University of Southampton

A STUDY OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN SUBJECTS WITH CHRONIC RHEUMATOID ARTHRITIS WITH RELATION TO THEIR AGE AND DURATION OF THE DISEASE

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ABSTRACT

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A STUDY OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN SUBJECTS WITH CHRONIC RHEUMATOID ARTHRITIS WITH RELATION TO THEIR AGE AND DURATION OF THE DISEASE

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Neurological manifestations are seen relatively frequently in patients with rheumatoid arthritis. The occurrence of a peripheral neuropathy is well recognised. Since the 1960s there has been a growing interest in the role of the autonomic nervous system in rheumatoid arthritis. There is conflicting evidence to support this view. The aim of this study was to investigate whether autonomic impairment occurs in rheumatoid arthritis, and if so, whether this is related to age, disease duration or rheumatoid factor status. The influence of disease activity was also investigated.

Clinical assessment of autonomic function was carried out using the battery of cardiovascular reflex tests as described by Ewing and Clarke, 1982. The use of these tests is established in clinical practice. Cardiovascular reflexes were measured in 62 rheumatoid arthritis outpatients aged between 38-84 years old (mean age 63.2yrs) and 41 healthy controls aged between 22-82 years old (mean age 48.0yrs) of either sex. None of these subjects had overt cardiovascular disease, other co-pathology known to interfere with autonomic function (such as diabetes), or were taking medication known to interfere with heart rate or blood pressure.

The results demonstrated significant differences between the rheumatoid and control group in heart rate responses to the Valsalva manoeuvre ($p=0.03$), to deep breathing ($p=0.01$), to standing ($p=0.001$) and in the rise in the diastolic pressure in response to sustained handgrip ($p<0.001$). These differences indicate autonomic impairment in the rheumatoid patients, which was not clinically apparent with a fall in systolic blood pressure. Significant differences were also demonstrated in the heart rate responses to the Valsalva manoeuvre between the control group and the rheumatoid factor positive patients ($p=0.02$), those who had had the disease for longer than 10 years ($p=0.01$) and in the older subjects ($p=0.02$). In general this trend is observed when each of the subgroups was compared against controls for the other cardiovascular autonomic reflexes. The exception being age group where no consistent pattern emerged. There was no difference observed in the cardiovascular reflexes when patients with or without peripheral neuropathy were compared with the controls. Furthermore there was no correlation with disease activity.

In conclusion, the results indicate that there is a tendency to impaired autonomic function as assessed by the cardiovascular reflexes. This exists on a subclinical level.

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Abbreviations

WHO	World Health Organisation
ARA	American Rheumatism Association
PIP	Proximal Interphalangeal joint
MCP	Metacarpophalangeal joint
h	hour
HLA	Human Leucocyte Antigen
hsp	Heat Shock Protein
IgM	Immunoglobulin M
N-linked	Nitrogen linked
Fc	Crystallizable fragment
CD	cellular differentiation classification
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgE	Immunoglobulin E
RF	Rheumatoid Factor
SCAT	Sheep cell agglutination test
SI	Système International d'Unités (International System of Units)
%	percentage
eg.	for example
MTP	Metatarsophalangeal
NSAID	Non steroidal anti-inflammatory drug
AD	Anno Domini
ATP	Adenosine triphosphate

N	Nicotinic
M	Muscarinic
α	alpha
β	beta
GABA	Gamma amino butyric acid
$mmsec^{-1}$	millimetres per second
$mVcm^{-1}$	millivolts per centimetre
mmHg	millimetres of mercury
ESR	Erythrocyte sedimentation rate
CRP	C reactive protein
RA	Rheumatoid Arthritis
p	probability
ECG	Electrocardiogram
secs	seconds
beats/min	beats per minute
g/l	grams per litre
+ve	positive
-ve	negative
pt(s)	patient(s)
n	number of subjects
f	female
m	male
mm/hr	millimetres per hour
mg/l	milligrams per litre
iu/l	international units per litre

max	maximum
min	minimum
diff	difference
yrs	years

Chapter One

Introduction

Introduction

In 1958 the World Health Organisation defined health as physical, mental and social well being (W.H.O. 1958). This led to increased interest on the impact that a chronic illness such as rheumatoid arthritis has on an individual's health, and its economic and social cost. Rheumatoid disease has multiple effects on a number of different systems in the body. The possible involvement of the autonomic nervous system in rheumatoid arthritis has been observed and needs further exploration as the neurological manifestations of the illness have a debilitating influence on an individual's health, and can lead to an increase in morbidity and mortality.

Given that rheumatoid arthritis is a common and widespread cause of disability and handicap in contemporary life, it is then perhaps not surprising that its relatively recent description in historical terms has prompted workers to observe that it is possibly a disease of modern times. In fact, there exists conflicting evidence that rheumatoid arthritis was present in ancient and medieval civilisations.

Paleontological studies of Old World and New World remains have unearthed the existence of spondyloarthropathy (Rothschild and Woods 1992[1]). However, the earliest dated findings of an erosive arthritis similar to rheumatoid arthritis have been recorded in pre-Columbian American Indians, with the oldest specimens coming from the Ohio River Valley and dating back some 3000-5000 years (Rothschild et al. 1992[2]). Some workers have expressed doubt about attributing erosive changes in bony remains to rheumatoid disease. A study in the West Country, where 800 skeletons were excavated, showed little or no rheumatoid disease (Rogers and Dieppe 1990). Early detailed accounts of rheumatoid arthritis have been reviewed in 18th century French and English literature. Charcot (1853) published an analysis of 41 cases on "Goutte Asthénique Primitive" which contains several illustrations, which lead one to suspect that he was describing rheumatoid arthritis. Later 18th century physicians, such as William Oliver and William Heberden recognised a chronic arthritis that was distinct from gout.

Jayson (1975) comments on a painting by William Hoare in 1742, which hangs in the Royal National Hospital for Rheumatic Diseases in Bath. It has been suggested that this shows three patients with rheumatoid-like disease involving the hands, leaving little doubt that this condition was recognised in 18th century England.

Alfred Baring Garrod (1859) first proposed the term rheumatoid arthritis, and highlighted the differences from gout and rheumatic fever (Short 1974). Furthermore, work has continued into distinguishing rheumatoid arthritis from other chronic inflammatory joint disorders, most notably the seronegative arthritides. Interestingly, until late into the 1950's North American physicians referred to ankylosing spondylitis as rheumatoid spondylitis, holding the view that it was part of the spectrum of rheumatoid disease.

Definition

Celsus stated the cardinal signs of inflammation as being:
(i). Rubor et tumor cum calore et dolore (redness and swelling with heat and pain).
(ii). Et functio laesa (loss of function).

These summarise the hallmark features of rheumatoid arthritis, which are characterised by inflammation of the lining of the joints (synovium), pericardium and pleura. Additionally, rheumatoid arthritis is a chronic disease that involves multiple systems of the body, often with a coexistent vasculitis.

In 1956 a committee of the American Rheumatism Association (ARA) proposed diagnostic criteria for rheumatoid arthritis (Ropes et al. 1956). This helped distinguish rheumatoid arthritis as classical, definite, probable and possible. These criteria were simplified in 1958 (Ropes et al. 1958). Since then further classifications have been proposed including the New York criteria, in an attempt to promote understanding and aid epidemiological work and clinical trials (Bennett and Burch 1966).

The American College of Rheumatology (1987) developed revised

criteria for rheumatoid arthritis (Arnett et al. 1988). Rheumatoid arthritis is diagnosed if at least four out of seven criteria are present with only one category of rheumatoid arthritis being recognised, and with exclusions being eliminated. They were derived from observations of "typical" patients with rheumatoid arthritis with mean disease duration of 7.7 years by experienced rheumatologists. These criteria demonstrate 91-94% sensitivity with 89% specificity for rheumatoid arthritis when compared with non-rheumatoid arthritis, rheumatic disease control subjects. (See table 1.1).

Table 1.1 The revised criteria for rheumatoid arthritis of the American College of Rheumatology (1987).

Criterion	
1. Morning stiffness	Duration > 1h lasting >6 weeks
2. Arthritis of at least three areas*	Soft tissue swelling or exudation lasting >6 weeks
3. Arthritis of hand joints	Wrist, metacarpophalangeal joints or proximal interphalangeal joints lasting >6 weeks
4. Symmetrical arthritis	At least one area lasting >6 weeks
5. Rheumatoid nodules	As observed by a physician
6. Serum rheumatoid factor	As assessed by a method positive in less than 5% of control subjects
7. Radiographic changes	As seen on anteroposterior films of wrists and hands

*For example, wrist, elbow, knee, ankle, PIP, and MCP joints.

Epidemiology

In clinical practice, the diagnosis of rheumatoid arthritis depends on clinical observations and laboratory investigations. Epidemiological studies rely on the use of various criteria that have been developed in order to allow a more meaningful comparison of research results that have been collected from different centres. There are limitations to this approach, as has been found in a population-based study in Sudbury, Massachusetts. Only 15% of cases with probable rheumatoid arthritis still had arthritis at follow up 5 years later (O'Sullivan et al. 1972). Many population-based studies have overcome this by using both old and new ARA criteria to try to provide a more reliable estimate of disease epidemiology.

A number of studies in North America and Europe have indicated the prevalence of rheumatoid arthritis as being between 0.5 - 1%, with larger studies quoting a range of 0.8 - 1% (Silman and Hochberg 1993[1]). Rheumatoid arthritis has a similar worldwide distribution with a 2-3:1 female preponderance. There is some variation in prevalence across different populations, for example, the relatively high prevalence of approximately 5% in the South American Pima Indians is thought to reflect interplay between genetic predisposition and the environment (Del Puente et al. 1989). Similarly, in some rural African populations, there is a relatively low prevalence of rheumatoid arthritis (Silman et al. 1993[2]). This may be explained by a number of factors, including poor survival of those with the disease, or under-representation of the elderly.

Incidence is a useful measure of disease occurrence especially for diseases such as rheumatoid arthritis, which have a relapsing and remitting course. Symmons et al. (1994) studied a population in Norfolk, England, using the 1987 ARA criteria to diagnose early cases of rheumatoid arthritis. They found an annual incidence of 36/100,000 for women and 14/100,000 for men. The incidence of rheumatoid arthritis increased in men from the age of 45 years, being rare before the age of 45. In females, the incidence increased until the age of 45 years, plateaued until the age of 75, and then fell in women beyond the age

of 75 years.

Some studies have suggested a decline in the incidence of rheumatoid arthritis (Hochberg 1990). This may be secondary to the increased use of oral contraceptives, a change in causal infectious agents, or a general improvement in living standards.

Aetiological Factors

(i). Genetics

In 1806 William Heberden first made references to rheumatoid arthritis having a genetic background. Family and twin studies show the incidence of rheumatoid arthritis is greater in first degree relatives of patients with rheumatoid arthritis especially if positive for rheumatoid factor (Lawrence 1970). Silman et al. (1993[3]) reported a 15% concordance of rheumatoid arthritis in monozygotic twins in the United Kingdom. Furthermore, disease concordance is increased in twins who have severe rheumatoid arthritis when compared with twins with mild disease.

The Human Leucocyte Antigen (HLA) system is composed of polymorphic genes located on the short arm of chromosome 6. It plays an important role in self-recognition by the cellular component of the immune system. The role of the HLA system in determining genetic susceptibility to rheumatoid arthritis was appreciated in the 1970s when Statsny (1978) demonstrated that 70% of Caucasian subjects with rheumatoid arthritis were HLA DR4 positive. The majority of concordant twins with rheumatoid arthritis type as HLA DR4 or DR1. The HLA system is thought to influence the severity and persistence of synovitis in susceptible patients (Ollier et al. 1984). There is an increased frequency of HLA subtypes observed in a number of racial groups, for example, HLA DR4 is increased in Japanese, Asian Indians, and Black Americans. A number of studies in recent years have led to the concept of the "shared epitope" on HLA molecules, leading to an increased susceptibility to

rheumatoid arthritis (Gregersen et al. 1987). The shared epitope is thought to comprise the 5 amino acid sequence: glutamine- (arginine or lysine)- arginine- alanine- alanine on the HLA DR B1 polypeptide, shared by all haplotypes associated with rheumatoid arthritis. The high frequency of rheumatoid arthritis in the Yakima Indians is related to the carriage of HLA Dw16, which is thought to be the region that carries the 5 amino acid sequence (Wilkins et al. 1991).

The shared epitopes act as co-dominant genes, therefore homozygosity for the genes further increases the risk of disease, especially in monozygotic twins (Jawaheer et al. 1994). Despite the body of evidence that exists to support the association of the shared epitope with rheumatoid arthritis, the majority of such gene carriers do not get rheumatoid arthritis. This implies that other genes may play a role, for example, T cell receptor genes; also, other genes may determine the clinical expression of disease.

(ii). The Role of Infection in Rheumatoid Arthritis

It has been proposed that rheumatoid arthritis may have an infectious cause. This has prompted many workers to try to find evidence for a transmissible aetiological agent. However, there is as yet no conclusive evidence to support this hypothesis. It is known that the joints are the sites of infection by organisms such as the gonococcus, chlamydia species and Borrelia burgdorferi. Infectious agents could lead to the initiation and perpetuation of rheumatoid arthritis by a number of different mechanisms. For example, retroviruses can integrate into the host genome leading to the production of abnormal proteins and alter clinical expression of the disease. Experiments in animal models have shown that mice can develop a chronic inflammatory arthritis when they have been genetically engineered to express Human T cell Leukaemia Virus -1 (Iwakura et al. 1995).

Bacteria produce toxins that can stimulate an immune response. Streptococci and Mycoplasma release T cell superantigens, which bind to particular regions on T cell receptors leading to the production of cytokines

(Kotzin et al. 1993). In certain strains of mice, retroviruses can alter the T cell repertoire via production of superantigens leading to sub-optimal immune responses to exogenous antigen. The Epstein-Barr virus may play an important part in rheumatoid arthritis by polyclonal activation of B-lymphocytes and subsequent autoantibody production (Venables 1988, Sample and Kieff 1991). Bacterial superantigens have been shown to induce joint inflammation and disease (Cole and Griffiths 1993). Albani et al. (1992) report that autoimmune responses can be induced by a molecular mimicry mechanism. In this model, a bacterium with structural similarity to joint components can attract lymphocytes to a joint synovium. These can cross-react with cryptic or stress proteins leading to a low-grade immune response and inflammation.

In historical terms, interest has long been focused on *Mycobacterium tuberculosis* as a possible trigger factor for rheumatoid arthritis. In 1935 Forrestier used gold salts to treat rheumatoid arthritis assuming that their antimicrobial activity would be directed against *M. tuberculosis*. Van Eden (1991) showed that a chronic arthritis could be induced in rats using mycobacterial heat shock protein. Heat shock proteins are produced by injured cells, and aid in the processing of denatured proteins. An antibody increase has been noted against foreign bacterial heat shock protein in normal subjects. It is thought that heat shock proteins act as potential autoantigens in rheumatoid arthritis. Human T cells are increased in the synovium in response to mycobacterial hsp65. This increase is proportional to inflammation observed, but it is not specific to rheumatoid arthritis (de Graeff-Meeder et al. 1990, Res et al. 1990).

(iii). Sex Hormones and other Aetiological Factors

The suggestion that sex hormones may have a role in the aetiology of rheumatoid arthritis has been stimulated by the observation that there is a preponderance of disease in pre-menopausal women compared with men, with a clustering of cases perimenopausally. A number of studies have reported that the

combined oral contraceptive pill exerts a protective influence against developing rheumatoid arthritis (Wingrave and Kay 1978). However, a meta-analysis concluded that the oral contraceptive pill use has no overall effect on rheumatoid arthritis risk, but it may delay the onset of disease (Romieu et al. 1989). A number of studies in the United Kingdom have shown an increased risk of rheumatoid arthritis in nulliparous women (Spector et al. 1990). If a subgroup of women who are nulliparous and do not use the contraceptive pill is selected, then the risks are even greater. It is unclear why this is the case.

The relationship between pregnancy and rheumatoid arthritis is a complex one. The features of inflammatory joint disease undergo a remission in pregnancy. This has previously been thought to be secondary to the immunomodulatory effects of a number of circulating substances, including α fetoprotein and glucocorticoids (Klipple and Cecere 1989). Nelson et al. (1993) reported that the remission is due to a difference in HLA DQ status between mother and foetus, suggesting that an anti-HLA immune response in the mother may be responsible.

A number of other factors including lifestyle, smoking and stress may also influence the expression of rheumatoid arthritis (Brooks 1998).

(iv). Rheumatoid Factor and other Autoantibodies

Waaler, in 1940, first identified immunoglobulin M (IgM) rheumatoid factor in the blood of patients with rheumatoid arthritis. It was the first immunological marker of rheumatic disease to be identified. A variety of rheumatoid factors are found in normal subjects and occur in a number of inflammatory and infectious disease states characterised by immune complex formation and hypergammaglobulinaemia. They are not specific to rheumatoid arthritis. Rheumatoid factors are defined as autoantibodies reactive to epitopes in the Fc region of IgG. The autoantibodies may be of the IgM, IgA, IgG, or IgE class. In rheumatoid arthritis, they are highly selective and this may reflect antigen specificity which has evolved through the presence of somatic mutations

in the genes which encode these antibodies (Deftos et al. 1994). The IgM-rheumatoid factor molecule forms a pentameric structure comprised of five sub-units, each with a molecular weight of 185,000 daltons, joined together by disulphide bridges (Stryer 1988).

B-lymphocytes produce autoantibodies, specifically rheumatoid factor, by promoting a T cell response to specific antigens trapped in immune complexes in the synovium (Andrew et al. 1991). The activated T cells then induce rheumatoid factor B cells to proliferate and mutate their immunoglobulin genes. B-lymphocytes also produce IgM rheumatoid factor in response to a non-specific polyclonal activation of B cells (Koopman et al. 1980). There are a number of theories to explain the mechanisms leading to rheumatoid factor induction. The selectivity of different rheumatoid factors varies depending on the disease process. Therefore, it is conceivable that there are a number of different processes leading to rheumatoid factor synthesis. Pokeweed mitogen, which is a T cell dependent B cell activator, induces lymphocytes from rheumatoid arthritis patients to produce IgM, IgA and IgG rheumatoid factors. Epstein-Barr virus simulates rheumatoid factor synthesis from lymphocytes of healthy subjects (Carson et al. 1981). This supports the view that rheumatoid factor B cells are constituents of the normal B cell population. It is likely that a transient synthesis of IgM rheumatoid factor occurs in response to polyclonal B cell activation, and this is part of immune regulation. However, a specific antigen response is likely to require the presence of both the humoral and the cellular components of the immune system and it is this mechanism which may play a role in the expression of autoantibodies in autoimmune disorders. It still remains to be elucidated what contribution polyclonal B cell activation and antigen driven B cell proliferation have to the expression of rheumatoid factor in disorders such as rheumatoid arthritis.

Abnormal IgG structure is also known to stimulate rheumatoid factor synthesis. Altered IgG glycosylation of some patients with rheumatoid arthritis has been demonstrated (Tomana et al. 1988). Normally IgG contains N-linked oligosaccharides located in the Fc portion of the molecule. Patients with

rheumatoid arthritis have been shown to have an increased amount of a galactose deficient oligosaccharide IgG. It may be that alteration of IgG has led to exposure of epitopes leading to induction of rheumatoid factor synthesis (Parekh et al. 1985). This abnormality of IgG has also been noted in normal ageing and inflammatory bowel disease (Parekh et al. 1988, Go et al. 1994). In the latter, RF is usually absent. The significance of this is unclear. It has been shown that IgG structure may also be altered by free radical reactions occurring in vivo (Lunec et al. 1985). The oxygen-derived free radicals are produced during inflammation by activated neutrophils and include the superoxide anion and the hydroxyl free radical.

During the inflammatory process rheumatoid factor is produced in the synovium (Wernick et al. 1985, Koopman et al. 1983). The levels of rheumatoid factor correspond with disease activity and severity (van Zeben et al. 1992). Rheumatoid factor might also play an important physiological role in addition to its association to rheumatoid arthritis. It is known to appear transiently following immunisation with viral or bacterial antigens (Svec and Dingle 1965, Johnson and Hall 1958).

Rheumatoid factor is measured in a variety of ways, usually by agglutination methods such as latex agglutination. Latex particles, which are coated with human IgG, agglutinate in the presence of IgM rheumatoid factor. The highest dilution of serum that causes aggregation is quoted as the result. The SCAT (sheep cell agglutination test) was developed by Waaler (1940) and Rose et al. (1948). It detects rheumatoid factor by agglutinating sheep erythrocytes sensitised with rabbit IgG anti-erythrocyte antibody. Despite its wide use it has proven to be technically difficult, therefore the latex fixation test has been more commonly used because it is more sensitive and easier to perform (Singer and Plotz 1956). Commercial kits for the latex fixation tests are now available and commonly used in clinical practice. Some variability has been demonstrated in the results using these kits but this is overcome by using reference standards and expressing results in SI units (Taylor et al. 1977). Other methods for measurement of rheumatoid factor include radioimmunoassay, indirect

immunofluorescence and enzyme linked immunoadsorbent assay. In larger laboratories laser nephelometry is also employed as an alternative to standard agglutination tests (Finley et al. 1979).

The significance of rheumatoid factor in rheumatoid disease needs careful consideration since it is present in normal individuals as well as in a number of other disease states including chronic infection and autoimmune disease. It has limited use in the diagnosis of rheumatoid arthritis within the general population. However, it is very useful in the context of rheumatological practice. Wolfe et al. (1991) found that measurement of rheumatoid factor conferred an 80% positive prediction of rheumatoid arthritis in rheumatology out patient clinics, where the prevalence of rheumatoid arthritis was 16.4%. The study group consisted of over 8000 rheumatoid arthritis patients.

If the rheumatoid factor titre is significantly elevated then by convention this is defined as being seropositive. The predisposition to seropositivity is associated with inheritance of major histocompatibility class II HLA DR4 or HLA DR1 alleles. Patients who have an absence of rheumatoid factor are denoted as having seronegative rheumatoid arthritis. Sometimes, rheumatoid factor can be detected in serum IgM of patients who are thought to have seronegative rheumatoid arthritis after separation from autologous IgG (Cracchiolo et al. 1970). Furthermore, patients who are thought to have seronegative rheumatoid arthritis in the early stages, have detectable levels of IgM rheumatoid factor as the disease becomes more advanced and the clinical picture becomes more apparent. Despite this, the clinical division of patients with rheumatoid arthritis depending on their rheumatoid factor status is clinically useful. Seropositive rheumatoid arthritis is a more aggressive disease with a higher frequency of extra-articular involvement. Rheumatoid factor seropositive status is also associated with increased mortality in rheumatoid arthritis (van Zeben et al. 1992, van Schaardenburg et al. 1993).

A number of other autoantibodies are also detected in rheumatoid arthritis including antinuclear antibodies, anticollagen antibodies, antikeratin antibodies and anti-perinuclear factors. Some of these are of limited use in the

diagnosis of rheumatoid arthritis, but it is likely that the disease process itself contributes to the formation of various antibodies as an immune response.

Presentation and Clinical Course

Rheumatoid arthritis can begin at any age. Its peak incidence is in the fourth or fifth decade with the prevalence increasing thereafter.

Patients often suspect a number of trigger factors such as trauma, stress or infections, but there is no definite evidence for this. There is also little evidence to support a seasonal variation for the disease (Eberhardt et al. 1990). The onset can be rapid or gradual, and the rate of progression varies widely. Similarly, the degree of impairment and disability is very variable. Typically the disease affects middle-aged females with a gradual onset of pain, stiffness and swelling in the small joints usually with a symmetrical pattern. Diagnostic criteria may provide helpful information in individual cases. They may not be definitive since the diagnosis may only become apparent with time (Arnett et al. 1988). Other patterns of presentation include an abrupt onset of polyarthritis affecting a number of joints. This can occur in any age group, especially in elderly people. The patient can often specify a date of onset. About ten per cent of patients suffer from palindromic rheumatism for a period of time before a more proliferative, chronic disease sets in (Schumacher 1982). Less commonly rheumatoid arthritis can present with a monoarthritis which can be acute or sub-acute in nature. In the former, the arthritis can be confused with a septic or gouty process. Sometimes, patients may complain of non-specific constitutional symptoms including malaise, loss of weight and fatigue. Kurki et al. (1992) have shown an increasing incidence of rheumatoid factor and antikeratin antibodies in the Finnish population in the years prior to the onset of rheumatoid arthritis. This would seem to indicate a preceding immune disorder. Any joint may be affected in rheumatoid arthritis but there seems to be a preferential localisation of symptoms to particular joints (see table 1.2).

Table 1.2 Involvement of joints in rheumatoid arthritis (Brooks 1998)

Site	Frequency (%)
MCP, PIP	90 (early)
MTP	90 (early)
Wrist	80 (early)
Knee	80
Ankle, Subtalar	80
Shoulder	60
Acromioclavicular	50
Elbow	50
Hip	50
Cervical Spine	40
Temporomandibular	30
Sternoclavicular	30
Cricoarytenoid	10

Rheumatoid arthritis behaves in a number of different ways. Early permanent remission of the disease can occur especially in patients who have a single acute presentation, but the majority of patients who have had the disease for more than six months go on to develop a more progressive and chronic pattern of disease. Sometimes clinical improvement can occur in patients who have had an initial severe reduction in functional status. Masi et al. (1983) traced the natural history of rheumatoid arthritis in a defined group of patients over a period of six years. They described three patterns of disease. These include monocyclic, polycyclic and progressive. It may be that in practice a mixed picture is observed in individual patients. Rheumatoid arthritis is a systemic disease and inflammation can extend beyond the joints to involve other organ systems. This occurs more frequently in patients who are seropositive and have rheumatoid nodules. Disease activity can be monitored clinically by studying joint inflammation, the erythrocyte sedimentation rate, C reactive protein and the level of haemoglobin.

Table 1.3 illustrates the extra-articular features of rheumatoid arthritis and consequent organ involvement.

Table 1.3 Extra-articular features of rheumatoid arthritis.

Non-Organ Specific	
	Weight loss, malaise and fever
	Lymphadenopathy
	Rheumatoid nodules
	Felty's Syndrome
	Amyloidosis
	Sjögren's Syndrome
Organ Specific	
Vasculitis	Splinter haemorrhages, nail fold infarcts
	Peripheral neuropathy
	Organ vasculitis
	Episcleritis
Cardiac	Pericarditis
	Endocarditis
	Myocarditis
Pulmonary	Pleurisy, pleural effusions
	Interstitial fibrosis
	Nodular lung disease
	Airways obstruction
Renal disease	Amyloid
	Drug induced eg. NSAIDs or second line agents
	Renal tubular acidosis (type 1)
Neurological	Compressive neuropathies (eg. carpal tunnel syndrome)
	Peripheral neuropathies (usually caused by vasculitis)
	Cervical myelopathies (secondary to atlantoaxial instability)

Neurological Involvement in Rheumatoid Arthritis

Neurological manifestations occur relatively commonly in rheumatoid arthritis. These primarily involve the peripheral component of the somatic nervous system. The most frequently documented abnormalities include the entrapment neuropathies. Nerve compression occurs secondary to the inflamed synovium, pressing the nerve against a fixed structure. The nerves that tend to be affected include the median and ulnar nerves, posterior tibial, and the posterior interosseous branch of the radial nerve. Neurological symptoms and clinical examination suggest the diagnosis in each case. Electromyographic studies show delayed nerve conduction. More rarely, a peripheral neuropathy, usually affecting the lower limbs, can occur. This is a form of mononeuritis multiplex. Its sudden onset usually has a poor prognosis and signals the onset of an aggressive vasculitic process.

A distal sensory neuropathy occurs in small vessel vasculitis. It may be seen in isolation without further progression to generalised vascular involvement. Cervical myelopathy in association with rheumatoid arthritis has been well documented (Marks and Sharp 1981). It occurs secondary to atlantoaxial vertebral subluxation. This is due either to erosion of the odontoid peg, or rupture of the transverse ligament of the first cervical vertebra, allowing the odontoid peg to slip posteriorly and cause compression of the spinal cord. Cord compression can also be caused by basilar invagination with upward impingement of the odontoid peg into the foramen magnum (Menezes et al. 1985). This is usually manifest clinically by a spastic paraparesis, sensory loss, loss of bladder and anal control, syncope and in some cases sudden death. This is more likely if cervical instability has not previously been noted.

There are several reports in the literature to suggest the existence of an autonomic neuropathy in rheumatoid arthritis (Edmonds et al. 1979, Toussirot et al. 1993). Autonomic dysfunction has also been noted in a number of other inflammatory joint conditions and connective tissue disorders (Gudesblatt et al. 1985, Lioté and Osterland 1994). Further understanding of the role of the

autonomic nervous system in chronic inflammatory joint disease depends on a detailed knowledge of the structure and function of the autonomic nervous system.

(i). The Autonomic Nervous System

Anatomists and physiologists have often classified the nervous system into the somatic (voluntary) nervous system and the autonomic (involuntary) nervous system. The somatic portion of the nervous system operates in a coordinated manner with somatic sensory information being detected through sensory receptors. These may be visual, auditory or tactile receptors. Sensory information is processed through the central nervous system and the subsequent effector functions of the somatic nervous system are manifested via the motor component. The motor component is primarily involved in controlling the skeletal musculature. The autonomic nervous system operates in parallel to the somatic nervous system and is primarily involved in regulating the involuntary or visceral functions of the body.

Whilst this classification has helped to promote understanding of the nervous system, it is more useful to think of one system as serving the body, with somatic and visceral functions being integrated by the higher centres of the brain and spinal cord.

Galen (130-201 AD) was the first to identify the nerves that supply the viscera. He proposed that they carried the sympathies; those emotional reactions thought to characterise human behaviour, for example, "heart leaps with joy", "bowels of mercy" and "tears of sorrow". Later, 17th and 18th century anatomists such as Sir Thomas Willis (1621-1675) helped to characterise the autonomic system. There is now general agreement that the autonomic nervous system, as defined by John Newton Langley (1898), consists of an efferent outflow from the brain and spinal cord with sympathetic and parasympathetic subdivisions. It is organised in a similar way to the somatic nervous system. For example, impulses initiated in the visceral receptors are relayed through afferent

autonomic pathways to the central nervous system, integrated within it at various levels, and transmitted via the efferent pathways to the visceral effectors. A third division of the autonomic nervous system, the enteric nervous system, is also recognised by some physiologists.

The peripheral motor components of the autonomic nervous system are made up of preganglionic and postganglionic neurones. The cell bodies of the preganglionic neurones are located in the intermediolateral grey column of the spinal cord or the motor nuclei of the cranial nerves. The axons of the preganglionic neurones are usually myelinated β fibres. These axons synapse on the cell bodies of postganglionic neurones. The postganglionic neurones are mainly unmyelinated C fibres, and terminate on visceral effector organs. Each preganglionic fibre synapses on several postganglionic neurones, leading to a divergence of autonomic outflow. The concept of chemical transmission and the discovery that autonomic nerves act through receptors was introduced in the 1900's. In 1921, Otto Loewi showed that vagal stimulation of a frog's heart released a chemical transmitter. He noted that this slowed the beating of a second heart and he coined the term "vagustoff". This was later identified as acetylcholine. In the 1930's Cannon showed that the sympathetic nervous system acts by liberating catecholamines (noradrenaline) (Cannon and Bacq 1931). It was also demonstrated that the adrenal medulla, which is composed of modified postganglionic neurones, is part of the sympathetic nervous system.

(ii). The Sympathetic Nervous System

The sympathetic nervous system is involved in the "fight or flight" response. The sympathetic nervous system acts on a number of organs and leads to pupillary dilatation, sweating, vasoconstriction, piloerection and reduced salivation. It also enables adrenaline to be released and leads to an acceleration of the heart rate. Furthermore, it influences metabolism to increase the availability of glucose in the body through the action of catecholamines on α adrenergic receptors in the liver, which then stimulate the breakdown of

glycogen. There is an increase in glycogenolysis in muscle and a subsequent increase in blood glucose concentration that is used in the "fight or flight" response. The metabolic effects are accompanied by an increase in the basal metabolic rate, muscle strength and mental alertness.

The sympathetic nervous system is made up of two chains of ganglia lying beneath the peritoneal lining of the thoracic and abdominal cavities, on either side of the vertebral column. These sympathetic chains extend from the superior cervical ganglion at the upper end of the neck to the sacral portion of the spinal cord. There are also collateral ganglia, namely the coeliac, superior and inferior mesenteric ganglia, lying closer to the viscera, which receive preganglionic fibres. The outflow of the preganglionic fibres arises from the 1st thoracic cord segment to the 3rd lumbar segment. In addition there are ganglia lying opposite each cord segment. The postganglionic nerves to the head originate in the superior and middle cervical ganglia, and stellate ganglion. The preganglionic fibres leave the spinal cord via the white rami communicantes to the paravertebral sympathetic ganglion chain. Not all of the preganglionic fibres end on the cell bodies of the postganglionic neurones. Some pass on through to the collateral ganglia, whilst others travel cranially or caudally for a few segments of the spinal cord before synapsing.

This organisation of the sympathetic nervous system enables a diffuse distribution of autonomic impulses throughout the body.

(iii). The Adrenal Medulla

The adrenal glands are located on the upper poles of the kidneys. Each gland is encapsulated in a sheath continuous with the peritoneal fascia and weighs approximately 5 grams. The adrenal glands have an outer cortex and an inner medulla. The medulla constitutes about 28 per cent of the mass of the adrenal gland. Embryologically, it arises from ectodermal cells of the neural crest. The adrenal medulla is in effect a sympathetic ganglion where the postganglionic neurones have lost their axons and become secretory cells. The

cells secrete catecholamines when stimulated by the preganglionic nerve fibres that reach the gland via the splanchnic nerves.

Within the adrenal medulla two cell types can be distinguished morphologically. The first is an adrenaline secreting type that has large dense granules. These comprise of approximately 90% of the cells. The second is a noradrenaline-secreting cell that has smaller and denser granules.

(iv). The Parasympathetic Nervous System

Not all of the tissues in the body are innervated by the parasympathetic nervous system. It plays a complementary role to the sympathetic nervous system. The parasympathetic nervous system has two major components. The cranial outflow supplies the visceral structures in the head via the oculomotor, facial and glossopharyngeal nerves. In addition the vagus nerve supplies a number of structures in the thorax and abdomen. The sacral outflow supplies the pelvic viscera via the pelvic branches of the 2^{nd} to the 4^{th} sacral spinal nerves that consists of preganglionic fibres (nervi erigentes). The preganglionic fibres in both outflow tracts end on short postganglionic neurones located on or near the visceral structures. This organisation of the parasympathetic nervous system leads it to be more circumscribed in its actions, which is in contrast to the sympathetic nervous system. The parasympathetic nervous system is concerned primarily with the conservation of energy and the maintenance of organ function during periods of minimal activity. It slows down the heart rate and lowers the blood pressure through vagal stimulation of the heart. The parasympathetic nervous system also promotes peristalsis and relaxation of sphincters in the gastrointestinal system. This propulsive effect is accompanied by a simultaneous increase in secretions by the glands located in the gastrointestinal tract and hence leads to an increase in absorption of nutrients. It has a slight effect on glycogen synthesis in the liver. The parasympathetic nervous system has a motor effect on the colon and rectum, and constrictor actions on the bladder. This leads to the emptying of the rectum and bladder respectively.

Two functions of the eye are controlled by the autonomic nervous system. These include pupillary size and focusing of the lens. The parasympathetic nerves protect the retina from excessive light by reducing the pupil size. The focusing of the lens is controlled almost entirely by the parasympathetic nervous system. Through actions on the ciliary muscle, it causes the lens to become convex and therefore focus on objects nearby. Parasympathetic fibres are involved in sexual function by producing engorgement of the erectile tissues.

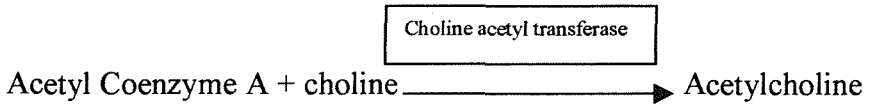
(v). Chemical Transmitters at Autonomic Junctions

Since the recognition that all nerves act by liberating transmitters there has been a lot of research to identify the chemical transmitters and modulators. Initially it was thought that all preganglionic neurones act through acetylcholine, as do the postganglionic fibres of the parasympathetic division, and the postganglionic fibres to the sweat glands. The majority of sympathetic postganglionic fibres were found to act through secretion of adrenaline or noradrenaline.

Acetylcholine:

Acetylcholine is an acetyl ester of choline. It exists enclosed in small, clear synaptic vesicles, in high concentration in the terminal buttons of cholinergic neurones. Acetylcholine is synthesised in the axoplasm of the nerve ending and it is then transported to the vesicles. Its synthesis is illustrated in figure 1.1

Figure 1.1 The synthesis of acetylcholine.

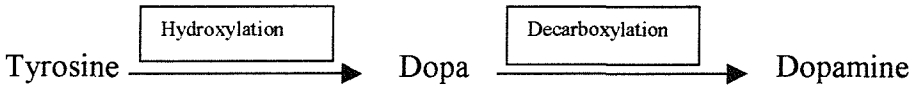


Once the acetylcholine has been released by the cholinergic nerve endings, most of it is split into an acetate ion and choline by the enzyme acetylcholinesterase that is present in the synaptic area (autonomic junction), bound with local collagen and glycosaminoglycans. The choline is recycled back into the nerve terminal for further synthesis of acetylcholine. Most of the acetylcholine is broken down within a few milliseconds after it is released.

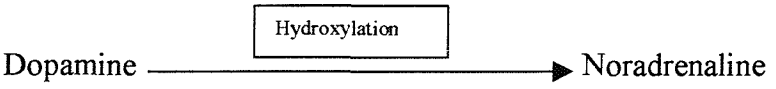
Noradrenaline/Adrenaline:

Noradrenaline is synthesised from tyrosine in the axoplasm of the terminal nerve endings of adrenergic nerve fibres, but the process is completed inside the vesicles. Its synthesis occurs through a number of enzymatic reactions. This is shown in figure 1.2, along with the synthesis of the other principal neurotransmitters, dopamine and adrenaline.

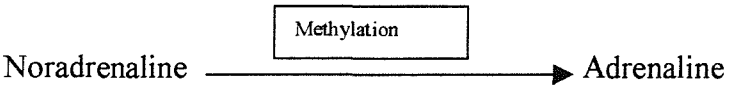
Figure 1.2 The synthesis of the principal neurotransmitters.



Dopamine is then transported into the vesicles:



In the adrenal medulla:



After the release of the noradrenaline by the terminal nerve endings, it is removed from the secretory site in a number of different ways. Firstly by re-uptake into the adrenergic nerve endings by active transport, removing around 50-80% of the noradrenaline. Secondly, by diffusion into the surrounding body fluids and blood. Finally, enzymes such as monoamine oxidase (usually found in

the nerve endings) or catechol-o-methyl transferase, (found in all tissues) can destroy it. Noradrenaline secreted by nerve endings is usually active for only a few seconds and then removed rapidly. Noradrenaline and adrenaline released by the adrenal medulla remain active until they diffuse into tissues where they are destroyed by catechol-o-methyl transferase. The main site of destruction is the liver. A number of other neurotransmitters have been identified that are secreted by nerve endings. They include dopamine, which is secreted by interneurones in the sympathetic ganglia, and gonadotrophin releasing hormone, which is secreted by other types of neurones. Other neurotransmitters include gamma amino butyric acid, glycine, glutamate, substance P, enkephalins and serotonin. Co-transmitters have also been identified in autonomic neurones. These are secreted alongside the principal chemical transmitters and may help to modify their action. Examples of this include vasoactive intestinal polypeptide, which is released with acetylcholine, ATP and neuropeptide Y, which are released with noradrenaline. The picture is further complicated by the fact that in tissue culture, potentially adrenergic neurones can be converted to cholinergic neurones and vice versa. These concepts provide insight into the functions and metabolism of neurotransmitters and demonstrate the fact that there is a state of dynamic flux with a number of regulatory factors operating to enhance neurotransmission.

(vi). Receptors

In 1907, Langley suggested that autonomic nerves act on the tissues through receptors. With the development of this idea it was found that drugs could block parasympathetic nerves. Muscarine, the alkaloid responsible for the toxicity of certain fungi, has little effect on the receptors in autonomic ganglia, but mimics the stimulatory action of acetylcholine on smooth muscle and glands. Acetylcholine acts on receptors that are, by convention, referred to as muscarinic receptors. They are blocked by atropine.

In sympathetic ganglia, small amounts of acetylcholine stimulate

postganglionic neurones, whilst large amounts appear to block transmission of impulses from pre to postganglionic neurones. These actions are unaffected by atropine, but are mimicked by nicotine. The receptors that they act on are called nicotinic receptors. Nicotinic receptors are further subdivided into those found at the neuromuscular junction (N_2) and those found at junctions between neurones (N_1).

Both muscarinic and nicotinic receptors are found in large numbers in the brain. Muscarinic cholinergic receptors differ from nicotinic receptors. Five types of muscarinic receptors have been identified, encoded by separate genes. These have been cloned and are coupled by G proteins to adenylate cyclase or phospholipase C. These receptors are designated in the following way:

M1 - Found in ganglia and secretory glands.

M2 - Found in myocardium and smooth muscle.

M3 - Found in smooth muscle and secretory glands.

M4 - Found in pancreatic acinar and islet tissue where they mediate increased secretion of pancreatic enzymes and insulin.

M1 to M5 - All five subtypes are found in the central nervous system.

Selective therapeutic interventions are not currently available for all of the five types of receptor.

Research experiments using sympathomimetic drugs have demonstrated two major types of adrenergic receptors, called the α and β receptors. Noradrenaline and adrenaline act on both types of receptor. Noradrenaline has a greater affinity for α-adrenergic receptors whilst adrenaline has a greater affinity for β-adrenergic receptors. There are at least five different subtypes of these adrenergic receptors, being $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$ and $\beta 3$. The first four of these are of current therapeutic importance.

With the advent of newly identified neurotransmitters, and drugs with

neurotransmitter properties, there have been a number of receptors discovered. The factors involved in the production of neurotransmitters are not fully understood. Receptors can be desensitised or blocked, sensitised or facilitated, and there are multiple receptor points on the receptor.

(vii). The Autonomic Reflexes

Many of the visceral functions of the human body are regulated through autonomic reflexes. The most important of these relate to the cardiovascular system. Several reflexes operate to control the blood pressure, cardiac output and heart rate. The baroreceptor reflex is central to this control mechanism.

Baroreceptors are stretch receptors located in the walls of the major arteries including the carotid arteries (the carotid sinuses) and the aorta (the aortic arch receptors). These receptors monitor the arterial pressure. Receptors are also located in the walls of the right and left atria, at the entrance of the superior and inferior venae cavae and the pulmonary veins, in the wall of the left ventricle, and in the pulmonary circulation. The receptors in the low-pressure part of the circulation and the left ventricle are referred to collectively as cardiopulmonary receptors. These baroreceptors are stimulated by distension of the structures in which they are located, and so they discharge at an increased rate when the pressure rises. Their afferent fibres pass via the glossopharyngeal and vagus nerves to the medulla oblongata. Most end in the nucleus of the tractus solitarius. The excitatory chemical transmitter they secrete is likely to be glutamate and there may also be an inhibitory pathway that employs the neurotransmitter gamma amino butyric acid (GABA). Impulses generated in the baroreceptors inhibit the tonic discharge of the vasoconstrictor nerves and stimulate the vagal innervation of the heart, producing vasodilatation, venodilatation, a drop in blood pressure, bradycardia and a reduction in cardiac output.

The afferent nerve fibres from the carotid sinus and the carotid body form a distinct branch of the glossopharyngeal nerve, the carotid sinus nerve.

The carotid sinus nerves and the vagal fibres from the aortic arch normally discharge at a slow rate. When the pressure in the sinus and aortic arch rises, the discharge rate increases and there is a fall in blood pressure due to an inhibition of nerve impulses in the nerves that cause vasoconstriction. The carotid receptors respond both to sustained blood pressure and pulse pressure. A decline in carotid pulse pressure without any change in mean pressure decreases the rate of baroreceptor discharge and provokes an increase in blood pressure and tachycardia. The receptors also respond to changes in pressure. The baroreceptors on the arterial side of the circulation, their afferent connections to the vasomotor centre, and the efferent pathways from this centre, constitute a reflex feedback mechanism that operates to stabilise the blood pressure and heart rate.

In chronic hypertension the baroreceptor reflex mechanism is "reset" to maintain an elevated rather than normal blood pressure. How and why this occurs is still unclear but this mechanism can be simulated in experimental animals. Furthermore, sectioning the nerves from the baroreceptors or bilateral lesions of the nucleus of the tractus solitarius, the site of termination of the baroreceptor afferents, can cause a severe hypertension that can be fatal. This is called neurogenic hypertension and is an acute form of hypertension. The changes in pulse rate and blood pressure that occur in humans on standing up or lying down, are due mainly to the baroreceptor reflexes.

Autonomic reflexes also control the upper part of the gastrointestinal tract and the rectum. For example, the smell of food stimulates afferent fibres from the nose and impulses are conducted via the vagal and glossopharyngeal nerves to the salivary nuclei in the brainstem. These transmit signals through the efferent fibres of the parasympathetic nerves to the secretory glands in the mouth and the stomach, causing secretion of digestive juices prior to ingestion of food. Other reflexes include those that control the emptying of the bladder, sexual function, and regulation of body temperature and blood glucose concentration.

The sympathetic and parasympathetic nervous systems act in synergy and are continuously firing nerve impulses. The basal discharge of impulses is

referred to as sympathetic or parasympathetic tone respectively. This allows the nervous system to regulate the nerve impulses to a particular organ thereby allowing control of its function.

Testing the Function of the Autonomic Nervous System

The assessment of autonomic function depends on testing the sympathetic and parasympathetic afferent and efferent components of the autonomic nervous system. In order to achieve this, there are a number of investigations available. Testing autonomic function depends on an understanding of the symptomatology of autonomic dysfunction. Hine et al. (1981) reviewed the symptoms of over three hundred subjects. They found that the commonest symptom was syncope (96%), followed by impotence in men. Weakness occurred in 90%, whilst failure to sweat occurs in 70%. Incontinence and constipation were found in 40% of patients. Finally, more than half of the cases demonstrated supine hypertension. This implies a failure of baroreceptors or afferent mechanisms.

In its simplest form, dysregulation of blood pressure can be studied using a sphygmomanometer. This allows observations of response to posture change (Ewing [1] 1978). More sophisticated methods include using an intra-arterial transducer or manometer system. The investigator can then monitor blood pressure continuously. This can also allow the effects of certain stimuli expected to cause an increase in blood pressure, to be studied; for example, a sudden unexpected noise such as a loud clap. Failure of this transient rise in blood pressure implies a lesion in the efferent sympathetic pathway. Tilt table studies can also be used to investigate orthostatic hypotension. Head up passive tilt testing refers to maintaining the subject in a 60 degree position for a brief period to provoke vasovagal syncope. Upright tilt leads to pooling of blood in the lower limbs, resulting in a reduced venous return. The normal compensatory response to the upright posture is reflex tachycardia, more forceful contraction of the ventricles, and vasoconstriction. This occurs as a result of an initial fall in

arterial pressure and as a consequence, the carotid sinus and aortic arch baroreceptors reduce their inhibitory drive to the vasomotor centre. However, in individuals susceptible to vasovagal syncope, the autonomic compensatory response is over ridden and fails to maintain arterial pressure. Furthermore, the forceful ventricular contraction in the setting of poor perfusion to the upper body may activate the left ventricular mechanoreceptors and hence a depressor reflex for sympathetic activity, thus triggering reflex hypotension and/or bradycardia. This is known as the Bezold-Jarisch reflex. Catecholamine release, by increasing ventricular contraction, may also activate the nerve endings responsible for triggering this reflex. Therefore catecholamines have been used to facilitate the responses during tilt testing. Kenny et al. (1986) report on the usefulness of tilt table testing in the investigation of unexplained syncope. They also reiterate that the vasovagal response to tilt is a separate phenomenon to orthostatic hypotension as a cause of dizziness and syncope. The advantage of using this technique is that the patient can quickly be returned to the supine position if he or she becomes symptomatic. However, tilt table testing does have its limitations. Wieling et al. (1983) showed an active change in posture does not necessarily produce the same vasomotor effects as passive head up tilt. Orthostatic hypotension can also be studied using lower body suction techniques. These generate a lower body negative pressure, thus simulating the upright posture. The release of suction mimics the increased venous return that occurs on return to lying (Bennett et al. 1980).

Heart rate generally reflects resting tone in the vagus nerve. Beat to beat change on standing has been used to quantify the likelihood of autonomic neuropathy. This is expressed as the 30:15 ratio (Ewing [2] 1978). During the change from the supine to the upright posture, a rapid increase in heart rate occurs. This is maximal around the fifteenth beat, with a relative bradycardia then occurring around the thirtieth beat. In the majority of cases of autonomic neuropathy, the heart rate remains relatively fixed, showing very little, if any, beat to beat variation. The fixed heart rate is usually relatively high, as seen in diabetic autonomic neuropathy.

The Valsalva manoeuvre is relatively simple to perform and is a recognised indicator of parasympathetic dysfunction (Levin 1966). During the strain period of the manoeuvre, the blood pressure falls and the heart rate rises. Following release, the blood pressure rises with overshoot of its resting value and the heart slows. The response is mediated by the vagus nerve, as is demonstrated by the fact that it is blocked by atropine, while propranolol has no effect. In subjects with sympathetic dysfunction, the heart rate changes still occur because the baroreceptors and vagus nerves remain intact. In patients with autonomic failure, a syndrome where there is widespread autonomic dysfunction, the heart rate changes are absent, and the blood pressure slowly falls during the strain and slowly normalises after release. There is no overshoot increase in blood pressure.

The blood pressure response to sustained handgrip can be used as a sensitive indicator of sympathetic damage. Ewing et al. (1974) showed that during a sustained handgrip, there is an increase in blood pressure. This is mediated by an increase in heart rate and a subsequent increment in cardiac output whilst the peripheral vascular resistance remains constant. Sympathetic dysfunction leads to an abnormally small rise in blood pressure.

Other tests dependent on a pressor response include the cold pressor test, in which the pressor response to immersion of a hand in cold iced water for a minute or so is tested. This response is absent or reduced in patients with sympathetic dysfunction. Carotid sinus massage can be used to detect hypersensitivity of the carotid artery baroreceptors. This can result in stimulation of the parasympathetic nervous system and lead to bradycardia and vasodilatation. In this condition, patients may describe dizziness or syncope when pressure is applied to the neck, for example, when wearing a tight collar. A positive response to carotid sinus massage may be found in 10% of the general elderly population. Less than a quarter of these patients suffer from spontaneous syncope. Digital blood flow can also be studied by using finger or hand plethysmography or monitoring heat elimination from the fingertips (Johnson and Park 1973). This gives an indication of reflex vasomotor control. Blood flow

in the fingertips is reflexly reduced by an inspiratory gasp and increased by the application of radiant heat to the trunk. Ocular and oral dryness are characteristic features of autonomic dysfunction. These can be investigated using pupillography (de Vos et al. 1989). This monitors the pupillary light reflex, which is regulated exclusively by the autonomic nervous system (Barendregt et al. 1996). Sweating is an easily demonstrable autonomic function and is mediated by sympathetic nerves. Stimulation of the pre-optic area in the anterior hypothalamus, either by excess heat or electrically, leads to sweating. The preganglionic fibres emerge via the thoracolumbar outflow and pass to the sympathetic ganglia. The postganglionic fibres exit through the sympathetic chain and pass to the periphery either with a main nerve trunk or in relation to a blood vessel. In the dermis the nerve supplies sweat glands, erector pili muscles and the smaller blood vessels. The fibres divide terminally and a single nerve fibre may innervate more than one structure. Postganglionic fibres mediate the sympathetic axon reflex. Nerve impulses pass up the postganglionic fibres and effect a response by stimulating sweat gland secretion. In normal subjects body heating leads to symmetrical sweating on the limbs and face. Lesions of the preganglionic or postganglionic sympathetic pathways lead to deficient or absent sweating. This can be tested in a number of ways including acetylcholine iontophoresis. Low et al. (1983) has described a quantitative method based on the sudomotor axon reflex test. Sweating can be shown more simply by using starch or iodine paper, or by dusting the skin with quinazarin powder. This method allows a topographical mapping of sweating abnormalities, especially in response to total body heating (Tuck and McLeod 1981).

More invasive tests of autonomic function include assessing the vagal integrity by measuring gastric acid production in response to insulin induced hypoglycaemia, and by monitoring clinical response to infusion of pressor agents on the sympathetic nervous system. For example, an exaggerated pressor response to infused angiotensin may be related to reduced baroreceptor sensitivity (Love et al. 1971).

With further advances in technology, increasingly sophisticated methods

of assessing autonomic function are available. An accurate assessment of the autonomic nervous system can be made by using a combination of tests and by being aware of the limitations of each of the methods.

Autonomic Dysfunction in Rheumatoid Arthritis

Since Young et al. (1969) described an acute onset autonomic neuropathy there has been research into, and a number of reports of, autonomic impairment in a variety of clinical disorders. These have included bacterial and viral infections. For example, an acute autonomic neuropathy has been described with herpes simplex encephalitis (Neville and Sladen 1984). Autonomic dysfunction has been detailed in association with Guillain-Barré syndrome (Persson and Solders 1983). More recently, Vassallo and Allen (1997) have demonstrated autonomic impairment after pneumonia. These examples illustrate that autonomic impairment can be demonstrated after an acute inflammatory condition.

Autonomic neuropathy has also been documented in a number of chronic disorders. Senaratne et al. (1984) have demonstrated autonomic deficits in a series of patients with multiple sclerosis. Hosking et al. (1978) have shown a similar impairment in patients with diabetes mellitus.

Since the late 1950s, there has been considerable interest shown in the demonstration of autonomic dysfunction in chronic inflammatory joint disease and connective tissue disorders. Autonomic dysfunction has been shown to occur in systemic lupus erythematosus (Lioté and Osterland 1994) and juvenile chronic arthritis (Kuis et al. 1996). In 1963 Kalliomäki et al. found that females with rheumatoid arthritis failed to sweat in response to an intradermal injection of nicotine on the forearm when compared with matched controls. Bennett et al. (1965) studied the sweating response in a series of patients after ingestion of a hot drink and the injection of acetylcholine in areas of anhydrosis. The authors concluded that there was an autonomic neuropathy in most rheumatoid arthritis patients who also had a co-existent peripheral neuropathy.

Later in the 1980s, there were several studies of patients with rheumatoid disease using cardiovascular tests based on the autonomic reflexes (Edmonds et al. 1979, Leden et al. 1983). These studies indicated that there might be an autonomic neuropathy in rheumatoid arthritis, which could be related to the degree of inflammation. The additional presence of a peripheral neuropathy was not mandatory. However, there seems to be conflicting evidence of this. Bekkelund et al. 1996[1] conducted a study in over 40 patients with rheumatoid arthritis. The authors studied autonomic function in these patients by using cardiovascular autonomic function tests. There was no significant difference between their study groups and their control subjects. In addition, the authors also explored the possibility that pancreatic polypeptide was a marker of autonomic impairment in rheumatoid disease. It is thought that certain neuropeptides such as substance P and calcitonin gene related peptide might contribute to the pathophysiology of rheumatoid arthritis (Larsson et al. 1991). The pancreatic polypeptide level has been shown to influence cholinergic tone as secretion of the polypeptide is blocked by atropine (Schwartz 1983). Bekkelund et al. (1996 [1]) found high basal and postprandial levels of pancreatic polypeptide in rheumatoid arthritis patients. They concluded that there was a relationship between rheumatoid arthritis and pancreatic polypeptide, but could not make a causal link between the pathophysiology of rheumatoid arthritis and neurological mechanisms. Toussirot et al. (1993), however, suggests that autonomic impairment occurs in rheumatoid arthritis on a subclinical level without an apparent motor or sensory neuropathy.

An assessment of autonomic function in chronic inflammatory joint disease also needs to be correlated with age. Little is known about age-related changes in the autonomic nervous system, but some degree of autonomic denervation does seem to occur with advancing age in healthy individuals. The mechanisms for this appear to be multifactorial (Collins 1983, O'Brien et al. 1986).

The research conducted to date to investigate the complex relationship between the autonomic system and rheumatoid arthritis has produced conflicting

results. A number of issues remain unresolved. This includes the fundamental question of whether there is any evidence of altered autonomic function tests based on the cardiovascular reflexes. An affirmative answer to this then poses a further dilemma as to whether this correlates with autonomic dysfunction in rheumatoid arthritis, and whether this appears to be a consequence of the rheumatoid disease process itself, or an independent effect of rheumatoid factor status or age? In an attempt to establish some of the answers to these questions and to explain some of the conflicting findings in previous research, the research presented in this thesis concentrates on assessing autonomic function in patients with rheumatoid arthritis. This is done by seeking evidence of disordered autonomic cardiovascular reflexes in rheumatoid arthritis compared with healthy control subjects. If so, is that dysfunction related to:

i. The age of the patient?

ii. The duration of the disease?

iii. Rheumatoid factor status?

This thesis aims to explore the effects that these variables have, if any, on autonomic function within the context of chronic inflammatory joint disease, and if so, whether it is of clinical importance. Finally, it is hoped that by studying this aspect of rheumatoid disease, recommendations can be made on treatment and management, which take the possibility of autonomic dysfunction into account.

Chapter Two

Methods

Methods

The study was carried out at the Royal Bournemouth and Christchurch Hospitals between December 1997 and September 1998. Ethical approval was granted by the Ethical Committee of the East Dorset Health Authority. Informed consent from all the participants in the study was obtained prior to testing.

Subject Selection

The control subjects were members of staff, relatives of patients and staff, and volunteers working at the Royal Bournemouth and Christchurch Hospitals. The control subjects were recruited over the same age range as the patients with rheumatoid arthritis.

The study group was recruited from patients with rheumatoid arthritis attending the rheumatology outpatients department for routine follow up appointments. For the purposes of this study rheumatoid arthritis is defined by the American Rheumatism Association Criteria 1987 (Arnett et al. 1988).

The patients attending the rheumatology outpatients department were tested with the author being blinded to the clinical details of their condition and any other co-existent pathology. This was done to minimise bias in the study. The subjects were then included or excluded according to the criteria outlined below.

Rheumatoid arthritis group inclusion and exclusion criteria

Inclusion criteria

- Absence of exclusion criteria
- Rheumatoid arthritis as defined by the American Rheumatism Association criteria 1987
- Adults of either sex who were ambulant and able to stand.
- The subjects were required to have normal cognitive function with an abbreviated mental test score of > 7/10, and be able to perform all of the tests.

Exclusion criteria

- Absence of inclusion criteria
- Taking medication known to interfere with heart rate and blood pressure.
- Known to have any medical condition complicated by autonomic neuropathy or any other chronic inflammatory condition.
- Unable to perform the autonomic function tests
- Recent ophthalmic surgery (less than six months), which precludes performing a Valsalva manoeuvre.

Control group inclusion and exclusion criteria

Inclusion criteria

- Absence of exclusion criteria
- Normal fit healthy adults of either sex and of all ages who were freely ambulant and without significant physical disease and not on regular medications.
- The subjects were required to have normal cognitive function with an abbreviated mental test score of > 7/10, and be able to perform all of the tests.

Exclusion criteria

- Absence of inclusion criteria.
- Taking medication known to interfere with heart rate and blood pressure.
- Known to have any medical condition complicated by autonomic neuropathy or any chronic inflammatory condition.
- Unable to perform the autonomic function tests
- Recent ophthalmic surgery (less than six months) which precludes performing a Valsalva manoeuvre.

Subject Numbers

The total number of participants in the study was 103. There were 41 subjects in the control group aged between 22 and 82 years (mean 48.0yrs). There were 62 people in the rheumatoid arthritis group aged between 38 and 84 years (mean 63.2yrs).

Method of measuring autonomic function

Autonomic function tests based on cardiovascular reflexes were performed on all of the subjects in this study. The tests used were based on Ewing's battery of tests (1982). Although these are cardiovascular reflex tests, they are indicative of damage elsewhere in the autonomic nervous system (Ewing et al. 1980[1]). The tests have been shown to be quick, reliable, non-invasive and easy to reproduce. Tests of cardiovascular reflexes are most often performed on diabetics but can be applied to the investigation of autonomic damage in other disorders (Vassallo and Allen 1997). The tests were conducted in a quiet room with a preceding period of rest to minimise the variable effects of noise and activity on the results (Ewing et al. 1980[2], Ewing and Clarke 1982).

All testing took place in the late morning; the subjects were almost all non-smokers, and those who smoked refrained for at least three hours. Furthermore, the subjects abstained from caffeine and alcohol from the preceding night. The five tests fall into two categories. The first group represents parasympathetic function and involve heart rate variation in response to the

Valsalva manoeuvre, heart rate variation during deep breathing, and the immediate heart rate response to standing. The second group reflects sympathetic function. Here the blood pressure response to standing and to sustained handgrip were measured. The tests took approximately twenty minutes to perform. They were conducted in the order listed in table 2.1.

Table 2.1 Ewing's battery of autonomic function tests in the order of performance (1982).

Autonomic function test	**Duration (minutes)**	**Posture**
Heart rate response to Valsalva manoeuvre	5	Sitting
Heart rate response to deep breathing	2	Sitting
Blood pressure response to sustained handgrip	5	Sitting
Immediate heart rate response to standing	3	Lying to standing
Blood pressure response to standing	5	Lying to standing

Equipment

The following equipment was used.

- An electrocardiogram machine calibrated at $25mmsec^{-1}$ and $1mVcm^{-1}$.
- An electrocardiograph ruler.
- A mercury in glass sphygmomanometer.
- A modified sphygmomanometer connected to a mouthpiece.
- A handgrip dynamometer.

Details of the Tests

Tests of parasympathetic function.

(i). The heart rate response to the Valsalva manoeuvre.

The Valsalva manoeuvre was performed by asking the subject to blow into a mouthpiece connected to a modified sphygmomanometer. The mercury column was held at a pressure of 40mmHg for 15 seconds. During this time an electrocardiogram was recorded. If the patient was unable to reach a pressure of 40mmHg, then a pressure of 20mmHg or more was felt to be acceptable (Korner et al. 1976).

The Valsalva manoeuvre was conducted three times with one-minute intervals between readings. The Valsalva ratio was calculated by dividing the shortest R-R interval during the manoeuvre by the longest R-R interval following the manoeuvre.

(ii). The heart rate variation during deep breathing.

The subject was asked to breathe in and out six consecutive times, whilst sitting quietly. Each breath was held in and out for 5 seconds respectively. An electrocardiogram was recorded throughout with each phase of the respiratory cycle being indicated on the electrocardiogram.

The maximum and minimum R-R intervals during each cycle were measured using a ruler and the result was expressed in beats per minute. The final result was calculated as the mean difference between the maximum and minimum heart rate for the six respiratory cycles.

(iii). Immediate heart rate response to standing.

The subject was asked to lie quietly on a couch whilst the heart rate was recorded on an electrocardiogram. The patient was then asked to stand up and this was indicated on the recording. The shortest R-R interval around the 15^{th} beat and the longest R-R interval around the 30^{th} beat were measured with an electrocardiogram ruler. The heart rate response was expressed as the 30:15 ratio.

Tests of sympathetic function

(iv). Blood pressure response to standing.

The patient's blood pressure was measured with a sphygmomanometer whilst he/she was lying down quietly, and then again when the patient had been standing up for two minutes. The postural fall in blood pressure was calculated as the difference between the systolic blood pressure lying and the systolic blood pressure standing. This was repeated three times, and the final result was expressed as an average.

(v). Blood pressure response to sustained handgrip.

The maximum voluntary contraction was initially determined using a handgrip dynamometer. The subject was then asked to maintain a contraction at a third of the maximum for as long as possible up to five minutes.

The diastolic blood pressure was measured three times before and at one-minute intervals during the handgrip test. The result was expressed as the difference between the maximum diastolic blood pressure during handgrip and the mean of the diastolic blood pressure prior to handgrip testing.

All of the results were tabulated and stored on a computer spreadsheet.

The results from the study group were analysed with respect to different age bands and duration of rheumatoid arthritis. In addition more subtle relationships were explored using background clinical information extracted from the medical records retrospectively. The clinical information that was collected included:

- Rheumatoid factor status
- The presence of extra-articular features
- The presence of peripheral neuropathy, and/or cervical myelopathy
- Haemoglobin
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive protein (CRP)

Statistical Analysis

The results were tabulated and stored on computer spreadsheets. Statistics were performed using the Microsoft Excel package. The mean and standard deviation of the control group were calculated for each of the different autonomic function tests. The results of the rheumatoid patients as a whole were analysed similarly. The rheumatoid patients were also divided into the following categories:

All rheumatoid patients

Rheumatoid factor positive patients

Rheumatoid factor negative patients

Those with RA for less than 5 years

Those with RA for 5 to 10 years

Those with RA for more than 10 years

Those less than 60 years old

Those more than 60 years old

The results of each of these groups were analysed and compared to the control group using Student's t test.

Next, the rheumatoid patients were divided into two groups. The first group consisted of rheumatoid patients who had three or more abnormal autonomic function tests. These patients were deemed to have impaired autonomic function. The second group consisted of rheumatoid patients with two or less abnormal autonomic function tests. These patients were considered to have unimpaired autonomic function tests. The association between these groups, the inflammatory markers and haemoglobin was tested using the chi-squared test.

A correlation study was conducted comparing each of the autonomic function tests of the rheumatoid subjects with several inflammatory markers. An additional correlation was performed to compare the autonomic function tests with age in both control and rheumatoid subjects, and disease duration in the study group. All correlation coefficients were calculated using the Pearson raw score method.

An analysis was attempted to try and assess the accuracy of the

autonomic function tests by calculating the coefficient of variation. One of the subjects in the control group volunteered to perform the autonomic function tests twenty times at spaced intervals.

Chapter Three

Results

Results

The first section of the results compares the results of the following subgroups with the control subjects:

1. All rheumatoid patients
2. Rheumatoid positive patients
3. Rheumatoid negative patients
4. Subjects with the disease for less than five years
5. Subjects with the disease for between five and ten years
6. Subjects with the disease for more than ten years
7. Subjects below the age of 60 years
8. Subjects 60 years or older

Each group was compared to the control group and the results are outlined in the following tables and graphs (3.1-3.5)

Table 3.1 shows the results of the heart rate response to the Valsalva manoeuvre, expressed as the Valsalva Ratio. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

When all rheumatoid patients were compared to the control group there was a statistically significant difference between the mean Valsalva ratio ($p=0.03$). Furthermore, when the rheumatoid patients were divided into those that were seropositive for rheumatoid factor and those that were seronegative, it was the seropositive group that showed a statistically significant difference from the controls ($p=0.02$), whilst the seronegative group did not.

The duration of rheumatoid arthritis only became statistically significant in those patients who had had the disease for longer than 10 years ($p=0.01$). When the age of the rheumatoid patients were compared to the control group, it was the patients over the age of 60 years who showed a statistically significant difference ($p=0.02$) whereas those under 60 did not. The mean values are graphically represented in figure 3.1, which also shows Ewing's reference ranges (Ewing and Clarke 1982).

Table 3.1 The results of the heart rate response to the Valsalva manoeuvre. The Valsalva ratio.

Subgroup	Number of patients in the group	Mean Result (Ratio)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	1.16	1.12	0.15	-
All rheumatoid patients	62	1.10	1.06	0.12	0.03 *
Rheumatoid positive	47	1.09	1.05	0.12	0.02 *
Rheumatoid Negative	15	1.12	1.11	0.10	0.40
Duration <5 yrs	30	1.13	1.11	0.13	0.32
Duration 5-10 yrs	13	1.09	1.05	0.12	0.15
Duration >10 yrs	19	1.07	1.04	0.08	0.01 *
Age <60	23	1.12	1.06	0.13	0.26
Age 60+	39	1.09	1.06	0.11	0.02 *

Key

* Denotes statistical significance.

Figure 3.1 The results of the heart rate response to the Valsalva manoeuvre. The Valsalva ratio.

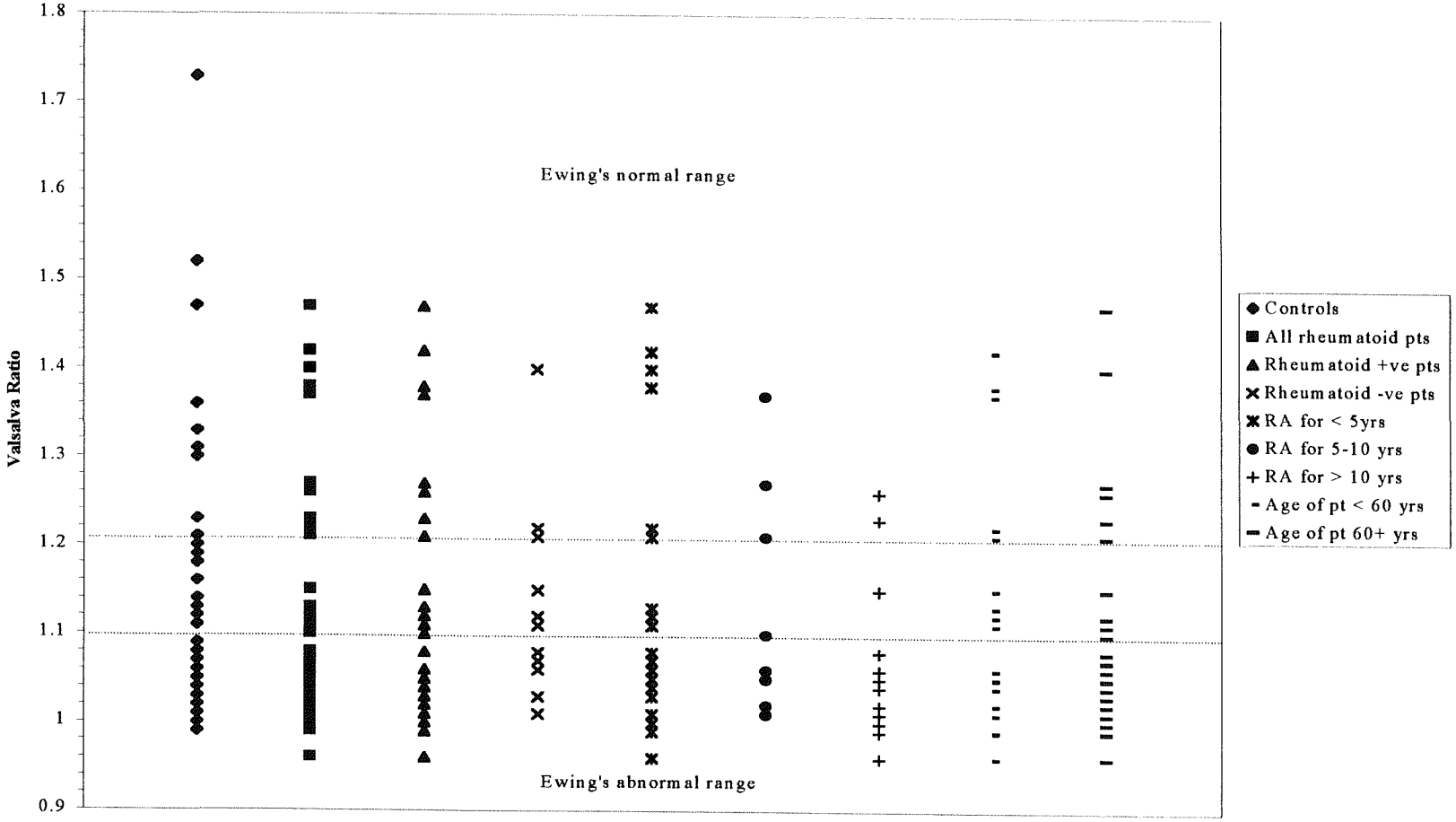


Table 3.2 shows the results of the heart rate response to deep breathing. This is expressed as the R-R interval. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

When all rheumatoid patients were compared to the control group there was a statistically significant difference between the mean R-R interval ($p=0.01$). The seropositive group showed a statistically significant difference from the controls ($p=0.01$), whilst the seronegative group did not.

Those rheumatoid patients who had had their disease either less than 5 years or more than 10 years both showed a statistically significant difference compared to control subjects with p-values of 0.04 and 0.003 respectively.

The patients over the age of 60 years showed a statistically significant difference ($p=0.002$), however those under 60 years did not. The mean values are graphically represented in figure 3.2.

Table 3.2 The results of the heart rate response to deep breathing. The R-R interval.

Subgroup	Number of patients in the group	Mean Result (beats/min)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	10.37	10	5.31	-
All rheumatoid patients	62	7.5	5.85	4.99	0.01 *
Rheumatoid positive	47	7.26	5	5.43	0.01 *
Rheumatoid Negative	15	8.27	7	3.24	0.16
Duration <5 yrs	30	7.79	6.7	5.11	0.04 *
Duration 5-10 yrs	13	8.91	7	5.95	0.41
Duration >10 yrs	19	6.08	5.2	3.85	0.003 *
Age <60	23	8.67	6.7	5.88	0.24
Age 60+	39	6.81	5.7	4.3	0.002 *

Key

* Denotes statistical significance.

Figure 3.2 The results of the heart rate response to deep breathing. The R-R interval.

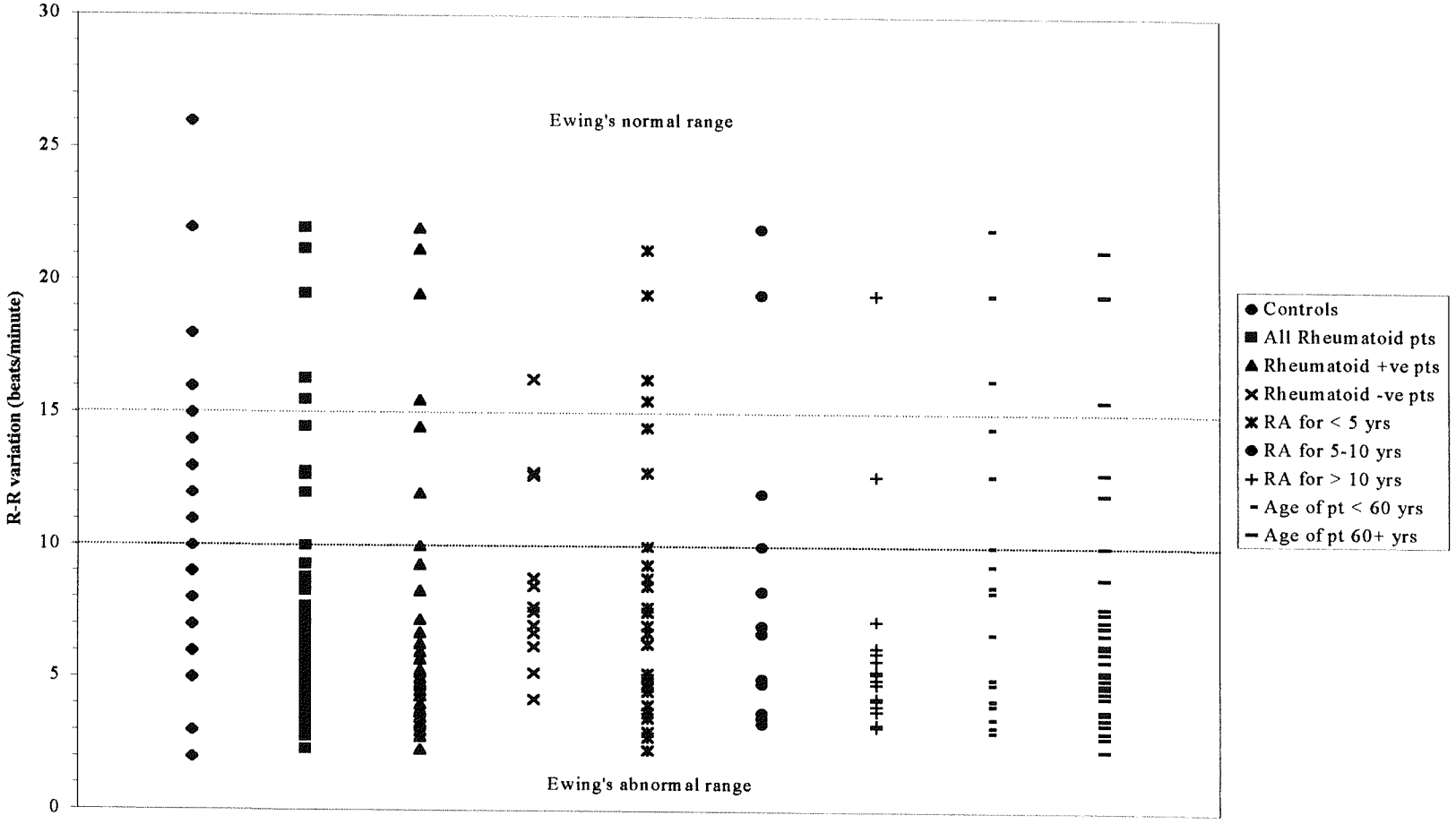


Table 3.3 shows the results of immediate heart rate response to standing. This is expressed as the 30:15 ratio. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

All subgroups analysed showed a statistically significant difference from the control group as indicated by the p-values in the table. The exception was the subgroup of patients who had had rheumatoid arthritis for between 5 and 10 years.

The mean values are graphically represented in figure 3.3.

Table 3.3 The results of immediate heart rate response to standing. The 30:15 ratio.

Subgroup	Number of patients in the group	Mean Result (Ratio)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	1.16	1.13	0.13	-
All rheumatoid patients	62	1.07	1.05	0.12	0.001 *
Rheumatoid positive	47	1.07	1.03	0.14	0.003 *
Rheumatoid Negative	15	1.06	1.08	0.05	0.01 *
Duration <5 yrs	30	1.08	1.06	0.1	0.01 *
Duration 5-10 yrs	13	1.09	1.03	0.21	0.16
Duration >10 yrs	19	1.04	1.03	0.06	<0.001 *
Age <60	23	1.06	1.06	0.06	0.001 *
Age 60+	39	1.08	1.03	0.15	0.01 *

Key

* Denotes statistical significance.

Figure 3.3 The results of immediate heart rate response to standing. The 30:15 ratio.

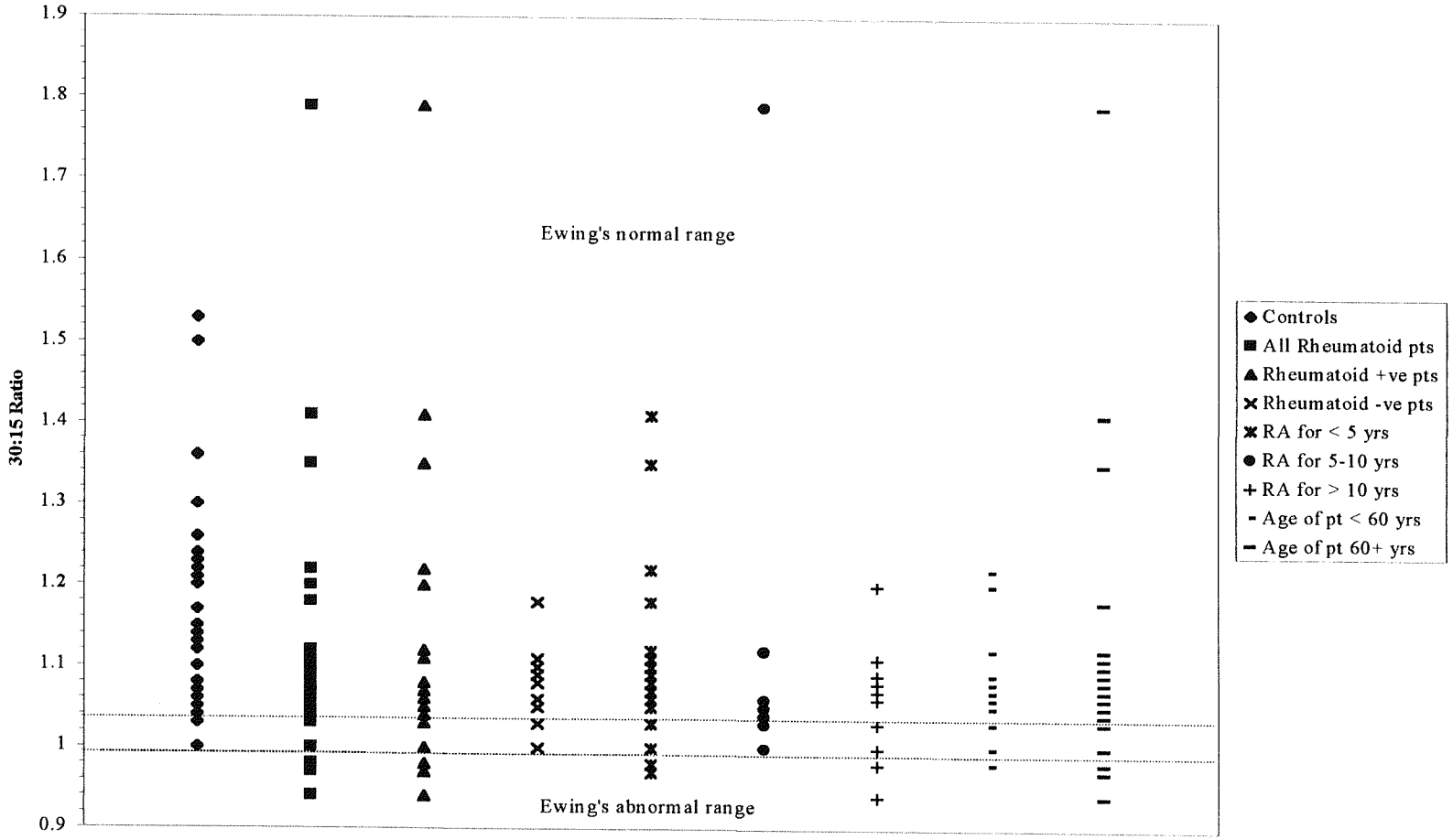


Table 3.4 shows the results of the rise in diastolic blood pressure in response to sustained handgrip. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

When all rheumatoid patients were compared to the control group there was a statistically significant difference between the two groups ($p<0.001$). Both the seropositive and seronegative group showed a statistically significant difference from the controls ($p<0.001$ and $p=0.002$ respectively).

All three subgroups concerning the duration of rheumatoid arthritis showed a statistically significant difference when they were compared to the control group. Also, both subgroups relating to the age of the rheumatoid patients demonstrated a statistically significant difference. The mean values are graphically represented in figure 3.4.

Table 3.4 The results of the rise in diastolic blood pressure in response to sustained handgrip.

Subgroup	Number of patients in the group	Mean Result (mmHg)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	17.39	20	7.4	-
All rheumatoid patients	62	9.55	10	5.58	<0.001 *
Rheumatoid positive	47	9.23	10	5.7	<0.001 *
Rheumatoid Negative	15	10.53	10	5.26	0.002 *
Duration <5 yrs	30	8.17	8	5.36	<0.001 *
Duration 5-10 yrs	13	12.38	10	4.96	0.03 *
Duration >10 yrs	19	9.79	10	5.82	<0.001 *
Age <60	23	8.26	10	4.37	<0.001 *
Age 60+	39	10.31	10	6.11	<0.001 *

Key

* Denotes statistical significance.

Figure 3.4 The results of the rise in diastolic blood pressure in response to sustained handgrip.

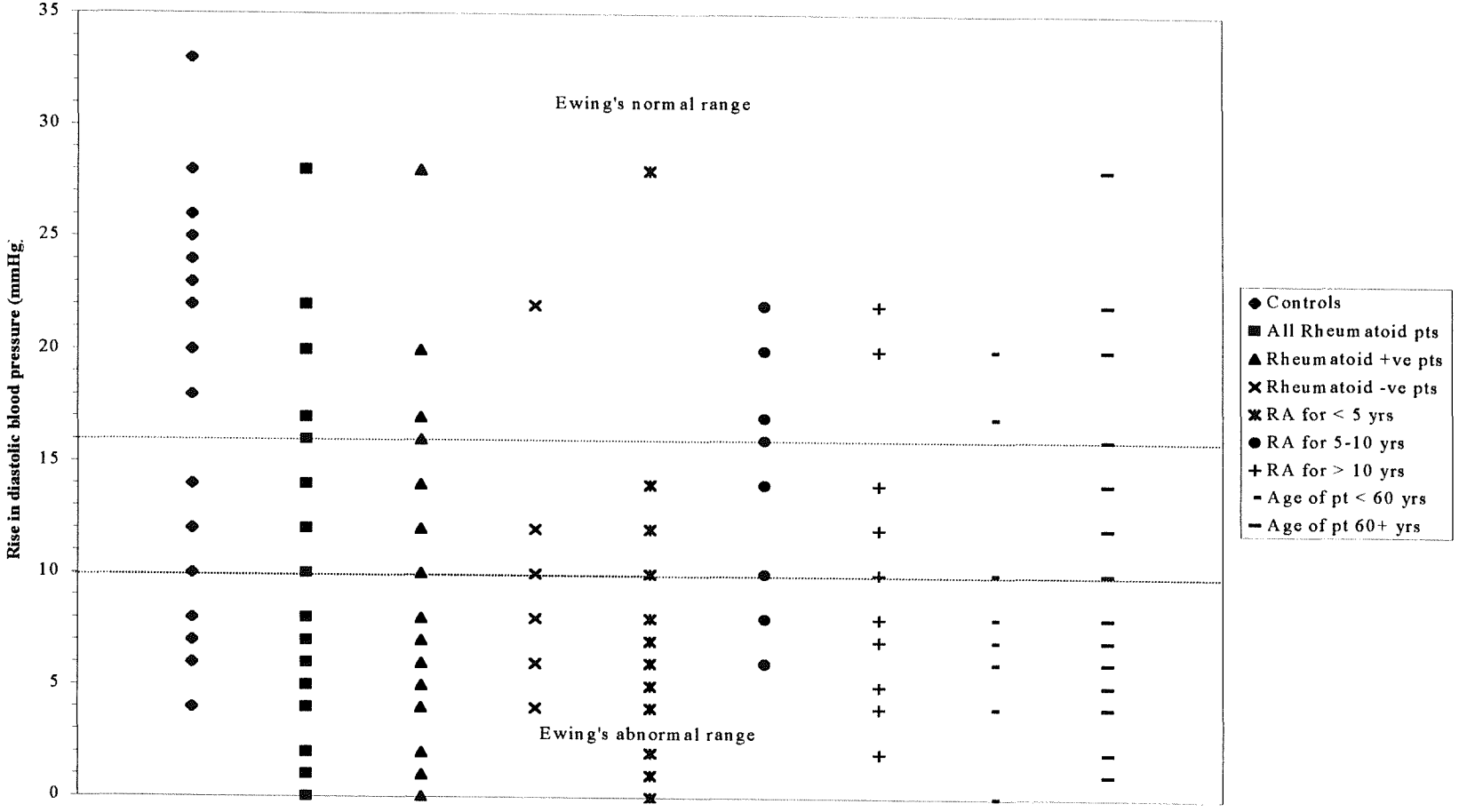


Table 3.5 shows the results of the fall in systolic blood pressure in response to standing. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

It can be seen from this table that there was no statistically significant difference between patients with rheumatoid arthritis and the control group. Indeed, when each of the subgroups was analysed there was no statistically significant difference between the means. These values are graphically represented in figure 3.5.

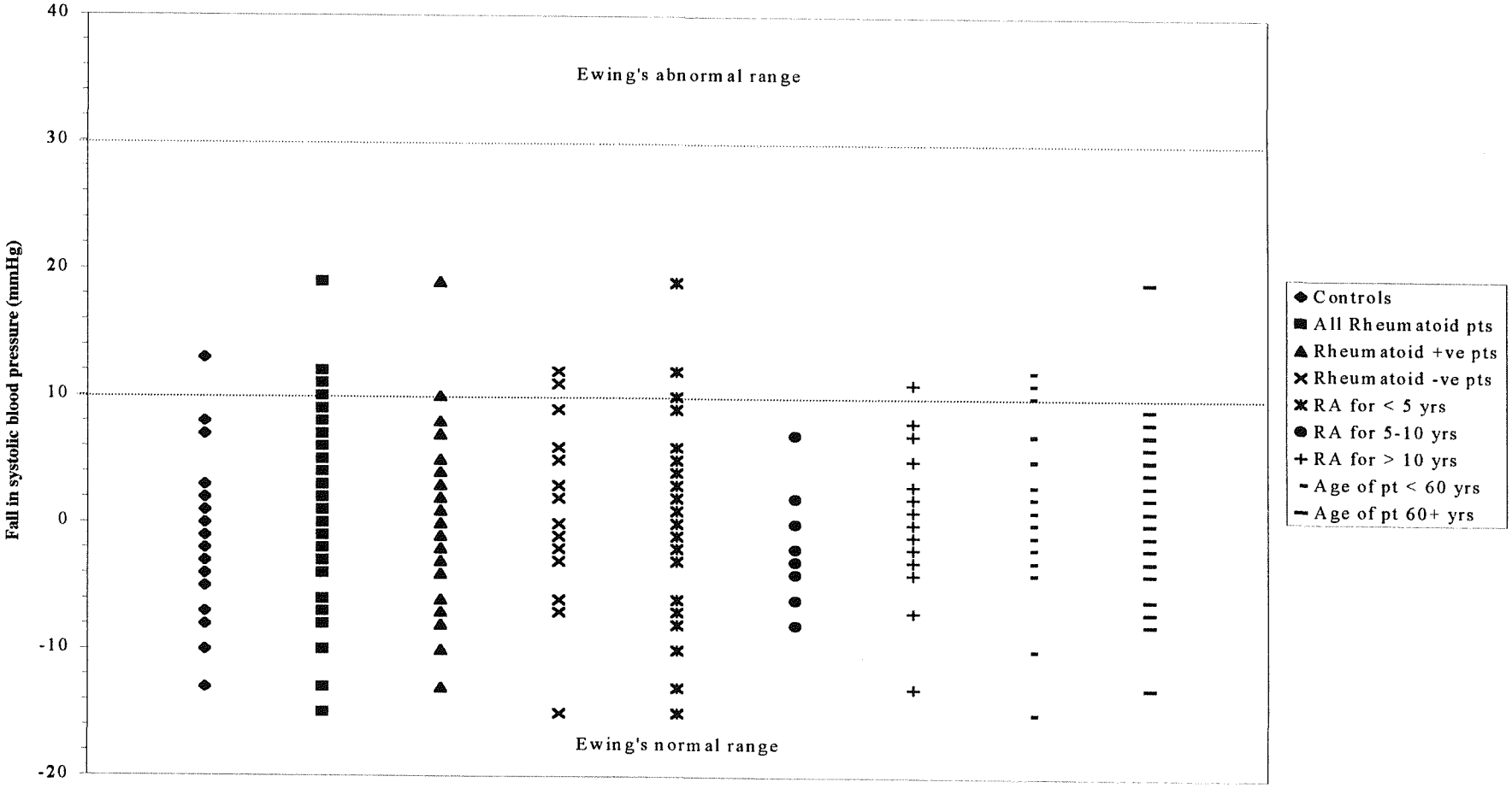
Table 3.5 The results of the fall in systolic blood pressure in response to standing.

Subgroup	Number of patients in the group	Mean Result (mmHg)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	-1.15	0	5.11	-
All rheumatoid patients	62	-0.69	-1	6.47	0.71
Rheumatoid positive	47	-1.21	-1	6.21	0.96
Rheumatoid Negative	15	0.93	0	7.23	0.23
Duration <5 yrs	30	-0.6	0	7.85	0.72
Duration 5-10 yrs	13	-2.23	-3	3.81	0.48
Duration >10 yrs	19	0.21	0	5.51	0.35
Age <60	23	-0.52	-2	6.66	0.68
Age 60+	39	-0.79	0	6.44	0.79

Key

* Denotes statistical significance.

Figure 3.5 The results of the fall in systolic blood pressure in response to standing.



The second part of the results reviews a new selection of subgroups. All rheumatoid patients were again compared with controls. In addition the subjects were divided into the following groups:

1. those patients who had a documented peripheral neuropathy
2. those who had no peripheral neuropathy
3. those patients who were rheumatoid factor positive with the disease for longer than ten years

Each group was compared to the control group and the results are outlined in the following tables and graphs (3.6-3.10)

Analysis was also performed comparing patients who were rheumatoid factor positive with rheumatoid arthritis for longer than ten years with those who were rheumatoid factor negative with the disease for less than five years. In fact no statistically significant difference was found in any of the tests except for the Valsalva ratio ($p=0.03$).

Table 3.6 shows the results of the heart rate response to the Valsalva manoeuvre, expressed as the Valsalva Ratio. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

As before, all rheumatoid patients were compared to the control group. The rheumatoid patients were also divided into those that had a documented peripheral neuropathy and those that did not. It can be seen that there was no significant difference in Valsalva Ratio in either of the groups when compared to the control group.

The final subgroup to be compared with the control group was those patients who had had rheumatoid arthritis for greater than ten years and who were rheumatoid positive. The Valsalva ratio in this subgroup was shown to be significantly different to that of the control group ($p=0.02$).

The mean values are graphically represented in figure 3.6, which also shows Ewing's reference ranges.

Table 3.6 The results of the heart rate response to the Valsalva manoeuvre. The Valsalva ratio.

Subgroup	Number of patients in the group	Mean Result (Ratio)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	1.16	1.12	0.15	-
All rheumatoid patients	62	1.10	1.06	0.12	0.03 *
Patients with a neuropathy	7	1.08	1.04	0.07	0.16
Patients without a neuropathy	54	1.11	1.06	0.12	0.06
Patients who are RF positive with disease for >10 yrs	16	1.06	1.04	0.08	0.02 *

Key

* Denotes statistical significance.

Figure 3.6 The results of the heart rate response to the Valsalva manoeuvre. The Valsalva ratio.

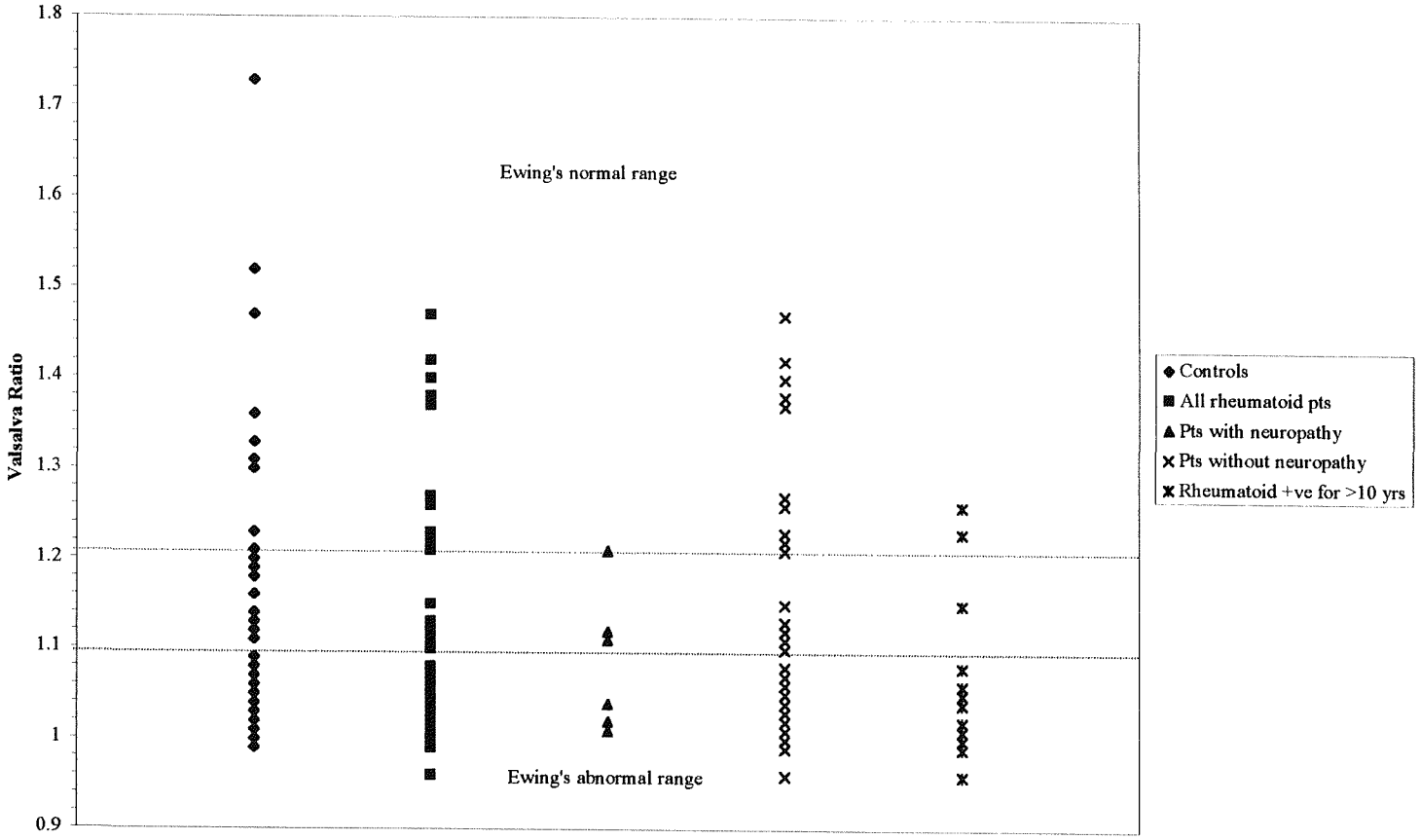


Table 3.7 shows the results of the heart rate response to deep breathing. This is expressed as the R-R interval. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

When all rheumatoid patients were compared to the control group there was a statistically significant difference between the mean R-R interval ($p=0.01$). Both those patients with a peripheral neuropathy and those patients without a peripheral neuropathy also showed a statistically significant difference in heart rate response to deep breathing when compared to the control group ($p=0.04$ and $p=0.02$ respectively).

Furthermore, those rheumatoid patients who had had their disease for more than 10 years and were rheumatoid factor positive, were also shown to have a statistically significant difference in R-R interval when compared to control subjects ($p=0.003$).

The mean values are graphically represented in figure 3.7.

Table 3.7 The results of the heart rate response to deep breathing. The R-R interval.

Subgroup	Number of patients in the group	Mean Result (beats/min)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	10.37	10	5.31	-
All rheumatoid patients	62	7.5	5.85	4.99	0.01 *
Patients with a neuropathy	7	5.96	6.30	1.8	0.04 *
Patients without a neuropathy	54	7.77	5.50	5.26	0.02 *
Patients who are RF positive with disease for >10 yrs	16	6.78	5.10	3.81	0.003 *

Key

* Denotes statistical significance.

Figure 3.7 The results of the heart rate response to deep breathing. The R-R interval.

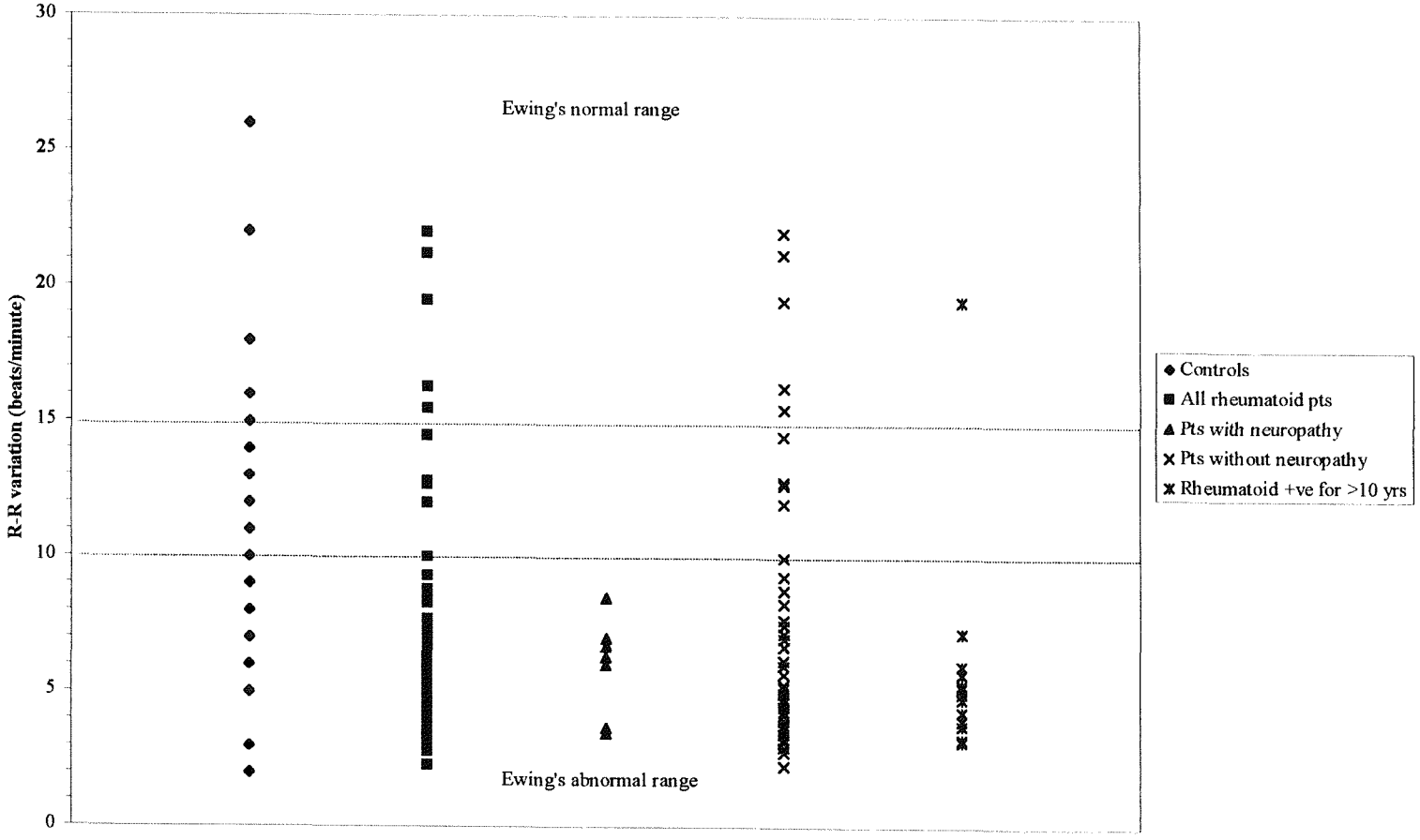


Table 3.8 shows the results of immediate heart rate response to standing. This is expressed as the 30:15 ratio. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

All subgroups analysed, with the exception of the subgroup of patients who had a peripheral neuropathy, showed a statistically significant difference from the control group as indicated by the p-values in the table.
The mean values are graphically represented in figure 3.8.

Table 3.8 The results of immediate heart rate response to standing. The 30:15 ratio.

Subgroup	Number of patients in the group	Mean Result (Ratio)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	1.16	1.13	0.13	-
All rheumatoid patients	62	1.07	1.05	0.12	0.001 *
Patients with a neuropathy	7	1.16	1.06	0.28	0.94
Patients without a neuropathy	54	1.06	1.03	0.08	<0.001 *
Patients who are RF positive with disease for >10 yrs	16	1.04	1.03	0.06	<0.001 *

Key

* Denotes statistical significance.

Figure 3.8 The results of immediate heart rate response to standing. The 30:15 ratio.

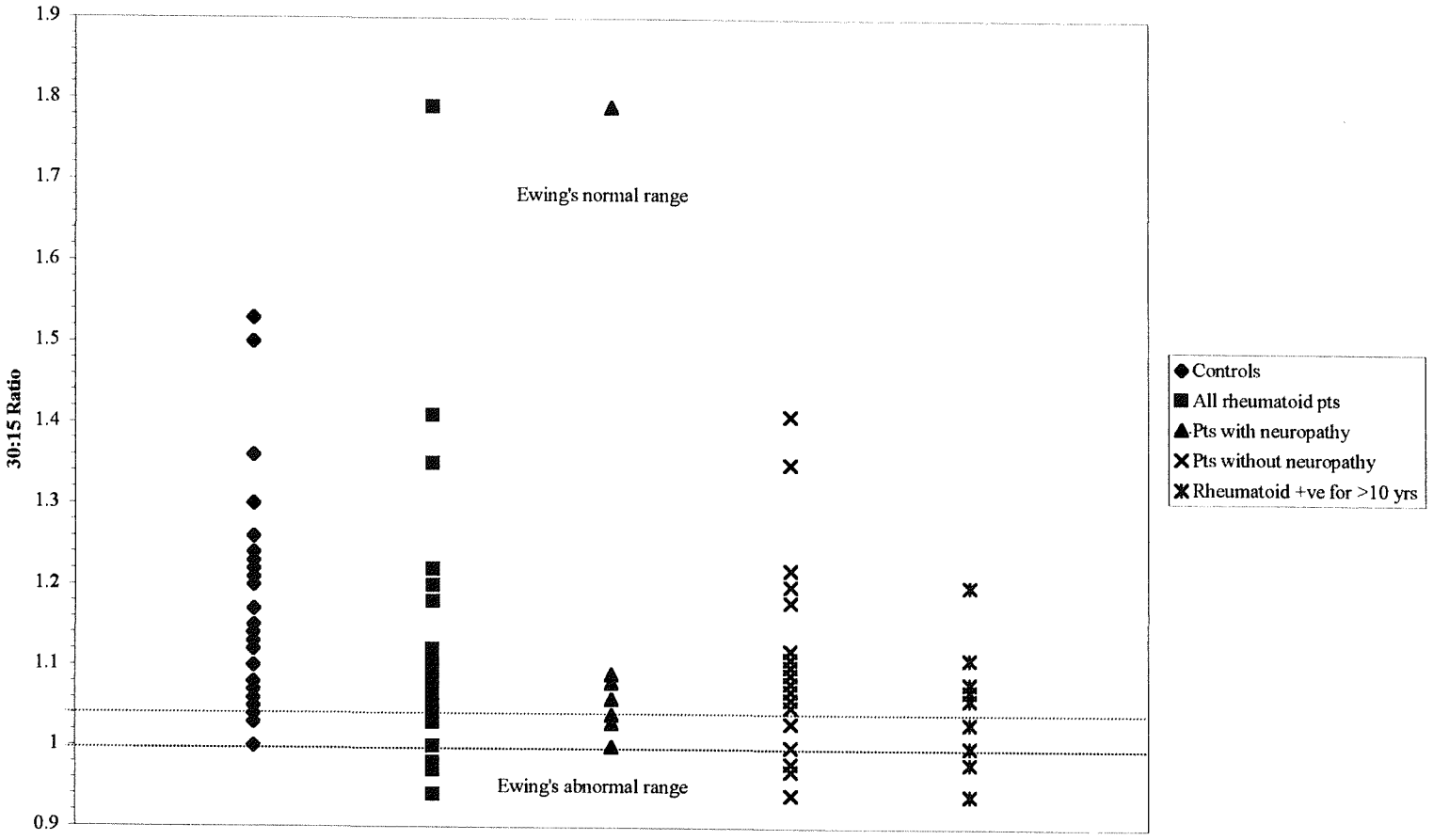


Table 3.9 shows the results of the rise in diastolic blood pressure in response to sustained handgrip. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

All subgroups analysed showed a statistically significant difference from the control group as indicated by the p-values in the table.

The mean values are graphically represented in figure 3.9.

Table 3.9 The results of the rise in diastolic blood pressure in response to sustained handgrip.

Subgroup	Number of patients in the group	Mean Result (mmHg)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	17.39	20	7.4	-
All rheumatoid patients	62	9.55	10	5.58	<0.001 *
Patients with a neuropathy	7	8.43	8.00	6.88	0.004 *
Patients without a neuropathy	54	9.74	10.00	5.50	<0.001 *
Patients who are RF positive with disease for >10 yrs	16	9.00	9.00	5.48	<0.001 *

Key

* Denotes statistical significance.

Figure 3.9 The results of the rise in diastolic blood pressure in response to sustained handgrip.

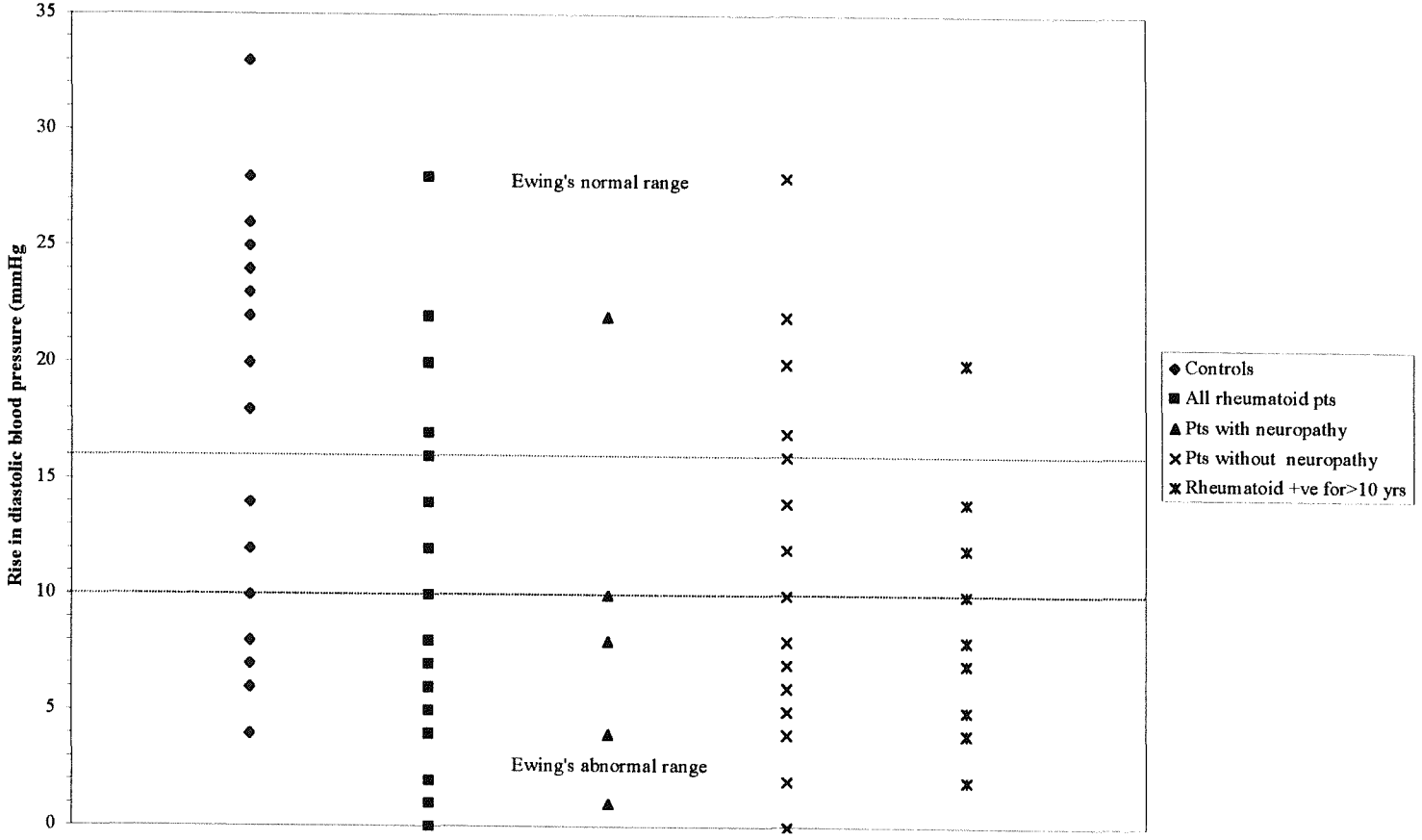


Table 3.10 shows the results of the fall in systolic blood pressure in response to standing. The mean, median and standard deviation for the control group and each of the rheumatoid subgroups is shown.

It can be seen from this table that there was no statistically significant difference between patients with rheumatoid arthritis and the control group. Indeed, when each of the subgroups was analysed there was no statistically significant difference between the means. These values are graphically represented in figure 3.10.

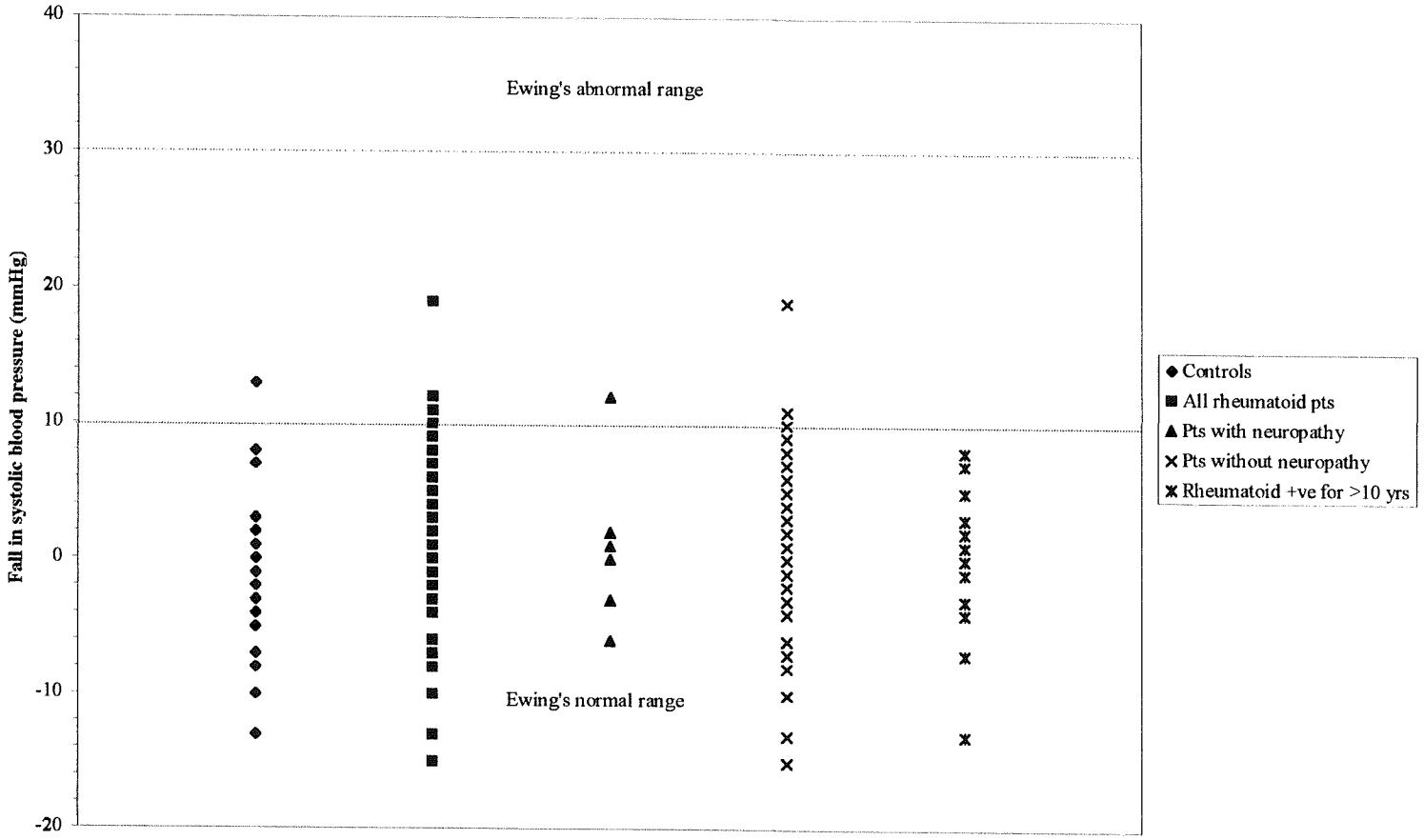
Table 3.10 The results of the fall in systolic blood pressure in response to standing.

Subgroup	Number of patients in the group	Mean Result (mmHg)	Median Value	Standard Deviation	p-value (compared to controls)
Controls	41	-1.15	0	5.11	-
All rheumatoid patients	62	-0.69	-1	6.47	0.71
Patients with a neuropathy	7	0.86	0.00	5.61	0.35
Patients without a neuropathy	54	-0.85	-1.00	6.65	0.81
Patients who are RF positive with disease for >10 yrs	16	-0.31	-0.50	5.30	0.59

Key

* Denotes statistical significance.

Figure 3.10 The results of the fall in systolic blood pressure in response to standing.



Additional Analysis carried out

A correlation study was conducted comparing each of the autonomic function tests of the rheumatoid subjects with their ESR, CRP and haemoglobin respectively. No correlation was found and hence a multivariate analysis was not attempted. The correlation coefficient values are outlined in table 3.11. An additional correlation was performed to compare the autonomic function tests with age in both control and rheumatoid subjects, and disease duration in the study group. Once again, no consistent correlation was demonstrated (table 3.12).

Non-parametric testing was conducted using the chi-squared test, which compared rheumatoid patients defined as having either impaired or non-impaired autonomic function with the ESR, CRP and haemoglobin respectively. Impaired autonomic function for the purposes of this analysis was defined as three or more abnormal autonomic function tests. The results were shown to be not statistically significant (table 3.13).

Table 3.11 Correlation coefficients found when comparing each of the autonomic function tests with various laboratory tests.

Clinical Parameter (rheumatoid pts)	Autonomic Function Test				
	Valsalva Ratio	R-R Interval	30:15 Ratio	Diastolic response to Handgrip	BP response to standing
Haemoglobin	0.04	-0.22	0.02	0.03	-0.02
ESR	-0.18	-0.22	-0.09	0.04	-0.13
C-reactive protein	0.03	-0.09	-0.05	0.31 ($p<0.05$)	-0.13

All p values were non-significant unless shown.

Table 3.12 Correlation coefficients found when comparing each of the autonomic function tests with age and duration of disease.

Clinical Parameter	Autonomic Function Test				
	Valsalva Ratio	R-R Interval	30:15 Ratio	Diastolic response to Handgrip	BP response to standing
Age of Rheumatoid Patients	-0.19	-0.23	0.07	0.21	-0.12
Age of Control Patients	-0.49 ($p<0.002$)	-0.41 ($p<0.01$)	-0.13	-0.14	0.02
Duration of rheumatoid disease	-0.25	-0.16	-0.18	0.02	0.07

All p values were non-significant unless shown.

Table 3.13 A non-parametric analysis of rheumatoid subjects defined as having impaired autonomic function with various laboratory tests.

		Patients with impaired autonomic function (three or more abnormal autonomic function tests)	
		Chi-squared	p-value
Low haemoglobin (f<115 & m<135 g/l) (n=14)		0.131	0.717
ESR mm/hr	>50 (n=11)	0.130	0.719
	>40 (n=14)	0.182	0.670
	>30 (n=22)	0.172	0.678
	>20 (n=26)	0.617	0.432
C-reactive protein (>10) (n=14)		0.103	0.749

Chapter Four

Discussion

Discussion

Rheumatoid arthritis has a complex and multifactorial aetiology in which both genetic and environmental components play a part (Wordsworth and Bell 1991). However, current concepts on the mechanisms involved do not completely explain the pathophysiology of the disease. The aim of this study was to investigate the possible role that the autonomic nervous system may contribute to the understanding of this disease.

The study used autonomic nervous system function tests based on the cardiovascular reflexes as described by Ewing and Clarke in 1982. The validity of these results depends on a number of factors. These include the reliability of using autonomic function tests based on the cardiovascular reflexes as indicators of autonomic damage. Cardiovascular reflex tests only measure damage to those particular reflexes and if they are to be used as autonomic function tests then it has to be assumed that impairment of the cardiovascular reflex tests implies damage elsewhere in the autonomic nervous system. Current evidence suggests that these tests are a highly sensitive and quantitative method of assessing autonomic damage (Ewing et al. 1980[2], Bennett et al. 1978). Historically they have been used to explore the presence of autonomic neuropathy in patients with diabetes mellitus with success, such that these tests have now become well established as an investigative tool in the management of such patients. Their use has been extended to a number of other conditions such as multiple sclerosis (Freeman and Miyawaki 1993, Thomaides et al. 1993), systemic lupus erythematosus (Lioté and Osterland 1994, Louthrenoo et al. 1999), chronic renal failure, alcoholism, Guillain Barre syndrome, and acute infections such as pneumonia (Vassallo and Allen 1997). Furthermore, the autonomic function tests give a global assessment of damage to the cardiovascular autonomic reflex arc and as such cannot be used to localise the lesion.

Although Ewing's cardiovascular reflex tests were simple to perform, each test has certain limitations, which must be understood when discussing the results. The Valsalva manoeuvre is effort dependent and requires the subject to blow into a mouthpiece however, the subject can cheat by placing their tongue

over the end. Although the latter was not a problem during testing, some of the older subjects may have encountered some difficulty in generating sufficient effort to perform the test. In this study all of the subjects were able to complete the test satisfactorily. Patients with defective vision may also have difficulty in seeing the graduations on the manometer, but this can be overcome by the tester indicating the level of mercury in the manometer with a pointer.

In normal subjects the heart rate varies constantly from moment to moment especially in association with breathing. The heart rate variation is maximal at six deep breaths per minute. This test has the advantage that it is objective, easily performed, and cannot be readily manipulated by the subject. The heart rate can only be measured in subjects with a normal sinus rhythm and few or no ectopic beats. During the course of the study none of the subjects encountered any problems in performing these tests, however some patients did have to be excluded from the study because of the presence of cardiac arrhythmias such as atrial fibrillation.

Changes in posture normally cause reflex alterations in the heart rate. The heart rate usually increases when the posture is changed from supine to upright (Ewing et al. 1978[2]). In this study, this was expressed as the 30:15 ratio. The majority of the subjects were able to stand up within 2-3 seconds but Ewing et al. in 1980[3] reported that even if a subject stood up slowly, ie. over a period of 10-15 seconds, the characteristic heart rate responses to standing still occurred. This observation is useful as it takes into account subjects who are frail or, by the nature of their disease, not able to stand very quickly. The 30:15 ratio is one of several methods available to express the heart rate response to standing (Ewing et al. 1978[2], MacKay et al. 1980, Sundkvist et al. 1980). This method relies on the fact that the maximum heart rate response occurs around the 15^{th} beat after standing, and that the minimum response around the 30^{th} beat. This ratio gives a simple numerical value that reflects the presence or absence of a bradycardia. One criticism of this method is that the actual points of tachycardia and bradycardia vary slightly between individuals. However, this can be overcome by analysing the shortest beat at or around the 15^{th} beat and similarly the longest beat at or around the 30^{th} beat.

The sustained handgrip test relies on the demonstration of an increase in

systemic blood pressure that occurs following sustained or isometric muscular exercise. This leads to an increase in cardiac output without a change in the peripheral vascular resistance, thus leading to the blood pressure changes as described. The test is highly sensitive and reproducible but it does suffer from the disadvantage that it requires effort and cooperation, and the subject may not exert the maximum voluntary contraction initially (Wheeler and Watkins 1978). This was noted to occur during the study, but the subject was then able to sustain the grip for longer before letting go. This did not appear to affect the eventual outcome of the blood pressure rise. Subjects were also able to cheat by letting go of the hand grip dynamometer but this was avoided by close observation and by explaining the test and exactly what was required from the subject in detail prior to testing. All the participants in this study were able to perform this test satisfactorily. The presence of hand deformities in the rheumatoid group did not prevent subjects from performing the test. One might have thought that rheumatoid hand deformities would have hindered testing but those affected were surprisingly resilient and showed a high degree of initiative and adaptability in the performance of the handgrip test. All participants were asked about the presence of pain prior to performing this test. All rheumatoid subjects were asked about the presence of active disease in the hands prior to testing, and any subjects who had obvious active synovitis in their hands were excluded from the study. Not withstanding these precautionary measures, the test is a useful measure of autonomic damage, and when abnormal implies extensive impairment of sympathetic efferent pathways.

The assessment of postural hypotension is the simplest of all the cardiovascular reflexes to measure. Its presence indicates overall damage to the baroreflex arc provided there is no decrease in the circulating blood volume or the subject is not on any hypotensive drugs. All the participants in the study were able to comply with this test. A number of the subjects had to be excluded from the study because of their hypotensive drug therapy. Drugs in this category most commonly included diuretics, tricyclic antidepressants, vasodilators, glyceryl trinitrate and phenothiazines.

The design of the study was such that testing occurred without the author being privy to the details of the subject's disease history and drug therapy. This

meant that exclusions were done retrospectively once the details had been obtained from the medical notes. Aside from drug therapy, the main reason subjects were excluded was a failure to meet the diagnostic criteria of rheumatoid arthritis set out in the methods section. The study was designed in this way in order to minimise inadvertent bias during testing.

A number of authorities have established normal ranges for autonomic function tests based on the cardiovascular reflexes (O'Brien et al. 1986, Ewing and Clarke 1982). Although in this study the protocol for Ewing's battery of cardiovascular tests was followed it was felt that the application of the reference ranges as described by Ewing and Clarke (1982) has a limited use when applied to older subjects. It is known that in the healthy elderly there is a natural decline in autonomic function, but that autonomic dysfunction is not a feature of normal ageing. This is due to a number of changes that occur in the autonomic nervous system with age. These include altered adrenoceptor function, reduced sensitivity to pharmacological agents that act on adrenergic receptors, and an increase in basal levels of noradrenaline in the elderly (O'Brien et al. 1986). Tests of autonomic function such as the Valsalva manoeuvre and the heart rate response to deep breathing also decline with age. Hence, in order to reflect this decline, normal ranges for tests of autonomic function need to be related to the age of the subject. Therefore the results obtained for the study group were compared directly with the control group in this study. When a comparison was made between Ewing's reference ranges and the results obtained from the control group it was found that the results from the control group fell within the band described as being borderline by Ewing. O'Brien and coworkers (1986) calculated reference ranges in over 300 healthy volunteers aged between 18 and 85 years of age, and found slightly lower limits for each of the tests. They agreed that this was probably due to the larger number of participants in the study, and the more uniform age distribution of their volunteers. Hence in this study, when the p-values were calculated for the non-parametric statistical tests, it was felt that combining Ewing's normal and borderline reference range bands gave acceptable cut off values for each of the autonomic tests. This reflected more accurately the results obtained from the control group.

The author of the manuscript undertook all the clinical measurements.

This reduced any errors due to observer variability.

Several workers have assessed autonomic cardiovascular function tests in order to ascertain their reliability as clinical tools. Hartwig et al. (1994) concluded that autonomic function tests were reliable and valid in the diagnosis of autonomic neuropathy in patients with diabetes mellitus. They applied the tests to three groups of subjects; healthy volunteers, those with symptomatic diabetes, and those with asymptomatic diabetes. Reliability was determined by intraclass correlation coefficients and validity was determined by analysis of variance procedures between the groups and the calculation of positive and negative predictive values as well as sensitivity and specificity. A reliable clinical test should give similar results when repeated on the same patient. In this study the autonomic function tests were repeated on a control subject. An attempt was made to calculate the coefficient of variation for each of the autonomic function tests. However repeated performance of Valsalva's manoeuvre and the heart rate response to breathing led to a minor degree of distress which compromised the results obtained and thus was felt to be a source of error. Further assessments of the coefficient of variation were not attempted. Furthermore ethical considerations precluded rheumatoid patients being included in the calculation of coefficient of variation. The autonomic function tests based on the cardiovascular reflexes have been assessed to justify their use in the diagnosis of autonomic neuropathy both in research projects and in clinical practice.

A full analysis of the results is only complete if one can draw meaningful conclusions from them and examine their potential clinical significance. The study showed that there was indeed impairment of autonomic function when rheumatoid patients were compared to the control group of healthy volunteers. This was statistically significant and was indeed more so in seropositive patients, those who had had the disease for longer than ten years, and in older subjects. By selecting out those seropositive patients who had had the disease for longer than ten years, statistical significance was again demonstrated (tables 3.6 to 3.10). It should be noted however that when this group was compared to those patients who were seronegative with the disease for less than five years, only the results for the Valsalva ratio showed any statistical difference. No statistical

difference was seen in the groups when comparisons were made for orthostatic hypotension.

In summary, this means that there is autonomic impairment present in rheumatoid patients compared to normal matched controls, but that it is not clinically detectable. This is in agreement with other published work on this subject over the last twenty years (Bennett and Scott 1965, Edmonds et al. 1979, Tan et al. 1993, Toussirot et al. 1993).

A detailed inspection of the results (tables 3.1 to 3.5) reveals that there are some notable exceptions to the general trend that has been obtained. The analysis of the heart rate response to deep breathing (table 3.2) shows that patients who had their disease for less than 5 years or more than 10 years showed statistical significance whereas the group who had had the disease for between 5 and 10 years did not. Similarly, when comparing the subgroups with the controls for the immediate heart rate response to standing (table 3.3), all the subgroups demonstrated a statistically significant difference except for those with duration of disease for 5 to 10 years. There were only 13 patients in this subgroup and this small number of patients may not be enough to demonstrate significance. In table 3.3 where significance has been demonstrated in all the subgroups for the heart rate response to standing, it can be seen that in general the p-value obtained demonstrates greater significance in seropositive patients ($p=0.003$) than in seronegative ones ($p=0.01$). Also, a similar situation is seen in patients who had had the disease for longer than 10 years ($p<0.001$) when compared with those who had had it for less than 5 years. The exception to this is the age of the patient where the reverse is seen. Furthermore, the seronegative group of patients was also fairly small and where no statistically significant result has been noted, it may be that the sample size was an influencing factor.

Finally, the analysis correlating the autonomic parameters with age in both the control and rheumatoid groups, and disease duration in the rheumatoid patients was shown in table 3.12. This indicated no consistent pattern although significant p values were noted for Valsalva and R-R interval in the control group. If the age of an individual was an independent variable predictive of autonomic dysfunction, one would expect to see a correlation in the study group. It seems more likely that these are chance findings.

A full analysis of the results obtained and their implications needs to be viewed with the understanding that, just as there are potential sources of error with the clinical methods, there are also limitations to statistical methods applied when processing the results. This may be illustrated with respect to conducting the Student's t-test on the various subgroups and the comparison with controls. In this study each subgroup was compared in turn with the control group, and hence the results obtained were derived from a comparison of two means. As such, none of the inherent errors with multiple t-testing of means were applicable.

In 1965 Bennet and Scott reported a decreased sweating response, in areas of cutaneous sensory disease, in patients who had seropositive rheumatoid arthritis with a peripheral neuropathy. Later, in 1979, Edmonds and coworkers described a relationship between peripheral neuropathy and autonomic dysfunction in patients with rheumatoid arthritis. In order to examine this relationship, this study also focussed on rheumatoid subjects with and without a peripheral neuropathy and looked at whether they were more likely to have autonomic impairment. In general, the results did not show that subjects with rheumatoid arthritis who also had a documented peripheral neuropathy were more likely to have impaired autonomic function tests. Closer inspection of the results (tables 3.6 to 3.10) shows that the rheumatoid patients without a peripheral neuropathy had autonomic impairment. This apparent anomaly can be explained by realising that only 7 rheumatoid patients had a peripheral neuropathy documented in the notes. Six of these had median nerve compression leading to carpal tunnel syndrome, one of whom also had an ulnar nerve entrapment neuropathy. The final patient had a lower lumbar nerve root compression manifesting as sciatica. None of the patients had documented cervical myelopathy or features to suggest that this may have been present. The subgroup that did not have a peripheral neuropathy was larger, comprising 55 patients. It is likely that, due to the smaller patient numbers with a neuropathy, a statistically significant difference could not be demonstrated. It is also possible that a proportion of the subgroup of patients without a peripheral neuropathy documented may have actually had symptoms of a peripheral neuropathy that were undetected at the time of testing.

A study by Toussirot et al. (1993) showed that autonomic nervous system involvement in rheumatoid arthritis subjects was not detectable clinically. In his study, autonomic dysfunction was found not to be related to markers of inflammation. In contrast to this however, the study by Edmonds et al. (1979) found that the mean erythrocyte sedimentation rate was higher in 9 rheumatoid patients with autonomic neuropathy. In the context of the current work there was no correlation detected between erythrocyte sedimentation rate, C-reactive protein or haemoglobin, and the presence of impaired autonomic function tests. Some workers have found diminished autonomic nervous system responsiveness in patients with rheumatoid arthritis (Geenen et al. 1996). This has mainly been manifested as elevated resting heart rates. Piha and Voipio-Pulkki in 1993 also noted elevated resting heart rates in patients with rheumatoid arthritis, but did not observe any correlation between this and the erythrocyte sedimentation rate.

The role of the nervous system in the pathophysiology of rheumatoid arthritis has been hypothesised and as a consequence of this many researchers have been keen to elicit evidence of autonomic impairment in rheumatoid arthritis and other related connective tissue disorders. Some support for this research comes from the fact that rheumatoid arthritis is an inflammatory condition with a symmetrical pattern of joint involvement, with certain joints being more commonly affected. Levine et al. (1985) proposed that this is likely to be due to the greater density of neural innervation in certain joints. It has also been noted that there is a sparing of arthritis in hemiplegic patients on the paretic side (Thompson & Bywaters 1962, Glick 1967). Furthermore there have been parallel observations that in hemiplegic patients with arthritis, fewer rheumatoid erosions and nodules are seen on the paralysed limbs. Neurological impairment is well recognised in extrapyramidal disorders, and autonomic dysfunction is seen in patients with idiopathic Parkinson's disease and Shy Drager's syndrome. Recently Ertan et al. (1999) have reported their observations on the occurrence of an extrapyramidal type rigidity in rheumatoid arthritis. The authors cannot entirely explain the possible mechanisms underlying their observations, but refer to historical suggestions emphasising the role of muscle tone and joint mechanics (Mumenthaler and Schliack 1991). However it is not inconceivable that the autonomic nervous system may be involved at this level. The

innervation of the synovium and tissues related to the joints indicates further support for the fact that the autonomic nervous system may play some part in the pathogenesis of rheumatoid arthritis. Schwab et al. (1997) conducted an anatomical study into the microtopography of the autonomic nerves in the rat knee. They found that in all the tissues of the knee joint, the neuropeptides calcitonin gene related peptide and neurokinin A, were found in high frequency. They were located in perivascular nerve fibres in and around arteries and arterioles. Furthermore, the density of these neuropeptides was enhanced after experimental induction of arthritis in adult rats. Other workers have also found that the local release of neurotransmitters such as substance P in the human synovium may modify the inflammatory response within it (Lotz et al. 1987). Observations such as these provide an exciting insight into the complex relationship that may be involved between the autonomic nervous system and chronic inflammatory joint disease.

The results obtained in this study suggest that there may be some impairment of autonomic function in patients with rheumatoid arthritis. There have been several theories proposed in the literature to try to provide an explanation for why this might be the case. The occurrence of peripheral neuropathy in rheumatoid arthritis patients is thought to be due to a vasculitic process (Scott et al. 1981, Salih et al. 1999). Vasculitic mechanisms that are clinically apparent exist in up to ten percent of patients with rheumatoid arthritis (Peyronnard et al. 1982). There is a wide spectrum of clinically detectable disease ranging from nail fold infarcts to major, albeit rare features, such as mononeuritis multiplex. This variation is thought to reflect the calibre of vessel involved, however it has not always been possible to obtain biopsy confirmation of vasculitis even in clinically active disease. Flipo et al (1994) report positive findings in biopsies taken of labial salivary glands in their control group of rheumatoid arthritis patients without clinically evident vasculitic disease. This indicates a widespread occurrence of subclinical systemic vasculitis. Bekkelund et al. (1996[2]) suggested that there may be a possibility of subclinical vasculitis having an impact on peripheral nerves in patients with rheumatoid arthritis. In the past some researchers have noted that peripheral neuropathy and autonomic neuropathy in rheumatoid arthritis may coexist (Bennett & Scott 1965). It would

therefore not seem to be unreasonable that similar vasculitic mechanisms may account for the occurrence of an autonomic neuropathy in rheumatoid arthritis (Edmonds et al.1979, Tan et al. 1993). This does seem to be an attractive proposition. There are some authorities who advise caution over such a hypothesis. One reason is that there has not been any supportive evidence to demonstrate histologically a vasculitic process in autonomic nerve fibres. Furthermore, no dysautonomia has been reported in vasculitis associated rheumatoid arthritis.

The effects of drugs may be thought to be contributing to the results observed. However, care was taken to exclude any patients who were on drugs that may have interfered with the autonomic nervous system, for example, beta-blockers and tricyclic antidepressants, and also medication that was thought to interfere with heart rate and blood pressure. In order to conduct a clinical study of this nature it was not practical to stop anti-rheumatic medication that rheumatoid subjects may have been taking or even to standardise it. However, it is thought that the majority of drugs used in the treatment of rheumatoid arthritis do not influence the autonomic nervous system function. There have been some reports in the literature that intramuscular gold may be linked to autonomic disturbances such as orthostatic hypotension, tachycardia, sweating, and myokimia, leading to "chorée fibrillaire de Morvan" (Hartfall et al. 1937, Fam et al. 1984). These symptoms were not observed in the participants in this study. A number of the patients in the study were also taking non-steroidal anti-inflammatory drugs. The possible sodium and water retentive effects of this class of drug counteracting the potential fall in systolic blood pressure on standing has also been considered by Toussirot et al. (1999). However it seems unlikely that these drugs would overall contribute a major influence on the circulation, especially as none of the patients studied had overt signs of oedema or heart failure. Also the possible role of steroid therapy needs to be considered. Lioté and Osterland (1994) reported that prednisolone has been shown to abolish the nocturnal fall of blood pressure in patients with systemic lupus erythematosus when compared to the period prior to starting glucocorticoid therapy. It has been suggested that the circadian blood pressure variation may be influenced by the adrenal axis through the autonomic nervous system. An awareness of the

possibility of this type of mechanism operating in rheumatoid arthritis should be considered with caution, however the fact that steroid therapy may operate as a confounding factor cannot be excluded.

Amyloidosis has also been proposed as a possible mechanism in rheumatoid autonomic neuropathy. Secondary amyloidosis is a recognised complication of rheumatoid arthritis (Cohen 1968, Husby 1975). The amyloid deposits that are found in most organs of the body comprise of amyloid P protein combined with a glycoprotein. Any organ system can be involved in amyloidosis complicating rheumatoid arthritis, and patients can present with renal failure, hepatosplenomegaly, cardiac abnormalities and gastrointestinal involvement. The most common mode of presentation is with proteinuria. Rarely, the peripheral nerves can be involved (Gertz 1992). Autonomic neuropathy has been reported in primary amyloidosis (AL) in approximately 15% of patients (Kyle and Greipp 1983). This is a very rare complication in secondary amyloidosis (AA). McGill et al. (1986) presented a case report of a 55 year old patient with rheumatoid arthritis and secondary amyloidosis (AA) where symptoms of autonomic neuropathy predominated in the final stages of the illness. These were mainly manifestations of postural hypotension. Although this is an interesting mechanism, it is rare and is unlikely to explain the frequency of autonomic impairment in rheumatoid arthritis patients observed in the literature and in the study presented herein. Clinical features consistent with amyloidosis were not noted in the rheumatoid subjects in this study.

Autonomic neuropathies in rheumatoid arthritis could be related to ageing. This seems unlikely, however, as a comparison in this study was made between rheumatoid subjects and controls over a similar age distribution. The changes of impaired autonomic function were noted despite taking age into account. In addition, Vassallo et al. (1997) showed that autonomic function, which was impaired following pneumonia, improved at follow up in elderly patients. This effect was observed independent of ageing. They also observed that prolonged bed rest in the pneumonia patients could not account for the observed difference in impaired autonomic function as they controlled for this with a group of patients who had been immobilised following neck of femur fracture. Interestingly, Piha et al. (1993) suggested that elevated resting heart

rate in rheumatoid patients, which has been thought to be secondary to diminished autonomic nervous system responsiveness, may be accounted for by physical deconditioning. Perry et al. (1989) found that baseline heart rate was elevated in patients with rheumatoid arthritis. They felt that this was due to reduced peripheral parasympathetic tone, as have other researchers (Leden et al. 1983). Another possibility is that the tachycardia seen is related to the anaemia often seen in these patients. Piha et al. (1993) could find no evidence between haemoglobin levels and resting heart rates in their study group of rheumatoids. They did comment, however, that they were unable to exclude the effects of anaemia on heart rate in patients with acute inflammatory arthritis. Geenen et al. (1996) suggests that the autonomic nervous system down regulates in patients with disease of recent onset. This would seem to refute the view that limited physical activity in rheumatoid arthritis patients contributes to observed autonomic impairment. They argue that other pathophysiological mechanisms probably contribute, and the impaired autonomic function that is observed cannot be explained by the long-term functional consequences of the disease alone.

Cardiovascular abnormalities such as pericarditis and myocarditis may also affect patients with rheumatoid arthritis. It is debatable whether these abnormalities are likely to influence results obtained from autonomic function tests based on the cardiovascular reflexes. Furthermore, Corrao et al. (1996) investigated left ventricular filling abnormalities in patients with rheumatoid arthritis without clinically evident disease using echo-Doppler techniques. They suggest that structural left ventricular changes could be responsible for these abnormalities. There have also been reports in the literature of cardiac arrhythmias and cardiac conduction defects in rheumatoid patients secondary to mononuclear cell infiltration into the myocardium. Tlustochowicz et al. (1995) investigated these problems with 24 hour ECG monitoring but found no difference in observed cardiac arrhythmias when compared with their control group. Although it is important to consider cardiac abnormalities as a possible confounding factor, it is unlikely that mild abnormalities may lead to autonomic dysfunction.

Abnormal autonomic dysfunction has been reported in other connective

tissue diseases such as systemic lupus erythematosus (Lioté and Osterland 1994), systemic sclerosis (Klimiuk et al. 1988), Sjögren's syndrome (Andonopoulos et al. 1998) and mixed connective tissue disease (Edelman et al. 1981). It has been postulated that autonomic impairment could be associated with connective tissue disorders through an immunological mechanism. Appenzeller et al. (1965) first induced a dysautonomia in animal models by injection of human sympathetic ganglion antigens, leading to the isolation of circulating antibodies to the autonomic nervous system. Maule et al. (1997) lend further support to this by suggesting that autonomic nervous function can be impaired in patients with connective tissue disorders. They report on the presence of autoantibodies directed against autonomic nervous system structures which might be implicated in the pathogenesis of autonomic dysfunction in these diseases. It is known that lymphocytes, monocytes and granulocytes possess receptors for catecholamines, especially the β2 subclass (Bisphoric et al. 1980). Felten et al. (1987) have demonstrated the close proximity of the nervous system and the immune system. Lymphatic tissues such as the spleen, lymph nodes and the thymus are richly innervated by sympathetic neural connections. There has been an accumulation of evidence to show that immune reactions are partly under the control of the sympathetic nervous system. Baerwald et al. 1997 report that in patients with rheumatoid arthritis, β-adrenergic receptors in synovial fluid lymphocytes were significantly reduced when compared to peripheral blood lymphocytes. They also found a reduction in β2 receptors on peripheral blood lymphocytes of the CD8 class in rheumatoid arthritis when compared to healthy donors. These were correlated with catecholamine levels and subsequently systemic inflammatory activity in patients with rheumatoid arthritis. The authors suggested that this supports the theory that impaired control of the immune response by the autonomic nervous system may contribute to the pathogenesis of rheumatoid arthritis. Kuis et al. (1996) explored the possible role of the immune system and the autonomic nervous system in juvenile chronic arthritis. They proposed a mechanism whereby lymphokines lead to an increased noradrenergic turnover in the brain, leading to a suboptimal immune response to dampen down ongoing inflammation in juvenile chronic arthritis. Steiner et al. (1999) suggest

that cytokines are produced by a subpopulation of T cells in rheumatoid synovial tissue leading to activated T cells playing an important role in the pathophysiology of rheumatoid arthritis. It may be that the immune system acts in concert with the autonomic system to contribute to the ongoing inflammatory disease process in rheumatoid arthritis.

Whether autonomic dysfunction occurs as an initiating event in the pathophysiology of rheumatoid arthritis or even as a consequence of a chain of events, requires further elucidation.

The questions posed in this study have been answered in that there does seem to be impairment of autonomic function in rheumatoid arthritis. This may not be evident clinically but it is related to features such as rheumatoid factor status, disease duration and the age of the patient. The mechanisms involved are complex but an immune mediated process seems likely. The importance of this can be explained by referring to work done in diabetics who are known to be at an increased risk of cardiorespiratory arrest during anaesthesia, where an autonomic neuropathy has been noted (Ewing et al. 1976). It may be that similar risks exist in patients with rheumatoid arthritis, and autonomic neuropathy may be an additional factor contributing to the increased morbidity and mortality in a patient group suffering from a multisystem disabling disease.

A review of the literature indicates that some rheumatoid patients with an autonomic neuropathy may have severe clinical symptoms, especially hypotension. These may be factors to consider in the management of these patients especially with respect to drug therapy.

Further work could be directed at discovering whether the intensity of inflammation plays a part in the severity of autonomic impairment, and if so what markers of this inflammation may be useful clinically. Further research directed at management strategies that target the immune system and autonomic nervous system concurrently remain a future aim.

Chapter Five

Appendix

Table 5.1 Age and sex distribution of the control subjects.

Subject	Sex	Age			Subject	Sex	Age
1	M	82			**22**	M	44
2	F	26			**23**	F	58
3	M	61			**24**	M	59
4	F	71			**25**	F	59
5	F	25			**26**	F	48
6	M	55			**27**	F	64
7	M	29			**28**	F	80
8	F	43			**29**	F	34
9	M	63			**30**	F	53
10	F	50			**31**	M	53
11	M	25			**32**	M	27
12	M	54			**33**	F	66
13	M	36			**34**	M	40
14	M	37			**35**	F	76
15	F	54			**36**	F	26
16	F	29			**37**	M	63
17	M	27			**38**	F	50
18	F	60			**39**	F	22
19	M	41			**40**	M	36
20	M	25			**41**	F	54
21	M	61					

Table 5.2 Valsalva ratio in control subjects.

Subject	Reading 1			Reading 2			Reading 3			Mean
	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Ratio
1	0.88	0.76	1.16	0.84	0.8	1.05	0.8	0.76	1.05	**1.09**
2	0.72	0.62	1.16	0.84	0.66	1.27	0.96	0.76	1.26	**1.23**
3	0.84	0.76	1.11	0.76	0.66	1.15	0.72	0.74	0.97	**1.08**
4	1.02	0.98	1.04	0.94	0.98	0.96	0.94	0.92	1.02	**1**
5	0.7	0.72	0.97	0.76	0.68	1.12	0.8	0.6	1.33	**1.14**
6	0.72	0.79	0.91	0.88	0.62	1.42	0.8	0.7	1.14	**1.16**
7	0.62	0.58	1.07	0.7	0.54	1.3	0.7	0.56	1.25	**1.21**
8	0.9	0.94	0.96	0.8	0.8	1	0.9	0.78	1.15	**1.04**
9	0.76	0.64	1.19	0.8	0.74	1.08	0.84	0.64	1.31	**1.19**
10	0.72	0.72	1	0.76	0.68	1.12	0.7	0.62	1.13	**1.08**
11	1.12	0.8	1.4	0.92	1	0.92	0.94	0.76	1.24	**1.19**
12	0.74	0.68	1.09	0.7	0.62	1.13	0.68	0.64	1.06	**1.09**
13	1.36	0.58	2.34	0.68	0.64	1.06	1.08	0.6	1.8	**1.73**
14	0.82	0.86	0.95	0.76	0.7	1.09	0.8	0.66	1.21	**1.08**
15	0.76	0.72	1.06	0.8	0.72	1.11	0.64	0.7	0.91	**1.03**
16	0.8	0.8	1	0.78	0.72	1.08	0.8	0.72	1.11	**1.06**
17	1.28	0.76	1.68	1.08	0.8	1.35	0.84	0.88	0.95	**1.33**
18	0.82	0.8	1.03	0.8	0.8	1	0.84	0.82	1.02	**1.02**
19	0.8	0.66	1.21	0.84	0.58	1.45	0.86	0.6	1.43	**1.36**
20	0.8	0.8	1	0.9	0.7	1.29	0.92	0.74	1.24	**1.18**
21	0.96	0.88	1.09	0.9	0.88	1.02	0.88	0.84	1.05	**1.05**
22	0.72	0.72	1	0.72	0.72	1	0.74	0.64	1.16	**1.05**
23	0.96	0.74	1.3	0.8	0.72	1.11	0.76	0.68	1.12	**1.18**
24	0.8	0.8	1	1.04	0.8	1.3	0.84	0.8	1.05	**1.12**
25	0.84	0.72	1.17	0.76	0.74	1.03	0.76	0.68	1.12	**1.11**
26	0.7	0.62	1.13	0.7	0.7	1	0.66	0.68	0.97	**1.03**
27	0.9	0.82	1.1	0.94	0.76	1.24	0.82	0.78	1.05	**1.13**
28	0.82	0.82	1	0.78	0.76	1.03	0.78	0.78	1	**1.01**
29	0.74	0.8	0.93	0.92	0.64	1.44	0.88	0.72	1.22	**1.2**
30	0.76	0.74	1.03	0.7	0.72	1.03	0.76	0.72	1.06	**1.04**
31	0.84	0.72	1.17	0.8	0.8	1	0.8	0.78	1.03	**1.07**
32	0.96	0.9	1.07	1.14	0.96	1.19	1.28	0.76	1.68	**1.31**
33	0.8	0.82	0.98	0.8	0.76	1.05	0.76	0.8	0.95	**0.99**
34	0.76	0.68	1.12	0.76	0.5	1.52	0.96	0.5	1.92	**1.52**
35	1.04	0.72	1.44	1	0.84	1.19	0.88	0.84	1.05	**1.23**
36	0.76	0.58	1.31	1	0.56	1.79	0.78	0.6	1.3	**1.47**
37	0.5	0.48	1.04	0.56	0.56	1	0.56	0.56	1	**1.01**
38	0.8	0.74	1.08	0.76	0.74	1.03	0.78	0.7	1.11	**1.07**
39	1.16	0.78	1.49	0.92	0.72	1.28	0.8	0.7	1.14	**1.3**
40	0.92	0.92	1	1	0.68	1.47	0.94	0.84	1.12	**1.2**
41	1	1.08	0.93	0.92	0.74	1.24	1.28	0.88	1.45	**1.21**

Table 5.3 R-R interval in control subjects.

Subject	Reading 1			Reading 2			Reading 3			Reading 4			Reading 5			Reading 6			Mean
	Max	Min	Diff.	Max	Min	Diff.	Max	Min	Diff.	Max	Min	Diff.	Max	Min	Diff.	Max	Min	Diff.	
	(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			
1	72	67	5	70	59	11	71	68	3	70	68	2	72	69	3	75	65	10	**6**
2	94	71	23	98	68	30	88	67	21	96	66	30	98	70	28	96	75	21	**26**
3	76	73	3	78	73	5	79	78	1	80	77	3	84	78	6	93	78	15	**6**
4	64	62	2	63	60	3	62	61	1	64	61	3	62	62	0	61	60	1	**2**
5	71	64	7	77	68	9	83	69	14	76	72	4	79	76	3	80	75	5	**7**
6	81	59	22	78	68	10	75	60	15	84	65	19	88	80	8	88	67	21	**16**
7	95	82	13	96	86	10	96	81	15	94	66	28	100	78	22	97	88	9	**16**
8	77	64	13	76	67	9	74	61	13	70	54	16	72	55	17	74	62	12	**13**
9	80	68	12	70	65	5	72	70	2	80	72	8	84	63	21	84	63	21	**12**
10	86	80	6	83	77	6	78	69	9	75	72	3	78	72	6	76	74	2	**5**
11	69	54	15	63	54	9	71	66	5	65	57	8	74	62	12	63	57	6	**9**
12	94	88	6	94	86	8	93	86	7	94	89	5	96	94	2	98	92	6	**6**
13	94	78	16	93	78	15	98	86	12	100	93	7	103	96	7	98	92	6	**11**
14	69	60	9	79	58	21	77	59	18	78	61	17	72	60	12	72	67	5	**14**
15	80	73	7	84	78	6	82	71	11	80	73	7	80	73	7	80	72	8	**8**
16	84	67	17	83	68	15	86	78	8	90	70	20	88	78	10	90	80	10	**13**
17	69	57	12	70	61	9	66	57	9	72	57	15	62	57	5	72	66	6	**9**
18	75	72	3	74	71	3	72	68	4	75	71	4	75	73	2	76	72	4	**3**
19	86	72	14	82	68	14	78	63	15	80	67	13	78	65	13	832	68	15	**14**
20	80	70	10	81	68	13	81	71	10	84	66	18	81	65	16	81	68	13	**13**
21	67	65	2	68	66	2	67	66	1	67	65	2	67	66	1	68	66	2	**2**
22	86	81	5	92	86	6	89	82	7	86	80	6	90	88	2	92	88	4	**5**
23	79	74	5	78	74	4	77	72	5	78	73	5	77	73	4	80	75	5	**5**
24	71	61	10	70	59	11	68	65	3	100	70	30	90	64	26	74	64	10	**15**
25	86	76	10	84	70	14	85	67	18	84	72	12	88	72	16	88	77	11	**14**
26	92	82	10	88	82	6	90	80	10	89	80	9	91	84	7	90	82	8	**10**
27	84	57	27	64	60	4	67	61	6	69	64	5	69	63	6	70	64	6	**9**
28	77	73	4	74	72	2	74	72	2	74	72	2	73	71	3	76	74	2	**3**
29	80	71	9	74	63	11	73	62	11	74	65	9	75	64	11	72	63	9	**10**
30	79	66	13	72	64	8	70	63	7	67	54	13	71	63	8	72	63	9	**10**
31	80	76	4	77	76	1	76	72	4	78	72	6	75	71	4	78	68	10	**5**
32	83	50	23	72	56	16	60	49	11	74	62	12	64	46	18	76	52	24	**18**
33	81	71	10	76	69	7	76	70	6	78	72	6	77	72	5	76	71	5	**7**
34	105	77	28	90	74	16	88	66	22	95	68	27	103	76	27	95	82	13	**22**
35	80	63	17	79	62	17	80	61	19	80	62	18	70	68	2	80	62	18	**15**
36	101	81	20	88	79	9	85	73	12	88	79	9	88	76	12	88	77	11	**12**
37	110	88	22	99	82	17	100	84	16	110	88	22	110	98	12	110	102	8	**16**
38	79	73	6	80	76	4	80	76	4	82	75	7	82	80	2	82	76	6	**5**
39	69	50	19	81	71	10	86	76	10	86	79	7	84	76	8	76	64	12	**11**
40	75	65	10	72	60	12	65	58	7	69	60	9	71	59	12	73	61	12	**10**
41	60	49	11	63	48	15	62	48	14	67	54	14	67	56	11	68	60	8	**12**

Table 5.4 30:15 ratio in control subjects.

Subject	30th beat (sec)	15th beat (sec)	Ratio
1	0.8	0.76	1.05
2	0.76	0.68	1.12
3	0.8	0.76	1.05
4	0.88	0.88	1
5	0.82	0.76	1.08
6	0.82	0.68	1.21
7	0.62	0.54	1.15
8	0.68	0.66	1.03
9	0.84	0.74	1.14
10	0.76	0.68	1.12
11	0.7	0.58	1.21
12	0.64	0.58	1.1
13	0.72	0.68	1.06
14	0.84	0.7	1.2
15	0.72	0.68	1.06
16	0.76	0.56	1.36
17	0.82	0.66	1.24
18	0.76	0.68	1.12
19	0.8	0.7	1.14
20	0.7	0.7	1
21	0.9	0.84	1.07
22	0.7	0.6	1.17
23	0.8	0.74	1.08
24	0.84	0.8	1.05
25	0.68	0.6	1.13
26	0.64	0.58	1.1
27	0.96	0.86	1.12
28	0.72	0.7	1.03
29	0.84	0.7	1.2
30	0.78	0.64	1.22
31	0.78	0.6	1.3
32	0.92	0.88	1.04
33	0.68	0.6	1.13
34	0.64	0.52	1.23
35	0.96	0.64	1.5
36	0.68	0.58	1.17
37	0.72	0.48	1.5
38	0.72	0.68	1.06
39	1.1	0.72	1.53
40	0.86	0.68	1.26
41	1.24	1	1.24

Table 5.5 Rise in diastolic blood pressure in response to sustained handgrip in control subjects.

Subject	Mean Baseline	Reading 1	Reading 2	Reading 3	**Max - Mean**
	(mmHg)		(mmHg)		(mmHg)
1	90	90	100	115	**25**
2	62	70	80	88	**26**
3	90	100	108	110	**20**
4	80	90	94	98	**18**
5	80	80	90	90	**10**
6	70	80	92	98	**28**
7	80	90	90	100	**20**
8	90	98	98	98	**8**
9	60	70	70	70	**10**
10	80	80	100	100	**20**
11	69	89	89	92	**23**
12	95	110	120	128	**33**
13	80	82	90	98	**18**
14	60	70	74	80	**20**
15	80	80	82	84	**4**
16	70	80	80	80	**10**
17	78	80	90	100	**22**
18	70	90	90	92	**22**
19	80	92	98	102	**22**
20	60	80	80	84	**24**
21	80	80	92	92	**12**
22	70	90	92	96	**26**
23	70	80	90	95	**25**
24	80	90	100	100	**20**
25	70	80	80	80	**10**
26	90	98	98	100	**10**
27	95	95	100	102	**7**
28	70	74	74	76	**6**
29	70	74	74	74	**4**
30	70	80	90	90	**20**
31	80	90	90	94	**14**
32	60	80	84	86	**26**
33	90	94	96	98	**8**
34	56	64	76	80	**24**
35	70	85	90	90	**20**
36	72	82	82	82	**10**
37	80	90	100	108	**18**
38	80	84	86	88	**8**
39	60	65	70	80	**20**
40	88	100	104	110	**22**
41	80	96	100	100	**20**

Table 5.6 Fall in systolic blood pressure on standing in control subjects.

Subject	Reading 1			Reading 2			Reading 3			Mean
	Lying	Standing	Drop	Lying	Standing	Drop	Lying	Standing	Drop	
	(mmHg)			(mmHg)			(mmHg)			(mmHg)
1	140	150	-10	170	170	0	170	165	5	**-2**
2	115	115	0	114	102	12	104	114	-10	**1**
3	130	130	0	130	135	-5	135	140	-5	**-3**
4	150	150	0	155	160	-5	155	155	0	**-2**
5	130	140	-10	130	140	-10	130	140	-10	**-10**
6	120	125	-5	120	130	-10	122	130	-8	**-8**
7	130	140	-10	13	140	-10	130	140	-10	**-10**
8	130	130	0	130	130	0	130	130	0	**0**
9	150	155	-5	150	150	0	150	155	-5	**-3**
10	150	150	0	150	150	0	150	150	0	**0**
11	118	110	8	116	104	12	114	110	4	**8**
12	150	150	0	142	142	0	142	145	-3	**-1**
13	140	124	16	128	118	10	130	118	12	**13**
14	110	120	-10	120	118	2	108	120	-12	**-7**
15	120	130	-10	130	130	0	130	130	0	**3**
16	120	120	0	120	120	0	120	115	5	**2**
17	120	122	-2	118	119	-1	118	120	-2	**-2**
18	130	130	0	130	130	0	130	130	0	**0**
19	140	150	-10	138	148	-10	140	142	-2	**-7**
20	114	120	-6	120	118	2	111	130	-19	**-8**
21	160	158	2	162	162	0	165	170	-5	**-1**
22	104	105	-1	104	102	2	102	104	-2	**0**
23	120	115	5	120	110	10	120	110	10	**8**
24	130	130	0	130	130	0	130	130	0	**0**
25	130	130	0	128	130	-2	130	130	0	**-1**
26	130	130	0	130	130	0	130	130	0	**0**
27	150	150	0	160	160	0	160	160	0	**0**
28	130	130	0	130	140	-10	135	140	-5	**-5**
29	100	110	-10	90	110	-20	100	110	-10	**-13**
30	110	110	0	110	110	0	110	110	0	**0**
31	150	150	0	152	150	2	148	150	-2	**0**
32	115	120	-5	119	122	-3	116	120	-4	**-4**
33	150	140	10	140	150	-10	140	160	-20	**-7**
34	112	110	2	110	110	0	111	110	1	**1**
35	130	130	0	130	130	0	130	130	0	**0**
36	100	90	10	90	100	-10	100	90	10	**3**
37	150	150	0	150	152	-2	152	155	-3	**-2**
38	140	135	5	140	135	5	140	130	10	**7**
39	120	110	10	120	110	10	110	100	10	**10**
40	140	14	0	138	138	0	140	135	5	**2**
41	162	158	4	160	162	-2	160	160	0	**1**

Table 5.7 Age and sex distribution of subjects with rheumatoid arthritis.

Subject	Sex	Age			Subject	Sex	Age
1	F	51			**32**	F	38
2	M	75			**33**	F	84
3	F	42			**34**	M	59
4	M	77			**35**	F	49
5	F	43			**36**	M	73
6	F	50			**37**	F	72
7	M	74			**38**	F	82
8	F	76			**39**	M	78
9	F	70			**40**	F	73
10	F	74			**41**	M	73
11	F	62			**42**	F	54
12	M	58			**43**	M	73
13	F	52			**44**	M	74
14	F	77			**45**	F	50
15	M	66			**46**	F	66
16	F	42			**47**	F	70
17	F	50			**48**	F	53
18	M	69			**49**	M	76
19	M	80			**50**	M	72
20	F	60			**51**	M	71
21	F	48			**52**	F	70
22	F	63			**53**	F	47
23	M	66			**54**	F	67
24	F	60			**55**	F	45
25	M	72			**56**	M	73
26	F	59			**57**	M	53
27	F	78			**58**	F	54
28	F	72			**59**	M	70
29	M	66			**60**	M	65
30	F	43			**61**	F	38
31	F	61			**62**	F	59

Table 5.8 Valsalva ratio in rheumatoid subjects

Subject	Reading 1			Reading 2			Reading 3			Mean
	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Ratio
1	0.88	0.74	1.19	0.92	0.72	1.28	0.76	0.64	1.19	**1.22**
2	0.78	0.78	1	0.78	0.76	1.03	0.76	0.75	1.01	**1.01**
3	0.8	0.76	1.05	0.8	0.8	1	0.76	0.76	1	**1.02**
4	0.9	0.88	1.02	0.94	0.82	1.15	0.86	0.9	0.96	**1.04**
5	0.84	0.64	1.31	0.88	0.64	1.38	0.88	0.56	1.57	**1.42**
6	0.56	0.56	1	0.6	0.6	1	0.76	0.56	1.36	**1.12**
7	0.74	0.72	1.03	0.84	0.72	1.17	0.8	0.76	1.05	**1.08**
8	0.8	0.76	1.05	0.9	0.6	1.5	0.84	0.78	1.08	**1.21**
9	0.74	0.74	1	0.7	0.72	0.97	0.7	0.68	1.03	**1**
10	0.92	0.88	1.05	0.92	0.92	1	0.92	0.92	1	**1.02**
11	0.8	0.76	1.05	0.82	0.82	1.12	0.78	0.72	1.08	**1.08**
12	0.68	0.68	1	0.72	0.66	1.09	0.72	0.76	0.95	**1.01**
13	0.8	0.84	0.95	0.8	0.78	1.03	0.76	0.7	1.09	**1.02**
14	0.74	0.7	1.06	0.72	0.68	1.06	0.8	0.64	1.25	**1.12**
15	0.8	0.64	1.25	0.84	0.68	1.24	0.84	0.64	1.31	**1.27**
16	0.76	0.52	1.46	0.76	0.56	1.36	0.68	0.52	1.31	**1.38**
17	0.48	0.44	1.09	0.48	0.44	1.09	0.46	0.48	0.96	**1.05**
18	0.82	0.8	1.03	0.82	0.8	1.03	0.76	0.78	0.97	**1**
19	1.2	1.16	1.03	1.2	1.2	1	1.24	1.16	1.07	**1.03**
20	0.9	0.8	1.13	0.84	0.7	1.2	0.76	0.76	1	**1.11**
21	0.8	0.8	1	0.8	0.82	0.98	0.76	0.76	1	**0.99**
22	0.72	0.64	1.13	0.76	0.6	1.27	0.68	0.64	1.06	**1.15**
23	0.8	0.84	0.95	0.82	0.9	0.91	0.8	0.78	1.03	**0.96**
24	0.82	0.8	1.03	0.84	0.82	1.02	0.82	0.8	1.03	**1.03**
25	1	0.96	1.04	1	0.98	1.02	0.96	0.96	1	**1.02**
26	0.98	0.96	1.02	0.96	0.92	1.04	0.98	0.92	1.07	**1.04**
27	0.68	0.64	1.06	0.68	0.64	1.06	0.66	0.66	1	**1.04**
28	0.94	0.88	1.07	0.9	0.88	1.02	0.86	0.84	1.02	**1.04**
29	0.72	0.76	0.95	0.72	0.68	1.06	0.7	0.68	1.03	**1.01**
30	0.68	0.72	0.94	0.72	0.84	0.86	0.64	0.6	1.07	**0.96**
31	0.8	0.82	0.98	0.8	0.74	1.08	0.84	0.64	1.31	**1.12**
32	0.78	0.64	1.22	0.82	0.64	1.28	0.72	0.64	1.13	**1.21**
33	0.82	0.84	0.98	0.86	0.84	1.02	0.82	0.82	1	**1**
34	0.78	0.66	1.18	0.72	0.72	1	0.68	0.68	1	**1.06**
35	0.76	0.8	0.95	0.84	0.72	1.17	0.8	0.76	1.05	**1.06**
36	0.76	0.56	1.36	0.72	0.56	1.29	0.72	0.64	1.13	**1.26**
37	1.04	0.96	1.08	1	0.95	1.05	0.94	0.94	1	**1.04**
38	1	0.84	1.19	0.96	0.96	1	0.96	0.96	1	**1.06**
39	1.16	0.96	1.2	1.24	1.06	1.17	1.2	1.36	0.88	**1.08**
40	0.92	0.92	1	0.88	0.88	1	0.82	0.84	0.98	**0.99**
41	1.24	0.76	1.63	1.16	0.84	1.38	1.12	0.8	1.4	**1.47**
42	0.72	0.68	1.06	0.72	0.7	1.03	0.7	0.64	1.09	**1.06**
43	0.88	0.72	1.22	0.84	0.8	1.05	0.9	0.84	1.07	**1.11**
44	0.92	0.84	1.1	0.92	0.8	1.15	0.88	0.92	0.96	**1.07**
45	0.78	0.7	1.11	0.78	0.76	1.03	0.74	0.74	1	**1.05**

Table 5.8 Continued.

Subject	Reading 1			Reading 2			Reading 3			Mean
	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Longest RR (secs)	Shortest RR (secs)	Ratio	Ratio
46	0.64	0.64	1	0.64	0.64	1	0.62	0.64	0.97	**0.99**
47	0.8	0.72	1.11	0.86	0.66	1.3	0.84	0.66	1.27	**1.23**
48	0.88	0.74	1.19	0.84	0.72	1.17	0.84	0.78	1.08	**1.15**
49	0.94	0.96	0.98	1	0.84	1.19	1	0.86	1.16	**1.11**
50	0.96	0.98	0.98	0.94	0.96	0.98	0.98	0.9	1.09	**1.02**
51	0.8	0.74	1.08	0.76	0.74	1.03	0.76	0.74	1.03	**1.05**
52	0.76	0.72	1.06	0.76	0.72	1.06	0.76	0.76	1	**1.04**
53	0.68	0.66	1.03	0.88	0.66	1.29	0.8	0.74	1.08	**1.13**
54	0.96	0.5	1.92	0.88	0.68	1.29	0.8	0.8	1	**1.4**
55	0.8	0.78	1.03	0.92	0.68	1.35	0.96	0.76	1.26	**1.21**
56	0.42	0.38	1.11	0.4	0.36	1.11	0.4	0.36	1.11	**1.11**
57	0.76	0.6	1.27	0.56	0.52	1.08	0.7	0.4	1.75	**1.37**
58	0.68	0.56	1.21	0.64	0.58	1.1	0.6	0.58	1.03	**1.11**
59	0.76	0.8	0.95	0.8	0.7	1.14	0.82	0.68	1.21	**1.1**
60	0.8	0.76	1.05	0.78	0.72	1.08	0.72	0.7	1.03	**1.05**
61	0.76	0.72	1.06	0.8	0.76	1.05	0.84	0.78	1.08	**1.06**
62	0.78	0.76	1.03	0.72	0.68	1.06	0.6	0.64	0.94	**1.01**

Table 5.9 R-R interval in rheumatoid subjects.

Subject	Reading 1			Reading 2			Reading 3			Reading 4			Reading 5			Reading 6			Mean
	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	
	(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			
1	80	59	21	79	63	16	82	69	13	82	68	14	82	38	14	84	64	20	**16**
2	81	75	6	77	73	4	75	72	3	76	72	4	75	74	1	76	74	2	**3**
3	82	74	8	71	68	3	75	63	12	76	63	13	69	65	4	75	65	10	**8**
4	77	62	15	66	64	2	66	61	5	69	67	2	69	68	1	68	66	2	**5**
5	94	82	12	98	74	24	96	74	22	96	71	25	90	71	19	90	75	15	**20**
6	86	82	4	88	80	8	86	82	4	110	75	35	92	80	12	94	70	24	**15**
7	80	75	5	80	72	8	77	72	5	79	75	4	80	75	5	80	73	7	**6**
8	95	72	23	90	69	21	92	80	12	81	78	3	86	74	12	90	68	22	**16**
9	84	79	5	80	78	2	80	77	3	79	77	2	79	77	2	80	77	3	**3**
10	57	52	5	55	54	1	57	53	4	64	56	8	56	54	2	56	55	1	**4**
11	78	71	7	76	71	5	80	68	12	77	62	15	80	60	20	80	62	18	**13**
12	88	83	5	88	84	4	88	82	6	88	84	4	90	84	6	90	86	4	**5**
13	75	63	12	75	63	12	79	70	9	78	70	8	77	66	11	76	70	6	**10**
14	86	76	10	84	79	5	84	80	4	86	83	3	94	80	14	88	84	4	**7**
15	78	70	8	79	67	12	82	67	15	78	71	7	80	71	9	78	69	9	**10**
16	105	94	11	110	98	12	110	100	10	105	94	11	105	100	5	105	98	7	**9**
17	130	125	5	130	127	3	135	130	5	135	130	5	135	130	5	137	130	7	**5**
18	77	73	4	77	74	3	74	72	2	71	69	2	80	69	11	75	71	4	**4**
19	53	50	3	53	49	4	54	51	3	55	53	2	56	55	1	56	55	1	**2**
20	76	66	10	73	69	4	76	72	4	75	69	6	74	69	5	75	73	2	**5**
21	73	70	3	74	70	4	73	71	2	75	72	3	77	73	4	80	75	5	**5**
22	88	84	4	86	82	4	90	84	6	88	84	4	92	82	10	92	84	8	**6**
23	67	63	4	68	63	5	71	68	3	71	69	2	68	65	3	77	71	6	**4**
24	76	66	10	72	66	6	73	66	7	71	66	5	70	65	5	71	65	6	**7**
25	60	53	7	56	51	5	60	53	7	61	55	6	59	56	3	60	57	3	**5**
26	61	57	4	60	55	5	59	56	3	59	57	2	60	57	3	60	58	2	**3**
27	84	79	5	86	81	5	87	82	5	87	84	3	88	82	6	88	84	4	**5**
28	71	66	5	73	63	10	70	68	2	71	64	7	71	66	5	72	68	4	**6**
29	86	76	10	84	77	7	88	82	6	88	82	6	90	83	7	90	84	6	**7**
30	94	88	6	90	86	4	92	90	2	92	86	6	92	88	4	86	84	2	**4**
31	86	74	12	78	72	6	79	75	4	79	73	6	79	77	2	83	75	8	**6**
32	90	79	11	84	79	5	83	75	8	79	71	8	83	75	8	85	74	11	**9**
33	71	68	3	70	67	3	72	70	2	74	71	3	75	73	2	75	74	1	**2**
34	92	88	4	88	84	4	86	82	4	90	84	6	94	92	2	92	86	6	**4**
35	72	67	5	75	64	11	67	61	6	67	61	6	67	60	7	67	62	5	**7**
36	110	76	34	105	76	29	115	75	40	86	78	8	90	86	4	90	88	2	**20**
37	59	54	5	55	52	3	59	58	1	66	54	12	61	57	4	61	57	4	**5**
38	64	62	2	62	61	1	61	60	1	62	61	1	67	64	3	70	59	11	**3**
39	58	52	6	50	44	6	58	46	12	44	41	3	54	50	4	46	40	6	**6**
40	79	69	10	68	64	4	72	67	5	72	68	4	74	70	4	74	69	5	**5**
41	69	44	25	75	58	17	75	50	25	75	60	15	72	50	22	73	50	23	**21**
42	86	76	10	80	77	3	80	77	3	80	77	3	80	78	2	82	78	4	**4**
43	72	64	8	70	61	9	67	64	3	67	63	4	72	66	6	74	64	10	**7**
44	66	59	7	68	57	11	64	57	7	64	56	8	65	57	8	64	59	5	**8**
45	86	78	8	81	77	4	82	78	4	82	79	3	80	79	1	84	80	4	**4**

Table 5.9 Continued.

Subject	Reading 1			Reading 2			Reading 3			Reading 4			Reading 5			Reading 6			Mean
	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	Max	Min	Diff	
	(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			(beats/min)			
46	85	79	6	86	80	6	88	83	5	88	82	6	88	84	4	90	86	4	**5**
47	83	77	6	82	72	10	84	77	7	84	75	9	82	75	7	80	76	4	**7**
48	78	62	16	80	61	19	81	67	14	72	64	8	77	68	9	77	67	10	**12.7**
49	76	68	8	72	61	11	79	70	9	90	75	15	82	76	6	78	74	4	**9**
50	65	60	5	64	61	3	65	61	4	66	63	3	66	63	3	66	62	4	**4**
51	82	77	5	82	78	4	82	80	2	84	80	4	84	81	3	84	82	2	**3**
52	80	72	8	78	71	7	78	74	4	80	75	5	80	77	3	80	75	5	**5**
53	88	76	12	86	82	4	86	82	4	87	83	4	90	88	2	90	87	3	**5**
54	76	70	6	75	66	9	70	97	3	74	66	8	75	66	9	76	66	10	**8**
55	88	63	25	84	62	22	84	63	21	88	62	26	86	64	22	88	71	17	**22**
56	160	145	15	160	145	15	150	145	5	150	145	5	160	145	15	150	145	5	**10**
57	98	80	18	94	72	22	98	78	20	110	84	26	105	88	17	98	84	14	**20**
58	102	94	8	98	90	8	96	90	6	98	90	8	100	94	6	98	94	4	**7**
59	88	69	19	75	69	6	75	67	8	81	68	13	81	71	10	85	70	15	**12**
60	80	77	3	80	77	3	78	76	2	78	73	5	79	74	5	80	76	4	**4**
61	78	75	3	77	72	5	78	74	4	78	76	2	80	77	3	79	77	2	**3**
62	79	69	10	73	68	5	72	67	5	72	68	4	75	72	3	73	70	3	**5**

Table 5.10 30:15 ratio in rheumatoid subjects.

Subject	30^{th} beat (secs)	15^{th} beat (secs)	Ratio
1	0.7	0.64	**1.09**
2	0.74	0.72	**1.03**
3	0.8	0.76	**1.05**
4	0.86	0.88	**0.98**
5	0.72	0.68	**1.06**
6	0.56	0.56	**1**
7	0.76	0.74	**1.03**
8	0.72	0.72	**1**
9	0.7	0.72	**0.97**
10	1	0.56	**1.79**
11	0.74	0.68	**1.09**
12	0.68	0.68	**1**
13	0.68	0.68	**1**
14	0.66	0.64	**1.03**
15	0.76	0.68	**1.12**
16	0.56	0.5	**1.12**
17	0.44	0.44	**1**
18	0.84	0.78	**1.08**
19	1.16	1.1	**1.05**
20	0.8	0.68	**1.18**
21	0.82	0.8	**1.03**
22	0.6	0.56	**1.07**
23	0.8	0.8	**1**
24	0.8	0.8	**1**
25	0.96	0.96	**1**
26	0.96	0.98	**0.98**
27	0.68	0.66	**1.03**
28	0.74	0.72	**1.03**
29	0.64	0.64	**1**
30	0.68	0.64	**1.06**
31	0.72	0.68	**1.06**
32	0.7	0.64	**1.09**
33	0.74	0.72	**1.03**
34	0.6	0.5	**1.2**
35	0.72	0.7	**1.03**
36	0.64	0.64	**1**
37	0.94	0.88	**1.07**
38	1.24	0.92	**1.35**
39	1.04	1.04	**1**
40	0.82	0.74	**1.11**
41	0.9	0.64	**1.41**
42	0.64	0.64	**1**
43	0.8	0.72	**1.11**
44	0.92	0.84	**1.1**
45	0.74	0.72	**1.03**

Table 5.10 Continued.

Subject	30^{th} beat (secs)	15^{th} beat (secs)	Ratio
46	0.68	0.66	**1.03**
47	0.72	0.68	**1.06**
48	0.96	0.88	**1.09**
49	0.76	0.72	**1.06**
50	0.96	0.92	**1.04**
51	0.74	0.74	**1**
52	0.68	0.72	**0.94**
53	0.64	0.6	**1.07**
54	0.8	0.76	**1.05**
55	0.76	0.72	**1.06**
56	0.4	0.4	**1**
57	0.6	0.58	**1.03**
58	0.56	0.52	**1.08**
59	0.72	0.68	**1.06**
60	0.72	0.7	**1.03**
61	0.78	0.64	**1.22**
62	0.76	0.68	**1.12**

Table 5.11 Rise in diastolic blood pressure in response to sustained handgrip in rheumatoid subjects.

Subject	Mean Baseline	Reading 1	Reading 2	Reading 3	**Max - Mean**
	(mmHg)		(mmHg)		**(mmHg)**
1	64	64	64	70	**6**
2	80	84	90	92	**12**
3	73	78	90	90	**17**
4	70	92	94	98	**28**
5	80	82	82	84	**4**
6	70	74	78	80	**10**
7	80	98	98	100	**20**
8	55	60	60	60	**10**
9	70	78	82	84	**14**
10	80	82	88	88	**8**
11	80	84	86	88	**8**
12	80	90	90	100	**20**
13	80	80	80	90	**10**
14	70	72	74	82	**12**
15	90	90	102	104	**14**
16	80	86	86	86	**6**
17	80	84	84	86	**6**
18	78	80	84	88	**10**
19	70	70	72	74	**4**
20	80	82	84	82	**4**
21	80	80	80	80	**0**
22	60	70	70	74	**14**
23	80	84	84	85	**5**
24	100	110	110	110	**10**
25	70	78	78	80	**10**
26	70	74	72	74	**4**
27	70	84	80	84	**14**
28	80	80	84	84	**4**
29	70	90	90	92	**22**
30	74	76	80	81	**7**
31	80	80	80	81	**1**
32	80	82	84	84	**4**
33	70	70	71	72	**2**
34	80	88	80	90	**10**
35	60	60	68	60	**8**
36	95	100	100	102	**7**
37	90	90	94	94	**4**
38	68	70	74	74	**6**
39	70	90	90	92	**22**
40	60	70	70	80	**20**
41	80	84	88	88	**8**
42	80	88	88	90	**10**
43	70	80	78	82	**12**
44	80	90	90	90	**10**
45	80	90	90	90	**10**

Table 5.11 Continued.

Subject	Mean Baseline	Reading 1	Reading 2	Reading 3	**Max - Mean**
	(mmHg)		(mmHg)		**(mmHg)**
46	70	70	70	72	**2**
47	90	90	92	98	**8**
48	65	75	75	75	**10**
49	80	82	90	90	**10**
50	70	80	78	80	**10**
51	78	88	88	94	**16**
52	70	72	72	74	**4**
53	80	82	82	84	**4**
54	80	86	86	88	**8**
55	90	90	100	100	**10**
56	60	60	60	70	**10**
57	70	78	80	80	**10**
58	80	82	88	90	**10**
59	70	80	80	80	**10**
60	60	72	74	74	**14**
61	50	50	60	60	**10**
62	68	72	70	70	**4**

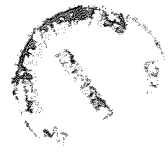


Table 5.12 Fall in systolic blood pressure on standing in rheumatoid subjects.

Subject	Reading 1			Reading 2			Reading 3			Mean
	Lying	Standing	Drop	Lying	Standing	Drop	Lying	Standing	Drop	
	(mmHg)			(mmHg)			(mmHg)			(mmHg)
1	88	104	-16	82	100	-18	90	100	-10	-15
2	130	140	-10	130	140	-10	140	140	0	-7
3	102	108	-6	100	102	-2	100	104	-4	-4
4	140	140	0	132	138	-6	140	140	0	-2
5	124	122	2	118	124	-6	122	122	0	-1
6	100	108	-8	100	104	-4	100	118	-18	-10
7	138	142	-4	132	132	0	132	140	-8	-4
8	150	150	0	150	160	-10	150	150	0	-3
9	150	130	20	150	134	16	150	130	20	19
10	170	170	0	180	185	-5	185	180	5	0
11	150	140	10	140	150	-10	150	150	0	0
12	130	132	-2	120	122	-2	122	130	-8	-4
13	130	120	10	140	140	0	150	140	10	7
14	150	150	0	160	150	10	150	152	-2	3
15	160	170	-10	150	160	-10	160	165	-5	-8
16	130	130	0	140	130	10	140	120	20	10
17	114	122	-8	112	130	-18	130	120	10	-5
18	160	162	-2	162	162	0	170	170	0	-1
19	140	140	0	140	150	-10	142	152	-10	-7
20	130	140	-10	130	140	-10	142	140	2	-6
21	110	104	6	110	108	2	110	104	6	5
22	100	98	2	108	98	10	111	119	-8	1
23	130	124	6	130	124	6	120	118	2	5
24	170	170	0	180	175	5	180	170	10	5
25	140	142	-2	140	130	10	130	130	0	3
26	154	150	4	152	154	-2	140	150	-10	-3
27	150	160	-10	150	170	-20	150	160	-10	-13
28	130	130	0	130	130	0	135	135	0	0
29	110	118	-8	120	130	-10	130	120	10	-3
30	145	150	-5	140	142	-2	140	142	-2	-3
31	120	120	0	120	118	2	120	118	2	1
32	120	120	0	120	110	10	115	120	-5	2
33	140	150	-10	140	150	-10	140	159	-19	-13
34	130	140	-10	135	135	0	138	140	-2	-4
35	104	100	4	99	104	-5	90	100	-10	-4
36	155	160	-5	160	155	5	160	162	-2	-1
37	140	140	0	140	142	-2	130	134	-4	-2
38	140	130	10	130	130	0	124	130	-6	1
39	150	140	10	140	144	-4	144	150	-6	0
40	110	120	-10	110	120	-10	110	128	-18	-13
41	135	145	-10	140	140	0	135	148	-13	-8
42	140	134	6	140	130	10	140	124	16	11
43	140	130	10	138	130	8	142	132	10	9
44	140	130	10	140	132	8	138	138	0	6
45	120	120	0	130	120	10	120	124	-4	2

Table 5.12 Continued.

Subject	Reading 1			Reading 2			Reading 3			Mean
	Lying	Standing	Drop	Lying	Standing	Drop	Lying	Standing	Drop	
	(mmHg)			(mmHg)			(mmHg)			(mmHg)
46	120	110	10	122	120	2	112	110	-2	**3**
47	140	130	10	150	150	0	140	130	10	**7**
48	115	110	5	110	110	0	100	110	-10	**-2**
49	140	150	-10	160	160	0	150	160	-10	**-7**
50	130	130	0	140	150	-10	142	150	-8	**-6**
51	130	140	-10	140	138	2	128	132	-4	**-4**
52	130	117	13	124	116	8	124	120	4	**8**
53	120	130	-10	118	130	-12	115	124	-9	**-10**
54	130	135	-5	140	140	0	138	137	1	**-1**
55	140	140	0	150	150	0	140	145	-5	**-2**
56	140	130	10	145	138	7	130	134	-4	**4**
57	94	98	-4	98	100	-2	100	102	-2	**-3**
58	120	100	20	118	104	14	116	115	1	**12**
59	130	120	10	125	130	-5	130	130	0	**2**
60	130	122	8	120	122	-2	124	130	-6	**0**
61	100	100	0	100	95	5	100	95	5	**3**
62	120	122	-2	125	120	5	119	120	-1	**1**

Table 5.13 Relevant clinical details of rheumatoid subjects.

Subject	Age	RF Status	RA Duration	Hb	ESR	CRP
	(years)		(years)	g/l	mm/hr	mg/l
1	51	neg	1	125	20	neg
2	75	pos	24	117	82	55
3	42	pos	9	116	31	neg
4	77	pos	1	127	35	neg
5	43	pos	2	134	12	neg
6	50	pos	3	127	19	36
7	74	pos	13	135	17	-
8	76	pos	4	94	87	-
9	70	pos	2	114	31	27
10	74	pos	7	113	38	neg
11	62	neg	2	140	24	neg
12	58	pos	5	115	79	78
13	52	pos	5	144	34	neg
14	77	neg	2	108	17	neg
15	66	pos	10	141	46	18
16	42	pos	1	116	37	neg
17	50	pos	5	115	115	65
18	69	pos	23	151	34	neg
19	80	pos	4	129	63	30
20	60	neg	2	120	36	neg
21	48	pos	0.5	127	30	35
22	63	pos	12	131	37	89
23	66	pos	35	133	43	18
24	60	neg	4	130	17	12
25	72	pos	30	118	44	neg
26	59	pos	26	109	80	16
27	78	pos	1	111	41	neg
28	72	pos	22	142	7	neg
29	66	neg	5	142	13	neg
30	43	pos	3	132	55	neg
31	61	pos	4	123	-	-
32	38	neg	1	117	6	neg
33	84	pos	2	121	25	neg
34	59	pos	11	125	71	19
35	49	pos	9	130	19	neg
36	73	pos	20	129	81	36
37	72	pos	18	136	57	-
38	82	pos	3	121	52	neg
39	78	neg	27	109	90	41
40	73	pos	11	129	78	24
41	73	pos	3	140	31	-
42	54	neg	19	99	37	-
43	73	neg	2	135	43	neg
44	74	neg	3	157	20	-

Table 5.13 Continued.

Subject	Age	RF Status	RA Duration	Hb	ESR	CRP
	(years)		(years)	g/l	mm/hr	mg/l
45	50	pos	22	99	79	32
46	66	pos	19	137	9	-
47	70	pos	14	129	38	neg
48	53	neg	18	122	20	neg
49	76	neg	2	128	28	-
50	72	pos	6	108	34	neg
51	71	pos	7	148	46	68
52	70	pos	11	111	96	21
53	47	pos	3	139	64	neg
54	67	neg	2	122	21	neg
55	45	pos	7	122	19	neg
56	73	pos	2	136	19	neg
57	52	pos	5	131	22	neg
58	54	neg	1	149	5	neg
59	70	pos	8	112	37	30
60	65	pos	1	132	27	neg
61	38	pos	1	117	25	neg
62	59	pos	2	127	29	53

Table 5.14 Clinical data collected from the notes of the rheumatoid subjects.

Subject	Age	RF Status	RA Duration (yrs)	Hb (g/l)	ESR (mm/hr)	CRP (iu/l)	Extra-articular features	Presence of neuropathy	Current Drugs
1	51	Neg	1	125	20	Neg	Mouth ulcers, rash	N	Sal, NSAID
2	75	Pos	24	117	82	55	N	N	Sal
3	42	Pos	9	116	31	Neg	N	N	Sal, MXT
4	77	Pos	1	127	35	Neg	N	N	MXT, Pred, NSAID
5	43	Pos	2	134	12	Neg	Nodules	N	MXT, Sal
6	50	Pos	3	127	19	36	N	N	Au
7	74	Pos	13	135	17	-	Nodules	N	MXT, Sal
8	76	Pos	4	94	87	-	Nodules	N	Sal, MXT, NSAID
9	70	Pos	2	114	31	27	Nodules	N	Au
10	74	Pos	7	113	38	Neg	Nodules	Sciatica	-
11	62	Neg	2	140	24	Neg	N	N	MXT, NSAID
12	58	Pos	5	115	79	78	Dry eyes	N	Sal
13	52	Pos	5	144	34	Neg	N	N	Pen
14	77	Neg	2	108	17	Neg	N	N	Sal
15	66	Pos	10	141	46	18	N	N	Sal, AZT, Pred
16	42	Pos	1	116	37	Neg	N	N	Sal, MXT
17	50	Pos	5	115	115	65	Sjogren's	N	MXT, Pred
18	69	Pos	23	151	34	Neg	N	N	AZT, Pen, Pred, Aspirin
19	80	Pos	4	129	63	30	N	N	-
20	60	Neg	2	120	36	Neg	N	N	MXT
21	48	Pos	0.5	127	30	35	N	N	Sal, Pred
22	63	Pos	12	131	37	89	N	N	Sal, Pen
23	66	Pos	35	133	143	18	N	N	Au
24	60	Neg	4	130	17	12	N	N	NSAID, Sal, MXT
25	72	Pos	30	118	44	Neg	N	N	MXT, Pred

Table 5.14 continued. Clinical data collected from the notes of the rheumatoid subjects.

Subject	Age	RF Status	RA Duration (yrs)	Hb (g/l)	ESR (mm/hr)	CRP (iu/l)	Extra-articular features	Presence of neuropathy	Current Drugs
26	59	Pos	26	109	80	16	Sjogren's, Nodules, thyroid	N	MXT
27	78	Pos	1	111	41	Neg	N	N	Pred
28	72	Pos	22	142	7	Neg	N	CTS	MXT, Coproxamol, Pred
29	66	Neg	5	142	13	Neg	Thyroid	CTS	MXT
30	43	Pos	3	132	55	Neg	-	-	MXT, NSAID
31	61	Pos	4	123	-	-	N	CTS, Ulnar	Au
32	38	Neg	1	117	6	Neg	N	CTS	Sal, NSAID
33	84	Pos	2	121	25	Neg	N	N	Au
34	59	Pos	11	125	71	19	Nodules	N	Pen, MXT, Pred
35	49	Pos	9	130	19	Neg	Alopecia	N	Au, Sal
36	73	Pos	20	129	81	36	N	N	-
37	72	Pos	18	136	57	-	Pulmonary	N	MXT
38	82	Pos	3	121	52	Neg	N	N	MXT, Pred
39	78	Neg	27	109	90	41	N	N	Azathioprine, Pred
40	73	Pos	11	129	78	24	Nodules	N	NSAID, Calci-Chew
41	73	Pos	3	140	31	-	N	N	Sal, Aspirin
42	54	Neg	19	99	37	-	N	N	Sal, Pred, NSAID
43	73	Neg	2	135	43	Neg	-	N	MXT
44	74	Neg	3	157	20	-	N	N	-
45	50	Pos	22	99	79	32	N	N	Cyclosporin A, NSAID
46	66	Pos	19	137	9	-	N	N	Sal, Pred
47	70	Pos	14	129	38	Neg	N	N	MXT, Coproxamol
48	53	Neg	18	122	20	Neg	N	N	Hydroxychloroquine, NSAID
49	76	Neg	2	128	28	-	N	N	MXT, Acemetacin
50	72	Pos	6	108	34	Neg	Nodules, thyroid	N	Sal, MXT

Table 5.14 continued. Clinical data collected from the notes of the rheumatoid subjects.

Subject	Age	RF Status	RA Duration (yrs)	Hb (g/l)	ESR (mm/hr)	CRP (iu/l)	Extra-articular features	Presence of neuropathy	Current Drugs
51	71	Pos	7	148	46	68	Nodules	N	MXT, Pred, NSAID
52	70	Pos	11	111	96	21	N	N	Pred, Iron, Lansoprazole, Coproxamol
53	47	Pos	3	139	64	Neg	N	N	MXT, Pen, Pred
54	67	Neg	2	122	21	Neg	N	N	Sal, Pred
55	45	Pos	7	122	19	Neg	Nodules, vitiligo	N	-
56	73	Pos	2	136	19	Neg	N	N	Sal, NSAID
57	52	Pos	5	131	22	Neg	Pleurisy	N	Sal
58	54	Neg	1	149	5	Neg	N	CTS	Sal, NSAID
59	70	Pos	8	112	37	30	Nodules	N	Pred
60	65	Pos	1	132	27	Neg	Nodules	N	Pred, Sal
61	38	Pos	1	117	25	Neg	Dry eyes	N	Chloroquine
62	59	Pos	2	127	29	53	Nodules	N	Sal, NSAID

Key

Sal	Salazopyrin	Pos	positive
MXT	Methotrexate	Neg	negative
Pred	Prednisolone	N	None
NSAID	Non-steroidal anti-inflammatory drug		
Au	Gold		
Pen	Penicillamine		
CTS	Carpal tunnel syndrome		

Chapter Six

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