**	**8.74**	**9.84**
Median	**18.36**	**-28.19**	**-11.55**	**-2.59**	**7.50**	**8.52**	**18.37**	**13.08**	**14.78**	**3.70**	**6.62**
Minimum	**-46.98**	**-67.16**	**-44.81**	**-31.23**	**-26.55**	**-36.83**	**-52.97**	**-66.01**	**-65.44**	**-9.09**	**-7.27**
Maximum	**135.29**	**18.82**	**70.21**	**107.45**	**139.36**	**169.68**	**828.30**	**184.04**	**227.66**	**29.99**	**32.95**

Appendix 32 continued/…

Legs cutaneous microcirculation during skin extension/relaxation in patients with frank venous ulcers

I.D.	Age	Sex	Measurement duration (min)	The flux (arbitrary units) measured at baseline	During extension	during relaxation phase 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
200	70	female	8	20.20	33.80	24.60	23.00	19.90	26.40	28.80	26.80	29.80	30.20	2.00
201	81	female	6	""34.7	""47.2	""34.3	""55	""58.3	""55.3	""50.2	""47.1			""3
202	49	female	8	142.80	94.40	28.70	38.90	44.50	48.90	53.70	58.70	63.40	63.10	1.00
203	72	female	7	""35.9	""44.2	""22.8	""37.2	""46.4	""47.1	""43.8	""42.4	""43.6		""2
204	62	female	8	26.10	34.50	18.50	25.50	25.40	27.40	30.50	32.30	30.90	31.90	3.00
205	61	male	8	27.90	32.90	20.50	23.90	22.50	25.30	29.00	27.40	29.50	30.90	2.00
206	65	female	8	74.10	63.00	28.40	35.40	40.60	42.60	40.80	42.00	36.60	45.20	2.00
207	73	male	3	""63.5	""69.3	""65.9	""72.5	""71.4						""2
208	74	female	8	36.30	44.70	30.30	34.20	34.30	33.50	34.60	32.60	30.80	32.30	5.00
209	57	male	5	""26.7	""31.6	""20.2	""23.2	""23.9	""23.5	""23.4				""2
210	66	female	8	36.30	31.60	23.60	26.00	27.00	26.80	27.40	29.40	27.30	26.70	6.00
211	56	female	7	""8.7	""36.1	""10.4	""9.4	""11.2	""10	""10.9	""10.2	""9.3		""2
212	72	female	8	51.30	78.80	64.90	79.20	74.90	73.40	83.10	94.30	79.20	74.10	6.00
213	34	male	7	""56.9	""66.1	""72	""86.7	""88.4	""99.3	""94.8	""97.3	""89.3		""8
214	60	female	8	50.80	37.10	30.10	42.20	41.50	46.60	40.80	38.30	44.20	55.40	1.00
215	73	male	7	""52.7	""34.7	""10.8	""14.6	""17.1	""19.2	""23.5	""25.1	""28.1		""3
216	75	female	7	""34.1	""45.4	""46.5	""40.9	""35.8	""31.7	""38.2	""31.3	""37.4		""5
217	85	female	8	63.50	74.20	73.60	74.70	68.50	76.70	84.50	89.60	71.80	83.00	4.00
218	58	male												
219	56	male	8	17.40	32.10	13.30	15.70	16.30	15.70	17.90	12.50	12.50	13.20	2.00
220	73	female	7	""88.8	""11.9	""73.5	""77.7	""90.3	""114.6	""118.3	""130.2	""133.9		""5
221	69	male												

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
Mean	**49.70**	**50.65**	**32.41**	**38.06**	**37.76**	**40.30**	**42.83**	**43.99**	**41.45**	**44.18**	**3.09**
Standard deviation	**35.72**	**22.80**	**19.06**	**20.75**	**19.20**	**19.89**	**22.25**	**26.28**	**20.98**	**21.95**	**1.87**
Median	**36.30**	**37.10**	**28.40**	**34.20**	**34.30**	**33.50**	**34.60**	**32.60**	**30.90**	**32.30**	**2.00**
Minimum	**17.40**	**31.60**	**13.30**	**15.70**	**16.30**	**15.70**	**17.90**	**12.50**	**12.50**	**13.20**	**1.00**
Maximum	**142.80**	**94.40**	**73.60**	**79.20**	**74.90**	**76.70**	**84.50**	**94.30**	**79.20**	**83.00**	**6.00**

Appendix 32 continued/…

Legs cutaneous microcirculation during skin extension/relaxation in patients with frank venous ulcers

				The %change in flux measured										
			Measurement	During	---------------------------during relaxation phase---------------------------								Slope of the %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
200	70	female	8	67.33	21.78	13.86	-1.49	30.69	42.57	32.67	47.52	49.50	1.46	5.68
201	81	female	6	""36.02	""-1.15	""58.50	""68.01	""59.37	""44.67	""35.74				
202	49	female	8	-33.89	-79.90	-72.76	-68.84	-65.76	-62.39	-58.89	-55.60	-55.81	0.32	3.42
203	72	female	7	""23.12	""-36.49	""3.62	""29.25	""31.2	""22.01	""18.12	""21.45			
204	62	female	8	32.18	-29.12	-2.30	-2.68	4.98	16.86	23.75	18.39	22.22	2.91	6.60
205	61	male	8	17.92	-26.52	-14.34	-19.35	-9.32	3.94	-1.79	5.73	10.75	1.94	5.09
206	65	female	8	-14.98	-61.67	-52.23	-45.21	-42.51	-44.94	-43.32	-50.61	-39.00	-0.75	2.02
207	73	male	3	""9.13	""3.78	""14.17	""12.44							
208	74	female	8	23.14	-16.53	-5.79	-5.51	-7.71	-4.68	-10.19	-15.15	-11.02	-2.34	-0.23
209	57	male	5	""18.35	""-24.34	""-13.11	""-10.49	""-11.99	""-12.36					
210	66	female	8	-12.95	-34.99	-28.37	-25.62	-26.17	-24.52	-19.01	-24.79	-26.45	-0.06	1.18
211	56	female	7	""314.94	""19.54	""8.05	""28.74	""14.94	""25.29	""17.24	""6.9			
212	72	female	8	53.61	26.51	54.39	46.00	43.08	61.99	83.82	54.39	44.44	2.03	3.07
213	34	male	7	""16.17	""26.54	""52.37	""55.36	""74.52	""66.61	""71.00	""56.94			
214	60	female	8	-26.97	-40.75	-16.93	-18.31	-8.27	-19.69	-24.61	-12.99	9.06	3.51	4.02
215	73	male	7	""-34.16	""-79.51	""-72.3	""-67.55	""-63.57	""-55.41	""-52.37	""-46.68			
216	75	female	7	""33.14	""36.36	""19.94	""4.99	""-7.04	""12.02	""-8.21	""9.68			
217	85	female	8	16.85	15.91	17.64	7.87	20.79	33.07	41.10	13.07	30.71	1.98	2.29
218	58	male												
219	56	male	8	84.48	-23.56	-9.77	-6.32	-9.77	2.87	-28.16	-28.16	-24.14	-7.93	-1.77
220	73	female	7	""-86.6	""-17.23	""-12.5	""1.69	""29.05	""33.22	""46.62	""50.79			
221	69	male												

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	During extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
Number of cases	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
Mean	**18.79**	**-22.62**	**-10.60**	**-12.68**	**-6.36**	**0.46**	**-0.42**	**-4.38**	**0.93**	**0.28**	**2.85**
Standard deviation	**38.86**	**33.55**	**34.17**	**29.39**	**31.52**	**37.39**	**41.90**	**36.06**	**34.77**	**3.21**	**2.52**
Median	**17.92**	**-26.52**	**-9.77**	**-6.32**	**-8.27**	**2.87**	**-10.19**	**-12.99**	**9.06**	**1.46**	**3.07**
Minimum	**-33.89**	**-79.90**	**-72.76**	**-68.84**	**-65.76**	**-62.39**	**-58.89**	**-55.60**	**-55.81**	**-7.93**	**-1.77**
Maximum	**84.48**	**26.51**	**54.39**	**46.00**	**43.08**	**61.99**	**83.82**	**54.39**	**49.50**	**3.51**	**6.60**

Appendix 33

The forearm cutaneous microcirculation during skin extension/relaxation, differences between elderly controls and elderly patients with CVI (with frank venous ulcers and without)

Forearm cutaneous microcirculation during skin extension/relaxation in elderly (61-90Y) asymptomatic controls																	
				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	At	During	---------During Relaxation phase-----				time to reach	During	-------During Relaxation phase------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
304	65	female	4	63.50	67.30	68.90	87.80	91.00	91.60	8.00	5.98	8.50	38.27	43.31	44.25	11.14	11.23
310	72	male	4	34.00	38.40	41.70	37.50	37.30	37.90	7.00	12.94	22.65	10.29	9.71	11.47	-1.59	-3.41
313	69	female	4	34.60	51.90	37.80	40.20	42.10	45.40	7.00	50.00	9.25	16.18	21.68	31.21	-2.52	7.14
330	63	male	4	38.00	49.50	37.00	46.30	41.40	44.40	5.00	30.26	-2.63	21.84	8.95	16.84	-1.53	4.55
338	65	female	4	40.20	55.30	38.30	35.60	34.80	33.40	1.00	37.56	-4.73	-11.44	-13.43	-16.92	-11.77	-3.86
339	69	male	4	31.70	45.70	26.50	31.50	41.70	44.90	6.00	44.16	-16.40	-0.63	31.55	41.64	4.29	20.63
340	70	female	4	24.60	30.70	22.10	28.30	31.70	29.80	4.00	24.80	-10.16	15.04	28.86	21.14	3.17	10.77
341	71	female	4	60.40	73.70	52.90	51.30	59.60	62.40	4.00	22.02	-12.42	-15.07	-1.32	3.31	-2.63	6.09
342	62	male															
343	69	female	4	20.50	24.40	26.90	28.10	34.20	36.20	4.00	19.02	31.22	37.07	66.83	76.59	15.08	16.59
344	69	female	4	20.20	21.90	19.40	21.10	17.20	22.00	1.00	8.42	-3.96	4.46	-14.85	8.91	-0.99	1.93
345	69	male	4	87.90	100.50	88.50	76.00	65.00	76.30	6.00	14.33	0.68	-13.54	-26.05	-13.20	-8.18	-5.42
346	74	female	4	23.20	32.30	34.40	42.80	52.40	75.30	2.00	39.22	48.28	84.48	125.86	224.57	44.83	57.03
347	69	male	4	39.60	47.50	45.60	41.50	39.80	41.80	3.00	19.95	15.15	4.80	0.51	5.56	-4.34	-3.31
348	71	female	4	68.00	67.50	100.20	114.80	107.90	108.40	8.00	-0.74	47.35	68.82	58.68	59.41	13.16	2.60
349	71	female	4	156.50	146.50	118.40	135.30	154.00	174.10	3.00	-6.39	-24.35	-13.55	-1.60	11.25	5.80	11.88
350	68	female	4	68.60	72.30	85.10	94.00	98.70	101.20	7.00	5.39	24.05	37.03	43.88	47.52	10.41	7.73
Number of cases				**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean				**50.72**	**57.84**	**52.73**	**57.01**	**59.30**	**64.07**	**4.75**	**20.43**	**8.28**	**17.75**	**23.91**	**35.85**	**4.65**	**8.89**
Standard deviation				**34.67**	**31.48**	**30.27**	**34.12**	**36.08**	**39.52**	**2.35**	**16.42**	**21.75**	**29.30**	**38.26**	**56.43**	**13.17**	**14.87**
Median				**38.80**	**50.70**	**40.00**	**42.15**	**41.90**	**45.15**	**4.50**	**19.49**	**4.59**	**12.67**	**15.69**	**18.99**	**1.09**	**6.62**
Minimum				**20.2**	**21.9**	**19.4**	**21.1**	**17.2**	**22.0**	**1.0**	**-6.39**	**-24.35**	**-15.07**	**-26.05**	**-16.92**	**-11.77**	**-5.42**
Maximum				**156.5**	**146.5**	**118.4**	**135.3**	**154.0**	**174.1**	**8.0**	**50.00**	**48.28**	**84.48**	**125.86**	**224.57**	**44.83**	**57.03**

Appendix 33 continued/…

Forearm cutaneous microcirculation during skin extension/relaxation in elderly (61-90Y) patients with CVI

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	At	During	---------During Relaxation phase-----				time to reach	During	-------During Relaxation phase------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
100	67	female	4	12.10	22.20	17.20	15.00	16.80	15.50	5.00	83.47	42.15	23.97	38.84	28.10	-11.41	-2.73
101	68	male	4	17.00	42.70	22.70	22.90	26.10	29.90	7.00	151.18	33.53	34.71	53.53	75.88	-13.06	14.59
105	74	female	4	26.60	42.50	48.20	47.80	56.20	58.00	5.00	59.77	81.20	79.70	111.28	118.05	14.66	14.21
108	63	male	1	""49.3	""76.3	""51.4				""5	""54.77	""4.26					
110	66	female	4	38.60	40.50	44.40	44.70	40.80	46.10	2.00	4.92	15.03	15.80	5.70	19.43	1.97	0.31
112	78	female	4	46.60	75.80	79.00	111.40	99.80	100.80	1.00	62.66	69.53	139.06	114.16	116.31	15.19	11.54
118	73	female	4	22.10	31.30	23.20	27.80	28.80	30.90	2.00	41.63	4.98	25.79	30.32	39.82	2.17	10.91
120	71	female	4	56.70	73.00	74.60	61.10	56.60	49.70	4.00	28.75	31.57	7.76	-0.18	-12.35	-11.40	-13.97
123	69	female	3	""32.7	""41.5	""76.50	""96.70	""104.10		""7	""26.91	""133.95	""195.72	""218.35			
125	73	female	4	21.70	29.80	18.80	28.20	22.40	21.90	7.00	37.33	-13.36	29.95	3.23	0.92	-5.62	1.61
126	72	female	4	71.60	94.40	85.40	81.40	67.10	61.70	7.00	31.84	19.27	13.69	-6.28	-13.83	-11.69	-11.93
127	81	male	2	""105	""140.10	""101.1(	""84.80			""1	""33.43	""-3.71	""-19.24				
129	70	female	4	16.90	27.00	19.50	14.40	13.50	13.00	2.00	59.76	15.38	-14.79	-20.12	-23.08	-20.12	-12.07
131	67	female	4	50.20	69.50	70.70	108.10	135.10	142.30	4.00	38.45	40.84	115.34	169.12	183.47	41.83	48.17
132	75	female	4	33.40	36.90	31.70	33.00	31.40	37.30	8.00	10.48	-5.09	-1.20	-5.99	11.68	0.15	4.55
133	73	male	4	44.60	61.70	22.90	24.70	22.80	28.90	4.00	38.34	-48.65	-44.62	-48.88	-35.20	-14.73	3.61
134	70	male	4	24.10	38.10	31.30	33.90	32.20	31.90	3.00	58.09	29.88	40.66	33.61	32.37	-4.77	0.04
136	74	female	4	121.40	130.30	115.10	113.70	120.90	119.50	6.00	7.33	-5.19	-6.34	-0.41	-1.57	-1.30	1.68
139	67	male	1	""34.70	""52.60	""33.10				""5	""51.59	""-4.61					
140	66	male	4	46.40	73.00	57.70	72.60	75.30	68.70	7.00	57.33	24.35	56.47	62.28	48.06	1.94	7.69
Number of cases				**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean				**40.63**	**55.54**	**47.65**	**52.54**	**52.86**	**53.51**	**4.63**	**48.21**	**20.96**	**32.25**	**33.76**	**36.75**	**-1.01**	**4.89**
Standard deviation				**27.18**	**29.14**	**29.70**	**34.77**	**37.72**	**37.73**	**2.22**	**35.09**	**31.52**	**47.11**	**57.15**	**59.80**	**15.14**	**14.59**
Median				**36.00**	**42.60**	**38.05**	**39.30**	**36.50**	**41.70**	**4.50**	**40.04**	**21.81**	**24.88**	**18.01**	**23.76**	**-3.04**	**2.64**
Minimum				**12.1**	**22.2**	**17.2**	**14.4**	**13.5**	**13.0**	**1.0**	**4.92**	**-48.65**	**-44.62**	**-48.88**	**-35.20**	**-20.12**	**-13.97**
Maximum				**121.4**	**130.3**	**115.1**	**113.7**	**135.1**	**142.3**	**8.0**	**151.18**	**81.20**	**139.06**	**169.12**	**183.47**	**41.83**	**48.17**

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Appendix 33 continued/...

Forearm cutaneous microcirculation during skin extension/relaxation in elderly (61-90Y) patients with venous ulcers

				The flux (arbitrary units) measured							The %chnge in flux measured						
			Measurement	At	During	----------During Relaxation phase-----				time to reach	During	-------During Relaxation phase------------				Slope of %change in flux	
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	peak (s)	extension	1min	2min	3min	4min	(ext-4min)	(1min-4min)
200	70	female	4	19.60	28.80	21.00	16.40	16.20	23.20	2.00	46.94	7.14	-16.33	-17.35	18.37	-8.16	3.27
201	81	female	4	20.10	36.10	29.10	23.40	29.40	28.50	7.00	79.60	44.78	16.42	46.27	41.79	-7.41	2.09
203	72	female	4	42.40	68.90	74.70	62.60	46.70	42.10	8.00	62.50	76.18	47.64	10.14	-0.71	-19.25	-26.82
204	62	female	3	""91.80	""102.70	""95.90	""121	""124.80		""1	""11.87	""4.47	""31.81	""35.95			
205	61	male	4	43.20	65.50	48.80	43.60	45.00	47.30	3.00	51.62	12.96	0.93	4.17	9.49	-9.31	-0.72
206	65	female	4	138.90	156.30	99.90	125.90	122.10	157.80	5.00	12.53	-28.08	-9.36	-12.10	13.61	1.81	12.23
207	73	male	4	55.30	48.80	35.80	37.80	42.70	41.20	3.00	-11.75	-35.26	-31.65	-22.78	-25.50	-1.50	3.82
208	74	female	4	71.60	86.60	61.80	62.70	61.70	49.70	8.00	20.95	-13.69	-12.43	-13.83	-30.59	-10.32	-5.21
210	66	female	4	31.60	44.40	30.20	38.70	50.80	51.60	5.00	40.51	-4.43	22.47	60.76	63.29	11.08	24.15
212	72	female	4	29.00	37.10	20.90	19.30	19.80	22.00	3.00	27.93	-27.93	-33.45	-31.72	-24.14	-10.79	1.31
215	73	male	4	28.10	45.30	23.70	28.60	34.90	39.10	3.00	61.21	-15.66	1.78	24.20	39.15	-0.43	18.69
216	75	female	4	51.00	76.00	80.00	95.30	107.00	95.80	3.00	49.02	56.86	86.86	109.80	87.84	13.06	11.59
217	85	female	4	167.80	134.90	72.50	96.70	142.60	150.50	3.00	-19.61	-56.79	-42.37	-15.02	-10.31	6.04	16.68
220	73	female	4	39.90	51.30	46.80	47.70	58.10	60.60	4.00	28.57	17.29	19.55	45.61	51.88	7.49	12.98

"" Measurement duration was less than 4 minutes and was not included in the statistical analysis

Number of cases	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**
Mean	**56.81**	**67.69**	**49.63**	**53.75**	**59.77**	**62.26**	**4.38**	**34.62**	**2.57**	**3.85**	**14.47**	**18.01**	**-2.13**	**5.70**
Standard deviation	**45.60**	**38.64**	**25.93**	**33.78**	**39.56**	**44.92**	**2.06**	**28.92**	**38.69**	**35.60**	**41.17**	**36.93**	**9.72**	**12.97**
Median	**42.40**	**51.30**	**46.80**	**43.60**	**46.70**	**47.30**	**3.00**	**40.51**	**-4.43**	**0.93**	**4.17**	**13.61**	**-1.50**	**3.82**
Minimum	**19.6**	**28.8**	**20.9**	**16.4**	**16.2**	**22.0**	**2.0**	**-19.61**	**-56.79**	**-42.37**	**-31.72**	**-30.59**	**-19.25**	**-26.82**
Maximum	**167.8**	**156.3**	**99.9**	**125.9**	**142.6**	**157.8**	**8.0**	**79.60**	**76.18**	**86.86**	**109.80**	**87.84**	**13.06**	**24.15**

Appendix 34

Changes in the leg cutaneous microcirculation during skin extension/relaxation in elderly patients with CVI (with frank venous ulcers and without)

The cutaneous microcirculation measured in the legs of elderly (61-90Y) asymptomatic controls

I.D.	Age	Sex	Measurement duration (min)	At baseline	During extension	The flux (arbitrary units) measured – During relaxation phase: 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
304	65	female												
310	72	male	8.00	38.40	36.50	22.70	26.80	28.50	31.40	34.00	34.40	35.80	35.00	1.00
313	69	female	8.00	19.50	29.30	17.50	20.60	24.50	29.10	30.40	31.00	34.00	33.10	3.00
330	63	male												
338	65	female	8.00	19.90	43.30	27.10	31.90	36.60	51.70	50.90	42.30	43.40	43.50	7.00
339	69	male	8.00	29.40	31.50	15.10	22.70	25.60	24.50	26.20	32.40	32.20	29.00	6.00
340	70	female	8.00	17.80	29.20	20.80	30.30	45.60	48.40	47.90	69.70	77.50	73.60	3.00
341	71	female	8.00	36.90	29.80	14.00	27.30	34.50	39.00	45.40	48.00	50.30	49.40	4.00
342	62	male	8.00	18.70	64.90	14.60	13.20	14.70	18.50	13.10	14.00	13.90	12.60	4.00
343	69	female	8.00	29.10	67.40	37.10	53.00	70.90	80.80	75.20	83.00	82.50	111.20	7.00
344	69	female	8.00	14.30	24.30	18.00	13.40	13.50	13.10	13.70	13.90	14.20	15.80	4.00
345	69	male	8.00	16.10	24.50	10.30	10.90	14.70	16.90	16.10	17.40	20.20	20.20	4.00
346	74	female	8.00	21.30	25.50	25.20	24.70	25.70	26.60	29.20	28.30	35.70	35.60	2.00
347	69	male	8.00	19.70	25.00	17.00	18.50	18.80	22.30	19.60	21.30	19.50	19.50	5.00
348	71	female	8.00	19.50	18.10	12.20	15.50	23.60	29.20	28.30	33.00	36.30	39.30	1.00
349	71	female	8.00	27.30	25.90	16.20	33.10	47.00	60.10	69.50	80.40	84.70	81.30	3.00
350	68	female	8.00	26.10	29.60	20.40	29.50	44.00	56.90	63.80	76.80	73.30	73.20	6.00
351	62	male	8.00	15.20	20.40	12.10	13.80	17.90	20.40	18.00	23.20	19.70	19.40	5.00
352	62	male	8.00	13.50	16.80	10.80	17.40	22.50	27.30	30.00	28.30	34.00	36.20	5.00
353	62	male	8.00	35.00	44.80	42.20	55.80	73.50	69.10	75.50	81.00	84.00	87.40	6.00
Number of cases				**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean				**23.21**	**32.60**	**19.63**	**25.47**	**32.34**	**36.96**	**38.16**	**42.13**	**43.96**	**45.29**	**4.22**
Standard deviation				**7.85**	**14.29**	**8.72**	**12.63**	**17.89**	**19.63**	**21.20**	**24.71**	**25.26**	**28.34**	**1.83**
Median				**19.80**	**29.25**	**17.25**	**23.70**	**25.65**	**29.15**	**30.20**	**32.70**	**35.75**	**35.90**	**4.00**
Minimum				**13.50**	**16.80**	**10.30**	**10.90**	**13.50**	**13.10**	**13.10**	**13.90**	**13.90**	**12.60**	**1.00**
Maximum				**38.40**	**67.40**	**42.20**	**55.80**	**73.50**	**80.80**	**75.50**	**83.00**	**84.70**	**111.20**	**7.00**

Appendix 34 continued/…

The cutaneous microcirculation measured in the legs of elderly (61-90Y) asymptomatic controls

I.D.	Age	Sex	Measurement duration (min)	During extension	1min	2min	3min	4min	5min	6min	7min	8min	Slope of %change in flux (ext-8min)	(1min-8min)
				The %chnge in flux measured	----during relaxation phase----									
304	65	female												
310	72	male	8.00	-4.95	-40.89	-30.21	-25.78	-18.23	-11.46	-10.42	-6.77	-8.85	2.34	4.69
313	69	female	8.00	50.26	-10.26	5.64	25.64	49.23	55.90	58.97	74.36	69.74	7.81	12.03
330	63	male												
338	65	female	8.00	117.59	36.18	60.30	83.92	159.80	155.78	112.56	118.09	118.59	7.10	11.28
339	69	male	8.00	7.14	-48.64	-22.79	-12.93	-16.67	-10.88	10.20	9.52	-1.36	3.48	6.76
340	70	female	8.00	64.04	16.85	70.22	156.18	171.91	169.10	291.57	335.39	313.48	40.15	45.31
341	71	female	8.00	-19.24	-62.06	-26.02	-6.50	5.69	23.04	30.08	36.31	33.88	10.82	13.22
342	62	male	8.00	247.06	-21.93	-29.41	-21.39	-1.07	-29.95	-25.13	-25.67	-32.62	-18.83	-1.15
343	69	female	8.00	131.62	27.49	82.13	143.64	177.66	158.42	185.22	183.51	282.13	21.52	28.51
344	69	female	8.00	69.93	25.87	-6.29	-5.59	-8.39	-4.20	-2.80	-0.70	10.49	-5.15	-0.80
345	69	male	8.00	52.17	-36.02	-32.30	-8.70	4.97	0.00	8.07	25.47	25.47	2.79	9.10
346	74	female	8.00	19.72	18.31	15.96	20.66	24.88	37.09	32.86	67.61	67.14	6.46	7.72
347	69	male	8.00	26.90	-13.71	-6.09	-4.57	13.20	-0.51	8.12	-1.02	-1.02	-0.69	1.65
348	71	female	8.00	-7.18	-37.44	-20.51	21.03	49.74	45.13	69.23	86.15	101.54	16.82	19.60
349	71	female	8.00	-5.13	-40.66	21.25	72.16	120.15	154.58	194.51	210.26	197.80	33.22	35.90
350	68	female	8.00	13.41	-21.84	13.03	68.58	118.01	144.44	194.25	180.84	180.46	28.58	31.65
351	62	male	8.00	34.21	-20.39	-9.21	17.76	34.21	18.42	52.63	29.61	27.63	4.13	7.37
352	62	male	8.00	24.44	-20.00	28.89	66.67	102.22	122.22	109.63	151.85	168.15	21.79	24.77
353	62	male	8.00	28.00	20.57	59.43	110.00	97.43	115.71	131.43	140.00	149.71	16.58	16.54
Number of cases				**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean				**47.22**	**-12.70**	**9.67**	**38.93**	**60.26**	**63.49**	**80.61**	**89.71**	**94.58**	**11.05**	**15.23**
Standard deviation				**64.47**	**29.88**	**37.18**	**56.64**	**67.38**	**71.56**	**88.75**	**95.79**	**101.98**	**14.40**	**13.21**
Median				**27.45**	**-20.20**	**-0.23**	**20.84**	**41.72**	**41.11**	**55.80**	**70.98**	**68.44**	**7.46**	**11.65**
Minimum				**-19.24**	**-62.06**	**-32.30**	**-25.78**	**-18.23**	**-29.95**	**-25.13**	**-25.67**	**-32.62**	**-18.83**	**-1.15**
Maximum				**247.06**	**36.18**	**82.13**	**156.18**	**177.66**	**169.10**	**291.57**	**335.39**	**313.48**	**40.15**	**45.31**

Appendix 34 continued/...

The cutaneous microcirculation measured in the legs of elderly (61-90Y) patients with CVI

I.D.	Age	Sex	Measurement duration (min)	The flux (arbitrary units) measured: At baseline	During extension	During relaxation phase: 1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
100	67	female	8.00	48.80	45.60	40.30	55.70	68.90	75.40	96.50	104.30	99.10	92.20	1.00
101	68	male	6.00	""14.7	""21.1	""13.7	""17.8	""24.8	""18.1	""18.1	""19.2			""2
105	74	female	8.00	49.80	41.60	25.40	30.80	38.30	37.90	44.60	39.50	41.50	37.00	2.00
108	63	male	8.00	31.80	36.90	22.70	27.90	33.00	30.40	30.30	28.30	28.40	30.70	1.00
110	66	female	8.00	27.90	38.40	22.50	24.40	27.30	26.90	27.10	26.00	30.70	30.80	7.00
112	78	female	8.00	25.30	36.90	13.20	15.70	18.80	19.20	21.70	24.30	24.50	27.50	2.00
118	73	female	8.00	8.20	13.10	6.90	7.50	7.60	7.60	7.90	7.80	8.30	8.20	2.00
120	71	female	8.00	62.90	52.40	33.40	41.80	48.70	46.20	49.10	52.10	53.50	59.10	2.00
123	69	female	8.00	18.80	29.20	20.90	32.00	39.00	45.00	50.70	51.70	53.40	61.60	3.00
125	73	female	8.00	10.50	11.10	9.90	12.80	12.90	13.00	11.60	12.60	12.00	12.10	7.00
126	72	female	4.00	11.2""	14.8""	21.3""	25.4""	25.7""	26.5""					""1
127	81	male	5.00	""38.3	""44.4	""37.4	""38.2	""38.6	""35.7	""36.5				""4
129	70	female	8.00	17.10	19.70	10.70	16.70	19.50	20.30	20.20	20.30	21.00	20.30	1.00
131	67	female	7.00	""84.1	""51	""49.2	""76.7	""97.9	""131.1	""142.5	""153.3	""152.4		""2
132	75	female	8.00	175.90	134.80	58.30	119.70	152.20	176.10	169.20	196.00	192.10	201.10	1.00
133	73	male	8.00	91.90	78.70	52.00	91.90	88.90	86.30	88.70	79.90	70.70	75.90	1.00
134	70	male	8.00	15.80	28.40	8.90	10.70	15.20	21.00	34.50	41.10	43.80	31.70	1.00
136	74	female	8.00	121.90	115.20	79.30	108.70	116.70	133.10	127.10	1131.60	114.40	123.10	2.00
139	67	male	4.00	""77.6	""46.7	""21.6	""28.2	""36.3	""43.9					""1
140	66	male	6.00	""54.4	""48.6	""44.8	""50.3	""54.1	""57.6	""64.5	""57.9			""2

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	At baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**
Mean	**50.47**	**48.71**	**28.89**	**42.59**	**49.07**	**52.74**	**55.66**	**129.68**	**56.67**	**57.95**	**2.36**
Standard deviation	**48.76**	**36.70**	**21.60**	**37.47**	**43.06**	**49.31**	**47.62**	**292.48**	**49.77**	**52.46**	**2.06**
Median	**29.85**	**37.65**	**22.60**	**29.35**	**35.65**	**34.15**	**39.55**	**40.30**	**42.65**	**34.35**	**2.00**
Minimum	**8.20**	**11.10**	**6.90**	**7.50**	**7.60**	**7.60**	**7.90**	**7.80**	**8.30**	**8.20**	**1.00**
Maximum	**175.90**	**134.80**	**79.30**	**119.70**	**152.20**	**176.10**	**169.20**	**1131.60**	**192.10**	**201.10**	**7.00**

Appendix 34 continued/…

The cutaneous microcirculation measured in the legs of elderly (61-90Y) patients with CVI														
				The %chnge in flux measured										
			Measurement	During	----------during relaxation phase----------								Slope of %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
100	67	female	8.00	-6.56	-17.42	14.14	41.19	54.51	97.75	113.73	103.07	88.93	16.65	17.26
101	68	male	6.00	""43.54	""-6.80	""21.09	""68.71	""23.13	""23.13	""30.61				
105	74	female	8.00	-16.47	-49.00	-38.15	-23.09	-23.90	-10.44	-20.68	-16.67	-25.70	1.79	3.47
108	63	male	8.00	16.04	-28.62	-12.26	3.77	-4.40	-4.72	-11.01	-10.69	-3.46	-0.50	1.66
110	66	female	8.00	37.63	-19.35	-12.54	-2.15	-3.58	-2.87	-6.81	10.04	10.39	-0.17	3.66
112	78	female	8.00	45.85	-47.83	-37.94	-25.69	-24.11	-14.23	-3.95	-3.16	8.70	1.08	7.68
118	73	female	8.00	59.76	-15.85	-8.54	-7.32	-7.32	-3.66	-4.88	1.22	0.00	-2.95	2.03
120	71	female	8.00	-16.69	-46.90	-33.55	-22.58	-26.55	-21.94	-17.17	-14.94	-6.04	2.86	4.76
123	69	female	8.00	55.32	11.17	70.21	107.45	139.36	169.68	175.00	184.04	227.66	24.66	27.59
125	73	female	8.00	5.71	-5.71	21.90	22.86	23.81	10.48	20.00	14.29	15.24	1.37	1.03
126	72	female	4.00	""32.14	""90.18	""126.79	""129.46	""136.61						
127	81	male	5.00	""15.93	""-2.35	""-0.26	""0.78	""-6.79						
129	70	female	8.00	15.20	-37.43	-2.34	14.04	18.71	18.13	18.71	22.81	18.71	4.02	6.34
131	67	female	7.00	""-39.36	""-41.5	""-8.8	""16.41	""55.89	""69.44	""82.28	""81.21			
132	75	female	8.00	-23.37	-66.86	-31.95	-13.47	0.11	-3.81	11.43	9.21	14.33	7.92	10.06
133	73	male	8.00	-14.36	-43.42	0.00	-3.26	-6.09	-3.48	-13.06	-23.07	-17.41	0.38	0.48
134	70	male	8.00	79.75	-43.67	-32.28	-3.80	32.91	118.35	160.13	177.22	100.63	20.89	31.37
136	74	female	8.00	-5.50	-34.95	-10.83	-4.27	9.19	4.27	828.30	-6.15	0.98	29.99	32.95
139	67	male	4.00	""-39.82	""-72.17	""-63.66	""-53.22	""-43.43						
140	66	male	6.00	""-10.66	""-17.65	""-7.54	""-0.55	""5.88	""18.57	""6.43				

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**	**14**
Mean	**16.59**	**-31.84**	**-8.15**	**5.98**	**13.05**	**25.25**	**89.27**	**31.94**	**30.93**	**7.71**	**10.74**
Standard deviation	**33.46**	**20.53**	**29.44**	**34.49**	**43.03**	**58.67**	**222.87**	**70.01**	**67.06**	**10.71**	**11.67**
Median	**10.46**	**-36.19**	**-11.55**	**-3.53**	**-1.74**	**-3.17**	**3.74**	**5.21**	**9.54**	**2.33**	**5.55**
Minimum	**-23.37**	**-66.86**	**-38.15**	**-25.69**	**-26.55**	**-21.94**	**-20.68**	**-23.07**	**-25.70**	**-2.95**	**0.48**
Maximum	**79.75**	**11.17**	**70.21**	**107.45**	**139.36**	**169.68**	**828.30**	**184.04**	**227.66**	**29.99**	**32.95**

Appendix 34 continued/…

The cutaneous microcirculation measured in the legs of elderly (61-90Y) patients with venous ulcers														
				The flux (arbitrary units) measured										
			Measurement	at	During	during relaxation phase								time to reach
I.D.	Age	Sex	duration (min)	baseline	extension	1min	2min	3min	4min	5min	6min	7min	8min	peak (s)
200	70	female	8.00	20.20	33.80	24.60	23.00	19.90	26.40	28.80	26.80	29.80	30.20	2.00
201	81	female	6.00	""34.7	""47.2	""34.3	""55	""58.3	""55.3	""50.2	""47.1			""3
203	72	female	7.00	""35.9	""44.2	""22.8	""37.2	""46.4	""47.1	""43.8	""42.4	""43.6		""2
204	62	female	8.00	26.10	34.50	18.50	25.50	25.40	27.40	30.50	32.30	30.90	31.90	3.00
205	61	male	8.00	27.90	32.90	20.50	23.90	22.50	25.30	29.00	27.40	29.50	30.90	2.00
206	65	female	8.00	74.10	63.00	28.40	35.40	40.60	42.60	40.80	42.00	36.60	45.20	2.00
207	73	male	3.00	""63.5	""69.3	""65.9	""72.5	""71.4						""2
208	74	female	8.00	36.30	44.70	30.30	34.20	34.30	33.50	34.60	32.60	30.80	32.30	5.00
210	66	female	8.00	36.30	31.60	23.60	26.00	27.00	26.80	27.40	29.40	27.30	26.70	6.00
212	72	female	8.00	51.30	78.80	64.90	79.20	74.90	73.40	83.10	94.30	79.20	74.10	6.00
215	73	male	7.00	""52.7	""34.7	""10.8	""14.6	""17.1	""19.2	""23.5	""25.1	""28.1		""3
216	75	female	7.00	""34.1	""45.4	""46.5	""40.9	""35.8	""31.7	""38.2	""31.3	""37.4		""5
217	85	female	8.00	63.50	74.20	73.60	74.70	68.50	76.70	84.50	89.60	71.80	83.00	4.00
220	73	female	7.00	""88.8	""11.9	""73.5	""77.7	""90.3	""114.6	""118.3	""130.2	""133.9		""5
221	69	male												

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

	at baseline	During extension	1min	2min	3min	4min	5min	6min	7min	8min	time to reach peak (s)
Number of cases	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean	**41.96**	**49.19**	**35.55**	**40.24**	**39.14**	**41.51**	**44.84**	**46.80**	**41.99**	**44.29**	**3.75**
Standard deviation	**19.16**	**19.79**	**21.27**	**23.14**	**21.21**	**21.47**	**24.42**	**28.29**	**20.95**	**21.95**	**1.75**
Median	**36.30**	**39.60**	**26.50**	**30.10**	**30.65**	**30.45**	**32.55**	**32.45**	**30.85**	**32.10**	**3.50**
Minimum	**20.20**	**31.60**	**18.50**	**23.00**	**19.90**	**25.30**	**27.40**	**26.80**	**27.30**	**26.70**	**2.00**
Maximum	**74.10**	**78.80**	**73.60**	**79.20**	**74.90**	**76.70**	**84.50**	**94.30**	**79.20**	**83.00**	**6.00**

Appendix 34 continued/…

The cutaneous microcirculation measured in the legs of elderly (61-90Y) patients with venous ulcers														
				The %chnge in flux measured										
			Measurement	During	----------during relaxation phase----------								Slope of %change in flux	
I.D.	Age	Sex	duration (min)	extension	1min	2min	3min	4min	5min	6min	7min	8min	(ext-8min)	(1min-8min)
200	70	female	8.00	67.33	21.78	13.86	-1.49	30.69	42.57	32.67	47.52	49.50	1.46	5.68
201	81	female	6.00	""36.02	""-1.15	""58.50	""68.01	""59.37	""44.67	""35.74				
203	72	female	7.00	""23.12	""-36.49	""3.62	""29.25	""31.2	""22.01	""18.12	""21.45			
204	62	female	8.00	32.18	-29.12	-2.30	-2.68	4.98	16.86	23.75	18.39	22.22	2.91	6.60
205	61	male	8.00	17.92	-26.52	-14.34	-19.35	-9.32	3.94	-1.79	5.73	10.75	1.94	5.09
206	65	female	8.00	-14.98	-61.67	-52.23	-45.21	-42.51	-44.94	-43.32	-50.61	-39.00	-0.75	2.02
207	73	male	3.00	""9.13	""3.78	""14.17	""12.44							
208	74	female	8.00	23.14	-16.53	-5.79	-5.51	-7.71	-4.68	-10.19	-15.15	-11.02	-2.34	-0.23
210	66	female	8.00	-12.95	-34.99	-28.37	-25.62	-26.17	-24.52	-19.01	-24.79	-26.45	-0.06	1.18
212	72	female	8.00	53.61	26.51	54.39	46.00	43.08	61.99	83.82	54.39	44.44	2.03	3.07
215	73	male	7.00	""-34.16	""-79.51	""-72.3	""-67.55	""-63.57	""-55.41	""-52.37	""-46.68			
216	75	female	7.00	""33.14	""36.36	""19.94	""4.99	""-7.04	""12.02	""-8.21	""9.68			
217	85	female	8.00	16.85	15.91	17.64	7.87	20.79	33.07	41.10	13.07	30.71	1.98	2.29
220	73	female	7.00	""-86.6	""-17.23	""-12.5	""1.69	""29.05	""33.22	""46.62	""50.79			
221	69	male												

"" Measurement duration was less than 8 minutes and was not included in the statistical analysis

Number of cases	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean	**22.89**	**-13.08**	**-2.14**	**-5.75**	**1.73**	**10.54**	**13.38**	**6.07**	**10.15**	**0.90**	**3.21**
Standard deviation	**28.75**	**31.43**	**32.07**	**26.80**	**28.96**	**35.46**	**40.11**	**35.60**	**32.73**	**1.77**	**2.37**
Median	**20.53**	**-21.53**	**-4.04**	**-4.10**	**-1.37**	**10.40**	**10.98**	**9.40**	**16.49**	**1.70**	**2.68**
Minimum	**-14.98**	**-61.67**	**-52.23**	**-45.21**	**-42.51**	**-44.94**	**-43.32**	**-50.61**	**-39.00**	**-2.34**	**-0.23**
Maximum	**67.33**	**26.51**	**54.39**	**46.00**	**43.08**	**61.99**	**83.82**	**54.39**	**49.50**	**2.91**	**6.60**

Appendix 35

The effects of CVI (with venous ulcers and without) on the postural vasoconstrictive response

The postural vasoconstrictive response in asymptomatic controls																			
				The flux (arbitrary units) measured							Time for flux to reach baseline (s)	The %drop in flux measured						Slopes of %drop in flux between	
				at	----------after passive leg lowering at-------------							----------after passive leg lowering at-----------							
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s		5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
101	23	female	right	16.60	25.70	25.20	16.20	14.50	10.70	6.40	15.0	-54.82	-51.81	2.41	12.65	35.54	61.45	1.20	1.02
103	28	female	right	21.60	63.30	48.70	38.50	45.90	21.90	11.80	19.0	-193.06	-125.46	-78.24	-112.50	-1.39	45.37	2.35	1.95
105	34	male	right	42.90	55.40	57.30	37.20	44.80	36.20	33.70	7.0	-29.14	-33.57	13.29	-4.43	15.62	21.45	0.51	0.41
106	25	female	right	215.50	145.40	94.80	227.10	161.50	61.90	43.20	3.0	32.53	56.01	-5.38	25.06	71.28	79.95	0.63	0.66
108	26	female	right	177.30	138.80	92.20	76.80	68.30	50.70	82.70	4.0	21.71	48.00	56.68	61.48	71.40	53.36	0.15	-0.02
112	29	female	right	43.20	54.80	41.80	32.50	31.60	27.20	20.70	7.0	-26.85	3.24	24.77	26.85	37.04	52.08	0.67	0.46
113	26	female	right	17.60	23.90	17.50	16.60	13.70	13.50	11.50	10.0	-35.80	0.57	5.68	22.16	23.30	34.66	0.56	0.35
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	18.0	-50.27	-12.10	-29.57	9.14	7.80	30.38	0.73	0.56
117	42	female	right	214.80	236.00	204.60	180.60	139.40	109.70	88.30	9.0	-9.87	4.75	15.92	35.10	48.93	58.89	0.68	0.55
118	58	male	right	67.10	115.20	84.30	88.70	93.40	97.70	89.20	54.0	-71.68	-25.63	-32.19	-39.20	-45.60	-32.94	0.16	-0.01
119	44	female	right	26.80	27.80	29.80	23.00	21.10	18.00	17.70	3.0	-3.73	-11.19	14.18	21.27	32.84	33.96	0.42	0.37
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	2.0	68.66	80.61	42.16	51.37	53.80	56.70	-0.10	-0.05
121	41	female	right	37.40	33.20	29.00	29.50	23.20	16.30	14.40	4.0	11.23	22.46	21.12	37.97	56.42	61.50	0.53	0.45
124	44	female	right	23.00	40.70	33.60	26.90	21.70	17.80	7.90	17.0	-76.96	-46.09	-16.96	5.65	22.61	65.65	1.40	1.16
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	12.0	-21.37	-2.82	7.90	21.51	33.43	59.31	0.81	0.68
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	9.0	-20.17	15.32	26.09	52.73	35.09	29.83	0.26	0.02
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	4.0	25.22	53.67	-0.29	41.94	48.39	60.12	0.38	0.35
128	52	male	right	37.20	47.80	41.80	37.90	38.80	36.90	21.50	9.0	-28.49	-12.37	-1.88	-4.30	0.81	42.20	0.72	0.65
130	51	female	right	39.40	24.70	20.10	11.40	13.70	11.30	14.00	1.0	37.31	48.98	71.07	65.23	71.32	64.47	0.17	0.05

Appendix 35 continued/...

The postural vasoconstrictive response in asymptomatic controls																			
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at-------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
131	42	male	right	144.70	85.80	78.80	78.00	82.80	34.20	60.60	3.0	40.70	45.54	46.10	42.78	76.36	58.12	0.19	0.15
132	43	female	right	247.40	255.30	224.60	269.90	272.00	216.00	38.50	6.0	-3.19	9.22	-9.09	-9.94	12.69	84.44	1.08	1.13
133	42	female	right	8.00	11.00	9.60	7.50	7.70	6.80	5.10	13.0	-37.50	-20.00	6.25	3.75	15.00	36.25	0.69	0.54
134	44	male	right	11.00	14.10	9.80	20.40	8.20	12.40	5.70	7.0	-28.18	10.91	-85.45	25.45	-12.73	48.18	0.88	0.87
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	44.0	-220.44	-91.97	-47.45	-31.39	-62.77	21.90	1.82	1.12
136	53	male	right	13.70	22.80	12.40	7.70	7.30	6.90	5.80	8.0	-66.42	9.49	43.80	46.72	49.64	57.66	0.82	0.36
137	46	female	right	10.10	12.20	13.80	9.50	10.10	9.70	6.00	16.0	-20.79	-36.63	5.94	0.00	3.96	40.59	0.73	0.71
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	2.0	6.84	33.41	53.53	45.72	48.92	20.01	-0.11	-0.31
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	4.0	14.30	18.94	4.26	31.47	27.07	44.43	0.36	0.36
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	2.0	52.92	77.16	72.63	51.60	32.94	48.47	-0.20	-0.25
141	48	female	right	32.70	30.20	12.80	18.10	11.30	13.40	7.00	5.0	7.65	60.86	44.65	65.44	59.02	78.59	0.51	0.29
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	19.0	-46.09	-33.27	-33.39	10.98	6.63	30.48	0.80	0.69
143	53	female	right	97.50	107.20	91.80	64.90	50.70	45.12	40.00	8.0	-9.95	5.85	33.44	48.00	53.72	58.97	0.61	0.43
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	3.0	0.83	14.97	8.25	11.20	28.34	23.74	0.21	0.15
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	10.0	-81.76	12.84	-55.41	-4.05	34.46	66.22	1.33	1.03
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	3.0	18.10	20.18	15.10	21.61	-50.13	20.44	0.00	0.07
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	2.0	64.88	55.06	8.78	11.64	35.79	20.58	-0.29	-0.12
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	1.0	-81.78	-50.58	50.00	-17.83	-14.73	29.26	0.83	0.52
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	2.0	69.68	62.53	61.47	77.47	76.63	68.21	0.02	0.02
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	7.0	-7.83	29.86	53.91	-1.16	48.99	47.25	0.39	0.21
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	2.0	26.69	47.21	57.17	58.76	62.35	81.87	0.49	0.37

Appendix 35 continued/…

The postural vasoconstrictive response in asymptomatic controls																		
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at----------						in flux between
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
101	23	female	left	9.10	12.80	12.80	12.50	9.90	10.20	5.80	17.0	-40.66	-40.66	-37.36	-8.79	-12.09	36.26	0.91	0.89
103	28	female	left	20.80	20.50	25.20	29.00	20.20	20.90	8.80	7.0	1.44	-21.15	-39.42	2.88	-0.48	57.69	0.89	1.04
105	34	male	left	7.10	16.10	18.00	11.00	8.20	4.10	4.70	17.0	-126.76	-153.52	-54.93	-15.49	42.25	33.80	1.78	1.52
106	25	female	left	80.70	67.50	66.40	51.90	22.40	6.70	27.70	1.0	16.36	17.72	35.69	72.24	91.70	65.68	0.49	0.35
108	26	female	left	98.30	126.10	103.90	100.90	127.00	82.00	138.60	11.0	-28.28	-5.70	-2.64	-29.20	16.58	-41.00	-0.30	-0.43
112	29	female	left	29.70	87.90	82.80	42.70	28.00	35.30	30.40	17.0	-195.96	-178.79	-43.77	5.72	-18.86	-2.36	1.66	1.11
113	26	female	left	17.50	19.80	20.10	18.10	17.40	18.90	9.80	13.0	-13.14	-14.86	-3.43	0.57	-8.00	44.00	0.67	0.68
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	29.0	-153.64	-91.95	5.75	-9.96	9.20	28.35	1.43	0.87
117	42	female	left	80.10	75.80	57.50	41.90	34.80	25.00	17.50	5.0	5.37	28.21	47.69	56.55	68.79	78.15	0.65	0.47
118	58	male	left	50.60	50.00	25.10	23.90	24.00	22.80	22.70	5.0	1.19	50.40	52.77	52.57	54.94	55.14	0.28	0.04
119	44	female	left	106.50	149.30	155.40	160.60	136.20	102.10	79.80	24.0	-40.19	-45.92	-50.80	-27.89	4.13	25.07	0.86	0.88
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	3.0	49.54	32.62	48.00	-21.85	-24.77	20.31	-0.20	-0.02
121	41	female	left	28.60	41.20	40.10	34.20	21.70	15.40	6.00	18.0	-44.06	-40.21	-19.58	24.13	46.15	79.02	1.37	1.25
124	44	female	left	16.70	52.40	40.50	27.50	22.70	11.50	5.60	26.0	-213.77	-142.51	-64.67	-35.93	31.14	66.47	2.62	2.01
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	6.0	-14.40	30.28	60.88	69.72	64.48	48.45	0.30	-0.03
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	8.0	-27.46	38.24	26.20	73.72	77.34	44.85	0.38	0.00
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	34.0	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00	0.08	-0.16
128	52	male	left	14.40	21.20	10.20	15.80	8.60	14.00	8.30	7.0	-47.22	29.17	-9.72	40.28	2.78	42.36	0.60	0.32
130	51	female	left	9.50	11.10	6.00	6.40	7.50	7.80	5.20	4.0	-16.84	36.84	32.63	21.05	17.89	45.26	0.39	0.19
131	42	male	left	110.70	68.90	118.60	96.80	101.90	94.90	71.40	4.0	37.76	-7.14	12.56	7.95	14.27	35.50	0.25	0.42
132	43	female	left	22.60	14.00	13.30	13.90	10.60	8.60	7.60	4.0	38.05	41.15	38.50	53.10	61.95	66.37	0.32	0.30
133	42	female	left	9.30	15.00	15.60	13.00	8.00	5.20	4.30	19.0	-61.29	-67.74	-39.78	13.98	44.09	53.76	1.31	1.17
134	44	male	left	5.70	17.20	9.60	15.40	8.50	10.40	10.80	120.0	-201.75	-68.42	-170.18	-49.12	-82.46	-89.47	0.61	0.10
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	91.0	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59	0.51	0.31

Appendix 35 continued/...

The postural vasoconstrictive response in asymptomatic controls

				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
136	53	male	left	17.80	16.70	26.20	13.40	13.80	15.20	6.50	2.0	6.18	-47.19	24.72	22.47	14.61	63.48	0.84	0.92
137	46	female	left	11.10	14.20	18.50	13.60	7.60	8.40	6.20	16.0	-27.93	-66.67	-22.52	31.53	24.32	44.14	0.95	0.93
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	3.0	13.45	12.85	49.22	21.13	-2.29	19.44	-0.04	-0.08
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	3.0	34.73	34.73	54.78	65.40	78.11	78.77	0.46	0.38
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	120.0	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66	-0.02	-0.09
141	48	female	left	20.20	18.80	16.80	13.00	8.70	7.90	6.20	5.0	6.93	16.83	35.64	56.93	60.89	69.31	0.60	0.47
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	4.0	16.36	41.41	60.99	44.22	60.69	74.74	0.48	0.34
143	53	female	left	132.50	100.50	93.80	89.80	81.40	59.90	29.70	2.0	24.15	29.21	32.23	38.57	54.79	77.58	0.61	0.59
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	5.0	2.51	18.66	-11.42	-8.64	-42.62	31.48	0.34	0.42
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	5.0	10.84	34.41	47.72	68.25	65.40	71.10	0.49	0.31
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	64.0	-75.82	-68.32	-26.92	-30.59	-23.99	23.81	1.03	0.91
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	2.0	77.43	25.14	66.99	28.83	93.91	87.38	0.43	0.59
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	3.0	-85.79	49.73	30.05	54.10	57.92	73.77	0.99	0.38
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	24.0	-28.56	-22.42	-32.84	-17.95	11.81	28.28	0.69	0.68
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	47.0	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26	2.24	1.03
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	16.0	-84.02	-156.19	-21.65	5.15	15.98	-16.49	0.83	0.68
Number of cases				**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Mean				**79.60**	**82.17**	**71.88**	**69.27**	**62.91**	**55.03**	**47.25**	**14.81**	**-32.50**	**-7.98**	**3.15**	**14.54**	**22.56**	**39.55**	**0.65**	**0.50**
Standard deviation				**94.00**	**105.61**	**97.38**	**104.08**	**84.64**	**80.28**	**72.58**	**22.61**	**74.89**	**56.29**	**47.49**	**41.01**	**43.15**	**37.18**	**0.57**	**0.48**
Median				**41.15**	**49.45**	**41.10**	**34.00**	**28.35**	**22.10**	**21.10**	**7.00**	**-18.51**	**7.53**	**8.08**	**21.20**	**29.74**	**45.32**	**0.60**	**0.42**
Minimum				**5.70**	**11.00**	**6.00**	**6.40**	**7.30**	**4.10**	**4.30**	**1.00**	**-350.46**	**-178.79**	**-170.18**	**-118.35**	**-118.97**	**-99.66**	**-0.30**	**-0.43**
Maximum				**542.6**	**792.7**	**723.1**	**723.8**	**483.0**	**506.6**	**377.2**	**120.0**	**77.43**	**80.61**	**72.63**	**77.47**	**93.91**	**87.38**	**2.62**	**2.01**

Appendix 35 continued/...

The postural vasoconstrictive response in patients with CVI																				
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
200	67	female	right	30.30	82.30	59.20	14.10	11.50	10.70	7.80	12.0	-171.62	-95.38	53.47	62.05	64.69	74.26	1.87	1.04
201	68	male	right	31.60	39.00	30.00	22.40	22.00	20.30	13.20	10.0	-23.42	5.06	29.11	30.38	35.76	58.23	0.70	0.51
202	39	female	right	11.40	35.90	21.40	24.40	18.90	14.70	14.00	75.0	-214.91	-87.72	-114.04	-65.79	-28.95	-22.81	1.47	0.87
203	72	female	right	11.70	21.90	22.40	11.70	14.10	8.70	7.80	15.0	-87.18	-91.45	0.00	-20.51	25.64	33.33	1.21	0.98
204	51	male	right	36.90	29.50	22.80	17.20	12.00	6.40	7.80	4.0	20.05	38.21	53.39	67.48	82.66	78.86	0.52	0.36
205	55	female	right	58.10	126.50	92.30	76.90	83.80	81.10	74.60	116.0	-117.73	-58.86	-32.36	-44.23	-39.59	-28.40	0.57	0.24
206	74	female	right	22.90	16.30	19.90	21.60	16.20	16.60	15.00	3.0	28.82	13.10	5.68	29.26	27.51	34.50	0.19	0.26
207	45	female	right	11.80	24.10	13.10	17.80	16.40	15.00	13.00	91.0	-104.24	-11.02	-50.85	-38.98	-27.12	-10.17	0.60	0.28
208	51	female	right	9.20	20.60	14.40	11.70	13.70	14.80	8.90	22.0	-123.91	-56.52	-27.17	-48.91	-60.87	3.26	0.97	0.65
209	63	male	right	52.90	46.30	36.60	34.50	31.90	29.10	17.30	4.0	12.48	30.81	34.78	39.70	44.99	67.30	0.52	0.43
210	35	female	right	24.30	34.30	27.20	24.10	22.40	21.90	19.70	15.0	-41.15	-11.93	0.82	7.82	9.88	18.93	0.46	0.28
211	53	male	right	30.50	47.90	28.50	19.80	15.00	12.50	12.30	9.0	-57.05	6.56	35.08	50.82	59.02	59.67	0.83	0.42
212	51	female	right	65.70	39.20	39.50	36.00	23.30	21.60	23.00	3.0	40.33	39.88	45.21	64.54	67.12	64.99	0.26	0.22
213	78	female	right	76.80	83.40	80.90	91.70	83.80	100.70	65.80	33.0	-8.59	-5.34	-19.40	-9.11	-31.12	14.32	0.30	0.35
214	55	female	right	10.40	33.00	29.10	23.40	26.70	21.40	14.40	120.0	-217.31	-179.81	-125.00	-156.73	-105.77	-38.46	1.78	1.53
215	73	female	right	138.50	83.10	93.60	68.70	66.30	51.00	42.70	2.0	40.00	32.42	50.40	52.13	63.18	69.17	0.35	0.33
216	50	female	right	100.80	73.00	76.50	40.40	39.80	25.20	35.90	2.0	27.58	24.11	59.92	60.52	75.00	64.38	0.35	0.24
217	58	female	right	257.00	220.00	81.30	15.00	14.60	115.70	35.70	5.0	14.40	68.37	94.16	94.32	54.98	86.11	0.36	0.06
218	35	male	right	26.90	41.20	26.90	31.20	23.70	25.50	15.70	10.0	-53.16	0.00	-15.99	11.90	5.20	41.64	0.80	0.58
219	71	female	right	40.90	69.60	52.80	56.50	46.50	38.50	28.50	27.0	-70.17	-29.10	-38.14	-13.69	5.87	30.32	0.95	0.76
220	50	female	right	159.10	257.00	160.50	131.20	85.10	65.00	26.20	10.0	-61.53	-0.88	17.54	46.51	59.15	83.53	1.23	0.86
221	32	female	right	25.20	33.40	29.10	21.30	20.70	13.80	6.30	13.0	-32.54	-15.48	15.48	17.86	45.24	75.00	1.09	0.93
222	73	female	right	26.60	67.30	40.90	30.20	34.70	34.50	21.80	33.0	-153.01	-53.76	-13.53	-30.45	-29.70	18.05	1.23	0.70

Appendix 35 continued/...

The postural vasoconstrictive response in patients with CVI																			
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
223	72	female	right	24.80	54.00	51.30	70.60	45.70	19.50	9.20	25.0	-117.74	-106.85	-184.68	-84.27	21.37	62.90	2.39	2.43
224	81	male	right	38.40	46.50	29.10	23.70	35.00	25.80	13.40	6.0	-21.09	24.22	38.28	8.85	32.81	65.10	0.72	0.53
225	53	male	right	55.00	79.90	24.80	21.80	12.70	14.00	20.00	9.0	-45.27	54.91	60.36	76.91	74.55	63.64	0.54	0.01
226	70	female	right	8.30	11.60	12.90	10.80	9.00	7.10	7.90	19.0	-39.76	-55.42	-30.12	-8.43	14.46	4.82	0.55	0.50
227	67	female	right	6.00	8.40	13.10	11.60	7.50	7.40	4.90	33.0	-40.00	-118.33	-93.33	-25.00	-23.33	18.33	1.14	1.36
228	70	female	right	81.40	108.90	59.60	33.10	82.10	95.60	105.60	6.0	-33.78	26.78	59.34	-0.86	-17.44	-29.73	-0.48	-0.77
229	58	female	right	132.60	28.50	61.80	41.30	120.50	106.30	123.70	38.0	78.51	53.39	68.85	9.13	19.83	6.71	-0.68	-0.53
230	43	female	right	36.80	42.00	17.00	13.60	14.80	9.00	23.70	6.0	-14.13	53.80	63.04	59.78	75.54	35.60	0.07	-0.31
231	76	female	right	45.40	37.90	19.40	19.30	20.70	17.90	12.20	3.0	16.52	57.27	57.49	54.41	60.57	73.13	0.40	0.22
232	54	female	right	14.30	80.20	61.60	50.90	31.30	75.20	25.00	39.0	-460.84	-330.77	-255.94	-118.88	-425.87	-74.83	3.22	2.52
233	28	female	right	31.20	39.10	21.60	22.20	20.20	20.80	6.10	6.0	-25.32	30.77	28.85	35.26	33.33	80.45	0.88	0.65
234	66	female	right	12.50	43.30	33.10	30.90	23.50	13.80	9.20	29.0	-246.40	-164.80	-147.20	-88.00	-10.40	26.40	2.65	2.13
235	40	female	right	19.50	35.10	25.60	24.80	20.10	21.20	46.00	112.0	-80.00	-31.28	-27.18	-3.08	-8.72	-135.90	-1.13	-1.51
236	55	female	right	259.40	379.60	371.10	335.90	390.40	204.20	310.50	27.0	-46.34	-43.06	-29.49	-50.50	21.28	-19.70	0.31	0.23
237	33	female	right	29.40	37.10	33.60	32.50	33.10	32.80	23.30	33.0	-26.19	-14.29	-10.54	-12.59	-11.56	20.75	0.48	0.44
239	73	male	right	27.00	47.00	33.60	23.70	18.40	12.00	4.50	13.0	-74.07	-24.44	12.22	31.85	55.56	83.33	1.41	1.05
240	70	male	right	19.40	53.50	34.10	36.00	24.50	14.20	4.30	21.0	-175.77	-75.77	-85.57	-26.29	26.80	77.84	2.37	1.86
200	67	female	left	11.10	39.20	69.50	47.70	17.70	12.10	5.40	29.0	-253.15	-526.13	-329.73	-59.46	-9.01	51.35	4.78	5.08
201	68	male	left	86.40	97.20	83.50	75.50	67.60	51.50	66.90	7.0	-12.50	3.36	12.62	21.76	40.39	22.57	0.27	0.14
202	39	female	left	7.80	25.10	21.80	29.90	27.10	31.80	11.40	69.0	-221.79	-179.49	-283.33	-247.44	-307.69	-46.15	2.22	2.51
203	72	female	left	6.50	13.90	14.80	10.00	6.80	7.70	5.60	22.0	-113.85	-127.69	-53.85	-4.62	-18.46	13.85	1.33	1.12
204	51	male	left	41.20	82.30	38.00	28.80	27.40	30.10	19.00	9.0	-99.76	7.77	30.10	33.50	26.94	53.88	0.99	0.43
205	55	female	left	24.20	59.00	55.80	46.00	38.40	34.20	16.70	40.0	-143.80	-130.58	-90.08	-58.68	-41.32	30.99	1.88	1.70

Appendix 35 continued/...

The postural vasoconstrictive response in patients with CVI																			
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
206	74	female	left	21.00	44.80	39.40	21.90	20.80	16.80	16.10	15.0	-113.33	-87.62	-4.29	0.95	20.00	23.33	1.17	0.78
207	45	female	left	132.20	161.40	106.70	66.50	52.70	45.10	36.70	2.0	-22.09	19.29	49.70	60.14	65.89	72.24	0.72	0.42
208	51	female	left	50.20	61.30	58.20	55.90	55.40	56.10	60.10	120.0	-22.11	-15.94	-11.35	-10.36	-11.75	-19.72	-0.04	-0.09
209	63	male	left	25.70	49.00	22.70	19.30	14.70	14.80	12.40	8.0	-90.66	11.67	24.90	42.80	42.41	51.75	0.91	0.36
210	35	female	left	17.60	21.50	20.10	16.50	15.70	17.20	12.00	13.0	-22.16	-14.20	6.25	10.80	2.27	31.82	0.52	0.44
211	53	male	left	48.90	24.00	21.30	16.50	17.60	14.80	23.10	3.0	50.92	56.44	66.26	64.01	69.73	52.76	-0.05	-0.12
212	51	female	left	56.10	81.10	71.70	61.80	56.70	29.40	22.10	16.0	-44.56	-27.81	-10.16	-1.07	47.59	60.61	1.12	0.97
213	78	female	left	77.40	118.10	125.20	127.40	112.00	102.60	102.70	53.0	-52.58	-61.76	-64.60	-44.70	-32.56	-32.69	0.31	0.33
214	55	female	left	24.50	268.80	60.00	35.20	95.40	59.90	23.40	91.0	-997.14	-144.90	-43.67	-289.39	-144.49	4.49	5.87	2.00
215	73	female	left	67.10	52.00	39.10	30.10	26.80	45.30	20.70	3.0	22.50	41.73	55.14	60.06	32.49	69.15	0.33	-0.07
216	50	female	left	72.00	115.60	153.30	138.30	118.80	102.10	63.60	49.0	-60.56	-112.92	-92.08	-65.00	-41.81	11.67	1.20	1.38
217	58	female	left	125.10	43.90	23.80	16.90	13.20	19.10	24.50	2.0	64.91	80.98	86.49	89.45	84.73	80.42	0.04	-0.06
218	35	male	left	70.60	253.80	58.40	42.50	43.80	40.80	41.70	9.0	-259.49	17.28	39.80	37.96	42.21	40.93	1.52	0.14
219	71	female	left	19.10	29.30	27.90	25.10	20.10	20.40	27.70	33.0	-53.40	-46.07	-31.41	-5.24	-6.81	-45.03	-0.05	-0.20
220	50	female	left	91.90	96.40	74.60	52.40	46.70	47.50	41.40	7.0	-4.90	18.82	42.98	49.18	48.31	54.95	0.46	0.27
221	32	female	left	16.10	50.20	63.50	55.10	42.00	23.60	9.70	58.0	-211.80	-294.41	-242.24	-160.87	-46.58	39.75	3.50	3.65
222	73	female	left	12.10	38.00	16.40	13.50	11.70	12.60	13.00	20.0	-214.05	-35.54	-11.57	3.31	-4.13	-7.44	1.08	0.13
223	72	female	left	13.10	132.90	75.80	48.90	22.40	7.80	3.20	26.0	-914.50	-478.63	-273.28	-70.99	40.46	75.57	7.92	4.92
224	81	male	left	118.70	98.90	124.30	89.80	57.00	63.70	34.10	4.0	16.68	-4.72	24.35	51.98	46.34	71.27	0.69	0.68
225	53	male	left	123.80	49.80	28.70	79.80	89.80	39.00	101.50	4.0	59.77	76.82	35.54	27.46	68.50	18.01	-0.46	-0.45
226	70	female	left	12.80	11.80	14.50	19.80	6.90	9.60	4.40	6.0	7.81	-13.28	-54.69	46.09	25.00	65.63	0.91	1.02
227	67	female	left	6.60	28.70	41.70	33.50	22.40	9.70	7.00	60.0	-334.85	-531.82	-407.58	-239.39	-46.97	-6.06	4.97	5.25
228	70	female	left	101.30	78.40	69.60	106.00	133.10	185.00	122.20	4.0	22.61	31.29	-4.64	-31.39	-82.63	-20.63	-0.44	-0.27

Appendix 35 continued/…

The postural vasoconstrictive response in patients with CVI																			
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
229	58	female	left	133.50	73.50	98.40	117.30	119.90	124.10	118.30	38.0	44.94	26.29	12.13	10.19	7.04	11.39	-0.22	-0.08
230	43	female	left	37.60	45.40	30.10	19.60	17.00	12.40	10.10	8.0	-20.74	19.95	47.87	54.79	67.02	73.14	0.74	0.45
231	76	female	left	23.10	23.50	51.50	33.50	46.50	23.60	11.60	30.0	-1.73	-122.94	-45.02	-101.30	-2.16	49.78	1.38	1.82
232	54	female	left	8.50	39.40	15.60	9.60	8.90	11.50	5.40	20.0	-363.53	-83.53	-12.94	-4.71	-35.29	36.47	2.52	1.03
233	28	female	left	24.00	52.20	44.10	22.20	15.80	8.10	4.80	14.0	-117.50	-83.75	7.50	34.17	66.25	80.00	1.81	1.33
234	66	female	left	15.40	91.90	70.20	53.70	39.90	24.00	11.50	25.0	-496.75	-355.84	-248.70	-159.09	-55.84	25.32	4.91	3.82
235	40	female	left	28.80	34.10	37.40	35.90	40.10	48.50	62.10	117.0	-18.40	-29.86	-24.65	-39.24	-68.40	-115.63	-1.14	-1.11
236	55	female	left	170.80	286.40	305.30	352.30	339.00	314.60	192.30	45.0	-67.68	-78.75	-106.26	-98.48	-84.19	-12.59	0.88	1.06
237	33	female	left	60.00	118.40	102.10	138.70	124.40	120.30	70.70	83.0	-97.33	-70.17	-131.17	-107.33	-100.50	-17.83	1.00	1.09
239	73	male	left	27.80	106.40	64.80	42.20	35.50	23.00	7.00	25.0	-282.73	-133.09	-51.80	-27.70	17.27	74.82	2.96	2.00
240	70	male	left	18.30	29.60	16.10	16.70	19.80	21.20	7.80	10.0	-61.75	12.02	8.74	-8.20	-15.85	57.38	0.95	0.70
Number of cases				**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Mean				**51.62**	**72.31**	**55.73**	**48.71**	**46.75**	**41.79**	**34.09**	**28.20**	**-102.58**	**-55.88**	**-31.20**	**-13.39**	**0.57**	**28.95**	**1.16**	**0.85**
Standard deviation				**52.27**	**68.15**	**56.11**	**56.97**	**60.38**	**49.83**	**46.84**	**31.14**	**178.57**	**124.03**	**99.80**	**75.46**	**77.29**	**45.66**	**1.50**	**1.23**
Median				**29.85**	**47.45**	**38.55**	**31.05**	**25.60**	**22.45**	**17.00**	**15.50**	**-52.87**	**-15.71**	**-7.40**	**-0.96**	**18.55**	**35.05**	**0.86**	**0.51**
Minimum				**6.00**	**8.40**	**12.90**	**9.60**	**6.80**	**6.40**	**3.20**	**2.00**	**-997.14**	**-531.82**	**-407.58**	**-289.39**	**-425.87**	**-135.90**	**-1.14**	**-1.51**
Maximum				**259.4**	**379.6**	**371.1**	**352.3**	**390.4**	**314.6**	**310.5**	**120.0**	**78.51**	**80.98**	**94.16**	**94.32**	**84.73**	**86.11**	**7.92**	**5.25**

Appendix 35 continued/...

The postural vasoconstrictive response in patients with venous ulcers

				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
300	70	female	right	9.90	42.40	28.00	26.70	32.80	25.60	26.90	120.0	-328.28	-182.83	-169.70	-231.31	-158.59	-171.72	0.88	0.22
303	49	female	right	20.00	31.20	16.50	17.60	29.80	19.00	10.20	7.0	-56.00	17.50	12.00	-49.00	5.00	49.00	0.86	0.65
304	73	male	right	181.70	90.60	77.70	62.40	63.60	70.40	87.30	3.0	50.14	57.24	65.66	65.00	61.25	51.95	-0.07	-0.13
308	65	female	right	109.20	130.00	88.50	80.40	82.10	79.20	115.50	7.0	-19.05	18.96	26.37	24.82	27.47	-5.77	-0.16	-0.38
311	74	female	right	20.60	34.30	24.50	23.40	22.30	16.20	11.70	22.0	-66.50	-18.93	-13.59	-8.25	21.36	43.20	0.98	0.74
312	57	male	right	172.40	142.50	203.00	208.50	236.90	244.30	155.70	42.0	17.34	-17.75	-20.94	-37.41	-41.71	9.69	0.21	0.46
314	34	male	right	94.00	78.60	42.70	32.60	35.80	24.70	28.80	3.0	16.38	54.57	65.32	61.91	73.72	69.36	0.33	0.12
315	56	female	right	40.00	47.20	22.70	13.60	9.70	7.70	16.30	5.0	-18.00	43.25	66.00	75.75	80.75	59.25	0.39	-0.01
316	73	female	right	29.10	85.60	33.50	22.10	19.60	7.30	15.50	11.0	-194.16	-15.12	24.05	32.65	74.91	46.74	1.46	0.45
317	75	female	right	14.40	15.30	20.10	18.60	13.90	9.00	6.50	20.0	-6.25	-39.58	-29.17	3.47	37.50	54.86	0.95	1.03
318	85	female	right	18.50	16.80	10.90	14.70	14.70	16.40	11.60	4.0	9.19	41.08	20.54	20.54	11.35	37.30	0.18	0.12
319	58	male	right	29.60	60.60	70.10	55.70	49.20	36.20	29.70	66.0	-104.73	-136.82	-88.18	-66.22	-22.30	-0.34	1.34	1.32
320	54	male	right	177.40	149.40	46.10	38.10	26.50	46.20	34.00	4.0	15.78	74.01	78.52	85.06	73.96	80.83	0.33	0.04
321	83	female	right	7.80	15.50	13.70	14.50	9.10	9.20	7.10	40.0	-98.72	-75.64	-85.90	-16.67	-17.95	8.97	1.11	0.95
301	60	female	left	94.80	50.80	55.30	55.90	55.10	53.50	176.00	4.0	46.41	41.67	41.03	41.88	43.57	-85.65	-1.61	-1.69
302	81	female	left	29.10	22.90	14.10	12.00	12.30	9.90	10.70	3.0	21.31	51.55	58.76	57.73	65.98	63.23	0.26	0.10
305	72	female	left	100.90	101.00	77.50	73.70	66.00	43.20	42.90	5.0	-0.10	23.19	26.96	34.59	57.19	57.48	0.52	0.38
306	62	female	left	133.60	116.50	108.50	101.70	106.50	104.90	94.00	4.0	12.80	18.79	23.88	20.28	21.48	29.64	0.15	0.12
307	61	male	left	154.60	142.20	101.20	65.40	123.00	193.00	189.40	5.0	8.02	34.54	57.70	20.44	-24.84	-22.51	-0.65	-0.77
309	77	female	left	124.50	268.30	273.90	247.50	255.30	266.20	276.20	110.0	-115.50	-120.00	-98.80	-105.06	-113.82	-121.85	-0.12	-0.16
310	73	male	left	70.40	18.20	11.20	16.80	24.10	40.90	43.60	70.0	74.15	84.09	76.14	65.77	41.90	38.07	-0.49	-0.49

Appendix 35 continued/...

				The postural vasoconstrictive response in patients with venous ulcers															
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
311	74	female	left	202.10	64.80	63.20	49.40	54.00	59.90	85.30	120.0	67.94	68.73	75.56	73.28	70.36	57.79	-0.16	-0.19
312	57	male	left	138.60	126.00	117.80	78.20	86.40	96.90	138.90	50.0	9.09	15.01	43.58	37.66	30.09	-0.22	-0.27	-0.40
313	66	female	left	138.90	59.10	54.20	43.30	34.70	38.30	62.60	2.0	57.45	60.98	68.83	75.02	72.43	54.93	-0.10	-0.16
319	58	male	left	15.40	31.60	40.00	41.50	28.40	18.80	14.90	38.0	-105.19	-159.74	-169.48	-84.42	-22.08	3.25	1.72	1.89
321	83	female	left	14.00	54.10	38.60	18.40	13.60	15.40	12.90	19.0	-286.43	-175.71	-31.43	2.86	-10.00	7.86	2.18	1.18
322	69	male	left	12.60	21.30	29.20	24.40	21.80	7.60	6.90	25.0	-69.05	-131.75	-93.65	-73.02	39.68	45.24	1.77	-1.01
Number of cases				**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**	**27**
Mean				**79.78**	**74.70**	**62.32**	**53.97**	**56.56**	**57.77**	**63.37**	**29.96**	**-39.33**	**-13.66**	**1.11**	**4.72**	**18.47**	**17.06**	**0.45**	**0.16**
Standard deviation				**65.08**	**58.36**	**60.21**	**56.08**	**62.38**	**69.99**	**70.19**	**36.94**	**100.70**	**83.58**	**74.03**	**71.24**	**57.72**	**59.17**	**0.84**	**0.75**
Median				**70.40**	**59.10**	**42.70**	**38.10**	**32.80**	**36.20**	**29.70**	**11.00**	**-0.10**	**18.79**	**24.05**	**20.54**	**30.09**	**38.07**	**0.33**	**0.12**
Minimum				**7.80**	**15.30**	**10.90**	**12.00**	**9.10**	**7.30**	**6.50**	**2.00**	**-328.28**	**-182.83**	**-169.70**	**-231.31**	**-158.59**	**-171.72**	**-1.61**	**-1.69**
Maximum				**202.1**	**268.3**	**273.9**	**247.5**	**255.3**	**266.2**	**276.2**	**120.0**	**74.15**	**84.09**	**78.52**	**85.06**	**80.75**	**80.83**	**2.18**	**1.89**

Appendix 36

The effects of CVI (with venous ulcers and without) on the postural vasoconstrictive response in the elderly

The postural vasoconstrictive response in elderly (61-90Y) asymptomatic controls																			
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
116	69	female	right	37.20	55.90	41.70	48.20	33.80	34.30	25.90	18.0	-50.27	-12.10	-29.57	9.14	7.80	30.38	0.73	0.56
120	64	male	right	61.90	19.40	12.00	35.80	30.10	28.60	26.80	2.0	68.66	80.61	42.16	51.37	53.80	56.70	-0.10	-0.05
125	68	female	right	141.80	172.10	145.80	130.60	111.30	94.40	57.70	12.0	-21.37	-2.82	7.90	21.51	33.43	59.31	0.81	0.68
126	69	male	right	197.80	237.70	167.50	146.20	93.50	128.40	138.80	9.0	-20.17	15.32	26.09	52.73	35.09	29.83	0.26	0.02
127	65	female	right	34.10	25.50	15.80	34.20	19.80	17.60	13.60	4.0	25.22	53.67	-0.29	41.94	48.39	60.12	0.38	0.35
135	71	female	right	13.70	43.90	26.30	20.20	18.00	22.30	10.70	44.0	-220.44	-91.97	-47.45	-31.39	-62.77	21.90	1.82	1.12
138	62	male	right	175.40	163.40	116.80	81.50	95.20	89.60	140.30	2.0	6.84	33.41	53.53	45.72	48.92	20.01	-0.11	-0.31
139	71	female	right	209.10	179.20	169.50	200.20	143.30	152.50	116.20	4.0	14.30	18.94	4.26	31.47	27.07	44.43	0.36	0.36
140	69	female	right	143.60	67.60	32.80	39.30	69.50	96.30	74.00	2.0	52.92	77.16	72.63	51.60	32.94	48.47	-0.20	-0.25
142	69	female	right	542.60	792.70	723.10	723.80	483.00	506.60	377.20	19.0	-46.09	-33.27	-33.39	10.98	6.63	30.48	0.80	0.69
144	69	male	right	156.30	155.00	132.90	143.40	138.80	112.00	119.20	3.0	0.83	14.97	8.25	11.20	28.34	23.74	0.21	0.15
145	74	female	right	14.80	26.90	12.90	23.00	15.40	9.70	5.00	10.0	-81.76	12.84	-55.41	-4.05	34.46	66.22	1.33	1.03
146	69	male	right	76.80	62.90	61.30	65.20	60.20	115.30	61.10	3.0	18.10	20.18	15.10	21.61	-50.13	20.44	0.00	0.07
147	71	female	right	433.90	152.40	195.00	395.80	383.40	278.60	344.60	2.0	64.88	55.06	8.78	11.64	35.79	20.58	-0.29	-0.12
148	66	female	right	51.60	93.80	77.70	25.80	60.80	59.20	36.50	1.0	-81.78	-50.58	50.00	-17.83	-14.73	29.26	0.83	0.52
149	62	male	right	47.50	14.40	17.80	18.30	10.70	11.10	15.10	2.0	69.68	62.53	61.47	77.47	76.63	68.21	0.02	0.02
150	62	male	right	34.50	37.20	24.20	15.90	34.90	17.60	18.20	7.0	-7.83	29.86	53.91	-1.16	48.99	47.25	0.39	0.21
151	62	male	right	50.20	36.80	26.50	21.50	20.70	18.90	9.10	2.0	26.69	47.21	57.17	58.76	62.35	81.87	0.49	0.37
116	69	female	left	26.10	66.20	50.10	24.60	28.70	23.70	18.70	29.0	-153.64	-91.95	5.75	-9.96	9.20	28.35	1.43	0.87
120	64	male	left	65.00	32.80	43.80	33.80	79.20	81.10	51.80	3.0	49.54	32.62	48.00	-21.85	-24.77	20.31	-0.20	-0.02

Appendix 36 continued/...

The postural vasoconstrictive response in elderly (61-90Y) asymptomatic controls

				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
125	68	female	left	61.10	69.90	42.60	23.90	18.50	21.70	31.50	6.0	-14.40	30.28	60.88	69.72	64.48	48.45	0.30	-0.03
126	69	male	left	127.10	162.00	78.50	93.80	33.40	28.80	70.10	8.0	-27.46	38.24	26.20	73.72	77.34	44.85	0.38	0.00
127	65	female	left	22.00	48.10	31.30	51.30	32.50	35.20	40.70	34.0	-118.64	-42.27	-133.18	-47.73	-60.00	-85.00	0.08	-0.16
135	71	female	left	5.80	12.30	7.50	8.30	10.60	12.70	7.40	91.0	-112.07	-29.31	-43.10	-82.76	-118.97	-27.59	0.51	0.31
138	62	male	left	218.60	189.20	190.50	111.00	172.40	223.60	176.10	3.0	13.45	12.85	49.22	21.13	-2.29	19.44	-0.04	-0.08
139	71	female	left	76.30	49.80	49.80	34.50	26.40	16.70	16.20	3.0	34.73	34.73	54.78	65.40	78.11	78.77	0.46	0.38
140	69	female	left	178.60	368.60	356.30	342.90	324.00	342.10	356.60	120.0	-106.38	-99.50	-91.99	-81.41	-91.55	-99.66	-0.02	-0.09
142	69	female	left	195.60	163.60	114.60	76.30	109.10	76.90	49.40	4.0	16.36	41.41	60.99	44.22	60.69	74.74	0.48	0.34
144	69	male	left	35.90	35.00	29.20	40.00	39.00	51.20	24.60	5.0	2.51	18.66	-11.42	-8.64	-42.62	31.48	0.34	0.42
145	74	female	left	52.60	46.90	34.50	27.50	16.70	18.20	15.20	5.0	10.84	34.41	47.72	68.25	65.40	71.10	0.49	0.31
146	69	male	left	54.60	96.00	91.90	69.30	71.30	67.70	41.60	64.0	-75.82	-68.32	-26.92	-30.59	-23.99	23.81	1.03	0.91
147	71	female	left	225.10	50.80	168.50	74.30	160.20	13.70	28.40	2.0	77.43	25.14	66.99	28.83	93.91	87.38	0.43	0.59
148	66	female	left	18.30	34.00	9.20	12.80	8.40	7.70	4.80	3.0	-85.79	49.73	30.05	54.10	57.92	73.77	0.99	0.38
149	62	male	left	107.50	138.20	131.60	142.80	126.80	94.80	77.10	24.0	-28.56	-22.42	-32.84	-17.95	11.81	28.28	0.69	0.68
150	62	male	left	10.90	49.10	20.70	17.70	23.80	15.90	11.80	47.0	-350.46	-89.91	-62.39	-118.35	-45.87	-8.26	2.24	1.03
151	62	male	left	19.40	35.70	49.70	23.60	18.40	16.30	22.60	16.0	-84.02	-156.19	-21.65	5.15	15.98	-16.49	0.83	0.68
Number of cases				**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**
Mean				**108.98**	**110.69**	**97.22**	**93.81**	**86.72**	**81.69**	**73.18**	**17.03**	**-31.50**	**1.37**	**8.95**	**12.61**	**16.05**	**32.03**	**0.50**	**0.33**
Standard deviation				**116.42**	**139.96**	**130.60**	**138.10**	**107.32**	**106.01**	**97.49**	**26.54**	**87.32**	**56.04**	**49.52**	**46.74**	**51.50**	**40.74**	**0.56**	**0.39**
Median				**61.50**	**59.40**	**49.75**	**39.65**	**36.95**	**34.75**	**34.00**	**5.00**	**-11.11**	**18.80**	**11.94**	**16.39**	**30.64**	**30.43**	**0.41**	**0.35**
Minimum				**5.80**	**12.30**	**7.50**	**8.30**	**8.40**	**7.70**	**4.80**	**1.00**	**-350.46**	**-156.19**	**-133.18**	**-118.35**	**-118.97**	**-99.66**	**-0.29**	**-0.31**
Maximum				**542.6**	**792.7**	**723.1**	**723.8**	**483.0**	**506.6**	**377.2**	**120.0**	**77.43**	**80.61**	**72.63**	**77.47**	**93.91**	**87.38**	**2.24**	**1.12**

Appendix 36 continued/…

The postural vasoconstrictive response in elderly (61-90Y) patients with CVI																		
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at----------						in flux between
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
200	67	female	right	30.30	82.30	59.20	14.10	11.50	10.70	7.80	12.0	-171.62	-95.38	53.47	62.05	64.69	74.26	1.87	1.04
201	68	male	right	31.60	39.00	30.00	22.40	22.00	20.30	13.20	10.0	-23.42	5.06	29.11	30.38	35.76	58.23	0.70	0.51
203	72	female	right	11.70	21.90	22.40	11.70	14.10	8.70	7.80	15.0	-87.18	-91.45	0.00	-20.51	25.64	33.33	1.21	0.98
206	74	female	right	22.90	16.30	19.90	21.60	16.20	16.60	15.00	3.0	28.82	13.10	5.68	29.26	27.51	34.50	0.19	0.26
209	63	male	right	52.90	46.30	36.60	34.50	31.90	29.10	17.30	4.0	12.48	30.81	34.78	39.70	44.99	67.30	0.52	0.43
213	78	female	right	76.80	83.40	80.90	91.70	83.80	100.70	65.80	33.0	-8.59	-5.34	-19.40	-9.11	-31.12	14.32	0.30	0.35
215	73	female	right	138.50	83.10	93.60	68.70	66.30	51.00	42.70	2.0	40.00	32.42	50.40	52.13	63.18	69.17	0.35	0.33
219	71	female	right	40.90	69.60	52.80	56.50	46.50	38.50	28.50	27.0	-70.17	-29.10	-38.14	-13.69	5.87	30.32	0.95	0.76
222	73	female	right	26.60	67.30	40.90	30.20	34.70	34.50	21.80	33.0	-153.01	-53.76	-13.53	-30.45	-29.70	18.05	1.23	0.70
223	72	female	right	24.80	54.00	51.30	70.60	45.70	19.50	9.20	25.0	-117.74	-106.85	-184.68	-84.27	21.37	62.90	2.39	2.43
224	81	male	right	38.40	46.50	29.10	23.70	35.00	25.80	13.40	6.0	-21.09	24.22	38.28	8.85	32.81	65.10	0.72	0.53
226	70	female	right	8.30	11.60	12.90	10.80	9.00	7.10	7.90	19.0	-39.76	-55.42	-30.12	-8.43	14.46	4.82	0.55	0.50
227	67	female	right	6.00	8.40	13.10	11.60	7.50	7.40	4.90	33.0	-40.00	-118.33	-93.33	-25.00	-23.33	18.33	1.14	1.36
228	70	female	right	81.40	108.90	59.60	33.10	82.10	95.60	105.60	6.0	-33.78	26.78	59.34	-0.86	-17.44	-29.73	-0.48	-0.77
231	76	female	right	45.40	37.90	19.40	19.30	20.70	17.90	12.20	3.0	16.52	57.27	57.49	54.41	60.57	73.13	0.40	0.22
234	66	female	right	12.50	43.30	33.10	30.90	23.50	13.80	9.20	29.0	-246.40	-164.80	-147.20	-88.00	-10.40	26.40	2.65	2.13
239	73	male	right	27.00	47.00	33.60	23.70	18.40	12.00	4.50	13.0	-74.07	-24.44	12.22	31.85	55.56	83.33	1.41	1.05
240	70	male	right	19.40	53.50	34.10	36.00	24.50	14.20	4.30	21.0	-175.77	-75.77	-85.57	-26.29	26.80	77.84	2.37	1.86
200	67	female	left	11.10	39.20	69.50	47.70	17.70	12.10	5.40	29.0	-253.15	-526.13	-329.73	-59.46	-9.01	51.35	4.78	5.08
201	68	male	left	86.40	97.20	83.50	75.50	67.60	51.50	66.90	7.0	-12.50	3.36	12.62	21.76	40.39	22.57	0.27	0.14
203	72	female	left	6.50	13.90	14.80	10.00	6.80	7.70	5.60	22.0	-113.85	-127.69	-53.85	-4.62	-18.46	13.85	1.33	1.12

Appendix 36 continued/...

				The postural vasoconstrictive response in elderly (61-90Y) patients with CVI															
				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	_----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
206	74	female	left	21.00	44.80	39.40	21.90	20.80	16.80	16.10	15.0	-113.33	-87.62	-4.29	0.95	20.00	23.33	1.17	0.78
209	63	male	left	25.70	49.00	22.70	19.30	14.70	14.80	12.40	8.0	-90.66	11.67	24.90	42.80	42.41	51.75	0.91	0.36
213	78	female	left	77.40	118.10	125.20	127.40	112.00	102.60	102.70	53.0	-52.58	-61.76	-64.60	-44.70	-32.56	-32.69	0.31	0.33
215	73	female	left	67.10	52.00	39.10	30.10	26.80	45.30	20.70	3.0	22.50	41.73	55.14	60.06	32.49	69.15	0.33	-0.07
219	71	female	left	19.10	29.30	27.90	25.10	20.10	20.40	27.70	33.0	-53.40	-46.07	-31.41	-5.24	-6.81	-45.03	-0.05	-0.20
222	73	female	left	12.10	38.00	16.40	13.50	11.70	12.60	13.00	20.0	-214.05	-35.54	-11.57	3.31	-4.13	-7.44	1.08	0.13
223	72	female	left	13.10	132.90	75.80	48.90	22.40	7.80	3.20	26.0	-914.50	-478.63	-273.28	-70.99	40.46	75.57	7.92	4.92
224	81	male	left	118.70	98.90	124.30	89.80	57.00	63.70	34.10	4.0	16.68	-4.72	24.35	51.98	46.34	71.27	0.69	0.68
226	70	female	left	12.80	11.80	14.50	19.80	6.90	9.60	4.40	6.0	7.81	-13.28	-54.69	46.09	25.00	65.63	0.91	1.02
227	67	female	left	6.60	28.70	41.70	33.50	22.40	9.70	7.00	60.0	-334.85	-531.82	-407.58	-239.39	-46.97	-6.06	4.97	5.25
228	70	female	left	101.30	78.40	69.60	106.00	133.10	185.00	122.20	4.0	22.61	31.29	-4.64	-31.39	-82.63	-20.63	-0.44	-0.27
231	76	female	left	23.10	23.50	51.50	33.50	46.50	23.60	11.60	30.0	-1.73	-122.94	-45.02	-101.30	-2.16	49.78	1.38	1.82
234	66	female	left	15.40	91.90	70.20	53.70	39.90	24.00	11.50	25.0	-496.75	-355.84	-248.70	-159.09	-55.84	25.32	4.91	3.82
239	73	male	left	27.80	106.40	64.80	42.20	35.50	23.00	7.00	25.0	-282.73	-133.09	-51.80	-27.70	17.27	74.82	2.96	2.00
240	70	male	left	18.30	29.60	16.10	16.70	19.80	21.20	7.80	10.0	-61.75	12.02	8.74	-8.20	-15.85	57.38	0.95	0.70

Number of cases	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**36**
Mean	**37.75**	**55.66**	**46.93**	**39.60**	**35.42**	**32.63**	**24.18**	**18.72**	**-113.64**	**-84.89**	**-47.96**	**-14.53**	**9.92**	**36.71**	**1.47**	**1.17**
Standard deviation	**33.82**	**33.25**	**29.58**	**29.03**	**29.58**	**36.68**	**30.43**	**14.10**	**181.24**	**152.42**	**112.08**	**63.31**	**35.84**	**35.46**	**1.74**	**1.47**
Median	**25.25**	**46.75**	**39.25**	**30.55**	**22.95**	**19.90**	**12.30**	**17.00**	**-57.58**	**-40.81**	**-12.55**	**-6.72**	**18.63**	**42.14**	**0.95**	**0.70**
Minimum	**6.00**	**8.40**	**12.90**	**10.00**	**6.80**	**7.10**	**3.20**	**2.00**	**-914.50**	**-531.82**	**-407.58**	**-239.39**	**-82.63**	**-45.03**	**-0.48**	**-0.77**
Maximum	**138.5**	**132.9**	**125.2**	**127.4**	**133.1**	**185.0**	**122.2**	**60.0**	**40.00**	**57.27**	**59.34**	**62.05**	**64.69**	**83.33**	**7.92**	**5.25**

Appendix 36 continued/...

The postural vasoconstrictive response in elderly (61-90Y) patients with venous ulcers

				The flux (arbitrary units) measured							Time for	The %drop in flux measured						Slopes of %drop	
				at	----------after passive leg lowering at------------						flux to reach	----------after passive leg lowering at-----------						in flux between	
I.D.	Age	Sex	Leg	baseline	5s	10s	15s	20s	30s	90s	baseline (s)	5s	10s	15s	20s	30s	90s	5s-90s	10s-90s
300	70	female	right	9.90	42.40	28.00	26.70	32.80	25.60	26.90	120.0	-328.28	-182.83	-169.70	-231.31	-158.59	-171.72	0.88	0.22
304	73	male	right	181.70	90.60	77.70	62.40	63.60	70.40	87.30	3.0	50.14	57.24	65.66	65.00	61.25	51.95	-0.07	-0.13
308	65	female	right	109.20	130.00	88.50	80.40	82.10	79.20	115.50	7.0	-19.05	18.96	26.37	24.82	27.47	-5.77	-0.16	-0.38
311	74	female	right	20.60	34.30	24.50	23.40	22.30	16.20	11.70	22.0	-66.50	-18.93	-13.59	-8.25	21.36	43.20	0.98	0.74
316	73	female	right	29.10	85.60	33.50	22.10	19.60	7.30	15.50	11.0	-194.16	-15.12	24.05	32.65	74.91	46.74	1.46	0.45
317	75	female	right	14.40	15.30	20.10	18.60	13.90	9.00	6.50	20.0	-6.25	-39.58	-29.17	3.47	37.50	54.86	0.95	1.03
318	85	female	right	18.50	16.80	10.90	14.70	14.70	16.40	11.60	4.0	9.19	41.08	20.54	20.54	11.35	37.30	0.18	0.12
321	83	female	right	7.80	15.50	13.70	14.50	9.10	9.20	7.10	40.0	-98.72	-75.64	-85.90	-16.67	-17.95	8.97	1.11	0.95
302	81	female	left	29.10	22.90	14.10	12.00	12.30	9.90	10.70	3.0	21.31	51.55	58.76	57.73	65.98	63.23	0.26	0.10
305	72	female	left	100.90	101.00	77.50	73.70	66.00	43.20	42.90	5.0	-0.10	23.19	26.96	34.59	57.19	57.48	0.52	0.38
306	62	female	left	133.60	116.50	108.50	101.70	106.50	104.90	94.00	4.0	12.80	18.79	23.88	20.28	21.48	29.64	0.15	0.12
307	61	male	left	154.60	142.20	101.20	65.40	123.00	193.00	189.40	5.0	8.02	34.54	57.70	20.44	-24.84	-22.51	-0.65	-0.77
309	77	female	left	124.50	268.30	273.90	247.50	255.30	266.20	276.20	110.0	-115.50	-120.00	-98.80	-105.06	-113.82	-121.85	-0.12	-0.16
310	73	male	left	70.40	18.20	11.20	16.80	24.10	40.90	43.60	70.0	74.15	84.09	76.14	65.77	41.90	38.07	-0.49	-0.49
311	74	female	left	202.10	64.80	63.20	49.40	54.00	59.90	85.30	120.0	67.94	68.73	75.56	73.28	70.36	57.79	-0.16	-0.19
313	66	female	left	138.90	59.10	54.20	43.30	34.70	38.30	62.60	2.0	57.45	60.98	68.83	75.02	72.43	54.93	-0.10	-0.16
321	83	female	left	14.00	54.10	38.60	18.40	13.60	15.40	12.90	19.0	-286.43	-175.71	-31.43	2.86	-10.00	7.86	2.18	1.18
322	69	male	left	12.60	21.30	29.20	24.40	21.80	7.60	6.90	25.0	-69.05	-131.75	-93.65	-73.02	39.68	45.24	1.77	-1.01
Number of cases				**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
Mean				**76.22**	**72.16**	**59.36**	**50.86**	**53.86**	**56.26**	**61.48**	**32.78**	**-49.06**	**-16.69**	**0.12**	**3.45**	**15.43**	**15.30**	**0.48**	**0.11**
Standard deviation				**66.90**	**64.33**	**62.45**	**56.00**	**60.66**	**70.20**	**72.97**	**42.15**	**117.21**	**85.58**	**71.56**	**75.55**	**63.52**	**64.16**	**0.80**	**0.61**
Median				**49.75**	**56.60**	**36.05**	**25.55**	**28.45**	**31.95**	**34.90**	**15.00**	**-3.17**	**18.87**	**23.97**	**20.49**	**32.49**	**40.64**	**0.22**	**0.11**
Minimum				**7.80**	**15.30**	**10.90**	**12.00**	**9.10**	**7.30**	**6.50**	**2.00**	**-328.28**	**-182.83**	**-169.70**	**-231.31**	**-158.59**	**-171.72**	**-0.65**	**-1.01**
Maximum				**202.1**	**268.3**	**273.9**	**247.5**	**255.3**	**266.2**	**276.2**	**120.0**	**74.15**	**84.09**	**76.14**	**75.02**	**74.91**	**63.23**	**2.18**	**1.18**

Appendix 37 Clinical history questionnaire

I.D. number (study number)
Date of Birth

Sex	Male	Female		
Marital status	Single	Married	With a partner	Widowed

Number of children

Please answer the following question with either YES or NO

	Yes	No
1) Do you suffer from swelling of the legs or ankles?		
2) Do you suffer from varicose veins?		
3) Have you had a CLOT/DVT previously?		
4) Have you had an ulcer in the leg or ankle previously? On which leg did you had the ulcer?		
5) If yes, how many? When did it start?		
6) Do you suffer from heart problems?		
7) Are you on any medication for your heart?		
8) Do you suffer from any skin disease that needed treatment with steroids cream?		
9) Are you diabetic?		
10) Are you pregnant?		
11) Have you had any treatment for cancer? If yes, please specify the condition and the medications used?		
12) Have you suffered from other conditions? Are you on any medication? If yes please specify?		