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Abstract

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M Phil

A Study of Autonomic Impairment in Elderly Patients with Pneumonia

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Autonomic impairment is increasingly recognized in association with infections .The object of this study was to see if elderly patients with pneumonia had evidence of impairment of autonomic cardiovascular reflexes when compared to healthy elderly people and people who were mobilizing after a fracture of the neck of femur , and if so how long did this persist . Thirty eight subjects were studied by means of a series of cardiovascular autonomic function tests . The study showed that the Valsalva ratio , 30 : 15 ratio , rise in diastolic blood pressure to sustained handgrip and postural drop in systolic blood pressure were significantly different when subjects tested immediately after a pneumonia were compared to healthy controls ($p = 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.01$ respectively) and to the fracture neck of femur controls ($p > 0.05$, $p = 0.001$, $p = 0.006$, $p = 0.04$) . There were no significant differences between the control groups . On follow - up of the pneumonia group 6 weeks after discharge , there was a significant improvement when compared to the initial reading ,in the first three tests listed above ($p = 0.03$, $p = 0.03$, $p = 0.001$) and at 6 months in postural drop in blood pressure ($p = 0.01$) . Throughout the study no significant relationships were observed in heart rate variation to deep breathing between any of the groups , nor within the pneumonia group . The data are discussed with special reference to possible mechanisms by which pneumonia can affect cardiovascular reflexes . The results suggest that there is a high prevalence of impairment of cardiovascular autonomic reflexes in the immediate post pneumonic phase .These abnormalities showed significant improvement when retested at 6 weeks and a further trend to improve at 6 months . The cause of these findings is not known and warrants further research . It is likely that this temporary impairment of autonomic function renders patients more susceptible to the development of postural hypotension if the cardiovascular reflexes are stressed by , for example , drugs or hypovolaemia for several weeks after pneumonia .The methods described are a very practical way of diagnosing impairment of autonomic cardiovascular reflexes at the bed side in a hospital and community setting .

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Preface

There has been a rapid increase of interest in various aspects of the autonomic nervous system over the past 30 years . Autonomic impairment is now recognized as accompanying a wide range of disease processes , infection being one of them . Pneumonia was once described as the old mans ' best friend as it was often a fatal event and was the means by which an old person , troubled by multiple ailing complaints eventually succumbed . Since the discovery of antibiotics in the 1930 ' s , and the development of medical technology for supporting critically ill people , treatment of pneumonia has become much more successful and the pathophysiology of the condition is better understood . There are still , however , some manifestations , such as atrial fibrillation , postural hypotension and the syndrome of inappropriate anti diuretic hormone secretion , whose pathogenesis is not well understood and which have been ascribed in other disease states to be due to autonomic impairment . The aim of this study was to see if there was any evidence of autonomic cardiovascular reflexes impairment in elderly patients with pneumonia and , if confirmed , to stimulate more research into the subject with the aim of throwing more light on further aspects of the pathophysiology of pneumonia . A practical , clinical objective of this study was to determine how long any autonomic reflex impairment detected immediately after pneumonia persisted , as this could have an important bearing on the management of coexisting conditions in such patients . Furthermore , we set out to demonstrate that ' simple ' , portable , equipment could be used to test cardiovascular autonomic reflexes in a way that was clinically useful and thereby make such testing widely available in clinical practice .

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List of Abbreviations

Central Nervous System	CNS
Autonomic Nervous System	ANS
Sympathetic Nervous System	SNS
Parasympathetic Nervous System	PNS
Intermediolateral (column)	IML
micrometre	*u*m
Non adrenergic non cholinergic	NANC
Vasoactive intestinal peptide	VIP
Monoamine oxidase	MAO
Cathechol - o - methyl transferase	COMT
Muscarinic	M
Arterial blood pressure	ABP
Gastrointestinal tract	GIT
Plasma renin activity	PRA
Acute autonomic neuropathy	AAN
Nerve growth factor	NGF
Transient ischaemic attack	TIA
Herpes simplex virus	HSV
Syndrome of inappropriate secretion of anti diuretic hormone	SIADH
Infectious Mononucleosis	IM
Ebstein - Barr virus	EBV
Electrocardiogram	ECG
Electromyogram	EMG

Chapter 1 :Introduction

Historical Perspective.

The Autonomic Nervous System (ANS) plays an important role in the body through its innervation of all the viscera, vasculature and endocrine glands. This relationship was first recognized by Claude Bernard (1813 - 1878) in his discussion "Stability of the Milieu Interieur" in 1877 [1] . He has been credited with initiating the modern era of ANS research since he was the first to conceptualise the notion of homeostasis and its regulation . Walter Gaskell [2] in the mid 1880 's performed detailed anatomic dissections that precisely defined the major outflows of the ANS . Since these initial observations , progress in the study of the ANS has been highlighted by a number of key discoveries . John Newton Langley [3] (1852 - 1925) , a physiologist at Cambridge , was the first person to use the term Autonomic Nervous System in 1898 . Following a series of experiments he established the two functional divisions of the ANS . He wrote ," I propose the term ANS for the sympathetic and the allied nervous system of the cranial nerves and the local nervous system of the gut" . Later , in 1905 Langley introduced the term parasympathetic .He also described " atropine resistant " neural effects in the bladder and stomach , an observation that preceded by several years the description of the nonadrenergic noncholinergic nervous system .

The idea of chemical transmission was first proposed in 1905 . In 1921 Loewi [4] showed that vagal stimulation of a perfused frog 's heart released a substance that slowed the beating of a second heart and stimulation of the sympathetic nervous system produced a substance that accelerated it . He called the former Vagusstoff and the latter Acceleranostoff respectively .He then identified the first as acetylcholine and

subsequently Cannon and Bacq in 1931 [5] showed that the second substance was noradrenaline . As reported by Pick [6] during the 1930 's it was shown that in the ANS all preganglionic and all postganglionic parasympathetic fibers released acetylcholine and the terms cholinergic and adrenergic to define nerves which released acetylcholine or adrenaline like substances were introduced .

The above observations have provided the foundations for the distinction of adrenergic from cholinergic transmission in the ANS and further developments were based on these fundamental observations . Further work on the anatomy and physiology was conducted between 1931 and 1970 by a number of scientists that has contributed greatly to understanding the ANS [7] .

Study of the ANS was made more interesting by relating known clinical manifestations to autonomic dysfunction .Syncope was a very well documented clinical observation since the nineteenth century . As quoted by Johnson [8] ,the following was written in the text "Edinburgh Practice of Physic Surgery and Midwifery (1803) ; " a syncope is when the action of the heart ,and along with it that of the arteries , is suddenly and very much lessened ; whence the animal powers ,the senses and voluntary motions immediately cease ". With the development of the sphygmomanometer it was noted that changes in blood pressure readings were related to clinical disorders that were already recognized . When postural hypotension was first described it was looked upon as a medical curiosity . However , we have now moved full circle to the point that this dysfunction is now recognized as a concomitant of a wide range of systemic diseases . The etiology may be unknown , as in primary autonomic failure , or may be the result of systemic diseases or conditions .A small subgroup of patients with primary

autonomic failure include those with acute and subacute dysautonomias .This syndrome was first reported by Young et al in 1969 [9] .The pathological basis and aetiology still remains unclear but infection , probably mediated by an autoimmune mechanism , has been proposed since the changes observed were very similar to an experimental autonomic neuropathy produced by Appenzeller et al [10] in 1965 . Hence autonomic dysfunction and infection has been the subject of much research fuelled by further reports of this syndrome .

Pneumonia has been described in medical texts for many centuries .Hippocrates was the first to describe the friction rub of pleurisy [11] .In the 17 th century it was felt that pneumonia was caused by malignant air . In 1834 the three stages of lung consolidation that are still used today were described and in the 1880 's , the fact that pneumonia was an infection due to bacteria was clarified when post mortem lung specimens were examined using the Gram stain technique . The pneumococcus and a capsulated bacillary organism later known as Friedlanders Bacillus were identified .The pneumococcus was later identified as the most common cause of infection . This rapidly led to work on the production of immunity to pneumococcal infection . By the early 20 th century microbiologists were able quickly to type and isolate pneumococci as a guide to specific serum therapy of the four types .However , serum therapy was only really effective against type A organisms , and the first real breakthrough in treatment was the discovery of sulphonamides in 1938 and penicillin in 1944 . Interest in pneumonias was further driven by the discovery of an atypical group of pneumonias resistant to penicillin but sensitive to other antibiotics .The next major event was the outbreak of Legionaire's Disease in 1976 in Philadelphia . Increasingly , unusual

pneumonias in immunosuppressed people and patients with AIDS still fuel interest in the subject .

The ubiquitous nature of the ANS has allowed a large variety of tests involving different systems . Generally , tests involving other systems are more complex but correlate well with the cardiovascular tests .The large number of tests available coupled with different methods of analysing results has led clinicians and researchers to be faced with difficulties of interpretation , and ,understandably , considerable debate exists regarding which tests to use . In 1981 Ewing , Clarke and co workers from Edinburgh adopted a battery of five tests with an additional sixth to be used for research purposes [12] .This went a long way in introducing uniformity but in 1987 David Ewing , as reported by Ryder [13] , in a lecture named "New Horizons for Diabetic Autonomic Neuropathy " in Leipzig called for more uniformity of tests. In 1988 the American Diabetes Association in conjunction with the Academy of Neurology produced a consensus statement that the heart rate response to the Valsalva manoeuvre , deep breathing and standing , and the blood pressure response to standing and sustained hand grip have been validated and shown to be reliable and reproducible , and to have prognostic implications [14] . Hence the Ewing battery of tests has been widely accepted for clinical and research work .

Overview of the Autonomic Nervous System

The ANS consists of two major divisions , the sympathetic and the parasympathetic nervous systems .There is an increasingly recognized third division ,the non adrenergic non cholinergic nervous system . The ANS is activated by centres located in the spinal cord ,brain stem and the hypothalamus . Parts of the cerebral cortex , via the limbic system , transmit impulses to the lower centres influencing autonomic control .Often the ANS operates through the visceral reflexes . Sensory input is integrated in the centres of the spinal cord , brainstem or hypothalamus and these in turn transmit reflex responses back to the visceral organs to control their activities .

The Sympathetic Nervous System (SNS)

The SNS has both central and peripheral pathways .The main control centre is in the hypothalamus but there are connections in the bulbar reticular formation ,orbito frontal cortex , cingulate gyrus , cerebral cortex ,amygdala and elsewhere . Descending pathways from the hypothalamus , medullary reticular formation , nucleus tractus solitarius , serotoninergic raphe nuclei and elsewhere synapse with the cells of the intermediolateral columns (IML) . The IML cells of the spinal cord extend from T1 to L2 segment . However they may start at C8 if the brachial plexus is prefixed or T2 if postfixed , and consequently extend to L 1 or L 3. There are about 5000 neurons for each segment and about 5 -8 % are lost due to ageing every ten years .The sympathetic nerves originate in the spinal cord , passing into the sympathetic chain .The sympathetic pathway consists of a preganglionic and a postganglionic neuron .The cell body of the preganglionic neuron lies in the intermediolateral horn of the spinal cord and its fibres

pass through an anterior root into a spinal nerve .On exit from the spinal canal the preganglionic fibres pass through the white ramus into one of the ganglia of the sympathetic chain . Once inside the ganglion they can either synapse with postganglionic neurons , pass up or down the chain before synapsing with a postganglionic neuron in another ganglion or pass right through the ganglion before synapsing with an outlying ganglion . Postganglionic fibres then pass into the spinal nerves via the grey rami .These are made up of Type C fibres extending to all parts of the body in the skeletal nerves . Approximately 8 % of fibres in an average skeletal nerve are sympathetic.

The sympathetic chain consists of a column of ganglia on either side of the spinal cord .There are three in the cervical region (the superior ,middle and cervico thoracic stellate ganglia) , eleven thoracic and four or five lumbar or sacral . At the level of the coccyx the two chains join to form the ganglion impar . Brooks ,Fournier and Coggerhall 1981 [15] have shown that each preganglionic axon will typically synapse with many post ganglionic neurons .This implies that activation of the SNS leads to a very diffuse discharge .

The sympathetic fibres from T1 generally pass up the sympathetic chain into the head , from T2 into the neck ,T3 - T11 into the thorax T7 - T 11 into the abdomen and L1 - L2 into the legs . The distribution of the sympathetic nerves to each organ is determined by the position in the embryo at which the organ originates .Some preganglionic fibres do not synapse but pass through the sympathetic chain forming splanchnic nerves innervating three paravertebral sympathetic coeliac , superior and inferior mesenteric ganglia . Second order neurons from these ganglia send post

ganglionic fibres to the hypogastric , splanchnic and mesenteric plexuses that innervate glands ,blood vessels ,and smooth muscles of abdominal and pelvic viscera .

In humans the histological structure of the sympathetic chain ,white rami and the greater splanchnic nerve is similar. Most myelinated fibres are in the 2 - 6 micrometre (*um*) diameter range and a smaller number of these fibres are of larger diameter with a peak of 12 *um* .The large diameter and some of the small diameter myelinated fibres are afferent .The pre ganglionic myelinated fibres range from 1.5 - 4.7 *um* in diameter .The numerous unmyelinated fibres are either postganglionic or afferent [7] .

The Adrenal Medulla

The preganglionic fibres travelling in the splanchnic nerves directly innervate the adrenal medulla .Thus the adrenal medulla may be regarded as a specialized sympathetic ganglion capable of secreting neurotransmitters into the blood for a more diffuse sympathetic discharge . About 80 % of adrenal secretion is adrenaline and 20 % is noradrenaline but the relative proportion of secretion alters considerably under different physiological stresses .The effect on end organs lasts about 10 times as long as direct stimulation due to slow removal of hormones from the blood . Usually , when any part of the sympathetic nervous system is stimulated the entire system or at least major parts of it are stimulated at the same time , thus adrenaline and noradrenaline are almost always released by the adrenal medulla at the same time that various organs are being stimulated by the sympathetic nerves .Hence organs are stimulated in a simultaneous and complementary way .This dual mechanism provides a safety factor , one substituting for the other if it is not working [16] .The secreted hormones can stimulate structures that are not innervated by direct sympathetic nerves .These hormones can directly stimulate the basal metabolic rate of the cells even though only a small proportion of the cells of the body have sympathetic nerves .

The Parasympathetic Nervous System (PNS)

The PNS , by virtue of its anatomy and circuitry , is more focal and less diffuse in keeping with its function to regulate specific organs . The cell bodies lie in certain cranial nerve nuclei and in the IML columns of the spinal cord .

About 75 % of all the fibres lie in the vagus , and many physiologists consider the vagus as synonymous with the PNS [16] . Its cell bodies lie in the Nucleus Ambiguus and the dorsal motor nucleus . Neurons from the former supply the visceral smooth muscle . The dorsal motor nucleus is predominantly secretomotor in function .The PNS again has preganglionic and post ganglionic fibres but with few exceptions the former pass uninterrupted to target organs which contain the ganglia from which the very short post ganglionic fibres arise . The cranial outflow of the PNS lies in the oculomotor , facial , glossopharyngeal and vagus nerves .The sacral parasympathetic fibres congregate in the form of nervi erigens , also called pelvic nerves , which leave the sacral plexus on each side of the cord and distribute their peripheral nerves to the descending colon ,rectum , bladder and lower ureters [7] .

The vagal afferent fibres consist of unmyelinated fibres and small myelinated fibres . Thus nerve fibres in both the sympathetic and parasympathetic divisions that participate in cardiovascular control mechanisms comprise mainly small 2 - 6 *um* myelinated and unmyelinated fibres .

Autonomic Supply to the Respiratory System

The autonomic nervous supply to the airways is more complex than originally believed .In addition to the parasympathetic and the sympathetic nervous system , there is an increasingly recognized third nonadrenergic noncholinergic nervous system [17] . The PNS supply is through the vagus . Preganglionic vagal fibres originating from the CNS pass to the parasympathetic ganglia located in the walls of the airways , and postganglionic fibres from these ganglia travel to the airway smooth muscle . Sympathetic nerve supply to the lungs originates from the upper thoracic preganglionic fibres that end in the extrapulmonary stellate ganglia . Postganglionic fibres enter the lungs and can be visualized in the walls of the airways and surrounding the blood vessels by fluorescent histochemical tests for catecholamines .There appears to be marked variability in adrenergic innervation between different species . In general , sympathetic innervation to airway smooth muscle is sparse and has not yet been demonstrated in humans , and the role of the sympathetic nervous system in regulating resting muscle tone is not clear . Experiments in dogs suggest that a small degree of sympathetic dilator tone exists that is dependent on an intact vagus [18] .

Branches of the vagus and the sympathetic form anterior and posterior pulmonary plexuses .The filaments from these plexuses accompany the bronchial tubes .In the trachea and main bronchi nerve bundles and ganglia are found mainly in the posterior membranous portion of the airway . On entering the lung the nerve bundles divide to form distinct peribronchial and perivascular plexuses .There are species differences in the extent to which this happens .The peribronchial plexus further divides to form the extra and endobronchial subepithelial plexuses .This division depends on the quantity

and extension of supporting cartilage in succeeding generations of intrapulmonary airways .In general the more distal bronchial plexus has fewer fibres than plexuses of airway generations of lower order .Nerve bundles have been shown by electron and light microscopy to be present in the alveoli [19] .

The efferent motor innervation has both excitatory and inhibitory components affecting submucosal glands ,bronchial smooth muscle and blood vessels.

The afferent sensory nerve endings present in both surface epithelium and the underlying submucosa are of three types, based on the position , pattern of firing , adaptation to stimuli and axonal myelination .Type 1 are rapidly adapting , comprising cough and irritant receptors , type 2 are slowly adapting pulmonary stretch reflexes thought to give rise to the Hering - Breuer reflex while type 3 are pulmonary juxta capillary receptors present deep in the lung .

The gastrointestinal tract is known to have its own autonomic nerve supply . Since the tracheobronchial tree arises from the foregut it has been suggested that a similar system exists in the lungs .Non adrenergic non cholinergic (NANC) bronchial nerves have since been identified and have been implicated in the pathogenesis of respiratory disease .Two physiologically distinct NANC mechanisms have been identified , one inhibitory and excitatory , abnormalities of which may be implicated in the pathogenesis of asthma [20] .

Neurotransmitters and Receptors

Neurotransmission is more complex than originally thought . Neurons do not necessarily have a single neurotransmitter and there is increased evidence of cotransmission in the peripheral nervous system of substances such as vasoactive intestinal peptide (VIP) , that is secreted together with acetylcholine .This explains why atropine cannot block all the effects of the parasympathetic stimulation . Neuropeptide Y, that is released with noradrenaline may be the reason why certain alpha blockers do not prevent the effects of sympathetic neural activation .Other neurotransmitters , like substance P and calcitonin related peptide , are also involved in afferent neurotransmission .Within the CNS several other neurotransmitters are known . A considerable number of amines and peptides act at different levels .These include substance P ,somatostatin ,vasopressin ,oxytocin , adrenaline and noradrenaline .The ultimate effect depends on the type of stimulus and the variety of interaction .The most well understood neurotransmitters are acetylcholine and noradrenaline . All preganglionic neurons are cholinergic in both the sympathetic and parasympathetic systems .The postganglionic neurons of the parasympathetic are all cholinergic while most postganglionic sympathetic neurons are adrenergic , secreting noradrenaline , except nerve fibres to sweat glands and blood vessels that are cholinergic .

Some of the ANS nerve endings , especially those of the PNS , are similar to the neuromuscular junction of skeletal muscle but much smaller .However , most of the sympathetic nerves merely touch the effector cells of the organs they innervate or terminate in connective tissue adjacent to effector cells .They usually end in bulbous enlargements known as varicosities .They contain vesicles of acetylcholine or

noradrenaline . Depolarization of these vesicles increases the permeability to calcium , causing the vesicles to fuse with the nerve membrane and to empty their contents to the exterior .The released acetylcholine has a very short half life and is destroyed almost immediately on secretion by the enzyme acetylcholinesterase present in the terminal nerve endings and in the surface of the receptor organs . It is split into an acetate ion and choline .The latter is transported back into the nerve terminal where it is used in the synthesis of acetylcholine again . A small amount diffuses into the surrounding fluids where it is quickly destroyed by another enzyme , serum cholinesterase .

Noradrenaline is secreted by the terminal nerve endings . It is removed from the secretory site in three different ways . Active reuptake into the nerve terminals , diffusion away from the nerve endings into the surrounding body fluids and the into the blood and destruction is by the enzymes , mono amine oxidase (MAO) found in nerve endings themselves and cathechol - o - methyl transferase (COMT) present in all tissues . Noradrenaline secreted into tissues usually lasts only a few seconds but when secreted into the blood by the adrenal remains active until it diffuses into tissue where it is destroyed by COMT . The noradrenaline circulating in the blood stream is almost entirely a spillover from nerve endings and does not normally contribute to the effects of sympatho - adrenal activation .The proportion of noradrenaline derived from different tissues depends on the width of the synaptic cleft .The wider the cleft the greater the likelihood of spillover [21]. Adrenaline is the major catecholamine secreted by the adrenal medulla . It is derived from noradrenaline . The major characteristic of the hormone is that its release is not subject to any negative feedback control but can be enhanced by a number of amplification loops such as

adrenocorticotrophic hormone and angiotensin - II release making it a true fight and flight hormone [21] .

Receptors

The neurotransmitters exert their effect by reacting with receptor substances in effector cells .The receptors are integral parts of the membrane and changes caused by combining with neurotransmitters leads to an alteration of the membrane properties causing altered permeability of the cell membrane to various ions or to activation of enzymes promoting chemical reactions within cells .

There are two types of acetylcholine receptors muscarinic and nicotinic . Muscarinic (M) receptors are found in all the effector cells stimulated by the postganglionic neurons of the parasympathetic and postganglionic cholinergic neurons of the sympathetic . At least three subtypes of muscarinic receptor have been recognized pharmacologically and five distinct receptor subtypes have now been cloned [22] . The muscarinic receptor subtypes have now been recognised in the airways [20] .

M_1 - receptors have a high affinity to pirenzepine , a selective muscarinic blocker of glandular secretion which causes little cardiac slowing . The receptors in ganglia may facilitate neurotransmission which is mediated via nicotinic receptors .These receptors appear to be important in chronic regulation of nerve impulse transmission whereas the nicotinic receptors may be more important in the rapid transmission of impulses as occur in reflexes .If they facilitate cholinergic reflexes they may be important in asthma especially nocturnal attacks where vagal tone is probably more important .

Other muscarinic receptors have a low affinity for pirenzepine and can be divided into

two depending on their affinity to AF DX 116 which is a pirenzepine analogue , which influences cardiac function . M_2 receptors have a high affinity to AF DX 116 and are found on postganglionic nerve terminals .They may inhibit the release of acetylcholine thus reducing the stimulation of post junctional M_3 receptors that have a low affinity to AF DX 116 .These receptors are located on bronchial smooth muscle and stimulation leads to bronchoconstriction .

Nicotinic receptors are found in synapses between the preganglionic and postganglionic neurons of both the sympathetic and parasympathetic systems , and also in the membranes of the skeletal muscle fibres at the neuromuscular junction .There are at least three separate nicotinic receptors determined by various studies using pharmacological methods or monoclonal antibodies .They are related to different organs , muscle , brain and autonomic ganglia . There are two types of adrenergic receptors , called alpha and beta . Noradrenaline predominantly excites alpha receptors but has a smaller effect on the beta receptor . Adrenaline on the other hand excites both receptors equally . Alpha receptors can be of two types , 1and 2 . The former are usually postsynaptic and excitatory and when activated increase cyclic AMP (c AMP) . The latter are presynaptic and inhibitory leading to a fall in c AMP , inhibiting noradrenaline release and thus inhibiting synaptic sympathetic function . In addition stimulation of these receptors leads to platelet aggregation , inhibition of lipolysis , inhibition of insulin secretion . Beta receptor stimulation results in an increase of c AMP . Beta 1 stimulation generally leads to a positive inotropic and chronotropic effect on the heart , stimulation of lipolysis and renin secretion from the kidney . Beta 2 stimulation relaxes smooth muscle in bronchi , uterus , gut , bladder detrusor , splenic

capsule , vascular smooth muscle , amylase secretion from the salivary gland , and gluconeogenesis from liver , as well as increasing lactate production by skeletal muscle .

Sympathetic stimulation causes excitatory effects in some organs but inhibitory effects in others and the same applies to parasympathetic stimulation . Also , when one stimulates one organ , the other inhibits it .The sympathetic and the parasympathetic systems are continually active and the basal rates of activity are known as sympathetic tone or parasympathetic tone . Increase or decrease in this tone can lead to different body responses to varying physiological conditions .

The Autonomic Reflexes

The ANS regulates visceral functions by means of autonomic reflexes .There are a large number of such reflexes , for example , those relating to the gastrointestinal system , bladder ,and sexual function . However , the most important cardiovascular reflex is the baroreceptor reflex . The arterial baroreceptor reflex is important since many of the tests of autonomic function , including the Valsalva response and ABP response to standing and tilt assess the integrity of this reflex .It is initiated by stretch receptors , called either baroreceptors or pressor receptors , located in the wall of large arteries . A systemic rise in blood pressure stretches the receptors causing them to transmit afferent signals to the central nervous system and efferent signals in turn influence the cardiovascular system to reduce arterial pressure to normal .

Baroreceptors are present in the walls of every large artery but are most abundant in the walls of the carotid sinuses above the carotid bifurcations and the walls of the aortic arch .They are spray type nerve endings . Impulses from the carotid sinus are transmitted via Hering's nerve to the glossopharyngeal nerve and then to the medullary area of the brain stem . Impulses from the aortic arch are transmitted to the medulla via the vagus .The baroreceptors respond extremely rapidly to changes in arterial pressure and the number of impulses is shown to increase in systole and decrease in diastole . The impulse intensity also responds rapidly to a change in blood pressure .The number of impulses for each unit rise in blood pressure is not linear and is greatest at a pressure level greater than the normal mean arterial pressure for that individual . When activated , the baroreceptor impulses inhibit the vasoconstrictor centre of the medulla and excite the vagal centre .This leads to vasodilatation throughout the

peripheral circulatory system , and decreased heart rate and strength of contraction of the myocardium thus lowering the blood pressure . A fall in blood pressure leads to the opposite effects .

The baroreceptors play a very important role during postural changes from lying to standing . Standing up causes a fall in ABP that stimulates the baroreceptors leading to a strong sympathetic discharge .These baroreceptors are probably of no importance in the long term regulation of blood pressure because they themselves adapt in one to three days to whatever pressure they are exposed to thus prolonged regulation of ABP requires other control systems , principally the renal body fluid pressure control system . The blood supply to muscles and the gastrointestinal tract (GIT) also plays a role in the short term BP regulation . Sympathetic activity to the muscles is influenced mainly by fluctuations in diastolic blood pressure . Sympathetic nerve fibre activity in muscles increases in response to a fall in BP , to changes in posture , and to the application of negative pressure to the lower half of the body .The splanchnic vascular bed also plays a part in the regulation of blood pressure .There is a marked decrease in the mesenteric blood flow in response to the above manoeuvres . Sympathectomy has little effect on the BP unless the splanchnic nerves are sectioned and patients with spinal cord lesions do not develop marked postural hypotension unless the lesion lies above the level of the splanchnic outflow at T 6 .

Hormonal changes with posture

Noradrenaline

Plasma noradrenaline rises in response to tilting . Patients with autonomic neuropathies affecting postganglionic sympathetic vasomotor fibres may have abnormally low plasma noradrenaline levels at rest . The blood pressure rise following infusion of noradrenaline may be increased in autonomic disorders affecting preganglionic and postganglionic sympathetic vasomotor fibres [16].

Plasma renin

Plasma renin increases in normal subjects as they assume the erect posture .This rise is attributed to increased sympathetic efferent activity as renin release is mediated in part via autonomic nerve endings in the juxtaglomerular apparatus .Plasma renin release does not require an intact autonomic nervous system but certain components of efferent sympathetic pathways to the kidneys may be important . Christlieb et al [23] showed a failure of plasma renin activity (PRA) to increase in response to standing in diabetic patients with postural hypotension .Patients with idiopathic postural hypotension due to probable afferent autonomic dysfunction have a normal increase in PRA on standing while those with a presumptive efferent lesion have an abnormal response .Thus the lack of a response in diabetics is probably due to neuropathy affecting the efferent nerves to the juxtaglomerular apparatus . Campbell et al [24] noted an inverse relationship between the degree of postural drop and rise in PRA on standing . It is , however, possible that in addition to lesions in efferent sympathetic nerves , impaired renin stores or renin releasing mechanisms due to neuropathy may be involved .

The role of a deficient renin response is still unclear in the pathogenesis of postural hypotension .The absence of PRA response may fail to compensate for the deficient sympathetic stimulation of the smooth muscle of the arterioles of the lower limbs which is widely recognized as being the principal lesion in diabetic postural hypotension .

Vasopressin

Release is dependent on the afferent stimuli from the baroreceptors .Baroreceptor dysfunction may therefore lead to abnormal control of plasma vasopressin release and consequently of blood volume .Elderly people with orthostatic hypotension of non neurological origin have an exaggerated release of vasopressin in response to standing [25] .

Investigation of the Autonomic Nervous System.

When autonomic neuropathy is suspected noninvasive tests may be used to confirm the diagnosis . Sometimes invasive tests may be required to localize more precisely the site of the lesion in the ANS .

The noninvasive tests of heart rate response to breathing , change in posture , and Valsalva ratio assess both afferent and efferent limbs of the vagus primarily ; the change in blood pressure on standing (or the application of lower body negative pressure) , response to isometric exercise , and plasma noradrenaline levels mainly evaluate sympathetic efferent function . Plasma vasopressin level tests the afferent limb of the sympathetic reflex arcs .Accurate noninvasive techniques like clamp photoplethysmography [26] to record beat to beat heart rate and BP , and doppler echocardiography and impedance cardiography to measure cardiac output are now available , as are sensitive spectral analysis techniques for the analysis of rhythmic fluctuations of these parameters [26] .

Sweat tests include quantitative sudomotor axon reflex test (QSART) and the thermoregulatory sweat test (TST) .Used in conjunction these tests can distinguish between pre and post ganglionic lesions .If both are abnormal the lesion is post ganglionic while if QSART is normal in the presence of an abnormal TST the lesion is preganglionic [27] .

Invasive tests are usually necessary only in doubtful cases or for research purposes . Intra arterial monitoring of blood pressure and heart rate changes to the Valsalva manoeuvre assess the afferent and the efferent limbs of the SNS . Baroreflex sensitivity is measured as the changes in heart rate ,vascular resistance and regional blood flow

during graded stimulation of the carotid sinus baroreceptors . It can also be measured by relating the changes in the RR interval to changes in blood pressure induced by drugs that have no effect on heart rate such as phenylephrine or angiotensin .By studying the slowing of heart rate with induced rises in BP it is possible to assess parasympathetic afferent and efferent limbs . A measure of steady state responses assesses the integrated sympathetic and parasympathetic activity of the heart . Infusion of pressor drugs can lead to a rise in BP thus testing adrenergic receptors and the subsequent slowing of the HR tests afferent and efferent parasympathetic limbs . Tests of peripheral vasomotor control include the skin vasoconstrictor response that regulates skin capillaries and arteriovenous circulation . Changes in peripheral blood flow in the hand , forearm , foot or leg in response to a variety of stimuli , including radiant heating of the trunk , immersion of the hand in hot water , the cold pressor test , emotional stress tests and the inspiratory gasp can also be measured .These test the integrity of the sympathetic efferent limb .Alterations in finger blood flow reflect a change in skin circulation and can be assessed using heat flow discs or laser doppler velocimetry .Changes in forearm blood flow approximately reflect changes in muscle blood flow .Other methods to measure muscle blood flow include isotope clearance techniques , measurement of changes in muscle temperature and measurement of the degree of oxygen desaturation in the deep veins draining forearm muscles .Abnormal autonomic innervation of the pupil may be associated with a variety of autonomic disorders and tests using 4 % cocaine , 0.1% adrenaline , 1% hydroxyamphetamine and 2.5% metacholine can be used to determine the site of the lesion [28] .

Disorders of the Autonomic Nervous System

Nerve fibres in both sympathetic and parasympathetic divisions that participate in cardiovascular control mechanisms comprise mainly small (2 - 6 um) myelinated and unmyelinated fibres .Conditions that affect these small fibres are therefore most likely to cause autonomic dysfunction [29] . Autonomic dysfunction may be primary where the etiology is unknown or secondary where the abnormality results from specific diseases or conditions .

The primary autonomic failure group is characterized by loss of cells from the intermediolateral columns of the spinal cord .Involvement of vagal nuclei in the brain stem can also occur .In this group fall the syndromes of chronic autonomic failure such as pure autonomic failure , multiple system atrophy , sometimes associated with striato nigral degeneration or olivopontocerebellar atrophy . A small subgroup of patients with primary autonomic failure includes those with acute and subacute dysautonomias . Secondary autonomic impairment may be due to lesions in the CNS (eg poliomyelitis , tetanus , multiple sclerosis) , spinal cord (eg. traumatic cervical and high thoracic transection , transverse myelitis , syringomyelia) , peripheral sites affecting afferent nerve fibres (eg. tabes dorsalis , Guillain - Barre syndrome) or efferent fibres (eg. diabetes mellitus , amyloid) or both (eg familial dysautonomia) or due to drugs that act at single or multiple sites [30] .

Acute and subacute autonomic neuropathy syndromes are usually idiopathic in origin but have been described after viral infections ,and in association with autoimmune disorders , mixed connective tissue disease , hypothyroidism , ulcerative colitis , botulism or hepatic porphyrias . Toxins such as podophyllin and paraneoplastic

syndromes , like the Eaton - Lambert Syndrome can also be associated . The syndrome affects relatively young people of most races or ethnic groups with a mean age of 30 years though it can be seen at any age [31] . Symptoms evolve for 1 - 3 weeks (rarely months) starting with gastrointestinal symptoms , followed by postural hypotension then urinary retention .There is a spectrum of clinical features ranging from pandysautonomias involving both sympathetic and parasympathetic components to purely cholinergic dysautonomia sparing sympathetic function , except sweating , and to those in which predominant dysautonomia overshadows variable degrees of motor or sensory involvement . Hyponatraemia due to the syndrome of inappropriate secretion of anti diuretic hormone and diabetes insipidus are known to occur in the acute phase . Cerebrospinal fluid protein is normal in the pure cholinergic form and elevated in pandysautonomias . Sural nerve biopsies show axonal degeneration , and a decrease in unmyelinated and myelinated small fibres . Several clinical features of acute autonomic neuropathy resemble the Guillain - Barre syndrome and it is tempting to suggest that pure AAN and Guillain Barre Syndrome are extremes on a clinical spectrum in which overlap exists [32] .

The Autonomic Nervous System and Ageing

The prevalence of autonomic dysfunction increases with age .This may be due to the presence of diseases that start in or persist in old age , drugs , and there is growing evidence that autonomic dysfunction may be associated with age related changes affecting both the sympathetic [33] or parasympathetic [34] nervous systems . The anatomical basis and pathological changes explaining this autonomic dysfunction are complex and imperfectly understood .There are not many studies of morphological changes in the central and autonomic fibres in relation to age and many of these are animal experiments . It seems , however , that the commonly accepted notion that nerve cells die throughout life does not apply widely .

Ageing changes do not occur uniformly throughout the ANS . Packing density of neurons in sympathetic ganglia is reduced in old age but in the superior cervical ganglion the numbers of preganglionic axons seems undiminished .In contrast , nerve cell loss occurs during adult life in the enteric nervous system with a reduction of 40 % of the total numbers . Both enteric and sympathetic neurons originate from similar neuroblasts in the neural crest [35] but exhibit different rates of cell loss . Age related neuronal loss has been shown in localized regions of the dorsal motor nucleus of the vagus and nucleus ambiguus .These supply parasympathetic targets in the myenteric plexus , the neuronal content of which is also compromised in old age .This observation led to the suggestion that prejunctional neurons in the hind brain are affected by deficits in their target nerve cells in the enteric plexus [35] . Axons projecting to different targets from the same source may show different changes with ageing . Experiments in rats have shown that the projections of the superior cervical

ganglion to the cerebral vessels show significant age changes while those to the iris are relatively unaffected , suggesting that target tissue influences some aspects of neuronal phenotype in old age .

Animal studies of mixed populations of autonomic nerves supplying a range of target tissues have shown that the developmental profile of each group of nerves is separately regulated .The density of terminal nerve plexuses may decrease , remain static or may even increase with age depending on the region being investigated .Neuropeptides associated with vasodilatation such as vasoactive intestinal peptide are expressed earlier in development than noradrenaline and in systemic blood vessels tend to decline during later development . In cerebral blood vessels expression of these neuropeptides increases in old age while noradrenaline appears to decline .It is possible that there is a competitive equilibrium between several different populations of autonomic nerves . The mechanisms by which age changes in target organs can influence cell numbers was investigated by Cohen et al [35] .Studies have shown that the number of neurons that survive into maturity is not predetermined but rather the result of competition amongst a population of nerves for access to an appropriate target tissue .The target tissue produces tropic factors , for example , Nerve Growth Factor (NGF) which are transported retrogradely and are required for the early survival and differentiation of sympathetic neurons .NGFs are being discovered in different regions of the brain . There is also experimental evidence to suggest that neuronal connectivity remains in dynamic equilibrium throughout life , retaining the capacity to grow and retract in response to varying stimuli . Again retrograde tropic stimuli from the target tissue is the most important stimulus . The retention of plasticity into maturity may enable the

nervous system to respond to continuous growth including the changes imposed by ageing . The microenvironment and the matrix surrounding nerve cells can also affect regulation of neuronal growth [35] .

This selective degeneration of nuclei is found in diseases most commonly present in old age . In Parkinson's disease the basis of the autonomic deficit is thought to be a degeneration of the dorsal nucleus of the vagus and locus ceruleus . Degeneration of these nuclei is also commonly found in the Shy - Drager syndrome . It is possible that degeneration of the locus ceruleus would account for the autonomic impairment observed in patients with Alzheimer's dementia [36] . In the CNS the motor neurons of the spinal cord , Purkinje cells of the cerebellum and the neocortex are most affected but there may be no changes in other parts .There is also a decline in the number of cells in the autonomic nervous system . Low et al in 1977 [37] showed approximately a loss of 370 neurons (about 8%) from the intermediolateral columns every decade . Similarly , first order and second order neurons outside the CNS showed deceasing cell numbers .Other reports showed an age related reduced number of neurons in the dorsal motor nucleus of the vagus nerve [38] .

Apart from declining numbers there are also anatomical abnormalities in remaining cells .These include accumulation of the pigment lipofuscin in neurons and Schwann cells , demyelination and remyelination , axonal degeneration , and loss of dendrites and dendritic spines in cortical neurons . Decreased communications between the fewer remaining cells leads to age related impairment of autonomic function .

There are also changes in receptors and target organs .Terminal regions of autonomic nerves exhibit changes in the distribution and content of acetylcholine and catecholamines that are localized both in time and place .

These anatomical and physiological changes are reflected in clinical manifestations of autonomic impairment . Some features of old age are being speculated to be related to autonomic impairment . Cronin [39] suggested that autonomic dysfunction is the abnormality underlying the tendency of the ageing aortic valve to calcify since valvular calcification is similar to medial arterial calcification , a condition in whose pathogenesis autonomic dysfunction is implicated . Autonomic denervation leads to withdrawal of neurotropic influences from cells and tissues . The resulting changes in function and in structure may give rise to a condition of vulnerability allowing other stresses , such as haemodynamic trauma , to result in calcification . However , the earliest recognized manifestation of impairment in the elderly was orthostatic hypotension , described by Johnson et al in 1965 [40] . Arterial blood pressure depends on the peripheral resistance and the cardiac output and is kept relatively constant by a number of mechanisms particularly the baroreceptor reflexes .In the elderly the usual range of the ABP increases the systolic more than the diastolic and the changes may be due to alterations in the sensitivity of the baroreceptor reflexes or the structure of the vessels themselves .Bristow et al 1969 [41] showed that when the baroreflex is activated by standing the heart rate increases by 10 - 15 beats / min in the elderly compared to 20 /min in the younger people implying a diminished baroreceptor activity with age .This may be due to decreased distensibility of the arterial wall of the carotid sinus , shown by Winston et al at postmortem studies [42] . Robinson et al [43]

found that changes in blood vessel walls themselves can bring about postural hypotension . Some patients with postural hypotension have impaired baroreflex function but normal afferent and efferent components of the arc , suggesting the disorder lies in the CNS .Necropsy studies showed arteriosclerotic changes in the brain , but since this is a common finding it could not be concluded that cerebral atherosclerosis and the impaired baroreflex are causally related . Appenzeller et al 1964 [44] suggested that stroke patients had impaired autonomic function most markedly during the acute phase .Thus cerebrovascular disease may be implicated in the pathogenesis of the impaired baroreflex .However , since cerebrovascular disease is age dependent it is difficult to distinguish which of the two is the major pathogenic factor . Gross 1970 [45] studied circulatory reflex function in a series of subjects with chronic ischaemic cerebrovascular disease compared to a group with no known cerebrovascular disease . The control group was not well matched being on average 12 years younger , though this eliminated to a degree the objection that they may have had occult disease . The results show that ageing is a more potent factor in the decline in performance of the baroreceptor reflexes and the only situation in which chronic ischaemic cerebrovascular disease appears to be a significant factor is in the case of the combined carotid and vertebrobasilar ischaemia and then only in relation to the heart rate changes .There was no significant difference found in the circulatory reflex function in subjects who suffered cerebral infarcts as opposed to transient ischaemic attacks (TIAs) .

The declining baroreceptor mechanism leads to a compensatory increase in the cardiovascular sympathetic system activity that could mask underlying functional

defects . Pfeifer et al [46] demonstrated declining sympathetic and parasympathetic inputs to the iris with ageing , suggesting a generalized decline in autonomic function . However , while detecting a declining cardiac parasympathetic function they found increased cardiac sympathetic activity .There was a positive relationship between plasma noradrenaline level and the mean arterial blood pressure when normally one would expect to see the reverse with an intact baroreflex system .The age related increase in noradrenaline was observed in supine and upright posture ,during mild exercise , cold pressor test , following oral glucose ingestion and during a mental stress procedure . It is unlikely that the increase in noradrenaline in the blood is due to decreased clearance although the evidence is unclear due to conflicting trial results [47 , 48] . Wallin et al [49] showed an increase in sympathetic muscle activity with age , suggesting an age related increase in noradrenaline since the wide sympathetic neuromuscular junctions in muscle are an important source of the hormone .

The probable mechanism of the above observation would be an impaired afferent input that would result in central recognition of the signal that the blood pressure was low , and as a result the efferent signals to the heart and smooth muscle would lead to a decrease in cardiac parasympathetic activity and an increase in sympathetic discharge ; thus resulting in spillover of the noradrenaline into the plasma and the rise in ABP observed with age .No effect of age on the adrenomedullary function was observed and plasma adrenaline did not increase with age [46] . The plasma adrenaline changes only minimally in response to a major baroreflex stimulus like standing . Some studies , however , have detected an increase in clearance of adrenaline with age and this could imply that there is an increase in adrenaline secretion despite stable blood levels .

Symptoms of orthostatic hypotension develop if there is cerebral hypoperfusion . Maintenance of an adequate blood flow to the brain depends on adequacy of the major arterial system and also on the autoregulation of the smaller arteries and arterioles within the brain itself . Autoregulation implies the maintenance of a constant blood flow despite changes in perfusion pressure . It is kept constant within a wide range of blood pressure in normal subjects . In normotensive subjects this ranges from 60 to 140 mmHg . In hypertensives the resistance is elevated to tolerate a higher blood pressure without an increase in blood flow . Conversely , the resistance may be shifted down to tolerate BPs as low as 40 mm Hg .Wollner et al 1979 [50] showed that in some elderly people with postural hypotension there is also a failure of cerebral autoregulation and this failure may contribute to the development of symptoms .It is uncertain why this may occur .They may have autonomic failure , altered blood volume control , abnormal control of vasopressin release or degenerative changes in the blood vessels themselves . Cerebral vessels are innervated by adrenergic and cholinergic fibres , probably derived from the superior cervical ganglion , and it is unclear if they are important in the maintenance of cerebral autoregulation .

Age also has an effect at the receptor level with altered adrenoceptor function and diminished responsiveness to adrenergic agonists and antagonists [47 ,51] .

Studies have established a decrease in responsiveness to both beta receptor agonists and antagonists .The contractile mechanism was found to be fully functional in animal experiments , thus the decreased responsiveness may be due to a change in the beta adrenoceptor or an alteration in the chain of processes linking the receptor to the contractile mechanism .Lymphocyte beta adrenoceptor density falls with increasing

age .It shows an inverted U distribution ,increasing up to middle life , then falling with senescence . Decreased responsiveness of the receptor in the presence of normal density suggests that a post receptor mechanism is important . Age related alterations in cell membrane structure or properties appear to be responsible .The production of cyclic AMP is diminished in cells from the elderly, in addition the time course was slower in cells from old people .There may also be a defect at a step after protein kinase activation but before calcium troponin interaction .

The evidence of a change in alpha adrenoceptor mechanisms with ageing is less clear , although it is a much less studied field .There is conflicting evidence on alpha receptor density but present consensus indicates no change in number or sensitivity with age .

The diagnosis of autonomic impairment frequently depends on tests which elicit reflex changes in heart rate .Variation in heart rate during different stimuli is mediated by the combined effects of cardiac ,vagal ,and sympathetic nerves acting on the sinoatrial node . Since ageing has an effect on the ANS allowance must be made for the physiological effects of ageing as diminished heart rate variation can be incorrectly attributed to disease .Sinus arrhythmia is enhanced during beta adrenergic blockade and abolished by atropine implying that the efferent pathway is vagal . It has been observed that changes in the heart rate during tidal breathing are reduced in the elderly [52] and this may be due to altered vagal activity since the chronotropic response to atropine is reduced in elderly subjects [53] .

The Valsalva ratio is a useful test . It is generally agreed that the ratio is age dependent and several age related normal ranges have been quoted [54] . This , however , has not been a universal finding [55] . More detailed information about the response can be

obtained by intraarterial catheter monitoring of the blood pressure . An abnormal Valsalva response can be recorded when the ratio is normal [53] .The extent of the overshoot of blood pressure in phase IV was noted to decrease with age , implying age related sympathetic dysfunction .

The increase in heart rate on standing has also been shown to diminish with age [54 ,55, 57] . Conventionally , the result is expressed as a ratio . A ratio of 1.00 indicates vagal damage but a value of less than 1.00 does not necessarily indicate more damage [58] .

Isometric exercise is followed by an increase in arterial blood pressure and cardiac output .The stimulus is derived from exercising muscle , that is , from the metabolic and / or mechanical changes in contracting muscle that activate small fibres in the afferent limb of the reflex arc , and central command .The early heart rate increase is due to vagal withdrawal while late changes are due to sympathetic activity .The increase in BP in healthy humans is mainly derived from an increase in cardiac output .Sustained handgrip , which is an effort dependent test , was the only test showing a significant difference between male and female subjects [55] . However , there does not seem to be any effect of age on the response to this test .

Autonomic Dysfunction and Infection .

Autonomic dysfunction has been observed in a variety of infections . The association is well established in a few but remains highly speculative in others .Impairment has been noted in association with viral infections (HIV [59 ,60] , HTLV 1 [61 , 62] ,Rubella [32] ,Guillain Barre syndrome [63] , Ebstein Barr [64 ,65] , Coxsackie B [66] , Herpes simplex [67] , pseudo rabies [68] , polio [74] , Varicella zoster [78]) , bacterial infections (tetanus [69] , tabes dorsalis [28] ,salmonella typhi [70] , Lyme disease [71] , leprosy [72] , diptheria [73] , botulism [75 ,76]) and parasitic infestations (Chagas ' disease [77]) .

By altering the functional activity of the ANS or by seeding the target organs , infections can produce a broad spectrum of manifestations. Few clinical or experimental studies have explored the mechanisms by which infection of autonomic neurons might produce impairment . It is reasonable to presume that manifestations of autonomic dysfunction would depend on how the ANS becomes infected , the types of virus - cell interactions and possible target organ sequelae .

Routes of access can be either haematogenous or via neural pathways .The former would lead to widespread infection and the latter more localized . However , more complex patterns of infection can be recorded such as distant organ involvement after haematogenous spread .

For infection to be established after blood spread the virus must penetrate or bypass the capillary endothelium, satellite or Schwann cells .Viral infections of target organs may involve autonomic nerves supplying the organ passing to the neuronal perikaryon with either perineural (infection passing progressively from one cell to another) or

axoplasmic pathways (an intraneural pathway whereby infection is carried centripetally within the axoplasm) . The nerve terminal is devoid of Schwann cells hence is easier to infect . Once within the cell , the virus is protected from neutralizing antibodies thus making eradication of infection difficult .

Considerable variability in the character of virus host cell interactions can be anticipated and the effects vary with the type and intensity of infection .Infection can be acute or chronic .The viral genome may be expressed fully , partially or remain latent .Chronic infection may be of a low grade productive type or else fluctuate amongst different types of genomic expression . The factors that determine what type of infection results is still unknown .Target organ sequelae and clinical manifestations of autonomic infection can result from three mechanisms , these are , viral seeding of target organs by infected autonomic neurons ,virus induced alterations in neuronal function and target organ denervation .

Viral infection of the ANS leads to centrifugal dispersal of virus by axoplasmic transport to the nerve terminals thereby infecting target organs tissue . Metabolic changes in infected cells may lead to a change in cell permissiveness and a reactivation of virus production . Since autonomic terminals are so widespread , supplying all the parts of the body , one may speculate that a large number of organs and tissues are susceptible to viral infections via their autonomic nervous system supply and , it has been suggested , that certain diseases such as viral myocarditis may be due to relapsing viral infection . Seeding of viruses along nerves to exocrine glands would also ensure viral transmission via body secretions , for example tears , saliva and semen .

In viral infections of neurons it is reasonable to assume that normal functional activity will be disrupted .The virus may alter DNA , leading to altered genome expression ,and thereby interfering with host enzymes or membrane function .There might be neuronal lysis or seeding that interferes with reception ,conduction or transmission of nerve impulses .Viral infection might also cause neuronal hyperactivity , hence infection of the autonomic supply to the glands , smooth muscle , or heart may lead to endocrine or exocrine dysfunction ,vascular spasm or arrythmias .If infection causes lysis of neurons , target organ denervation will follow . Permanent loss of neurons leads to target organ atrophy or denervation hypersensitivity . If the organs are reinnervated the dysfunction is transient [78] .

The mechanisms by which viral infections can impair autonomic function are various but which ones are involved in specific infection is usually unknown .

Human Immunodeficiency Virus .

Autonomic dysfunction , detected by autonomic testing , has been observed in HIV infection and appears to be part of the continuum from AIDS related complex (ARC) to AIDS ,although one cannot exclude toxins , malnutrition and medications as playing a role in the manifestations of this syndrome .It is also thought to be present in the early stages of HIV infection when the infection is still subclinical . Freeman et al [59] showed that patients with ARC represented a heterogenous group , some showing declining autonomic function while others showed exaggerated normal responses .This may be due to denervation supersensitivity , described by Bannister in 1988 [79] . A significant increase in heart rate in patients with AIDS was noted to be similar to that

observed in diabetic patients with a vagal neuropathy , most likely representing unopposed cardiac sympathetic activity [80] . Damage to the ANS has been documented in HIV infection . However , there has been no correlation between the clinical stage of the disease and the degree of pathological change . Pathological changes , with a reduction in axonal density of the autonomic nerves in the jejunal mucosa of patients with AIDS and gastrointestinal symptoms , have been shown . Although the degeneration tended to be greater in the patients with more severe diarrhoea this was not always the case and was even present in the asymptomatic stage indicating that autonomic neuropathy may develop early in the disease .

Some AIDS patients have an inappropriately low level of catecholamines for their degree of postural hypotension . The levels were normal when they would be expected to be high .This would suggest a preganglionic defect as well as a post ganglionic defect in autonomic nerves .

Herpes Simplex

The herpes simplex virus (HSV) is known to infect autonomic and sensory ganglia . Infection is characterized by a chronic relapsing course .Studies show a rapid passage of the HSV to ganglia after inoculation .This suggests that an axoplasmic transport mechanism is involved in movement of the virus up and down the nerve . On reaching the ganglion an initial acute productive infection can be detected by homogenization of the ganglia or by fluorescent antibodies . A latent infection follows during which it is difficult to detect the presence of the viral genome in the ganglion [81] .

Guillain Barre Syndrome (Acute Post infective Polyneuritis)

The syndrome usually starts about four weeks after a viral illness , often trivial in nature . There is inflammatory oedema and demyelination of the spinal nerves near the nerve root junction .Cerebrospinal fluid (CSF) shows a normal cell count but the protein may be raised . The Guillain Barre Syndrome (GBS) may produce an interruption of the autonomic reflex pathways in the sympathetic and the parasympathetic [82] systems .In one series [63] mild autonomic disturbance was reported in 65 % of patients with the syndrome , and 59% had cardiovascular autonomic impairment .Since patients now rarely die from respiratory failure , autonomic impairment has become an important cause of morbidity and mortality .This can cause cardiovascular , bowel , bladder or sexual dysfunction in addition to abnormalities of pupils , lachrymal , salivary and bronchial smooth muscle function . Also , the syndrome of inappropriate secretion of anti diuretic hormone (SIADH) , glucose intolerance and an abnormal response to drugs have been reported . The cardiovascular abnormalities detected include sinus tachycardia , labile heart rate , postural hypotension , sustained hypertension , paroxysmal hypertension , vagal spells , other arrythmias and abnormal response to drugs . Sinus tachycardia is clinically most significant in patients with severe disease . It is not necessarily present at the height of the illness but may be present in the relatively early stages , pointing to later complications . Patients with tachycardia have a diminished RR interval and slowing in response to carotid sinus massage is preserved implying vagal integrity .It is possible that a mechanism known as phase dependent block accounts for the tachycardia

(impulses arriving at the sinus node during certain phases of the cardiac cycle fail to produce cardiac slowing or may produce a tachycardia) . In GBS slowing of impulses in either the afferent or the efferent vagal pathways of the baroreflex can cause signals to arrive at the sinus node on the refractory path , resulting in a tachycardia .

No significant association between heart rate lability and disease process has been found and this could be explained by an exagerated normal response to a variety of physiological stimuli . The incidence of postural hypotension is high . Mechanical factors such as lack of muscle contraction with decreased venous pumping in quadriplegic patients play a part but dysautonomia is probably the major contributing factor .This may be due to lesions in the efferent sympathetic vasoconstrictor fibres or to baroreflex afferent fibre lesions . Hypertension can be sustained but is more commonly labile .The latter was significantly associated with quadriplegia and respiratory failure .The explanation for the irritable blood pressure could be a lesion on the afferent side of the baroreflex and could also account for any concomitant postural hypotension . It is unclear whether there is increased excretion of urinary catecholamines .Some studies have documented an increased plasma renin .Vagal spells are the most ominous type of dysautonomia in the GBS .They refer to episodes of bradycardia , episodic heart block and asystole occurring spontaneously or in response to a vagotonic stimulus . Such episodes occur more commonly during tracheal suctioning or during Valsalva - like manoeuvres . Other arrythmias have been noted but it is unlikely that autonomic dysfunction plays a part in the etiology . Morphological ECG abnormalities have been noted ,for example , depressed or elevated ST segments , flat or inverted T waves , QT interval prolongation and increased QRS voltage .These

can occur in the absence of ischaemic heart disease and the mechanism for these could be autonomic imbalances causing regional changes in ventricular repolarisation .
Other manifestations in the GBS include urinary retention , urinary incontinence , impotence , constipation , ileus and faecal incontinence .
The syndrome of inappropriate anti diuretic hormone secretion (SIADH) can be present in patients with GBS and there is a significant correlation between SIADH and respiratory failure . It is likely that this may result from abnormalities of afferent fibres from the baroreceptors leading to a resetting of the osmostat with resulting hyponatraemia .There may be other contributing factors , for example , positive pressure ventilation or a reduction in venous return due to paraplegia .
Finally , glucose intolerance may be a transient feature of the GBS especially in patients with increased circulation of catecholamines and steroids .

Infectious Mononucleosis

Infectious Mononucleosis (IM) sometimes involves the nervous system . It is accepted that the causative organism is the herpes like Epstein - Barr (EB) virus .Acute neurological conditions of virtually any sort or variety , in young people , can be the only manifestation of the disease . Dysautonomia is rare and can present as pure autonomic dysfunction [64] or else accompanied by sensory and motor disturbances . The autonomic defects that have been demonstrated were referable to post ganglionic involvement of the ANS .The pathogenic mechanism by which involvement of the nervous system occurs is far from clear . In the few pathological studies carried out the findings are compatible either with a viral infection or an immunological

process . Direct viral invasion of the peripheral autonomic ganglia or post ganglionic neuronal elements is possible [78] .It is also possible that changes may be due to an abnormal immune response by neural tissue , cross reacting with a microbial antigen . In this regard the disorder may represent the human counterpart of the experimental autonomic neuropathy described by Appenzeller et al [10] .Cases complicated by sensory or motor disturbances have severe loss of myelinated and unmyelinated fibres . In all the cases so far reported recovery has been slow and incomplete .

Coxsackie B

Pavesi et al (1992) [66] reported a case of acute sensory and autonomic neuropathy associated with Coxsackie B infection .Electrophysiological studies suggested an axonal neuropathy and a sural nerve biopsy showed axonal degeneration with virtual absence of unmyelinated fibres and a moderate loss of myelinated fibres , mainly affecting small fibres .Thus it seems that the mechanisms involved in the pathogenesis of this condition are similar for different viruses .

Poliomyelitis

Autonomic involvement can occur in the acute phase and as a late complication of the infection . During the acute phase there is involvement of the anterior horn cells .Cells of the intermediolateral (IML) columns lying adjacent can also be involved causing bladder paralysis , excessive sweating and peripheral vasoconstriction .This latter responds to paravertebral sympathetic block . It may also be due to involvement of the brain stem centres . Postural hypotension has recently been reported . Autonomic

involvement as a late complication has not been confirmed in a series by Borg et al 1988 [83] but Tenharkel et al 1991 [74] describe a case of past polio presenting with postural hypotension and an abnormal Valsalva response . Further investigation led to a diagnosis of hypoadrenergic orthostatic hypotension with a predominantly preganglionic sympathetic lesion and intact vagal baroreflex pathways . Pure autonomic failure , multiple system atrophy (MSA) and motor neuron disease were excluded . Since the intermediolateral cells are affected in the acute stage patients have a diminished cell number . Ageing also reduces the number of cells in the IML column hence it is conceivable that the postural hypotension is due to age related loss of cells from a pool that is already diminished by disease .

Human T lymphotropic Virus Type 1 (HTLV - 1)

HTLV 1 infection is associated with a slowly progressive spastic paraparesis , pyramidal signs , mild sensory impairment and sphincter disturbances . Antibodies to HTLV 1 are found in the CSF and serum . The myelogram is normal .Other reported neurological symptoms include tremor, double vision , cerebellar ataxia and facial nerve palsy . Akizuki et al [62] reported pathological lesions in the brain stem , cerebrum and cerebellum as well as spinal cord . A patient with autonomic impairment with MSA was found to be positive to HTLV 1 antibodies in serum and CSF , and symptoms improved with oral corticosteroids . Yokota et al [66] evaluated 21 patients with similar neurology but none was positive to HTLV 1 .Thus such infection is uncommon in autonomic failure with MSA but worth seeking .

Diphtheria

Diphtheria is a common infectious disease in developing countries and occurs occasionally elsewhere . It is caused by the toxin of Corynebacterium diptheriae . Commonly , it starts as pharyngeal diphtheria that can then be complicated by myocarditis , demyelinating motor neuropathy , paralysis of the soft palate , palsies of the IX, X, and XI cranial nerves and generalized peripheral neuropathy .Idiaquez et al 1992 [73] studied the prevalence of autonomic impairment in 10 diptheria patients with generalized peripheral neuropathy . Sympathetic function was shown to be normal when assessed using postural fall .These results would be in keeping with the finding of small histological lesions in the sympathetic nervous system of doubtful significance . Parasympathetic function was abnormal . Necropsy studies showed lesions in the nodose ganglion of the vagus . Results showed evidence of vagal neuropathy and the finding agrees with the classic description of diphtheritic neuropathy which states that tachycardia can be present without myocarditis . So far as the mechanism of vagal abnormalities in diphtheria is concerned , there is little information about vagal pathological processes in acute demyelinating neuropathies .

Salmonella typhi

Blumenfeld et al [70] reported the first case of acute autonomic neuropathy with Salmonella typhi infection .Typhoid has been associated with numerous neurological conditions for example coma , semi coma , confusional states , meningitis , convulsions , generalized myoclonus , focal neurological signs , deafness , hemiplegia , facial palsy , Parkinsonism , spasticity , hypotonicity , schizophrenia , symmetrical

sensorimotor polyneuropathy and mononeuritis . It is possible that the relative bradycardia and constipation occurring during the first week of typhoid could be due to autonomic impairment .No explanation is known for these features .

Chagas ' disease

Caused by infection with the protozoan Trypanosoma cruzi , it has an acute and a chronic form . In non endemic areas it is easily missed since it mimics coronary artery disease and also idiopathic dilated cardiomyopathy .The impairment of the autonomic control of heart rate , particularly of the parasympathetic component , has been shown in many patients with chronic Chagas' heart disease , sometimes associated with digestive disease of the same etiology , on the basis of reduced heart rate responses to atropine , Valsalva manoeuvre , dynamic exercise , postural changes and hyperventilation .These methods detect patients with gross defects in autonomic function . L F Junqueira Jr et al [77] identified cardiac autonomic impairment in Chagastic patients with overt heart , or associated heart and gastrointestinal , disease who have normal responses to more conventional tests . Baroreflex sensitivity was determined by relating the beat-to-beat pulse intervals to systolic pressure values during transient phenylephrine and amyl nitrate - induced changes in arterial pressure . Patients with only digestive disease or without overt heart disease showed no evidence of autonomic damage .There seems to be a relationship between the pattern of organic involvement in Chagas' disease and cardiac autonomic impairment expressed by disturbed baroreflex sensitivity .The exact mechanism of the cardiac autonomic lesion remains unknown , though there is evidence to suggest that it may be a process

resulting from a continuous autoimmune mechanism triggered during the acute phase of the disease .The relevance of the impairment of cardiac baroreflex control in Chagas' disease remains to be determined.

Tetanus

Tetanus is caused by Clostridium tetani , a Gram positive rod .There are at least 10 types but all produce the same exotoxin .The exotoxin has a great affinity for animal nervous tissue .The controversy over the mechanism and the route of absorbtion of the tetanus toxin has not been finalized but the evidence favours a retrograde intraaxonal route .There are tissue spaces in the endoneurium between nerve fibers connecting with the subarachnoid spaces of the cord and the toxin is pushed into these spaces when tissue pressure rises in exercising muscle .When the wound is superficial and toxin is produced in subcutaneous tissues that generate low tissue pressure it might be that the toxin is transported by lymph currents and distributed to the nervous system via the blood stream .The toxin binds irreversibly with certain sialic acid containing gangliosides . It blocks inhibition of spinal reflexes , resulting in muscle spasms . Post mortem examination does not usually reveal pathological changes in nerve tissue due to toxin . One case was reported as having degenerative changes in motor neurons especially in the medulla and upper spinal cord [84] .

Autonomic impairment is evidenced by tachycardia , labile blood pressure , sweating and cardiac arrythmias . Irritability of BP appears after the patient has been on treatment for about a week . Sometimes the BP rises to 200 / 120 and remains at this level for the rest of the illness and into convalescence . In others the BP may oscillate ,

and hypertension may be followed by prolonged hypotension that can lead to death due to hypotensive shock .Tachycardia is common and may be accompanied by ECG changes and T wave inversion .These cardiovascular complications appear to be due to the action of tetanus toxin on the brain stem though myocardial damage has sometimes been found at postmortem .Severe sweating is sometimes seen in patients with this instability of BP .Sweating may be followed by peripheral circulatory failure with vasoconstriction of the skin .This may have its origin in brain stem intoxication or it may be due to overactivity of the sympathetic system due to the action of the toxin on the lateral horn of the spinal cord .These changes in heart rate and blood pressure may be accompanied by rises in the concentration of plasma catecholamines , adrenaline or noradrenaline . Hyperpyrexia is a common feature of tetanus . It is not related to any complication of treatment and again appears to be due to brainstem intoxication . In some elderly patients low rather than high temperature may be recorded .The most severe cases may be complicated by stomach and intestinal dilatation followed by paralytic ileus .This is invariably fatal .This condition also occurs in severe cases of polio where there is severe brainstem involvement .

Botulism [85]

This is caused by a Gram positive rod with a terminal or subterminal spore .It is strictly anaerobic and there are at least seven known types (A - G) . Each strain produces a potent neuro toxin . The clinical syndrome is characterized by muscle paralysis , acute autonomic dysfunction and gastrointestinal symptoms caused by absorbtion of the toxin from the gastrointestinal tract . Once in the blood stream the toxin acts in the region of the myoneural junction and it affects only cholinergic fibres , leaving the adrenergic and sensory nerves unimpaired . It acts on the unmyelinated fibres just proximal to the acetylcholine release zone and blocks the passage of impulses along these fibrils so that no acetylcholine is released .The muscle itself remains normally active .The acetylcholine release zone itself is not affected and in perfusion bath preparations it reacts to the stimulus of an electric current in the fluid by the production of acetylcholine .The brain and spinal cord seem to be resistant even to the direct injection of toxin . The action of toxin is not due to actual physical contact . Histological examination of the neuromuscular junction does not reveal any consistent abnormalities and it may be that the change induced by toxin is a chemical one .The electrophysiological features are similar to those seen in the Eaton Lambert syndrome . Acute autonomic dysfunction may be present without associated muscular weakness in which case the condition may be difficult to distinguish clinically from acute autonomic neuropathy .

Lyme Disease

This is a recently recognised disease first described in 1976 , caused by the spirochete Borrelia burgdorfei that is transmitted by a tick , Ixodes dammini . It is characterized by a typical skin lesion , erythema chronicum migrans . Neurological complications usually start within a few weeks or months after the rash .These include aseptic meningitis , encephalitis , motor or sensory polyneuropathy ,cranial neuropathy , mononeuritis multiplex , ataxia and myelitis . Several syndromes can occur in one patient . Sterman et al [71] described a case of GBS complicating Lyme disease with evidence of autonomic dysfunction causing a resting tachycardia .

Leprosy

Leprosy is the leading cause of neuropathy in developing countries .This is due to the affinity of the M.leprae to the Schwann cell . Autonomic neuropathy is reported in varying degrees as indicated by sweat function tests and bed side tests for cardiovascular involvement . There is involvement of the sympathetic chain and the vagus with an infiltrate of acid fast bacilli .There is post ganglionic sympathetic nerve damage in the iris .Pedal oedema in leprosy is due to autonomic nerve involvement of the capillaries of the leg . Ramachandran et al 1987 [72] showed involvement of both divisions of the ANS .The parasympathetic system was involved early and more commonly than the sympathetic . Sympathetic involvement is always associated with involvement of the parasympathetic . DP Gupta et al [86] showed that the severity of neuropathy was greater in leprosy of longer duration but involvement of the ANS occurs irrespective of the duration of leprosy and treatment .

The Autonomic Nervous System and Respiratory Disorders

Autonomic dysfunction has been observed in patients with various respiratory disorders , bronchial carcinoma ,asthma , chronic airflow limitation , cystic fibrosis , viral respiratory tract infections , allergic rhinitis and atopic dermatitis . The precise contribution of autonomic dysfunction in diseases presenting with overlapping manifestations is not known .

Bronchial Carcinoma

Patients with bronchial carcinoma are known sometimes to have forms of neuropathy and myopathy .They are often very non specifically unwell , and whether autonomic dysfunction contributes to this is unknown .The majority of cases show no definite changes , only subtle ones , in autonomic function . However , isolated cases are documented with direct neoplastic involvement of the vagus or a non metastatic vagal neuropathic complication of carcinoma .

Direct vagal involvement with malignant disease may be relatively common but is only rarely associated with clinically significant changes . Carcinoma of the oesophagus involving the sensory branches of the upper part of the vagus is known to cause pain . Involvement of the recurrent laryngeal branch of the vagus causes hoarseness due to vocal cord paralysis . Cases of neoplastic auto vagotomy leading to gastric stasis complicated by gastric bezoar or volvulus have been recorded .Below the level of the lung roots the vagus forms quite an extensive oesophageal plexus .For autovagotomy to occur both vagal trunks or the whole of this plexus need to be involved and this may be the reason why this complication is rare [89] .

Cases of autonomic impairment as a non metastatic effect of carcinoma of the lung are known to occur .The presence of orthostatic hypotension and an abnormal vasoconstrictor response , and variability of the pulse interval in the Valsalva manoeuvre indicate a failure of the baroreceptor reflex arc . Further investigation shows that the defect is probably on the afferent side or in the central connections . Treatment of the primary lesion can lead to reversal of the autonomic dysfunction [90] . There is evidence of autonomic dysfunction as a feature of bronchial carcinoma , though a causal relationship has not been established [91] . There is a significant effect of the carcinoma on resting heart rate , with lower supine BP and increased postural fall in BP, but more specific markers of cardiovascular autonomic function , like the Valsalva ratio , are not significantly affected .

Cystic Fibrosis

Davis et al [92] demonstrated abnormal autonomic responses in patients with cystic fibrosis . There was reduced cardiovascular sensitivity to beta adrenergic stimulation and increased sensitivity to alpha adrenergic and cholinergic stimulation .Alpha sensitivity was significantly related to the severity of the disease but cholinergic sensitivity was not .These autonomic responses are similar to those observed in asthma . Thus patients with asthma and cystic fibrosis show an increased frequency of atopy , increased sensitivity to inhaled methacholine , hypertrophy and hyperplasia of the mucus secreting apparatus in the upper and lower airways . The autonomic defects observed in cystic fibrosis patients are also observed in obligate heterozygotes , suggesting that these defects are genetically determined rather than being a reflection of

the disease process, chronic illness ,drug administration or malnutrition .Thus one gene for cystic fibrosis seems to be enough to produce a measurable alteration in autonomic sensitivity .It also implies that since these abnormalities are present in the asymptomatic state they are not sufficient to produce the phenotype of cystic fibrosis .The end organ responsiveness indicates a lesion in alpha adrenergic ,beta adrenergic and cholinergic systems at or beyond the level of the receptor .

Asthma

Possible causes of bronchial hyperreactivity include a decrease in baseline airway calibre , increased responsiveness of the smooth muscle itself , an abnormality due to epithelial damage with an increased accessibility of stimulus to target cells or disorders of autonomic regulation .

Autonomic nervous control of the airways is complex since the non adrenergic and non cholinergic (NANC) system and several neuropeptides have been recognised in addition to the more classical cholinergic and adrenergic mechanisms [93] . Airway hyperreactivity could be due to increased parasympathetic and alpha adrenergic activity or decreased beta adrenergic or non cholinergic activity [94] .

Vagal nerves cause bronchoconstriction by release of acetylcholine at postganglionic endings on muscle .The distribution of constriction mediated via the vagi has been shown to be maximal in the small bronchi and absent in bronchioles and alveolar ducts . Vagal activity is thought to be increased , explaining the increased muscle tone in asthma .This could be due to changes in the sensory pathways, central connections or efferent pathways of the vagus . Bronchomotor tone has been shown to be affected by

stimulation of receptors in the nose , larynx ,lungs , chemoreceptors and baroreceptors . Stimulation of these receptors brings about reflex bronchoconstriction via vagal efferent pathways . It is thought that various feedback mechanisms may decrease or increase the degree of reflex bronchoconstriction , for example , stimulation of the airways causes bronchoconstriction which in turn stimulates airways receptors .Damage to airway epithelium may also sensitize sensory receptors and thus cause reflex responses .Viral upper respiratory tract infections and ozone cause reversible damage to airway epithelium and this may predispose subjects with colds to bronchoconstriction . Neural output from the central nervous system (CNS) in the absence of sensory input from the lungs could also be responsible for vagal efferent activity . In asthma , the role of emotions on airways control is assumed to be expressed via the parasympathetic system .These pathways might play a role in airway reactivity .The exact mechanism is unclear because the various stimuli causing an exaggerated bronchospasm all stimulate sensory receptors in the airways with subsequent vagal reflex bronchoconstriction . There may be enhanced neuro transmission in cholinergic ganglia because of release of other neurotransmitters or mediators , or facilitation of acetylcholine release from post ganglionic nerve terminals .There may be an increased effect of cholinergic stimulation of airway smooth muscle due to increased muscarinic receptor density or affinity , or due to increased efficacy of signal transduction . A specific enhancement of muscarinic receptors is unlikely since similar effects are observed with other substances , for example , histamine ,leucotrienes and prostaglandins and is more likely to be explained by mechanical factors .

The sympathetic nervous system to the lungs originates from the upper thoracic preganglionic fibres that end in the extrapulmonary stellate ganglion . Sympathetic nerves to the smooth muscle in man have not been demonstrated conclusively and the role of sympathetic nerves in regulating resting tone is therefore not clear . Experiments in dogs suggest a small degree of sympathetic dilator tone exists dependent on an intact vagus . Normal healthy adults show no response to beta blockade but asthmatics given propranolol may develop severe bronchoconstriction reversed by atropine suggesting that unopposed parasympathetic activity is the main cause of beta blocker induced bronchoconstriction .This is also partly due to beta receptor hyporesponsiveness in asthmatics [95] shown also in allergic rhinitis and the preallergic state .

There are reports of alpha receptors in human airway smooth muscle that produce constriction when stimulated [95] . Studies in guinea pigs , later confirmed on human lung tissue , have suggested that the relative density of alpha adrenergic to beta adrenergic receptors is increased during experimentally induced asthma , although there do not seem to be pharmacological implications of this .

The gastrointestinal tract in humans is known to have its own autonomic nerve supply . Since the tracheobronchial tree arises from the foregut , it has been suggested that a similar system exists in the lungs . NANC inhibitory bronchodilator nerves are prominent in human airways and these nerves may be defective in asthma .These nerve terminals secrete various neurotransmitters and in humans nitric oxide is responsible for bronchodilatation [96] .This is the only known neural bronchodilator pathway in human airways .

Viral Upper Respiratory tract infections

Viral infections lead to production of virus specific IgE , upregulation of leucocyte inflammatory activity , enhancement of factors involved in the generation of late phase allergic responses . In addition , autonomic dysfunction has been noted with alterations in *B* adrenergic and cholinergic activity possibly enhanced by damage to the airway [97] . Consequently , changes in airway responsiveness after viral upper respiratory tract infections (URTI) have been noted . Experiments on guinea pigs have shown that influenza virus may result in a selective loss of M 2 receptors compared with M 3 receptors , due to the action of viral muraminidase on the sialic acid residues on the M2 receptors which are necessary for their function .This results in loss of autoreceptor function and enhanced cholinergic bronchoconstriction .

Summary

It seems that all the variables involved in the subject of this thesis , respiratory disease , infection and age , have been found to have an adverse effect on autonomic function . The association between autonomic impairment and infection has been recognized . Darowski et al [98] have found that patients admitted with hypothermia had evidence of definite or probable infection usually of the respiratory or of the urinary system . Infection can complicate hypothermia but the latter may also come about if there is failure of peripheral vasoconstriction [99] . Autonomic impairment has also been reported in association with a large number of infectious diseases and it may complicate infective processes both as a result of involvement of specific parts of the anatomy of the ANS or as a generalized effect of infection itself .

An important factor to consider is the age of the sample studied . Postural hypotension is common in elderly people and it may be the only feature suggestive of autonomic damage . It is , however , difficult to decide whether this is due to primary autonomic failure or due to the ageing process itself . It is possible that postural hypotension is the " tip of the iceberg " and is manifested only when all the compensatory mechanisms of autonomic failure have been exhausted [100] and if a minor insult is inflicted on an already degenerating ANS .

Autonomic impairment has been shown in a wide range of respiratory disorders , infective , inflammatory and neoplastic . Pneumonia carries considerable morbidity and mortality and is the fifth leading cause of death in those above 65 years [101] . Some of the features of pneumonia , such as postural hypotension or arrythmias , are known to be precipitated by autonomic instability in other circumstances . Another

manifestation that may be related to dysfunction of the ANS is hyponatraemia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) .This syndrome is a well recognised complication of pneumonia . It is possible that a mechanism similar to that in Guillain - Barre syndrome or vincristine neuropathy is responsible .There may be a resetting of the osmostat due to an abnormality of the afferent fibres from baroreceptors (low pressure , high pressure or both) . A correlation between SIADH and respiratory failure with retention of carbon dioxide was noted . Mechanical haemodynamic factors such as positive pressure ventilation or a reduction in venous return due to prolonged bed rest may contribute to the development of the SIADH in pneumonia [44] .

To date the association between autonomic impairment and pneumonia has been shown in children with familial dysautonomia having increased autonomic activity and gastro oesophageal reflux predisposing to lower respiratory tract infections [102] .

Elderly people are generally presumed to be increasingly susceptible to infection and this is usually assumed to be due to the inevitable decline in immunological resistance against microorganisms . But it is surprising how circumstantial the evidence is for this popular notion since most of the immunological defences of the body are relatively intact [101] and some infections , for example URTIs , are not more frequent in old age . Indirect evidence includes a decline in the number of T cells and immunoresponsivity and an increase in autoimmune disorders with age . It is possible that other factors may be responsible for increasing susceptibility to infection , since the attack rate for pneumonia , however , rises steadily with age and increases 100 fold

between the third and the ninth decades of life . Pontopidden et al 1960 [103] showed a progressive reduction in the sensitivity of the cough reflex with increasing age . The increasingly recognised association between autonomic impairment and infection and the possibility that some of the clinical manifestations of pneumonia may be due to autonomic impairment were the motives behind this study . The questions adressed by the research described in this thesis are 1- Do patients with pneumonia have evidence of impairment of autonomic cardiovascular reflexes when compared with healthy elderly people and 2 - if so how long does this persist .

Chapter 2 : Patients and methods

2/1 Subjects

The number of subjects included in the study was 38 .They were grouped as follows .

1 - 15 normal elderly controls aged 71 - 93 .

2 - 11 elderly people who sustained a fracture of the neck of the femur aged 70 - 90 . 3 patients with abnormal results were followed up at 6 weeks .

3 - 12 elderly people admitted with a pneumonia aged 74 - 96 . These were followed up at 6 weeks and 6 months .

2/1.1 Sources

The first group were volunteers ,both men and women recruited from relatives and friends of patients admitted for treatment .The second group was collected from patients in the orthogeriatric wards in Christchurch Hospital where they were admitted for rehabilitation following a fracture of the neck of femur . The third group was made up of patients admitted to the Department of Medicine for the Elderly at the Royal Bournemouth Hospital for treatment of a pneumonia .

2/1.2 Approval and Consent

Permission to carry out the studies was obtained from the Ethical Committee of the East Dorset Health Authority .Informed consent was obtained from all subjects and patients .

2/1.3 Mode of Approach

All the groups of subjects were invited to participate in this study by the author .

2/1.4 Criteria for Inclusion of Subjects in the Study

2/1.4 .1 Group One

a - Normal fit elderly people , defined by Woodhouse et al [104] as being over 65 years , living independently at home or in sheltered accomodation , freely ambulant and without significant hepatic , renal , cardiac , respiratory or metabolic disorder on either clinical examination or laboratory investigation , and not receiving regular prescribed medication .

b - Non - smokers , alcohol intake less than 10 units per week .

c - Communicative and co - operative , willing and able to perform and complete the full study .

d - Absence of exclusion criteria .

2/1.4 .2 Group two

a - Patients just mobilizing after a fracture of the neck of femur sustained after an accidental fall .

b - Defined (as above) as normal fit elderly people prior to the accident .

c - Non - smoker , alcohol intake less than 10 units per week .

d - Communicative and co - operative willing to perform and complete the full study .

e - Absence of exclusion criteria .

2/1.4 .3 Group three

a - Patients admitted with pneumonia with chest radiograph changes compatible with consolidation ***and*** a clinical setting of pneumonia , that is , two of the following symptoms or signs ; systemic upset , pyrexia , pleuritic chest pain , cough , discoloured sputum , haemoptysis , confusion , signs of consolidation , localised crepitations or tachypnoea (> 24 / min)

b - Defined (as above) as healthy elderly people prior to this illness . Any medication that the patient was on was not considered an exclusion criterion as long as it did not interfere with heart rate or blood pressure , in this group .

c - Non - smokers , alcohol intake less than 10 units per week , mobile communicative and co - operative .

d - Absence of exclusion criteria .

2/1.5 Criteria for Exclusion of Subjects in the study

2/1.5 .1 Group 1

a - Absence of inclusion criteria .

b - Unable to co - operate with the regimen of the Autonomic Function Tests (AFTs)

c - A recent (< 6 months) ophtalmic operation , for example cataract operation .

d - Medical conditions known to be complicated by autonomic neuropathy .

e - Any medication that might alter heart rate or blood pressure .

2/1.5 .2 Group 2

a - Absence of inclusion criteria .

b - Unable to co - operate with the regimen of the AFTs .

c - An inability to stand up without support on a walking frame .

d - Medical conditions known to be complicated by autonomic neuropathy .

e - Any medication that might alter heart rate or blood pressure

f - Ophtalmic surgery in last 6 months .

g - Subject on warfarin ; thought by author to be a relative contraindication to the Valsalva manoeuvre .

h - Dehydration ; diagnosed clinically or biochemically with a disproportionate rise in urea compared to creatinine and / or a high haematocrit .

2/1.5 .3 Group 3

a - Absence of inclusion criteria

b - Unable to co - operate with the regimen of the AFTs .

c - Ophtalmic surgery in last 6 months .

d - Subject on warfarin ; thought by author to be a relative contraindication to the Valsalva manoeuvre .

e - Dehydration ; diagnosed clinically or biochemically with a disproportionate rise in urea compared to creatinine and / or a high haematocrit .

f - Medical conditions known to be complicated by autonomic neuropathy [8] .

2/2 Methods

2/2.1 Apparatus

a - An ECG Machine calibrated at 25 mm per second and 1 mV per cm .

b - A sphygmomanometer (Health Aid) The same instrument was used throughout the study .

c - An anaeroid manometer connected to a mouth piece .

d - An ECG Ruler .

e - A Hand Grip Dynamometer .

2/2.2 Tests Performed

A -Tests reflecting parasympathetic damage .

1 - Heart rate response to the Valsalva Manoeuvre

2 - Heart rate (RR variation) during deep breathing .

3 -Immediate heart rate response to standing .

B - Tests reflecting Sympathetic Damage

4 - Blood Pressure response to standing .

5 - Blood Pressure response to sustained hand grip .

2/2.3 Patient preparation

One source of confounding variables in testing of autonomic function resides in the test subject . The subjects were asked to avoid food , coffee ,tea , or nicotine for three hours before the study since all of these can increase the baseline heart rate .The level of anxiety or discomfort was kept to a minimum .Subjects in pain or obviously distraught

were not tested .The tests were conducted in a comfortable ,warm ,quiet environment since any anxiety or discomfort would lead to an increased plasma catecholamine level with a consequent tachycardia .Compressive clothing and corsets were not worn on the morning of the tests and subjects were asked to avoid alcohol for 24 hours prior to testing [27] .

2./2.4 *Tests reflecting parasympathetic damage* .

1 - The heart rate response to the Valsalva manoeuvre .

While sitting the subject was asked to blow into a mouth piece connected to an anaeroid manometer and hold a pressure of 40 mm Hg for 15 seconds .The test was repeated until two reproducible responses were obtained .Koener et al (1976) [106] showed that a pressure below 20 mmHg was inadequate and above 60 mmHg less reproducible . Hence a pressure of 40 mmHg seems to yield reproducible results .If the patient was unable to reach the level of 40 mmHg ,20mmHg or more was considered as acceptable . The manoeuvre was repeated three times with one minute intervals between . An ECG was recorded during the test and the Valsalva ratio calculated .The ratio is the maximum heart rate in response to the Valsalva manoeuvre divided by the minimal response occurring within 30 seconds of the peak heart rate .

2 - Heart Rate variation during deep breathing .

While sitting the subject was asked to breath in deeply and hold for five seconds and then out and hold for five seconds .This was repeated six consecutive times . An electrocardiogram was recorded throughout , and the onset of each inspiration and expiration was marked .The maximum and minimum RR intervals during each breathing cycle were measured with a ruler and converted to beats per minute .The result was then expressed as the mean difference between the maximum and minimum heart rate for the six measured cycles .

3 - The immediate response of the heart rate on standing .

The heart rate (HR) was recorded while the patient was lying .The point was marked on the ECG trace when the patient was asked to stand up .The shortest RR at around the 15 th beat and the longest RR at around the 30 th beat were measured .The HR responses was expressed as the 30 : 15 ratio , that is , the ratio of the RR intervals at (or nearest to) the 30 th and 15 th beats . This test was performed once .

2/2.5 *Tests reflecting Sympathetic Damage* .

4 - The blood pressure response to sustained handgrip .

While sitting down the patient was asked to produce a maximum voluntary contraction using a handgrip dynamometer .The subject was then asked to hold the grip at 30 % of the maximum contraction for as long as possible up to 5 minutes .BP was measured three times before and at one minute intervals during handgrip .

The result was given as the difference between the highest diastolic blood pressure during sustained handgrip and the mean of the three diastolic BP readings before handgrip .

5 - Blood Pressure response to standing .

The patient was asked to lie down and rest for 20 minutes . Ten Harkel et al [107] showed that the orthostatic reduction in BP is greater after 20 minutes of preceding rest than 1 minute ,increasing from a mean systolic / diastolic decrement of 8 / 9 to 17 / 19 mmHg .The arm was at heart level since arm position influences measurement of BP . The subjects blood pressure was measured while laying down and again 1 ,2 and 5 minutes after standing up .

2/2.6 *Performing the tests* .

Two batteries of tests have been described by O'Brien [54] and Ewing [12] .The former battery is shorter and less demanding and would have been easier to perform , however , in this study we used the battery of tests as suggested by Ewing as this was likely to provide better information .

The group of pneumonia patients was first tested after antibiotic therapy , when their temperature was normal , increasing appetite and mobilizing prior to discharge . All the patients received antibiotic therapy , and various combinations of the other forms of treatment (Table 3) . The patients were not receiving any of these treatments other than physiotherapy when tested for the first time .

After the patient was prepared , the tests were performed in the following order in the sitting position ; heart rate response to the Valsalva manoeuvre , heart rate response to deep breathing and blood pressure response to sustained hand grip .The patient was then asked to lie down on a couch or bed for 20 minutes . Three blood pressure readings were taken in the supine position . The heart rate was then recorded using an electrocardiogram and the patient was asked to stand up while the heart rate was being recorded . The blood pressure was then recorded while the patient was standing . Once the tests were performed the results were calculated using an ECG ruler .The same ruler was used throughout the study and all measurements were made by one observer .Results were grouped as normal , borderline or abnormal (Table 1) . The results were then categorized into one of four groups .Normal , early parasympathetic damage with one of the three tests of parasympathetic function abnormal ,definite parasympathetic damage with results of at least two of the parasympathetic function tests abnormal ,combined parasympathetic and sympathetic damage if there is one abnormal parasympathetic test in addition to one sympathetic test .

2/2.7 Problems encountered during the study .

Although there were many patients admitted to the acute Care of the Elderly wards with a diagnosis of lower respiratory tract infection or clinical pneumonia , many were unsuitable for the study (Table 2) .The reasons were mainly failure to meet the criteria for inclusion , and several were too frail and ill to cooperate with the protocol .Some could not perform a Valsalva manoeuvre correctly , others could not stand up unaided

and several could not perform the sustained handgrip test due to easy fatigueability and lack of understanding of what the test entailed .

Others could not be included because of medical contraindications such as the presence of diseases that could cause autonomic impairment , drugs that interfered with heart rate and cardiac arrhythmias , most commonly atrial fibrillation , that make the calculation of heart rate changes unreliable using the method adopted in this study .

Once a patient was considered suitable for the study , by meeting the inclusion criteria and absence of any exclusion criteria , consent was obtained .Only one patient declined to take part . The fact that the tests were non invasive and not having to undergo painful procedures was reassuring to the patients .One patient did not come for the first follow up and his results have been omitted .Two patients were excluded from the study simply because they were taking warfarin and it was considered prudent not to ask them to do a Valsalva manoeuvre .

2/3.1 Statistics

Statistical analysis was performed using Fisher's Exact Probability Test and Yate's Chi squared test . When analysed the results were grouped as normal and not normal , the latter group including borderline results as well as the abnormal ones .

Test	Normal	Borderline	Abnormal
Valsalva Ratio	> 1.21	1.11 - 1.20	< 1.10
RR variation with deep breathing	> 15 Beats / min	11 - 14 Beats / min	< 10 Beats / min
30 : 15 Ratio	> 1.04	1.01 - 1.03	< 1.00
Fall in systolic blood pressure on standing	< 10 mmHg	11 - 29 mmHg	> 30 mmHg
Rise in diastolic blood pressure during sustained handgrip	> 16 mmHg	11 - 15 mmHg	< 10 mmHg

Table 1 - Normal , borderline and abnormal values in tests of cardiovascular autonomic function [12]

1 - Inability to co - operate with the protocol	a - Frailty and illness .
	b - Lack of understanding of the test involved .
2 - Medical contraindications	a - Presence of diseases that can cause autonomic impairment .
	b - Drugs that interfere with heart rate and blood pressure .
	c - Arrhythmias , most commonly atrial fibrillation .

Table 2 - Summary of the main reasons for exclusion from the study .

1 - Intravenous fluids
2 - Oxygen
3 - Intravenous or oral antibiotics
4 - Nebulised salbutamol and / or ipratropium
5 - Anti pyretics (eg paracetamol)
6 - Physiotherapy
7 - Continuous positive airways pressure

Table 3 - Summary of treatment of pneumonia patients

Study Group	First study	Second study	Third study
Pneumonia Group	Patients tested after initial treatment , when afebrile , not ' toxic ',and mobilizing 3 - 7 days after coming off all supportive therapy	6 weeks after discharge	6 months after discharge
Fracture neck of femur group	Mobilizing after a fracture neck of femur . Approximately at the same stage of mobilization as the pneumonia group ie 3 - 7 days after coming off supportive therapy , or operation .	6 week follow up only if initial results were abnormal	No follow up
Healthy controls	Tested at subject 's convenience	No follow up	No follow up

Table 4 - Summary of study .

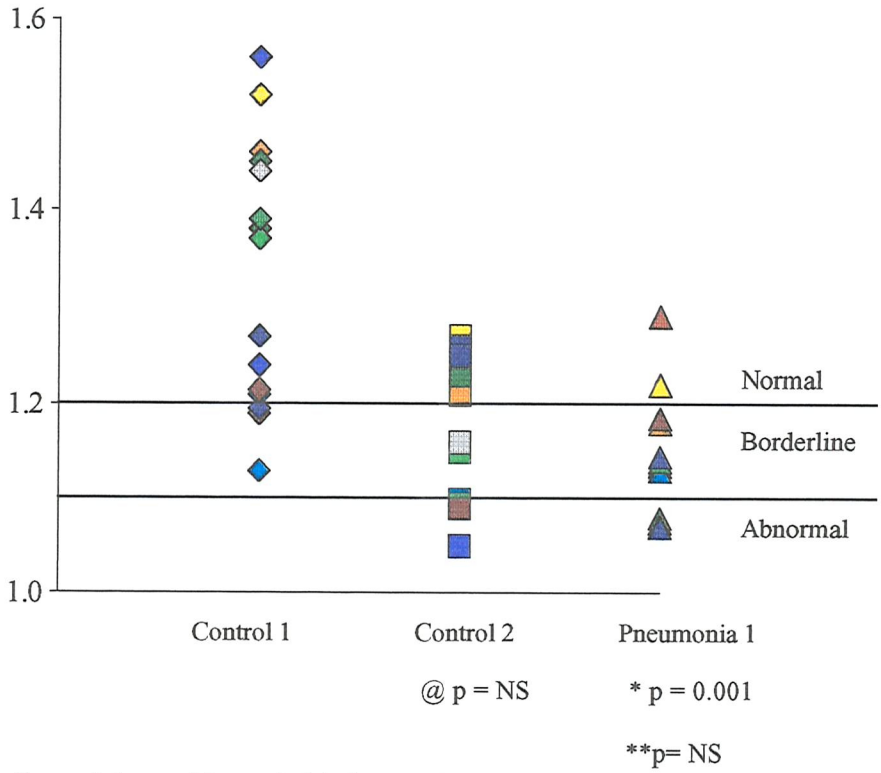
Chapter 3 : Results

The results are presented in a series of tables for each of the autonomic function tests (the Valsalva manoeuvre ; table 5 : heart rate variation with deep breathing ; table 6 : 30:15 ratio ; table 7 : postural drop in blood pressure ; table 8 and blood pressure changes during sustained hand grip ; table 9) . Results obtained in each of the study groups are shown in the relevant table . Each table is followed by two graphs showing the relation between each of the study groups . The first graph shows the results obtained in the healthy elderly people group (control 1) , elderly with a fracture neck of femur (control 2) and the pneumonia group immediately after treatment (pneumonia 1) . The second graph shows the results in the different pneumonia groups : 1 , (immediately after recovery from pneumonia) ; 2 , (6 weeks after discharge) and 3 , (6 months after discharge) . Results of the statistical analysis of the relationship between each of the groups are shown on the relevant graph .

Groups	Number Mean Age in Years (Range)	Sex	Mean Valsalva Ratio	Valsalva Ratio Range	Normal >1.21 (%)	Borderline 1.11 - 1.20 (%)	Abnormal < 1.10 (%)
Healthy Elderly Controls	15 81.7 (71-93)	7 F 8 M	1.34	1.19 - 1.56	13 (86.6)	2 (13.3)	0 (0)
Fracture neck of femur control	11 83.1 (70 - 89)	8 F 3 M	1.17	1.05 - 1.27	6 (54.5)	2 (18.2)	3 (27.3)
Immediately post pneumonia	12 84.8 (73 - 95)	5 F 7 M	1.14	1.07 - 1.29	2 (16.6)	7 (58.3)	3 (25)
6 weeks post pneumonia	12 84.8 (73 - 95)	5 F 7 M	1.25	1.05 - 1.46	8 (66.6)	3 (25)	1 (8.3)
6 months post pneumonia	10 83.1 (73 -92)	4 F 6 M	1.23	1.06 - 1.52	7 (70)	2 (20)	1 (10)

Table 5 : Test 1 - The Valsalva Ratio .

The results show that only 16.6% of elderly patients with pneumonia had a normal Valsalva manoeuvre . There was a significant improvement at follow up , both at 6 weeks (66.6 % normal ; $p = 0.03$) and at 6 months (70% normal ; $p = 0.03$) . The first control group of healthy elderly people showed a normal manoeuvre in 86.6% ,and this was significantly different from pneumonia 1 ($p = 0.001$) but not significantly different from the second control group . Control group 2 however showed a normal response in 54.5% of subjects and this was not significantly different to any of the pneumonia groups .



Control 1 : Normal elderly people.

Control 2 : Elderly patients mobilising after a fractured neck of femur .

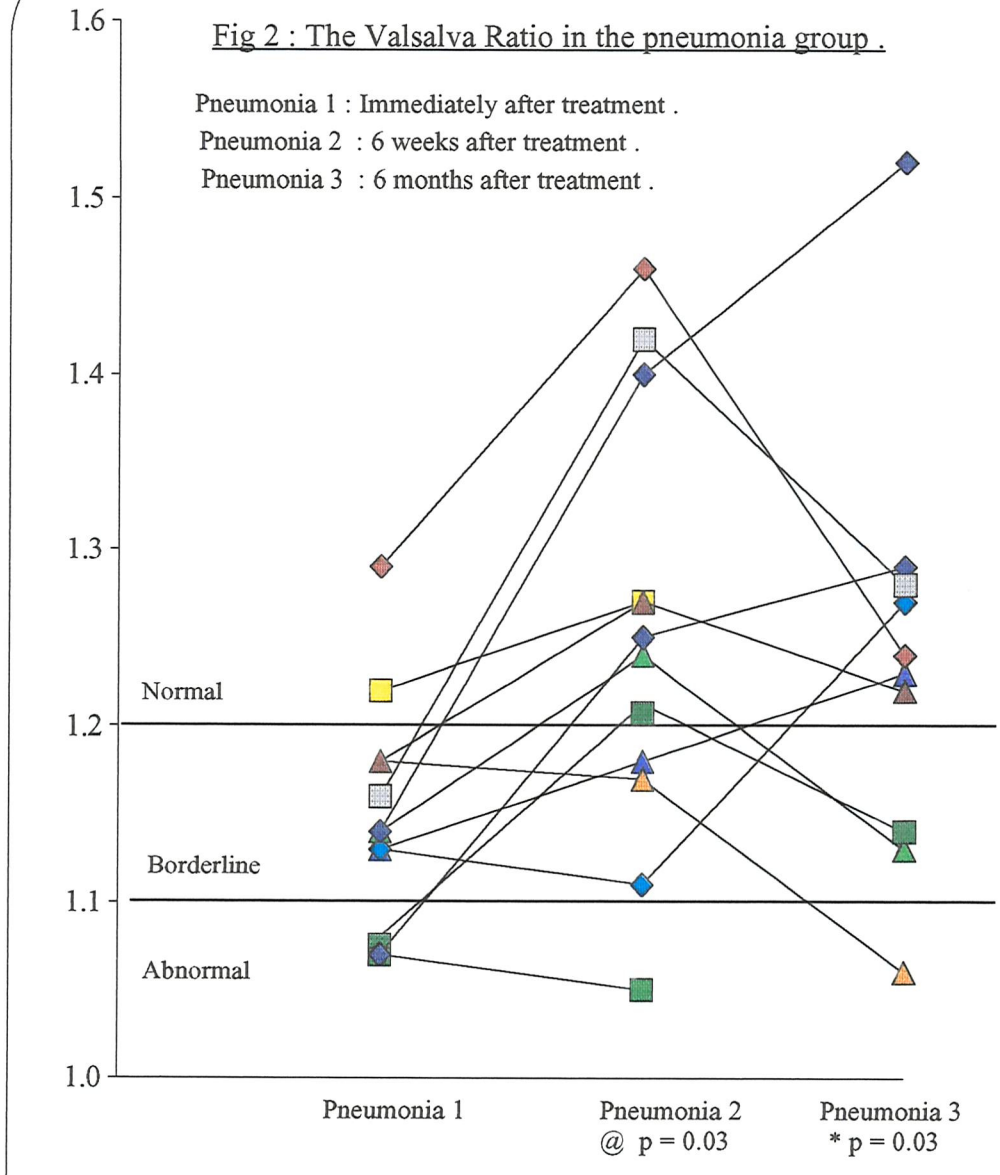
Pneumonia 1 : Immediately after treatment .

Fig 1 : The Valsalva Ratio.

@ Comparing control 2 with control 1 .

* Comparing pneumonia 1 with control 1 .

** Comparing pneumonia 1 with control 2 .



@ Comparing pneumonia 2 with pneumonia 1 .

* Comparing pneumonia 3 with pneumonia 1 .

Groups	Number Mean Age in Years (Range)	Sex	Mean Heart Rate difference	Heart Rate difference Range	Normal > 15 / min (%)	Borderline 11 - 14 / min (%)	Abnormal < 10 / min (%)
Healthy Elderly Controls	15 81.7 (71 - 93)	7 F 8 M	11.9	1.3 -29	5 (33.3)	6 (40)	4 (26.7)
Fracture Neck of femur control	11 83.1 (70 - 89)	8 F 3 M	7.1	0.41 - 18.8	2 (18.2)	0 (0)	9 (81.8)
Immediately post pneumonia	12 84.8 (73 - 95)	5 F 7 M	5.4	1.48 - 9.9	0 (0)	0 (0)	12 (100)
6 weeks post pneumonia	12 83.1 (73 - 95)	5 F 7 M	8.8	2.13 - 23.6	1 (8.3)	2 (16.6)	9 (75)
6 months post pneumonia	10 83.1 (73 - 92)	4 F 6 M	9.2	4.5 - 17.1	2 (20)	2 (20)	6 (60)

Table 6 : Test 2 - Heart Rate variation to deep breathing .

In this test no significant relationships were found . In the first pneumonia group none of the subjects had a normal result , and although 33.3 % of the first control group and 18.2% of the second control group had a normal result , the differences were not significant ($p > 0.05$) .There was no significant improvement in subsequent pneumonia groups , 8.3% at first and 20% at second followup ($p > 0.05$) , though there was a trend toward normal values .

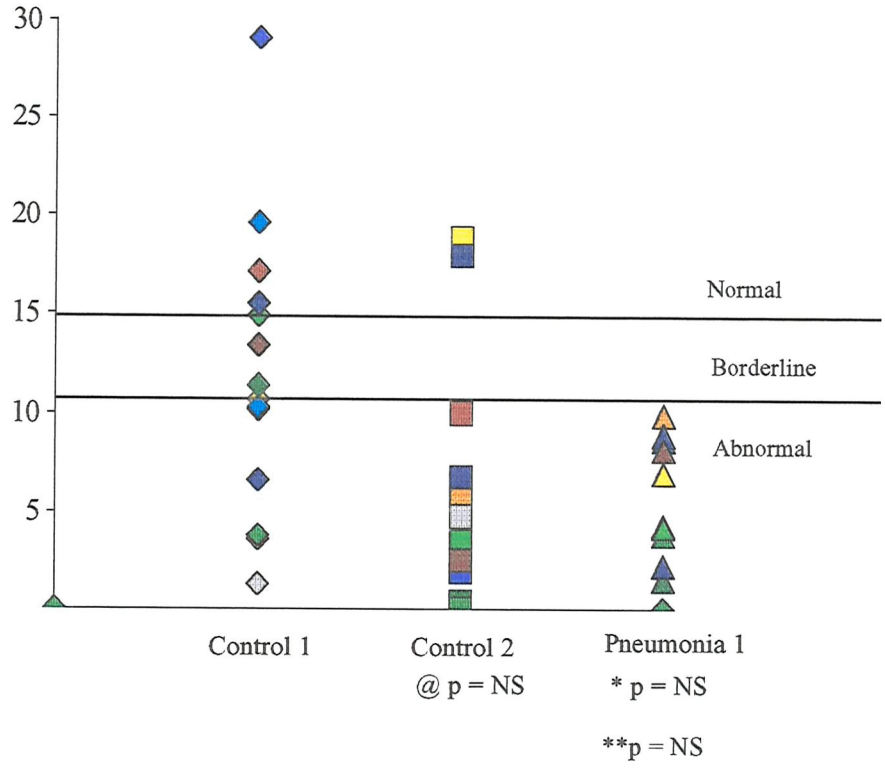


Fig 3 : Heart Rate variation with deep breathing .

@ Comparing control 2 with control 1

* Comparing pneumonia 1 with control 1 .

** Comparing pneumonia 1 with control 2 .

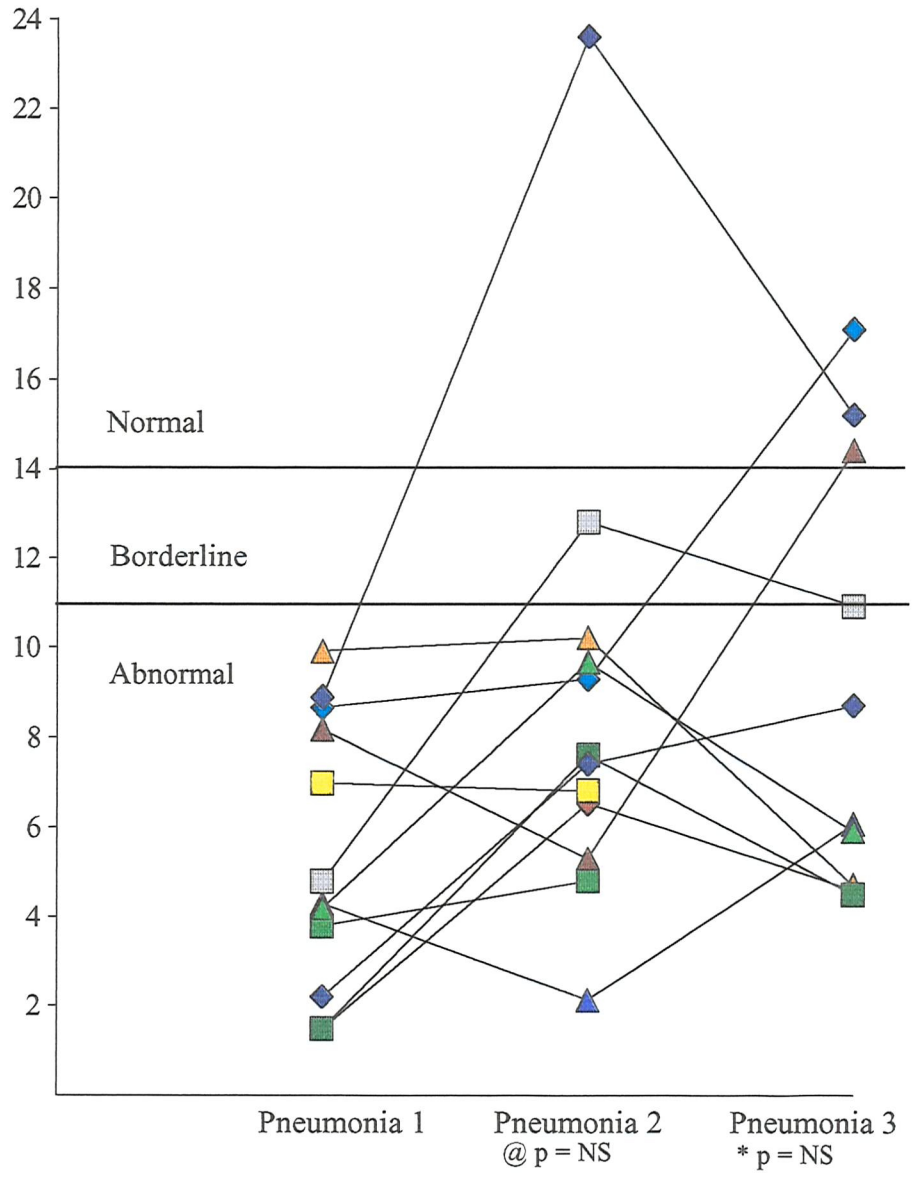


Fig 4 : Change in Heart Rate Variation in the Pneumonia Groups .

@ Comparing pneumonia 2 with pneumonia 1 .

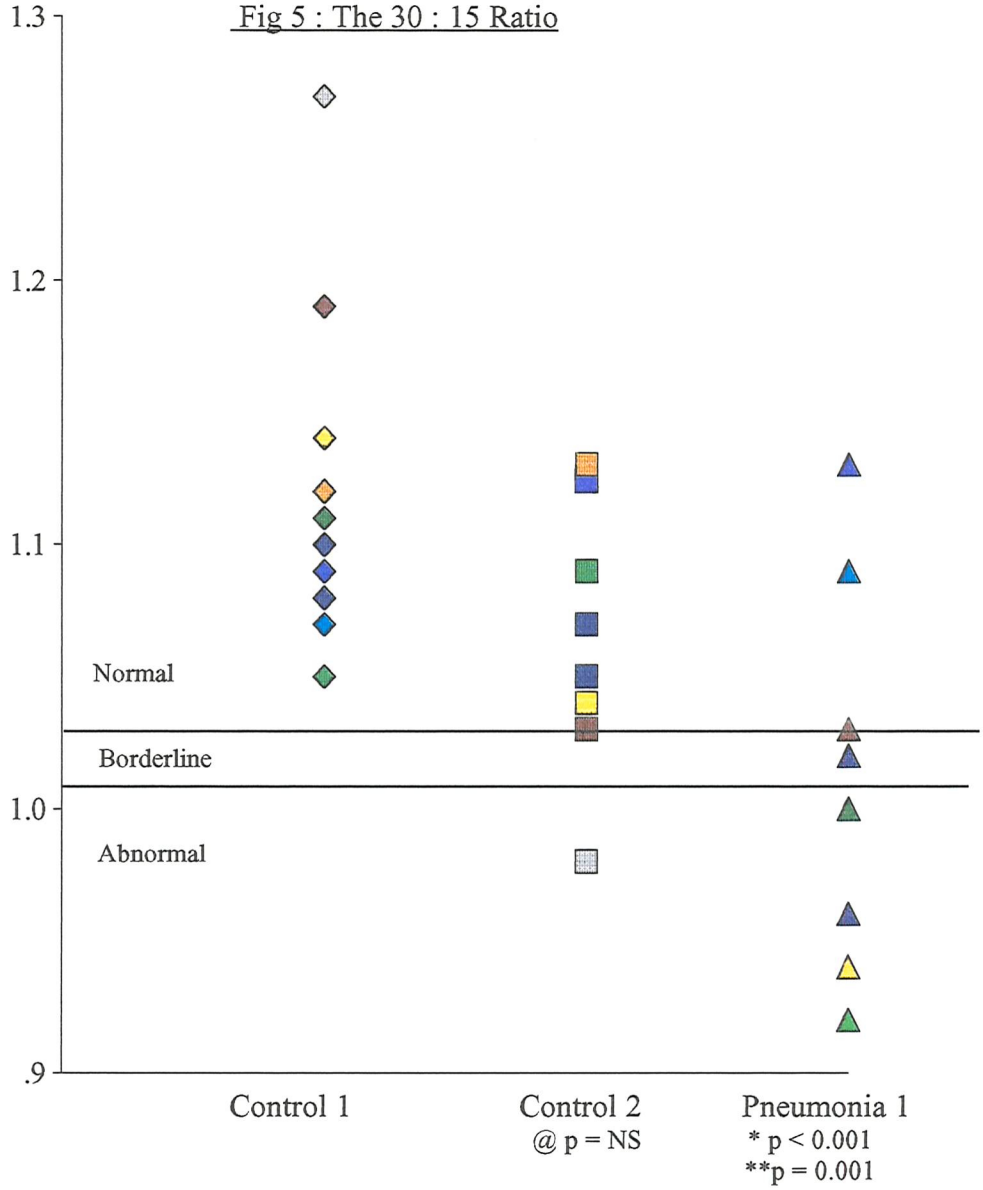
* Comparing pneumonia 3 with pneumonia 1 .

Groups	Number Mean age in Years (Range)	Sex	Mean 30 : 15 Ratio	30 : 15 Ratio Range	Normal > 1.04 (%)	Borderline 1.01 -1.03 (%)	Abnormal <1.00
Healthy Elderly Controls	15 81.7 (71 - 93)	7 F 8 M	1.11	1.05 - 1.27	15 (100)	0 (0)	0 (0)
Fracture Neck of Femur control	11 83.1 (70 -89)	8 F 3M	1.06	0.96 - 1.13	10 (90.9)	0 (0)	1 (9.1)
Immediately post pneumonia	12 84.8 (73 - 95)	5 F 7 M	1.01	0.92 - 1.13	2 (16.6)	2 (16.6)	8 (66.6)
6 weeks post pneumonia	12 84.8 (73 - 95)	5 F 7 M	1.06	0.98 - 1.12	8 (66.6)	3 (25)	1 (8.3)
6 months post pneumonia	10 83.1 (73 - 92)	4 F 6 M	1.04	0.96 - 1.13	6 (60)	3 (30)	1 (10)

Table 7 : Test 3 - Immediate Heart Rate Response to Standing (30 : 15 Ratio)

Only 16.6% of elderly patients with pneumonia had a normal 30 : 15 ratio . At 6 weeks 66.6 % were normal ($p = 0.03$) . The first control group had a normal result in 100% of subjects , while in the second group 90.9% were normal . Both were significantly different fron the first pneumonia group , $p = < 0.001$ and $p = < 0.01$ respectively . Statistically the control groups were not different from each other .

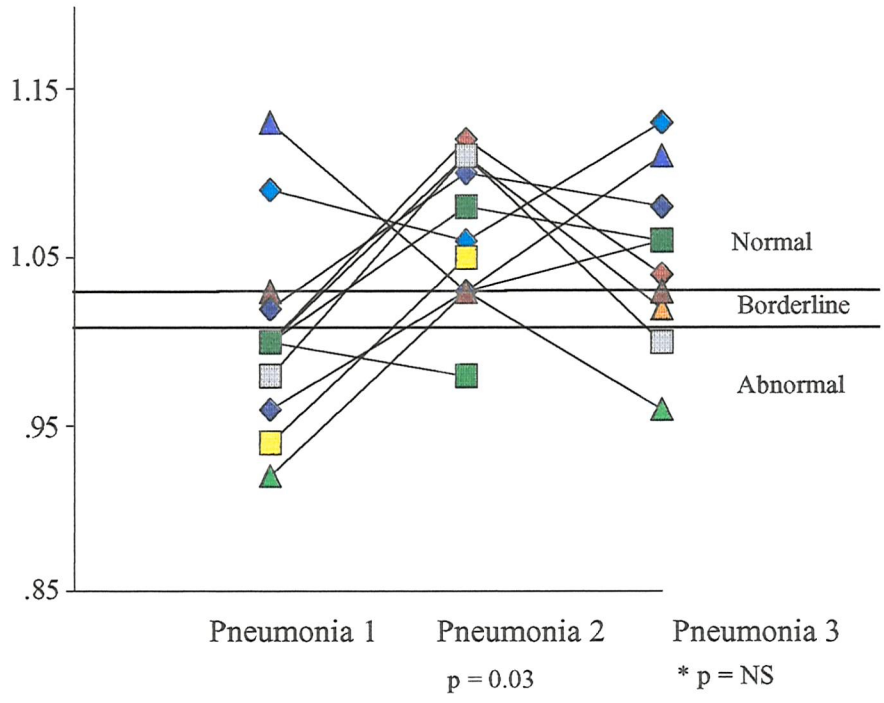
Fig 5 : The 30 : 15 Ratio



@ Comparing control 2 with control 1 .

* Comparing pneumonia 1 with control 1

** Comparing pneumonia 1 with control 2 .



@ comparing pneumonia 2 with pneumonia 1

* comparing pneumonia 3 with pneumonia 1

Fig 6 - 30 : 15 Ratio in the Pneumonia groups.

Groups	Number Mean Age in Years (Range)	Sex	Mean Supine Blood Pressure (mmHg)	Mean Standing Blood Pressure (mmHg)	Mean Postural Drop in Systolic blood pressure (mmHg)	Normal < 10 (%)	Borderline 11 - 29 (%)	Abnormal >30 (%)
Healthy Elderly Controls	15 81.7 (71 - 93)	7 F 8 M	162 / 86	157 / 85	5.8	14 (93.3)	1 (6.7)	0 (0)
Fracture Neck of Femur controls	11 83.1 (70 - 89)	8 F 3 M	156 / 86	149 / 85	7.9	10 (90.9)	1 (9.1)	0 (0)
Immediately post pneumonia	12 84.8 (73 - 95)	5 F 7 M	159 / 88	143 / 81	15.8	5 (41.6)	4 (33.4)	3 (25)
6 weeks post pneumonia	12 84.8 (73 - 95)	5 F 7 M	166 / 83	150 /82	11.8	7 (58.3)	3 (25)	2 (16.7)
6 months post pneumonia	10 83.1 (73 - 92)	4 F 6 M	166 / 86	160 / 86	5.6	10 (100)	0 (0)	0 (0)

Table 8 : Test 4 - Blood Pressure response to standing .

In the first pneumonia group 41.6% had a normal result .On follow up 58.3% were normal at 6 weeks (p= NS) and 100% at 6 months (p = 0.02) . 93.9% and 90.9% of results were normal in the first and second control groups respectively .These were not significantly different from each other but were different from the first pneumonia group , p = 0.01 and p = 0.04 respectively .

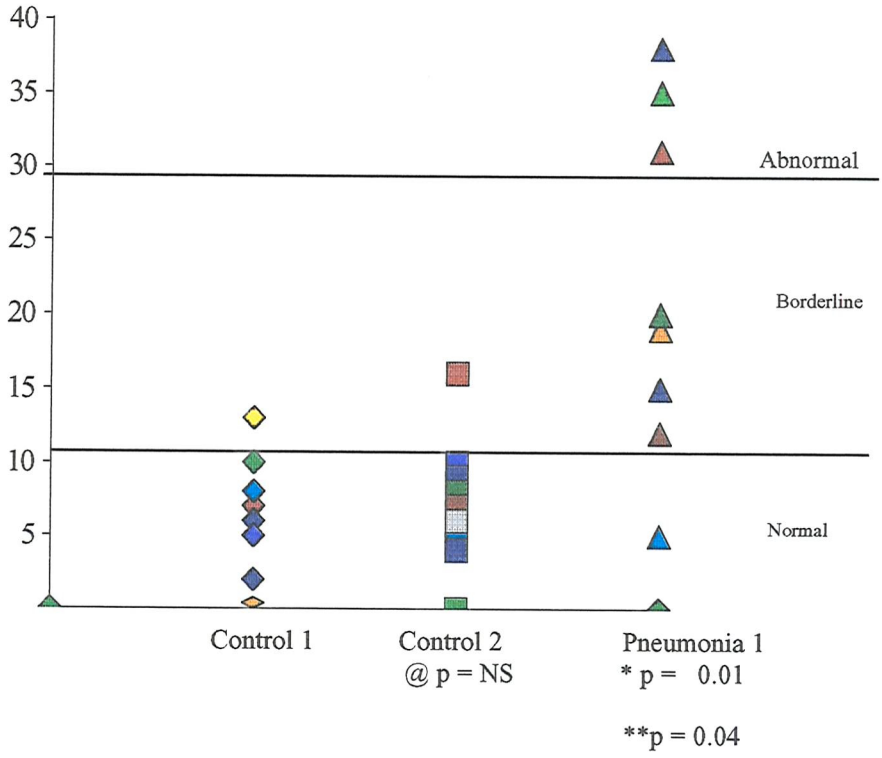


Fig 7 : Postural drop in Blood Pressure (mmHg) .

@ Comparing control 2 with control 1 .

* Comparing pneumonia 1 with control 1 .

** Comparing pneumonia 1 with control 2 .

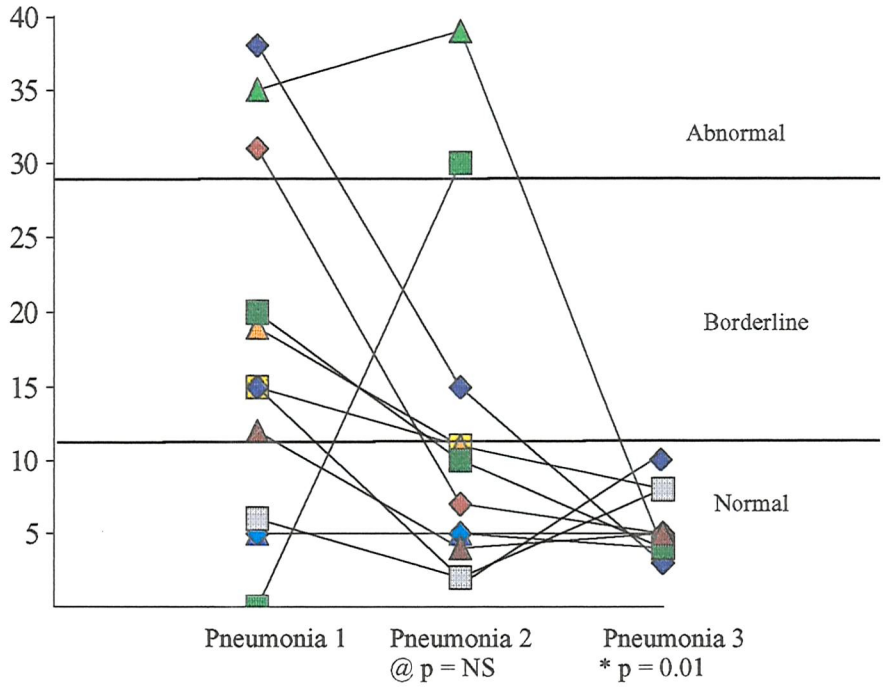


Fig 8 : Postural drop in Blood Pressure in the Pneumonia Groups (mmHg)

@ : Comparing Pneumonia 2 with Pneumonia 1 .

* : Comparing Pneumonia 3 with Pneumonia 1 .

Groups	Number Mean age in years (Range)	Sex	Mean resting Blood Pressure (mmHg)	Mean BP during sustained hand grip (mmHg)	Mean rise in diastolic BP (mmHg)	Normal >16 (mmHg)	Borderline 11 - 15 (mmHg)	Abnormal < 10 (mmHg)
Healthy Elderly Controls	15 81.7 (71 - 93)	7 F 8 M	163 / 83	177 / 103	22	14 (93.3)	1 (6.7)	0 (0)
Fracture Neck of Femur control	11 83.1 (70 - 89)	8 F 3 M	158 / 86	168 / 103	17.9	8 (72.8)	2 (18.1)	1 (9.1)
Immediately post pneumonia	12 84.8 (73 - 95)	5 F 7 M	160 / 88	168 / 96	10.6	1 (8.4)	5 (41.6)	6 (50)
6 weeks post pneumonia	12 84.8 (73 - 95)	5 F 7 M	166 / 82	172 / 99	19.6	10 (83.3)	1 (8.3)	1 (8.3)
6 months post pneumonia	10 83.1 (73 - 92)	4 F 6 M	122 / 65	172 / 103	17.1	8 (80)	1 (10)	1 (10)

Table 9 : Test 5 - Blood Pressure response to sustained handgrip .

The first pneumonia group had a normal result in 8.4% of cases . On follow up 83.3% were normal at 6 weeks ($p = 0.001$) and 80 % at 6 months ($p < 0.01$) . The first control group was normal in 93.3% of cases and 72.8% in the second group . This difference was not significant ($p > 0.05$) ,but both groups were significantly different from the first pneumonia group , $p < 0.001$ and $p < 0.01$ respectively .

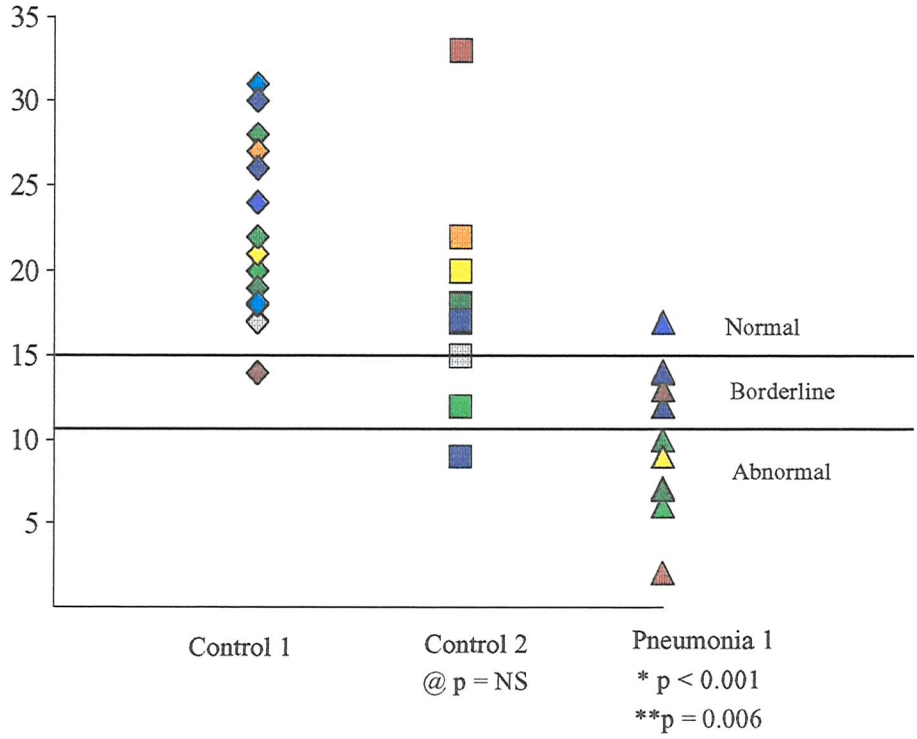


Fig 9 : Rise in diastolic blood pressure to sustained hand grip (mmHg) .

@ Comparing control 2 to control 1.

* Comparing Pneumonia 1 to control 1 .

** Comparing Pneumonia 1 to control 2 .

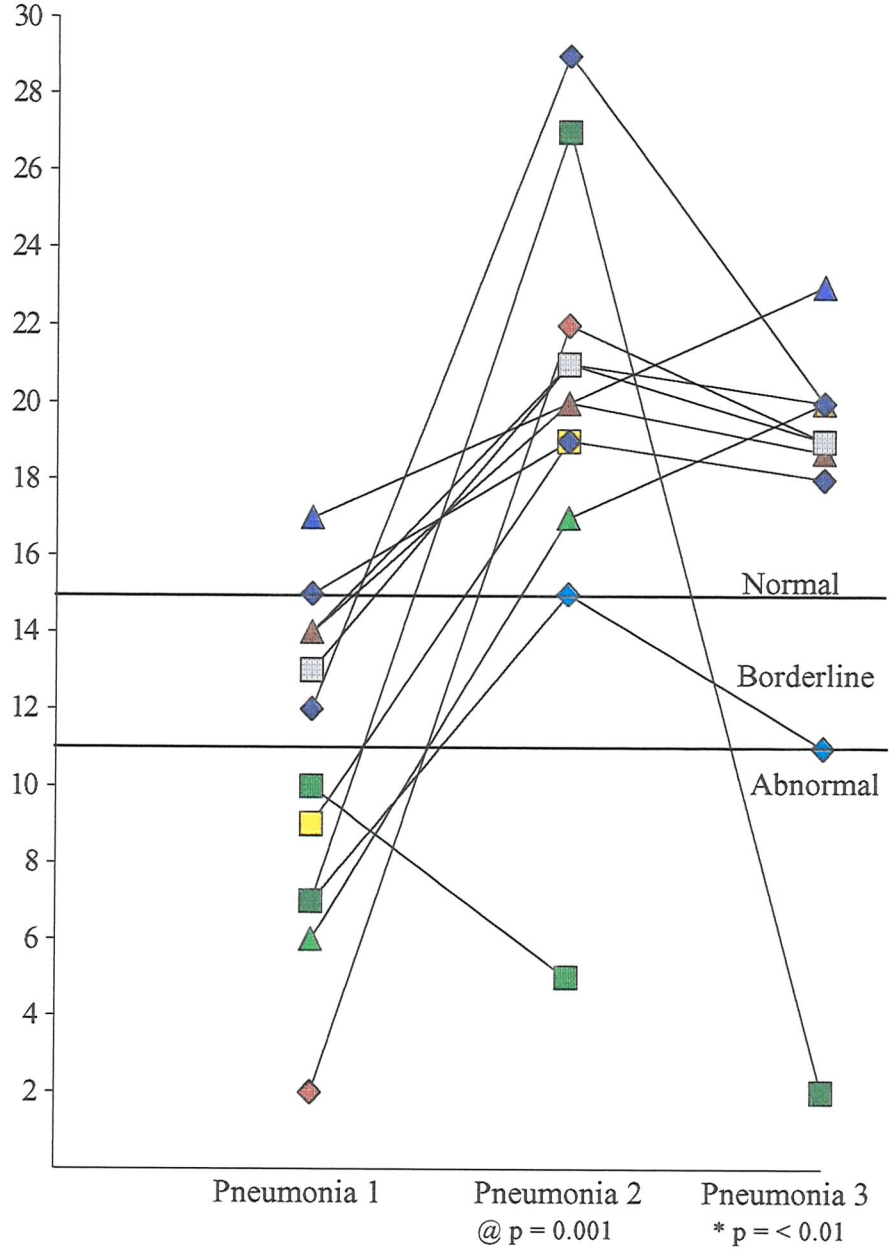


Fig 10 : Rise in diastolic blood pressure in the Pneumonia Groups
(mmHg)

@ : Comparing Pneumonia 2 with Pneumonia 1
* : Comparing Pneumonia 3 with Pneumonia 1

Chapter 4 : Discussion

Despite the use of antibiotics , pneumonia is still a major cause of death in elderly people .It is also a cause of substantial morbidity and a large burden on the health care system with hospital stays 3 - 5 days longer in the elderly compared to younger people [101] . American and British based studies show mortality rates of 24 % - 33 % in the elderly compared to 5.7 - 8.0 % in younger people . Even higher mortality rates are observed in nursing homes and in patients with hospital acquired pneumonias [101] . Factors predicting mortality from pneumonia include prexisting coronary heart disease , dementia , urinary incontinence and impaired mobility impaired mental status , absence of fever , tachypnoea , hypotension , cyanosis and diffuse abnormalities on chest examination [108] . With an aged population , and pneumonia the fifth leading cause of death in this age group ,there is a need for a thorough understanding of the effects of pneumonia .

Pathological features of Pneumonia

Pneumonia is an inflammatory process characterized by consolidation due to the presence of exudate involving the alveolar tissue and terminal bronchioles of the lungs . It can be classified anatomically into three main types , bronchopneumonia ,lobar pneumonia and interstitial pneumonia or according to the etiological agent .In lobar pneumonia , the causative bacteria lead to the production of a watery inflammatory exudate in the alveoli .This flows directly into the bronchioles and related alveoli , filling them and spilling over into adjacent lobules and segments of the lung . Damage to the bronchiolar walls is present although this is thought to be relatively unimportant

[109] .The exudate and bacteria spread through the lumens rather than the walls of the terminal airways .The consolidation is always confined to the affected lobe , which is diffusely involved . In bronchopneumonia , the inflammation occurs primarily in the terminal and respiratory bronchioles .The walls are damaged so that infection and exudation extend into the surrounding and peribronchiolar alveoli and into the acinus supplied by the affected terminal bronchiole [109] . The occurance of lobar or bronchopneumonia could be seen to depend on the balance between the rapid formation of infected oedema fluid and the localisation of infection by leucocyte defences [110] .

For the purposes of the study no distinction was made between the different pathological forms of pneumonia since clinically the distinction is largely irrelevant because a clear cut distinction between them cannot always be made , management is similar and the same organism can cause a variable clinical picture [110] .

Importance of Patient preparation

The evaluation of autonomic function starts from the initial interview of the patient in the office or at bed side . The office evaluation , consisting of the history , examination and preferably routine laboratory tests is a necessary prelude and complement to the formal testing of autonomic function . The clinician needs to recognize the presence and distribution of autonomic dysfunction with particular reference to aspects of dysautonomia that do not lend themselves to laboratory measurements such as intermittent problems like paroxysmal tachycardia or hypertension and certain orthostatic presyncopal symptoms , time pattern in the

development of symptoms and response to any therapy . The clinician must also attempt to recognize patterns of autonomic failure that fit into specific syndromes . As the clinical importance of autonomic neuropathy is increasingly recognized the need to reach a diagnosis as quickly and easily as possible increases . Tests based on cardiovascular reflexes are reliable , reproducible , simple and non invasive . In addition they reflect damage elsewhere in the ANS [111 , 112] . The investigator must however resist the temptation of ignoring patient preparation prior to testing , which is a prerequisite to a successful completion of autonomic function tests .

As suggested by Low [27] the subjects were asked to avoid food , coffee , alcohol and smoking for three hours before the tests because each of these factors effects the measurement of autonomic function in several ways.

Dietary intake is known to exert an influence on the autonomic nervous system as both a long term and a short term effect [113] . Lipsitz et al [114] found that in healthy elderly subjects , the maintenance of blood pressure homeostasis after food ingestion is associated with an increase in heart rate , forearm vascular resistance , cardiac index and plasma noradrenaline .In addition power spectral analysis showed an increase in heart rate and noradrenaline levels in young people while healthy elderly people showed an impairment in post prandial autonomic modulation of heart rate despite increasing noradrenaline levels . This may predispose dysautonomic patients to post prandial hypotension when they fail to maintain systemic vascular resistance . Postprandial reductions in blood pressure have been described in frail institutionalized elderly people after a morning meal and also in healthy community dwelling elderly people after a noon meal [115 , 116] . Possible mechanisms for this postprandial hypotension

include , impaired reflex cardioacceleration , impaired baroreflex - mediated peripheral vasoconstriction due both to age and hypertension , splanchnic blood pooling reducing venous return to the heart and meal related insulin release blunting baroreflex activity [116] . Dietary intake exerts a profound influence on the sympathetic nervous system with insulin acting as a powerful intermediary signal . Subsequently the sympathetic system activation helps to regulate mammalian thermogenesis [117] . Tle long term effects of food have been studied by Peterson et al [118] who have shown that increased body fat has been shown to depress both parasympathetic and sympathetic activity .

Alcohol ingestion can influence autonomic function tests .Chaudhuri et al [119] have shown that it lowers blood pressure and dilates the superior mesenteric artery in patients with primary autonomic failure . Blood pressure fell further if the patient was subjected to head up tilt .There was no change in muscle or cutaneous blood flow . Autonomic neuropathy of vagal origin has been shown in chronic alcoholics and there is also evidence of vagal neuropathy in alcoholic cirrhosis [120] .

Smits et al [121] have shown that caffeine induced a significant increase in blood pressure with a decrease in heart rate while nicotine alone was associated with an increase in both heart rate and blood pressure . At rest both substances have an additive effect while during conditions of sympatho adrenal stimulation like standing up , their combined effect is less than additive .

In addition , whenever possible the tests were performed at the same time of the day usually around 10 - 11 .00 am . This is because variations in autonomic function have been shown to occur at different times of day . Variations also occur during sleep .

Sleep is a process that is both natural and repeatable [122] . Non rapid eye movement sleep (slow wave sleep) is accompanied by a downward resetting and increased sensitivity of the arterial baroreflex characterised by hypotension , decreased variation in blood pressure , bradycardia , reduction in cardiac output and systemic vascular resistance . These changes are due to an increase in vagal activity causing the bradycardia and reduced sympathetic vasomotor tone causing hypotension . During rapid eye movement sleep , the stage of sleep associated with dreaming , sympathetic drive decreases in the sphlanchnic and renal circulation but increases in skeletal muscle vessels . An initial pronounced decrease in blood pressure is interrupted by large transient increases in blood pressure and heart rate during which sympathetic vasoconstriction in muscle further increases . This blood pressure instability could be due to an impairment of the baroreceptor reflex .

All subjects were tested in a warm ,quiet comfortable envionment and levels of anxiety or discomfort were kept to a minimum to avoid activation of the sympathetic nervous system .

Since the autonomic nervous system is affected by all the above factors , particular attention was paid to them in an attempt to test all subjects under standard conditions . Every attempt was made to select patients and controls who were matched for age , since clearly this has a very important bearing on the result . Whenever possible they were matched for sex although this was not so important since there is no evidence that it has an effect on autonomic function or that pneumonia affects males and females differently .

Interpreting the results

The normal values given by Ewing and Clarke [11] are somewhat unclear when it comes to interpreting results since there is no continuity between the range of values given for the different groups (Ref table 1) . Hence a result may lie between normal and borderline ranges and the result may be put in either group arbitrarily leading to some inconsistency in interpretation . To avoid this , the results were included as definitely normal or definitely abnormal if they did not fall in the borderline category . To analyze statistically the results , they were grouped as normal and not normal , the latter group including borderline results .

All the autonomic function tests immediately after treatment of the pneumonia , with the exception of the RR variation to deep breathing were significantly impaired when compared to the control group of normal elderly people . This was followed by a statistically significant improvement at early or late follow - up in all tests with the exception of the heart rate variation to deep breathing where no statistically significant relationships were found between the pneumonia groups .

It is possible that the impaired autonomic function noted was due to impairment of the baroreflex associated with a period of prolonged bed rest during the pneumonic illness and the subsequent improvement was due to a retraining of these reflexes during mobilization . To account for this variable I studied another control group of patients who sustained a fractured neck of femur , matched to pneumonia group in having suffered a major illness requiring a similar period of bed rest (mean 3 days) and who had their autonomic function tested during early mobilization . I found that while this group was not statistically different from healthy controls , there were significant

differences from the pneumonia group in the heart rate response to standing , blood pressure change to posture and sustained hand grip which gave normal responses . Although 54.5% of these subjects had a normal Valsalva ratio compared to 16.6% of the pneumonia group , this difference was not significant (Refer Table 5) . Follow up of the femoral fracture patients exhibiting the abnormal Valsalva ratio showed no significant improvement in any of the autonomic function tests . The heart rate variation to deep breathing again showed no statistically significant difference between any of the groups and the apparently limited value of this test in the diagnosis of autonomic impairment in the elderly will be discussed .

While the second control group may have had some background autonomic impairment perhaps due to age , or bed rest , or selection bias (in view of the small number of subjects) , there was , however , still a significant difference between this group and the pneumonia group in three out of the five tests of autonomic function . On the other hand , there was no significant difference from the healthy control group in any of the five tests . Hence , it seems that patients with pneumonia are different from the second control group , and they possibly exhibit autonomic impairment by some other mechanism / s other than bed rest alone . Other possible causes leading to abnormal baro reflexes , such as dehydration , were excluded by the entry criteria for the study .

Possible mechanisms by which pneumonia could affect cardiovascular reflexes .

The possible mechanisms by which pneumonia could lead to blunting of the cardiovascular reflexes as shown by individual autonomic function tests , which essentially test different reflex pathways , are speculative . Generally , for a reflex to be abnormal there must be structural or functional derangements in the afferent and / or efferent components of the reflex . The possible mechanisms are discussed below .

Damage to pulmonary nerves .

The afferent stimulus during the Valsalva manoeuvre is derived from stimulation of baro receptors in the heart , lungs , aorta , carotid sinuses and , possibly , stretch receptors in the lung and muscles of the chest wall .The efferent pathways are via the cardiac vagal efferents and sympathetic vasomotor nerve fibres . Lesions of any of these autonomic pathways or of their central connections result in abnormalities of the Valsalva response .

One possible reason for the abnormal result is an anatomical lesion . There is physiological evidence that unmyelinated afferent nerve fibres and their receptors exist in a juxtacapillary position within the alveolar wall of the cat , rabbit , rat and mouse [19] . Autonomic nerves from the pulmonary nerve plexuses have been found in the respiratory bronchioles . Fox et al ,1980 [19] using ultrastructural techniques , studied the innervation of alveolar walls in the human lung . Any nerve fibre found closer than 200 um to ciliated epithelium was not studied to minimize the possibility that the nerve fibres seen were innervating the bronchioles . Finding the nerve fibres was difficult , probably because they are not easily recognizable .Their size ranged from

1.6 - 13.8 *u*m and were as close as 1.2*u*m from the air space .The nerves were unmyelinated and contained vesicles , the majority of which were agranular which is thought to indicate they are sensory in function .

Hence nerves have been found innervating the terminal bronchioles and alveoli , and the inflammatory process associated with pneumonia could lead to direct damage of these nerve endings and might , through an indirect mechanism, cause damage to other parts of the ANS , possibly accounting for an impaired afferent stimulus leading to the observed impaired Valsalva response . Since both sympathetic and parasympathetic nerves are intermingled , one would expect any such mechanisms to involve both components of the ANS .

The mechanism of damage to nerve fibres by a remote pathological process is not new . In carcinoma of the lung autonomic impairment is thought to be due to a non - metastatic effect though direct invasion of the vagal nerve plexus does occur [89] . In leprosy the acid fast bacilli have a high affinity to the schwann cell and have been found directly infecting the sympathetic chain and the vagus [72] .To produce manifestations of autonomic impairment by an indirect mechanism the involvement of autonomic nerves must be quite extensive unless a major structure is involved ,where direct damage would be more probable . In this study all the patients with pneumonia had evidence of consolidation on the chest x ray and it can be implied that there was a significant intrapulmonary inflammatory reaction . The close proximity of the nerve ending to the alveolar space would suggest that they are easily damaged during a pneumonic process . It might be argued that resolution of the direct (pneumonia) process would be followed by an improvement of the indirect impairment of autonomic

function . In normal subjects who stand up from the lying position there is a tachycardia maximal around the 15 th beat followed by a relative bradycardia . The initial tachycardia has two phases , an initial exercise reflex at 3 seconds followed by a vagal mediated baroreflex that also accounts for the bradycardia . The baro reflex is the key component of this test ,and the test of postural drop in blood pressure .The afferent limb is mediated via the glossopharyngeal nerve while the efferent limb is mediated via the vagus . If the vagal efferent nerve fibres are indirectly affected by damage to its afferent fibres in the lung the 30 : 15 ratio would be abnormal as would be the heart rate variation to deep breathing .

Generalized damage to the ANS during septicaemia

Since pneumonia is caused by a variety of micro organisms it is possible that different parts of the ANS might be directly infected as part of a septicemia or toxaemia . A wide variety of microorganisms have been shown to have a predilection for different parts of the ANS . This possibility is , however , difficult to sustain since autonomic impairment has not been shown to occur with any of the organisms that commonly cause pneumonia [101] . In addition , to date , the syndrome of acute autonomic neuropathy ,both cholinergic or pandysautonomic , has not been described following a pneumonia . There may be exceptions , and infections of Legionella pneumophila are complicated in 50% of cases by gastrointestinal symptoms ,with nausea ,vomiting , diarrhoea and abdominal pain . Mental confusion and neurological signs have also been described .

Autoimmunity

Autoimmunity has also been widely speculated to be involved in the pathogenesis of autonomic failure following infection causing acute cholinergic and pandysautonomic failure and the Guillain Barre' syndrome . The evidence for this is not convincing and largely rests on indirect evidence based on animal experiments by Appenzeller et al [10] . A disorder of vasomotor function was produced in rabbits immunized with human sympathetic ganglia . A circulating antibody specific to sympathetic tissue accompanied the experimentally induced disorder .

In humans , antibodies against neuronal constituents have so far been identified in serum and cerebrospinal fluid of patients with various degenerative diseases , like Alzheimer's disease and Idiopathic Parkinson's disease , that specifically recognize components of cholinergic and dopaminergic neurons respectively . Murphy et al [123] found antibodies against the same protein in patients with organic sympathetic failure of different causes suggesting that antibody production is secondary to neuronal damage , rather than being an initiating cause , although autoimmune attack might contribute to the severity of neurological deficits . To date , autoantibodies to the autonomic nervous system as a consequence of infective illness have been shown in Chagas' disease . Goin et al [124] have detected a higher cholinergic antibody activity in sera of patients with Trypanosoma.cruzi .This IgG antibody was responsible for a progressive receptor block in the parasympathetic branch of the ANS .

None of the organisms that commonly cause pneumonia has previously been implicated in the production of autoimmune disease and acute dysautonomia has never been

reported following pneumonia , hence it is unlikely that this mechanism could be responsible for the autonomic impairment noted in the study .

Down regulation of the Baro reflex

The pneumonic state could be associated with increased activity of the ANS leading to a down - regulation of the baroreflex .The concept of down - regulation or up - regulation in response to physiological or pathological changes in the body has been described in a number of conditions .

The dynamic nature of the ANS has been described by Cohen [35] . Autonomic modulation is a process that can occur very rapidly and has been shown to occur in sleep [122] .The ANS provides further examples of down - regulation or up -regulation in disease states where a change in agonist concentration leads to a reciprocal change in receptor number . Patients with a phaeochromocytoma are relatively insensitive to their own catecholamines while in autonomic neuropathy denervation hypersensitivity is known to occur .

Catecholamine levels have not been measured in pneumonia but have been measured in asthma , a condition that has some similarities to it . Wind et al [125] have shown that plasma noradrenaline concentration was two or three times normal in all patients . Plasma adrenaline , however , was not increased . This failure to increase during the stress of an acute attack was unexplained and contrasts with the pronounced rise both in adrenaline and noradrenaline in acute myocardial infarction , heart failure and septicaemia . The failure of adrenaline to rise may be due to impaired secretion from the adrenal medulla . Guyton [16] suggests that when any part of the sympathetic

nervous system is stimulated the entire system is stimulated thus adrenaline and noradrenaline are almost always released by the adrenal medulla .

If this pattern of catecholamine secretion is present in pneumonia it could account for the abnormalities in the tests of sympathetic function found in this study . The pharmacological actions of adrenaline and noradrenaline complement each other and clearly if one component of this combination is missing during the stressful condition of pneumonia one might expect a degree of impaired sympathetic function such as that demonstrated .

The heart is an important end organ of the baro reflex and downregulation of cardiac receptors and impaired autonomic function has been described in heart failure . Pneumonia is known to be complicated by heart failure and elevated levels of noradrenaline similar to those shown in asthma could affect the baroreflex by a mechanism similar to that seen in heart failure .

The baroreflex is down regulated in heart failure [126] . The mechanisms that lead to this are not entirely clear , but are presumably related in some way to exposure to increased levels of catecholamines . Elevated urinary and plasma catecholamines have been documented and chronic exposure to this *B* agonist may contribute to the down regulation . Patients with long standing CCF have high plasma noradrenaline concentrations due to heightened sympathetic activity , resulting in vasoconstriction and impaired myocardial function , thereby worsening the prognosis .These changes occur in spite of arterial pressure and cardiac output being normal and an expanded blood volume . Baroreceptor responsiveness is depressed in CCF and this may contribute to the long term maintenance of sympathetic drive in this disorder .

Ferguson et al [126] have found impaired muscle sympathetic activity when the baroreflex was stimulated by intravenous infusion of phenylephrine . Marin - Neto et al [127] found that the baroreflex responses improved with treatment of CCF . A mechanism of desensitization has been suggested by Colucci et al [128] . Circulating catecholamines can influence B receptors in the same way that clinically relevant concentrations of administered sympathomimetic agents may affect *B* adrenergic density in human beings . This has been observed in patients in heart failure given the agonist pirbuterol [128] .The reciprocal effects of agonists on receptor number may be exaggerated by accompanying changes in the coupling processes . At a cellular level , the combination of a cathecholamine and its membrane bound B adrenergic receptor activates the enzyme adenylate cyclase . Bristow et al [129] showed that in patients with heart failure , decreased B receptor density was transmitted to more distal loci in the adrenergic pathway as demonstrated by a reduction in isoproterenol - stimulated adenylate cyclase activity .The reduction was of the same order as the decline in receptor density . Sometimes changes in the coupling processes occur alone ,and can in turn affect the response through an unrelated receptor that uses the same intracellular signal . A good example is the potentiation caused by chronic *B* blockade of responses through other receptors in the heart that are coupled to the adenylate cyclase . Selective *B*1 blockers not only fail to protect against stimulation of the cardiac *B*2 receptors , which are equally important in the human atrium , but potentiate by 5 - 10 fold the effects of adrenaline , salbutamol , 5 hydroxy tryptamine and possibly more potentially arrythmogenic compounds .This may explain the apparent benefit noted from using *B* blockers in heart failure [130] .

Radioligand - binding methods have been used to demonstrate that long term therapy with adrenergic agonists in asthmatic patients results in a decrease in *B* - adrenergic receptor density on polymorphonuclear leucocytes [131] . Indeed , many patients with pneumonia (including several of those in this study) are treated with the *B* adrenergic stimulant salbutamol which has a pharmacological effect on B_2 receptors in the heart as well as those in the lung and this may affect receptors at this site of the baroreflex . Though short term treatment would not be expected to alter *B* receptor density . Autonomic impairment has been noted in a number of disease states , infective or otherwise , and no specific mechanism is apparent . It seems that the greater the degree of frailty the greater the autonomic impairment . The mechanism of denervation hypersensitivity is well known and has been described by Bannister et al [79] , and it could be that this mechanism is responsible for the increased autonomic reflexes associated with the ARC of HIV infection .The opposite mechanism may be involved that is disease states associated with an increased autonomic activity lead to hyposensitivity of the reflexes .

Hypoxia and metabolic changes accompanying pneumonia

Appenzeller et al found [44] autonomic impairment during the acute phase of cerebrovascular disease , implying that the hypoxic injury to the brain may lead to abnormalities of cardiovascular reflexes . In isometric exercise sustained muscle contractions lead to a rise in systolic and diastolic blood pressure and heart rate . The stimulus is derived from exercising muscle (due to metabolic and / or mechanical

changes) and central command . The reflex is impaired in conditions complicated by neuropathy .

Muscle weakness associated with the acute phase of the infection can account for a reduction in afferent impulses .Hypoxia and metabolic abnormalities can affect peripheral and central input to the reflex . Kiriachkov et al [132 , English abstract] have described five types of " neurovegetative reactions " affecting central and peripheral parts of the autonomic nervous system aimed at maintaining the oxygen balance in the blood of human subjects breathing a gaseous hypoxic mixture . Undoubtedly pneumonia can lead to hypoxia that might have an effect on the autonomic nervous system . Apart from affecting the CNS and the ANS , hypoxia can also lead to myocardial suppression .

There may also be metabolic abnormalities that can affect muscle from where the afferent part of the reflex starts . It is also possible that toxins produced during the pneumonia might induce vasodilatation that would explain the abnormal blood pressure responses observed during this study .

It is possible that both hypoxia and metabolic abnormalities can affect the heart's ability to increase cardiac output when the sympathetic nervous system is stimulated .

This study has established a high prevalence of impairment of cardiovascular autonomic reflexes in the immediate post - pneumonic phase . It has also been shown that sympathetic nervous system impairment is particularly prevalent in patients who have had pneumonia . These abnormalities show improvement when retested at 6 weeks in a significant proportion of patients , and a further trend to improvement at 6 months . The cause of these findings is not known and warrants further research .

Problems with the measurement of autonomic dysfunction

There are many aspects of the measurement of autonomic impairment that are the cause of contention .These include the choice of tests to be used , the normal range , additional tests available and different normal ranges using the same test at different ages . In 1988 [14] the American Diabetes Association and the Academy of Neurology produced a statement validating the use of heart rate response to the Valsalva manoeuvre , deep breathing and standing , and the BP response to standing and sustained hand grip .However , different batteries of tests for heart rate variability have been suggested using the above tests , including the Ewing and the O'Brien batteries [12 , 54] . The former battery of tests has been described previously . The latter battery consists of measuring the heart rate continuously during four procedures , quiet supine rest for 60 seconds , a single deep breath , the Valsalva manoeuvre and standing for 60 seconds to calculate the 30 : 15 ratio .In this final test the recording was started once the patient was standing up . Both have their advantages and disadvantages . Although these two batteries measure the same thing there are subtle but very important differences between them .

In the O'Brien battery only one Valsalva manoeuvre is used rather than three , resulting in more patient comfort . It is , however , possible that the patient produces this one Valsalva manoeuvre incorrectly and hence averaging the three should be more accurate . In the Ewing Battery the result of the Valsalva manoeuvre is expressed as a ratio of the shortest to the longest RR interval during and after the Valsalva manoeuvre respectively . In practice , however , the RR interval continues to shorten for several seconds after the Valsalva manoeuvre finishes .The O'Brien test accounts for this

and hence might be a more sensitive measure , although it can be argued that the difference obtained in the ratio is only slight and not relevant to an abnormal heart where the response varies less .

In the O'Brien battery one deep breath instead of six is taken and is an extremely quick test . Furthermore , the time taken to measure the RR intervals from the ECG 's is considerably less if computer analysis is not available .This is acceptable if the changes induced by a single breath are the same as those induced by repeated breaths .This has been shown to be the case by Bennett et al [87] but this was not a confirmed observation , hence in view of the uncertainty it seems sensible to take an average of six breaths rather than one .

For the 30 : 15 ratio O'Brien suggests that the counting should start as soon as the patient is upright to avoid the considerable distortion in the ECG tracing while the patient is standing up .There is , however , a physiological misconception in this since the RR shortening begins at the moment when the patient starts standing , irrespective of whether this is done slowly or more rapidly and in any case the ECG tracing would usually have steadied by the time the 15 th beat is reached .

It seems that both batteries of tests have their advantages and disadvantages but I opted for the Ewing battery since it seems more physiologically sound . It is argued that the O'Brien battery of tests is shorter and more comfortable for the patient , and this can be very relevant to our elderly study group . However , it seems that most of the time is spent setting up the experiment and this is the same for both batteries , and the short cuts taken in the Valsalva manoeuvre and deep breathing might compromise the result .

The interpretation of the results is another cause for contention .The Ewing approach [88] is that there are lower limits of the normal range that apply at any age . However certain tests from the above battery , that is the heart rate response to deep breathing , 30 : 15 ratio and blood pressure response to standing decline with age . On the contrary , the Valsalva ratio and the blood pressure response to sustained handgrip appear to be unrelated to age [58] . In research , patients are compared to a control group and this is appropriate , but the approach must be different when a single patient is involved and a clinician wishes to decide whether or not he has autonomic impairment , and if so whether this is age related or not . Hence the importance of having age related normal values . It seems , however , that different investigators have found different normal ranges . It could be argued that every lab should preferably establish its own control values over a wide range of age groups , based on large population samples .

It is also a contentious issue as to whether the response to tests of autonomic function should be expressed as the difference or the ratio of the induced change in the heart rate . The relation between these two indices is linear , the slope is dependent on basal heart rate [54] .Heart rate and blood pressure have physiological limits and so their ability to respond must be limited . It is not known if a change in heart rate from 60 to 80 is comparable physiologically to a change from 100 to 120 . The resting heart rate has an important effect when the result is expressed as a ratio in the resting ,deep breathing and standing up test, but not in the Valsalva manoeuvre . A low correlation between age and resting heart rate underlines the fact that both factors have independent effects on the ratio . When the test result is expressed as a difference

between heart rates , resting rate is not important . Because of a large amount of variance in expression of the result using ratios it is best to use differences in heart rate [133] . This confirms earlier reports that autonomic dysfunction would be diagnosed more frequently if ratios rather than differences are used [54] .

The Individual Tests

The Valsalva ratio is more complicated than heart rate response to deep breathing in that although it primarily reflects cardio vagal function it is dependent on BP alterations and cardiac sympathetic function .Although it is easy to perform and the ratio easy to derive the true stimulus of the manoeuvre is not recorded .The true stimuli are the reduction in BP in phases 2 and 3 and the BP overshoot in phase 4 .Currently , blood pressure changes are not measured . Although the test is standardized the actual haemodynamic changes generated may be quite different from individual to individual , depending on such variables as muscle volume and muscle strength . Some individuals can maintain the column of mercury by blowing on a closed glottis alone . The BP changes are also the result of compensatory baroreflex changes .

There are problems with the execution of the test .It requires patient cooperation , so severely ill patients or those with weak expiratory , facial , or oropharyngeal muscles may be unable to cooperate .The test should be avoided in proliferative retinopathy due to the risk of intraocular haemorrhage .The ratio may be spuriously normal in patients with parasympathetic failure who have preserved cardiac sympathetic function . Such subjects have a tachycardia during the manoeuvre without subsequent bradycardia but the ratio is normal . Factors that affect the Valsalva ratio include age , position of the

subject , expiratory pressure , duration of effort , inspiratory volume , circulatory volume status and medications [134] .

Heart rate response to deep breathing is probably the most reliable of the cardiovascular heart rate tests since both the major afferent and efferent pathways are vagal. It is affected by age , deep breathing , the analytical methods used , hypocapnia , the influence of sympathetic activity ,the position of the patient , the depth of breathing and medications , including salicylates [134] .

The analytical method significantly affects the derived results .There are three main methods of evaluation . The expiratory : inspiratory ratio (E : I) is affected by the drifting heart rate , is suppressed by resting tachycardia and is affected by ectopic beats ; it takes about 30s to reach a stable value . The heart rate range is affected by the drifting heart rate and is insensitive to the mean heart rate . It is affected by ectopic beats and takes about thirty seconds to reach a steady state . The mean circular resultant is a direct measure of the synchronization between heart rate variation and respiration . It needs a long recording period of several minutes since the value is highly cyclic and may be a problem in subjects who develop hypocapnia - induced tachycardia and suppression of respiratory sinus arrhythmia . It is unaffected by shifting heart rate or ectopic beats but is significantly affected by asynchrony of respiration , resulting in lower values .The preferred analytical method is the heart rate method .

The heart rate response to standing has a more complex physiology . The initial tachycardia is due to an exercise reflex at about 3 seconds after standing while the subsequent tachycardia and bradycardia are baroreflex - mediated . Ziegler et al

[135] have shown that there is a wide variation of the longest RR interval within beats 21 - 39 and the shortest RR interval within beats 6 - 24 in response to standing , hence the use of the original 30 : 15 ratio appears to be invalid .However , the appropriate range around the 15 th and the 30 th beat has not been defined .

Sustained handgrip causes a rise in systolic and diastolic blood pressure and heart rate . The test is of limited sensitivity and specificity . The role of central command versus muscle afferents is controversial and confounding variables are not well known [134] .

Moreover , many tests are influenced by both the parasympathetic and sympathetic system at the same time . In healthy subjects standing up from the supine position induces characteristic heart rate and blood pressure responses . Two stages are recognized , the initial heart rate response during the initial phase is mainly vagally mediated while the heart rate and blood pressure responses during the early steady state depend exclusively on sympathetic stimulation [136] .

Though simple , these tests require considerable co-operation from the patient and the results can be modified by his or her emotional status . Some tests might also be dangerous for some patients ; for example , sustained handgrip in patients with cerebrovascular disease or cardiac disease and the Valsalva manoeuvre in those with proliferative diabetic retinopathy , all common ailments in elderly people . Recently , two simple and non- invasive tests , RR interval variation and sympathetic skin response have been described . They have been used successfully in patients with Alzheimer's disease since they require minimal patient cooperation . These tests however require an electromyographic (EMG) machine limiting their availability for routine clinical use .

The effect of age on the results

Age related deterioration in the anatomy and function of the ANS is known to occur . The lungs have an abundant supply of *B* receptors that are known to decrease in number and efficiency as one grows older .Target tissue influences on the autonomic nervous system have been demonstrated , so a declining number of *B* receptors and the age related changes in the lung could promote a decline in the autonomic nerve supply to the lung . It is possible that the ageing lung has a decreasing number of autonomic nerve fibres leading to an increased predisposition to clinical manifestations of autonomic impairment and a decreased capacity to heal completely following damage . Hence while in young people autonomic impairment remains subclinical , elderly people develop more readily the clinical manifestations of ANS failure due to decreased reserve .

The increased levels of noradrenaline and possibly adrenaline found in elderly people might also contribute to down regulation of *B* receptors in the lung and heart .

The observation on follow up that there was not a complete return to normal of the autonomic function tests suggests that there could have been some initial underlying impairment . The elderly are generally presumed to be susceptible to infection due to a decline in the immune system although the evidence for this is not very strong . It is possible that a declining local ANS could contribute to the increased predisposition to infection by impairing local reflexes that tend to remove pathogens .This could be the mechanism explaining the age related changes in cough threshold .

My results suggest that resolution of the autonomic impairment is more complete in the sympathetic nervous system . Plasma catecholamines are known to increase with age ,

possibly due to the declining baroreflex that is responsible for maintaining blood pressure .It is possible that this increased demand under normal circumstances would diminish the capacity to secrete more in times of stress . An improvement in the general condition of the patient would lead to rapid reversion to normal of the tests since this mechanism does not depend on the healing of any nerve fibres damaged in the pneumonic process . In addition it seems that sympathetic fibres in the lung are less abundant and may extend less deeply into the alveoli than the parasympathetic fibres and consequently resolution of the pneumonia would lead to a more complete improvement in sympathetic function .

Heart rate response to Deep Breathing

In view of the results obtained , this test deserves special mention .This test is reported as the most reliable of the cardiovascular HR tests of autonomic function . The vagal afferent fibres that are involved in the reflex innervate pulmonary stretch receptors [28] . In this study , however , most of the abnormalities noted were in the R-R variation to deep breathing with no significant relationship between any of the groups studied . This pattern of results was also noted by other investigators studying autonomic impairment using the Ewing battery of tests [137] .

Ewing and Clarke have recommended a normal range of more than 15 beats / minute , 11 - 14 being borderline and less than 10 as abnormal .This normal range may be valid for a younger age group but it is possibly not appropriate in the elderly . O'Brien et al [54] studied the effect of age on the heart rate variability in 310 healthy subjects and derived a normal range for different tests . Multiple correlation analysis showed that

age accounted for 15 - 33 % of variations in heart rate responsiveness in normal subjects . In addition the relative changes in heart rate in response to the various procedures was greatest for the Valsalva manoeuvre , followed by standing , then inspiration and least of all resting . Hence age affected the R - R variation to deep breathing more than it did the Valsalva ratio or standing tests . Since this study was conducted in the very elderly with an average age of more than 80 years , care should be used in the interpretation of the R - R variation to deep breathing . O' Brien quotes the lower 90% confidence limits and the lower 95% confidence limits (borderline and abnormal) as 3 beats / min and 2 beats / min respectively at the age of 75 years .Other researchers have quoted similar normal values [42] . Our results show that the normal controls had a wide range of results ranging from 1.3 to 19.6 beats per minute (Figure 3) with only 26 % being completely normal . All the subjects in the patient group had an abnormal result of which only 4 (33 %) returned to normal at follow up . It is possible that the grossly abnormal results obtained are just the result of the high average age of the trial . In view of the uncertainty of the age related normal ranges , this test is probably of limited value in the very elderly unless more sensitive methods of measuring heart rate variation are adopted .

Further Research

This study has shown that pneumonia in the elderly is associated with impaired autonomic cardiovascular reflexes during the acute phase . The exclusion criteria for subjects in the study excluded known causes of autonomic neuropathy , drugs and hypovolaemia which would have interfered with the interpretation of the results . Usually research raises more questions than it answers and clearly two questions arise from this study ; what are the possible causes for this observation and what are the possible treatment and prognostic implications ?

Elderly people exhibit a decline in autonomic function as part of the physiological process of ageing . It is possible that the autonomic impairment observed is just due to the effect of the infective process on an already precarious autonomic nervous system and younger patients would not exhibit the same manifestations due to their increased physiological reserves . Hence it is unclear how much age itself has contributed to the result . The same protocol adopted for this study could be used in a younger age group of patients admitted with pneumonia . Preliminary observations indicate that extensive autonomic impairment does not occur in young people with pneumonia .

Indirect evidence for nerve damage can be tested by assessing the threshold of the cough reflex to varying concentrations of an inhaled airways irritant such as citric acid or ammonia in patients during and after a pneumonia and in healthy controls matched for age and sex .

This possibility of damage to autonomic nerves can also be studied in a controlled experiment involving rats (shown to have nerve fibres within the alveolar wall) who would have an artificial pneumonia induced . Sections of lung can be examined by an

electron microscope comparing them to lung tissue from healthy rats .This can be coupled with electrophysiological studies of nerve impulses along the vagus before and after inducing a pneumonia . This would add evidence in favour or against nerve damage . The role of hypoxia , or metabolic abnormalities like hyponatraemia ,on brainstem centres or the peripheral autonomic nerves coordinating autonomic function is unknown . Whether a low PaO_2 has any effect on the autonomic cardiovascular reflexes can be studied by relating O_2 saturations on admission and recovery to the Ewing and Clarke battery of tests . Any positive correlation between the two would be important in emphasizing the need for oxygen treatment in pneumonia in preventing short and long term complications . Such a study would present considerable difficulties of interpretation as the mean and trough O_2 saturation levels before admission would be unknown .

Useful information about the activity of the ANS during pneumonia might be obtained by studying what happens to catecholamine levels during this condition . Increased levels have been shown in septicaemia [138] . Information is lacking about what happens to the heart during pneumonia ; there is no firm knowledge regarding the etiology of heart failure and atrial fibrillation (AF) . Both these conditions complicate the recovery of pneumonia and can increase the morbidity and mortality of the condition . It is unclear what precipitates AF . It is thought that pericardial involvement by the infective process or an increase in the cardiac output due to the febrile state may be involved . There have been no studies measuring noradrenaline levels in patients with pneumonia compared to controls matched for age .The finding of raised catecholamine levels would provide a more plausible explanation of why there might be

a down regulation of the baroreflex and of the pathogenesis of AF and heart failure . In planning any future studies an important consideration would be the age of the subjects since noradrenaline and possibly adrenaline have been shown to increase with age . Catecholamine levels and receptor changes may have prognostic implications . A scenario that is not uncommonly encountered in the management of pneumonia is the patient who is not getting better , with a bubbly chest , progressive respiratory and cardiac failure , on antibiotics ,bronchodilators , CPAP , diuretics and nitrates that do not seem to improve the patients condition , and who eventually dies . The cardiac *B* receptor may be important in the pathophysiology of this clinical picture . One of the commonly used drugs in the treatment of pneumonia is the sympathomimetic , salbutamol which stimulates the B_2 receptor . Sympathomimetics have been shown to decrease the concentration of *B* receptors in the heart . This will lead to a downregulation of the baroreflex which in itself might lead to an increase in plasma noradrenaline concentration . This raises the question ; does pneumonia lead to a vicious circle with an increased level of catecholamines (that predispose to heart failure by causing peripheral vasoconstriction , increasing venous return) , leading to a downregulation of the baroreflex by reducing *B* receptors ,which in turn further increases catecholamine levels ,and does treatment with selective B_2 sympathomimetics in the high doses commonly used , affect the cardiac B_1 receptor fuelling this positive feed back by downregulating the B receptor ?

Conditions of chronic B_1 blockade potentiate the effects of adrenaline by stimulation of the same pathway through the B_2. If there is a downregulation of the B_1 receptor in pneumonia due to changes in catecholamine concentration ,the heart would be more

susceptible to side effects from the use of salbutamol and other B_2 stimulants . This mechanism , if shown to be present , might explain why some patients who do not respond to an initial course of antibiotics to interrupt " the vicious circle " before it becomes established , take a long time to recover and why chronic bronchitics taking long term bronchodilators are especially susceptible to the effects of lower respiratory tract infections .

Clinical implications of the study

In spite of the limitations of non - invasive tests of autonomic function , the battery of tests of autonomic function used in this study has proved to be reliable in achieving a clinically relevant finding with relatively simple tools . The use of portable equipment made it possible to follow up some patients at home quite easily , patients who otherwise would have been lost to follow - up . Hence a diagnosis of autonomic impairment can be made easily at the bedside , at home , or in hospital using equipment that is easy to use and widely available , and which requires a minimum of training . The importance of careful prescribing in the elderly cannot be underestimated , not only because of the disproportionately high expenditure of drugs in this age group compared to other age groups , but because there is no doubt that drugs are the most important single cause of iatrogenic disorders in old age [139] . This study shows that elderly people , after a pneumonia have impaired cardiovascular reflexes and these recover to a significant extent over the subsequent weeks .No matter what the causes are ,the most important clinical message from the finding is that in this time period , until these reflexes return to their pre pneumonia state , elderly people are particularly susceptible

to the consequences of impaired autonomic function , and in prescribing medication care must be taken to avoid if at all possible medicines that can further upset the baroreflex .

Autonomic impairment in diabetic patients has been shown to carry a poor prognosis [140] . It is certainly impossible to come to any definite conclusion regarding prognostic implications of transient autonomic impairment after pneumonia due to the relatively small sample of patients and the relatively short follow up . More research is needed into the possible role of sympathomimetics in the treatment of pneumonia , and whether changes in receptors or catecholamine levels have any prognostic implications .

Chapter 5 : References

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Chapter 6 : Appendices

	First Reading			Second Reading			Third Reading			
Case No	Longest RR (sec)	Shortest RR(sec)	Ratio	Longest RR (sec)	Shortest RR (sec)	Ratio	Longest RR(sec)	Shortest RR (sec)	Ratio	Mean Valsalva Ratio
1	0.82	0.66	*1.24*	0.79	0.66	*1.19*	0.88	0.68	*1.29*	1.24
2	0.64	0.59	*1.08*	0.64	0.56	*1.14*	0.84	0.6	*1.4*	1.21
3	0.83	0.55	*1.51*	0.87	0.56	*1.55*	0.64	0.58	*1.1*	1.38
4	0.8	0.56	*1.42*	0.85	0.62	*1.37*	0.8	0.6	*1.33*	1.37
5	0.82	0.69	*1.18*	0.82	0.7	*1.17*	0.8	0.66	*1.21*	1.19
6	0.92	0.56	*1.64*	0.94	0.58	*1.62*	0.84	0.64	*1.31*	1.52
7	1.04	0.68	*1.53*	1.04	0.72	*1.44*	0.98	0.69	*1.42*	1.46
8	0.9	0.79	*1.14*	0.95	0.77	*1.23*	0.92	0.77	*1.19*	1.19
9	1.04	0.69	*1.53*	1.1	0.68	*1.61*	0.86	0.71	*1.21*	1.45
10	0.72	0.6	*1.2*	0.75	0.61	*1.23*	0.74	0.62	*1.19*	1.21
11	0.88	0.68	*1.29*	0.9	0.7	*1.28*	0.85	0.68	*1.25*	1.27
12	1	0.7	*1.43*	0.98	0.63	*1.56*	0.98	0.73	*1.34*	1.44
13	0.68	0.52	*1.3*	0.86	0.5	1.72	0.9	0.54	*1.66*	1.56
14	1.3	0.92	*1.41*	1.18	0.94	1.25	1.14	0.92	*1.24*	1.3
15	1.12	0.74	*1.51*	1.05	0.77	1.36	1.09	0.84	*1.29*	1.39

Appendix 1 - Valsalva Ratio in normal healthy controls .

	First Reading			Second Reading			Third reading			
Case No	Longest RR (sec)	Shortest RR (sec)	Ratio	Longest RR (sec)	Shortest RR (sec)	Ratio	Longest RR(sec)	Shortest RR (sec)	Ratio	Mean Valsalva ratio
1	0.8	0.68	1.17	0.76	0.62	1.22	0..86	0.62	1.38	1.26
2	1	0.84	1.19	0.92	0.81	1.13	0.92	0.8	1.13	1.15
3	0.76	0.67	1.13	0.76	0.72	1.05	0.76	0.7	1.08	1.09
4	0.78	0.71	1.09	0.8	0.7	1.14	0.78	0.74	1.05	1.1
5	0.68	0.62	1.09	0.66	0.64	1.03	0.66	0.64	1.03	1.05
6	1	0.8	1.25	0.98	0.8	1.22	0.98	0.72	1.36	1.27
7	1.04	0.9	1.15	1.04	0.86	1.21	1.13	0.9	1.25	1.21
8	1.08	0.8	1.35	1	0.84	1.19	1.04	0.84	1.23	1.26
9	0.8	0.74	1.16	1.05	0.8	1.31	0.98	0.82	1.19	1.23
10	0.64	0.6	1.06	0.66	0.59	1.11	0.66	0.6	1.1	1.09
11	0.77	0.64	1.2	0.78	0.62	1.26	0.8	0.62	1.29	1.25

Appendix 2 - Valsalva Ratio in elderly patients mobilizing after a fractured neck of femur .

	First Reading			Second Reading			Third Reading			
Case No	Longest RR (sec)	Shortest RR (sec)	Ratio	Longest RR (sec)	Shortest RR (sec)	Ratio	Longest RR (sec)	Shortest RR (sec)	Ratio	Mean valsalva ratio
2	1	0.84	1.19	0.92	0.81	1.13	0.92	0.8	1.13	1.15
2	***0.98***	***0.78***	***1.25***	***0.9***	***0.76***	***1.18***	***0.9***	***0.78***	***1.15***	***1.19***
3	0.76	0.67	1.13	0.76	0.72	1.05	0.76	0.7	1.08	1.09
3	***0.7***	***0.66***	***1.06***	***0.7***	***0.66***	***1.06***	***0.69***	***0.64***	***1.08***	***1.07***
5	0.68	0.62	1.09	0.66	0.64	1.03	0.66	0.64	1.03	1.05
5	***0.58***	***0.56***	***1.04***	***0.6***	***0.56***	***1.07***	***0.62***	***0.56***	***1.11***	***1.07***

Appendix 3 - Valsalva ratio in patients 2 , 3 , 5 at follow-up after 6 weeks

Follow-up results in bold and italics .

Patient 4 declined follow-up while patient 10 was lost to follow-up .

	First Reading			Second Reading			Third Reading			
Case No.	Longest RR(sec)	Shortest RR (sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Mean Valsalva Ratio
1	0.7	0.62	*1.13*	0.7	0.62	*1.13*	0.72	0.64	*1.13*	1.13
2	0.8	0.64	*1.25*	0.76	0.72	*1.05*	0.79	0.72	*1.09*	1.13
3	0.78	0.72	*1.08*	0.75	0.7	*1.07*	0.76	0.72	*1.05*	1.07
4	0.7	0.58	*1.2*	0.64	0.56	*1.14*	0.65	0.6	*1.08*	1.14
5	0.85	0.66	*1.28*	0.88	0.68	*1.29*	0.89	0.68	*1.3*	1.29
6	0.8	0.62	*1.29*	0.76	0.6	*1.26*	0.78	0.7	*1.11*	1.22
7	0.74	0.64	*1.15*	0.75	0.65	*1.15*	0.76	0.61	*1.25*	1.18
8	0.68	0.62	*1.09*	0.72	0.6	*1.2*	0.7	0.62	*1.13*	1.14
9	0.86	0.8	*1.07*	0.92	0.82	*1.12*	0.9	0.85	*1.05*	1.08
10	0.62	0.54	*1.15*	0.66	0.54	*1.22*	0.64	0.54	*1.18*	1.18
11	0.9	0.83	*1.08*	0.89	0.83	*1.07*	0.9	0.85	*1.05*	1.07
12	0.72	0.63	*1.14*	0.74	0.62	*1.19*	0.72	0.62	*1.16*	1.16

Appendix 4 - The Valsalva Ratio in the elderly patients immediately after pneumonia .

	First Reading			Second Reading			Third Reading			
Case No	Longest RR (sec)	Shortest RR(sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Mean Valsalva Ratio
1	0.8	0.64	*1.25*	0.74	0.66	*1.12*	0.74	0.63	*1.17*	1.18
2	0.84	0.74	*1.14*	0.84	0.78	*1.08*	0.87	0.77	*1.13*	1.11
3	0.84	0.8	*1.05*	0.84	0.8	*1.05*	0.85	0.8	*1.06*	1.05
4	0.8	0.62	*1.29*	0.78	0.64	*1.21*	0.78	0.64	*1.21*	1.24
5	0.98	0.66	*1.48*	0.9	0.64	*1.4*	0.96	0.64	*1.5*	1.46
6	0.72	0.58	*1.24*	0.68	0.52	*1.3*	*	*	*	1.27
7	0.98	0.82	*1.19*	0.98	0.82	*1.19*	0.98	0.86	*1.14*	1.17
8	0.88	0.62	*1.41*	0.88	0.61	*1.44*	0.9	0.66	*1.36*	1.4
9	0.76	0.62	*1.23*	0.74	0.63	*1.17*	0.76	0.62	*1.23*	1.21
10	0.84	0.7	*1.2*	0.86	0.66	*1.3*	0.84	0.64	*1.3*	1.27
11	1	0.79	*1.26*	1	0.78	*1.28*	0.96	0.78	*1.23*	1.25
12	0.92	0.66	*1.39*	0.96	0.66	*1.45*	0.94	0.66	*1.42*	1.42

Appendix 5 - The Valsalva Ratio in elderly patients 6 weeks after pneumonia .

* inadequate Valsalva .

	First Reading			Second Reading			Third Reading			
Case No	Longest RR(sec)	Shortest RR(sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Longest RR(sec)	Shortest RR(sec)	Ratio	Mean Valsalva Ratio
1	0.76	0.64	*1.18*	0.78	0.62	*1.26*	0.8	0.64	*1.25*	1.23
2	0.64	0.56	*1.14*	0.76	0.56	*1.35*	0.74	0.56	*1.32*	1.27
3	*	*	*	*	*	*	*	*	*	*
4	0.64	0.6	*1.06*	0.68	0.62	*1.09*	0.7	0.56	*1.25*	1.13
5	0.76	0.6	*1.26*	0.74	0.6	*1.23*	0.74	0.6	*1.23*	1.24
6	*	*	*	*	*	*	*	*	*	*
7	1.02	0.95	*1.07*	1	0.9	*1.11*	0.98	0.96	*1.02*	1.06
8	1	0.61	*1.63*	0.86	0.62	*1.38*	1.04	0.66	*1.57*	1.52
9	0.88	0.76	*1.16*	0.86	0.76	*1.13*	0.88	0.78	*1.13*	1.14
10	0.9	0.73	*1.23*	0.9	0.72	*1.25*	0.94	0.79	*1.19*	1.22
11	0.63	0.48	*1.31*	0.65	0.49	*1.32*	0.59	0.47	*1.25*	1.23
12	0.9	0.7	*1.28*	0.92	1.72	*1.27*	0.92	0.72	*1.27*	1.28

Appendix 6 - The Valsalva Ratio in elderly patients 6 months after pneumonia .

* patients deceased

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR Exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Ave HR diff
1	0.76	0.88	10.7	0.76	0.88	10.7	0.76	0.91	13	0.88	0.94	4.3	0.78	0.9	10.3	0.75	0.88	11.8	10.2
2	0.6	0.98	38.8	0.75	0.8	5	0.66	0.78	13.9	0.6	0.92	34.7	0.74	0.79	5.1	0.68	0.88	20.1	19.6
3	0.62	0.7	11.2	0.62	0.68	8.5	0.61	0.68	10.1	0.62	0.68	8.5	0.61	0.68	10.1	0.6	0.71	15.5	10.7
4	0.66	0.85	20.3	0.67	0.82	16.4	0.68	0.8	13.2	0.68	0.78	11.3	0.69	0.86	17.1	0.68	0.78	11.3	15
5	0.8	0.96	12.5	0.86	1.1	15.1	0.88	1.2	18.2	0.86	1.2	19.7	0.72	0.98	22.1	0.76	0.94	15.1	17.1
6	0.84	0.9	4.8	0.76	0.94	15.1	,78	0.94	13.1	0.78	0.92	11.7	0.75	0.9	13.4	0.76	0.83	6	10.7
7	0.91	1.01	6.5	0.96	1.12	8.9	0.94	0.96	1.3	0.9	0.92	1.4	0.91	0.91	0	..84	0.88	3.2	3.6
8	0.84	0.93	6.9	0.84	0.91	5.5	0.84	0.94	7.6	0.86	0.94	5.9	0.86	0.95	6.6	0.89	1	7.3	6.6
9	0.84	1.14	18.8	0.84	1.02	12.6	0.84	0.96	8.9	0.82	0.96	10.7	0.83	0.98	11.1	0.84	0.92	6.2	11
10	0.68	0.72	4.9	0.66	0.85	20.4	0.67	0.84	18.1	0.69	0.84	15.4	0.7	0.76	6.8	0.68	0.82	15	13.4
11	0.78	1.1	22.4	0.78	1.07	20.8	0.84	1.06	14.8	0.84	1.03	13.1	0.82	1.02	14.3	0.83	0.93	7.7	15.5
12	0.99	1.02	1.8	0.95	0.96	0.6	0.98	0.98	0	0.98	1	1.2	1	1.03	1.8	0.98	1.02	2.4	1.3
13	0.6	0.8	25	0.58	0.92	38	0.58	0.9	36	0.6	0.76	20	0.56	0.85	26	0.58	0.82	30	29
14	0.92	1.22	16	0.96	1.06	5.9	0.87	1.12	15.4	0.92	1.02	6.4	0.92	1.1	10.7	0.92	1.04	7.6	10.3
15	0.82	0.85	2.6	0.86	0.9	3.1	0.86	0.94	5.9	0.82	0.84	1.7	0.88	0.92	2.7	0.78	0.86	7.2	3.8

Appendix 7 - Heart Rate variation with deep breathing in normal elderly people .

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR Exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Ave HR diff
1	0.68	0.78	11.3	0.7	0.82	12.6	0.78	0.68	11.3	0.84	0.76	7.5	0.82	0.74	8	0.76	0.68	9.3	10
2	0.88	0.92	3	0.92	0.94	1.4	0.84	0.92	6.2	0.94	0.88	4.4	0.92	0.84	6.2	0.88	0.88	0	3.5
3	0.72	0.76	4.4	0.74	0.76	4.2	0.72	0.76	6.4	0.72	0.78	6.4	0.72	0.76	4.4	0.72	0.78	6.4	5.3
4	0.73	0.76	3.29	0.72	0.82	10.1	0.77	0.82	4.72	0.75	0.8	5	0.73	0.74	1.1	0.72	0.8	8.36	5.42
5	0.6	0.6	0	0.66	0.68	2.7	0.6	0.62	3.3	0.62	0.62	0	0.62	0.62	0	0.64	0.68	5.5	1.91
6	0.74	0.89	12.3	0.72	0.92	18.1	0.68	0.88	20.1	6.7	0.94	21.8	0.74	0.84	9.6	0.54	0.75	31	18.8
7	0.9	1.16	14.9	0.92	1	5.2	0.92	0.98	4	0.92	1.04	7.5	0.88	0.94	4.4	0.92	0.92	0	6
8	0.76	0.88	10.8	0.8	0.9	8.4	0.82	0.84	1.7	0.75	0.8	5	0.72	0.78	6.4	0.78	0.88	8.7	6.8
9	0.78	0.8	1.9	0.82	0.82	0	0.8	0.84	3.6	0.82	0.84	1.7	0.82	0.8	-1.9	0.82	0.79	-2.8	0.41
10	0.64	0.66	2.9	0.66	0.69	4	0.66	0.68	2.7	0.66	0.68	2.7	0.66	0.68	2.7	0.66	0.66	0	2.5
11	0.68	0.92	23	0.69	0.9	20.3	0.7	0.85	15.2	0.7	0.88	17.5	0.7	0.86	16.5	0.68	0.82	15.1	17.9

Appendix 8 - Heart rate variation with deep breathing in elderly patients mobilizing after a fractured neck of femur .

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR Exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Aver HR diff
2	0.88	0.92	3	0.92	0.94	1.4	0.84	0.92	6.2	0.88	0.94	4.4	0.84	0.92	6.2	0.88	0.88	0	3.5
2	***0.98***	***1.04***	***2.4***	***1.02***	***1.04***	***2.4***	***1***	***1.06***	***3.4***	***1***	***1.06***	***3.4***	***1***	***1.04***	***2.4***	***0.96***	***1***	***2.5***	***2.8***
3	0.72	0.76	4.4	0.74	0.78	4.2	0.72	0.78	6.4	0.72	0.78	6.4	0.72	0.76	4.4	0.72	0.78	6.4	5.4
3	***0.68***	***0.69***	***1.3***	***0.7***	***0.72***	***2.4***	***0.68***	***0.7***	***2.5***	***0.68***	***0.7***	***2.5***	***0.68***	***0.71***	***3.7***	***0.66***	***0.7***	***5.2***	***2.9***
5	0.6	0.6	0	0.66	0.68	2.7	0.6	0.62	3.3	0.62	0.62	0	0.62	0.62	0	0.64	0.68	5.5	1.91
5	***0.6***	***0.64***	***6.25***	***0.6***	***0.62***	***3.23***	***0.6***	***0.66***	***8.1***	***0.6***	***0.64***	***6.25***	***0.6***	***0.62***	***3.23***	***0.6***	***0.66***	***8.1***	***6.2***

Appendix 9 - Heart rate variation with deep breathing in patients 2 , 3 , 5 at follow-up after 6 weeks .

Follow-up results in bold and italics .

Patient 4 declined follow-up while patient 10 was lost to follow-up .

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR Exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Ave HR
1	0.7	0.72	2.4	0.68	0.72	4.9	0.62	0.7	11	0.68	0.7	2.5	0.68	0.7	2.5	0.67	0.69	2.6	4.3
2	0.8	0.92	10	0.88	0.9	1	0.88	0.92	3	0.8	0.88	7	0.85	1.05	14	0.68	0.85	17	8.6
3	0.75	0.8	5	0.78	0.8	1.9	0.78	0.8	1.9	0.76	0.8	3.9	0.76	0.76	0	0.74	0.8	6.1	3.8
4	0.64	0.65	3.8	0.62	0.62	0	0.6	0.6	0	0.54	0.6	11.1	0.51	0.56	10.5	0.56	0.56	0	4.2
5	0.82	0.88	4.9	0.88	0.9	1.6	0.86	0.88	1.5	0.88	0.88	0	0.84	0.84	0	0.84	0.85	0.9	1.5
6	0.74	0.8	6.1	0.76	0.8	3.9	0.72	0.8	8.3	0.72	0.78	6.4	0.74	0.81	7	0.72	0.82	10.2	6.9
7	0.72	0.88	15.1	0.73	0.8	7.2	0.7	0.8	10.7	0.71	0.78	7.6	0.72	0.82	10.1	0.7	0.78	8.8	9.9
8	0.63	0.74	14.2	0.64	0.74	12.6	0.68	0.74	7.1	0.67	0.72	6.2	0.66	0.74	9.8	0.69	0.72	3.57	8.9
9	0.86	0.88	1.58	0.86	0.88	1.58	0.84	0.86	1.66	0.86	0.88	1.57	0.86	0.87	0.79	0.82	0.84	1.74	1.5
10	0.6	0.64	6.25	0.58	0.6	3.5	0.58	0.66	12.5	0.58	0.62	6.6	0.58	0.64	9.7	0.56	0.62	10.4	8.2
11	0.92	0.94	1.4	0.9	0.95	3.5	0.9	0.94	2.8	0.9	0.94	2.8	0.9	0.92	1.4	0.9	0.92	1.4	2.2
12	0.66	0.71	6.4	0.7	0.71	1,2	0.68	0.76	9.3	0.68	0.71	3.7	0.68	0.7	2.5	0.7	0.75	5.7	4.8

Appendix 10 - Heart rate variation with deep breathing in elderly patients immediately after pneumonia .

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR Exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Ave. HR diff
1	0.72	0.76	4.4	0.7	0.72	2.4	0.7	0.72	2.4	0.72	0.72	0	0.69	0.69	0	0.69	0.72	3.62	2.1
2	0.78	0.9	10.3	0.78	0.92	11.7	0.72	0.9	16.8	0.82	0.88	5	0.88	0.94	4.4	0.82	0.92	7.5	9.28
3	0.76	0.81	4.87	0.8	0.86	5.24	0.8	0.86	1.66	0.83	0.87	0.85	0.72	0.84	11.8	0.81	0.86	4.31	4.8
4	0.69	0.79	11	0.72	0.8	8.3	0.69	0.79	11	0.71	0.82	11.4	0.7	0.79	9.8	0.72	0.78	6.4	9.6
5	0.84	0.96	8.92	0.86	0.94	5.96	0.85	0.92	5.38	0.86	0.94	5.96	0.9	1	6.66	0.89	0.98	6.19	6.52
6	0.68	0.76	9.3	0.66	0.74	9.8	0.67	0.72	6.2	0.7	0.74	4.6	0.7	0.76	6.8	0.7	0.74	4.6	6.8
7	0.84	1	11.4	0.84	1	11.4	0.84	1.02	12.6	0.85	1	10.5	0.95	0.98	2.9	0.84	1.02	12.6	10.2
8	0.68	0.94	24.4	0.7	0.83	13.4	0.76	0.88	10.7	0.6	0.9	33.3	0.56	1.02	48.2	0.78	0.92	11.6	23.6
9	0.68	0.8	13	0.7	0.75	5	0.68	0.74	7	0.68	0.73	6	0.68	0.74	7	0.68	0.75	8	7.6
10	0.78	0.84	5.5	0.74	0.88	13	0.73	0.79	6.3	0.78	0.86	7.2	0.8	0.82	1.9	0.76	0.9	3.9	5.3
11	0.94	1.02	4.9	0.9	1.08	11.1	0.92	1.02	6.39	0.88	0.99	7.5	0.88	0.98	6.9	0.84	0.94	7.59	7.4
12	0.82	1.04	15.5	0.81	1.03	15.8	0.82	1.02	14.4	0.82	0.98	12	0.85	0.98	9.4	0.84	0.98	10.2	12.8

Appendix 11 - Heart rate variation with deep breathing in elderly patients 6 weeks after pneumonia .

Case No	RR Ins 1	RR Exp 1	HR diff 1	RR Ins 2	RR Exp 2	HR diff 2	RR Ins 3	RR Exp 3	HR diff 3	RR Ins 4	RR exp 4	HR diff 4	RR Ins 5	RR Exp 5	HR diff 5	RR Ins 6	RR Exp 6	HR diff 6	Ave HR diff
1	0.7	0.72	2.4	0.66	0.72	7.6	0.68	0.74	7.1	0.68	0.72	4.9	0.66	0.76	12	0.7	0.72	2.4	6
2	0.54	0.68	22.9	0.56	0.72	23.7	0.6	0.68	11.8	0.61	0.7	12.6	0.6	0.75	20	0.6	0.68	11.8	17.1
3	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
4	0.66	0.72	7.6	0.64	0.68	5.5	0.64	0.68	5.5	0.64	0.68	5.5	0.62	0.66	5.8	0.64	0.68	5.5	5.9
5	0.7	0.74	5.6	0.7	0.72	2.4	0.7	0.78	8.8	0.7	0.74	4.6	0.72	0.74	2.2	0.72	0.76	4.4	4.6
6	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
7	0.95	1.02	4.4	0.94	1.03	5.6	0.94	1,03	5.6	0.96	1.02	3.7	0.94	1.03	5.6	0.96	1.02	3.7	4.7
8	0.8	0.96	12.5	0.74	0.96	18.6	0.66	0.79	15	0.76	0.86	9.1	0.64	0.82	20.6	0.82	1.04	15.5	15.2
9	0.86	0.9	3.2	0.82	0.9	6.6	0.8	0.9	8.4	0.84	0.86	1.6	0.88	0.9	1.6	0.86	0.89	2.4	4.5
10	0.78	0.9	10.3	0.72	0.9	16.7	0.72	1.04	25.6	0.77	0.97	16.1	0.84	0.94	7.6	0.8	0.92	9.8	14.4
11	0.58	0.64	9.7	0.6	0.65	7.7	0.59	0.66	10.7	0.6	0.68	11.7	0.59	0.64	7.9	0.59	0.64	4.8	8.7
12	0.88	1.2	18.1	0.94	1.12	10.3	0.96	1.1	8	0.9	1.08	11.1	0.88	1.04	10.6	0.9	1.02	7.8	10.9

Appendix 12 - Heart rate variation with deep breathing in elderly patients 6 months after a pneumonia .

* patients deceased

Case No	RR around 30 th beat	RR around 15 th beat	Ratio
1	0.75	0.69	1.08
2	0.58	0.55	1.05
3	0.6	0.56	1.07
4	0.74	0.62	1.19
5	0.89	0.82	1.08
6	0.78	0.68	1.14
7	0.82	0.73	1.12
8	0.86	0.78	1.1
9	0.8	0.72	1.11
10	0.74	0.62	1.19
11	0.8	0.74	1.08
12	1.06	0.83	1.27
13	0.72	0.66	1.09
14	0.88	0.82	1.07
15	0.72	0.68	1.05

Appendix 13 - 30 : 15 ratio in normal elderly people .

Case No	RR around 30 th beat	RR around 15 th beat	Ratio
1	0.78	0.69	1.13
2	0.88	0.8	1.1
3	0.68	0.62	1.09
4	0.73	0.7	1.04
5	0.6	0.62	0.96
6	0.82	0.79	1.04
7	1	0.88	1.13
8	0.9	0.84	1.07
9	0.8	0.76	1.05
10	0.63	0.6	1.04
11	0.65	0.62	1.05

Appendix 14 - 30 : 15 ratio in elderly patients mobilizing after a fractured neck of femur .

Case No	RR around 30th beat	RR around 15 th beat	Ratio
2	0.88	0.8	1.1
2	***0.91***	***0.72***	***1.26***
3	0.68	0.62	1.09
3	***0.7***	***0.63***	***1.11***
5	0.6	0.62	0.06
5	***0.6***	***0.6***	***1***

Appendix 15 : 30 : 15 ratio in patients 2 , 3 , 5 at follow up after 6 weeks .

Follow-up results in bold and italics .

Patient 4 declined follow-up while patient 10 was lost to follow-up .

	Immediately post pneumonia			First follow up			Second follow up		
Case No	RR around 30th beat	RR around 15th beat	Ratio	RR around 30th beat	RR around 15th beat	Ratio	RR around 30th beat	RR around 15th beat	Ratio
1	0.72	0.64	1.13	0.69	0.66	1.04	0.76	0.68	1.11
2	0.72	0.66	1.09	0.8	0.75	1.06	0.77	0.68	1.13
3	0.68	0.68	1	0.78	0.8	0.98	*	*	*
4	0.52	0.56	0.92	0.7	0.68	1.03	0.58	0.6	0.96
5	0.68	0.68	1	0.74	0.66	1.12	0.74	0.71	1.04
6	0.64	0.68	0.94	0.64	0.61	1.05	*	*	*
7	0.66	0.66	1	0.78	0.7	1.11	1	0.98	1.02
8	0.6	0.62	0.96	0.72	0.7	1.03	0.68	0.64	1.06
9	0.82	0.82	1	0.66	0.61	1.08	0.78	0.73	1.06
10	0.58	0.56	1.03	0.72	0.7	1.03	0.77	0.75	1.03
11	0.88	0.86	1.02	1	0.9	1.1	0.54	0.5	1.08
12	0.6	0.61	0.98	0.83	0.75	1.11	0.82	0.82	1

Appendix 16 - 30 : 15 ratio in elderly patients immediately following pneumonia and first (6 week) and second (6 month) follow up .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
1	190/92	185/90	180/90	180/90	190/90	190/90	0
2	173/85	177/87	175/85	169/80	172/80	170/80	5
3	160/80	155/83	162/85	150/80	153/80	160/85	5
4	150/83	153/85	153/83	145/80	143/83	149/85	7
5	168/80	160/80	164/80	155/80	160/83	158/80	7
6	160/100	165/95	163/93	149/90	146/85	153/90	13
7	190/100	180/95	180/93	190/102	185/100	182/98	0
8	160/80	162/83	159/81	160/80	155/75	160/80	2
9	160/80	163/78	157/82	155/80	152/80	158/83	5
10	145/85	147/83	146/90	140/85	138/87	140/85	6
11	190/90	190/90	190/90	185/90	183/90	185/90	6
12	165/80	160/83	165/80	155/90	153/85	155/85	8
13	145/80	145/80	145/80	140/83	140/90	140/85	5
14	153/95	155/93	153/95	145/90	145/90	145/90	8
15	143/80	145/75	145/75	130/80	133/80	135/80	10

Appendix 17 - Postural drop in blood pressure in normal elderly people .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
1	148/85	150/90	150/90	138/92	138/90	140/88	10
2	160/80	165/83	163/85	155/90	158/90	160/90	5
3	170/80	173/85	168/88	165/80	165/80	168/85	4
4	160/84	155/86	156/88	150/83	146/85	148/88	9
5	140/80	144/85	142/80	126/80	128/80	130/80	16
6	145/86	148/90	145/86	136/84	140/86	140/86	8
7	163/85	163/85	165/88	155/80	156/80	156/80	8
8	150/85	153/88	153/88	145/80	142/85	142/85	9
9	155/80	160/80	156/80	148/90	150/92	150/90	8
10	168/90	170/94	168/90	160/90	163/90	163/90	7
11	150/85	153/90	153/88	150/80	145/85	150/90	4

Appendix 18 - Postural drop in blood pressure in elderly patients mobilizing after a fracture of the neck of femur .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
2	160 / 80	165 / 83	163 / 85	155 / 90	158 / 90	160 / 90	5
2	***165 / 90***	***165 / 92***	***160 / 93***	***155 / 90***	***158 / 90***	***158 / 90***	***6***
3	170 / 80	173 / 85	168 / 88	165 / 80	165 / 80	168 / 85	4
3	***165 / 94***	***165 / 94***	***165 / 94***	***160 / 90***	***158 / 92***	***160 / 90***	***6***
5	140 / 80	144 /85	142 / 80	126 / 80	128 / 80	130 / 80	16
5	***145 / 80***	***144 / 85***	***148 / 83***	***140 / 80***	***138 / 80***	***142 / 84***	***5***

Appendix 19 : Postural drop in blood pressure in patients 2 , 3 , 5 at follow-up after 6 weeks .

Follow-up in bold and italics .

Patient 4 declined follow-up while patient 10 was lost to follow-up .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
1	160/83	163/80	160/85	155/80	155/80	160/80	5
2	190/100	190/100	185/100	185/95	190/100	185/95	5
3	160/80	158/80	155/83	163/80	160/80	153/80	0
4	170/95	167/98	168/98	135/90	130/90	133/92	35
5	120/80	120/75	123/73	90/40	95/45	85/50	31
6	180/100	183/95	180/100	170/90	164/90	165/90	15
7	160/80	160/83	160/80	140/80	143/80	140/70	19
8	162/96	158/94	156/94	118/90	118/95	125/90	38
9	180/100	190/100	185/90	170/85	165/85	174/90	20
10	160/93	164/95	162/93	152/93	150/90	152/93	12
11	140/78	140/80	140/80	128/65	125/65	132/70	15
12	120/68	125/75	120/70	115/80	117/80	115/80	6

Appendix 20 - Postural drop in blood pressure in elderly patients immediately following pneumonia .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
1	130/80	135/72	130/70	125/70	128/70	130/68	5
2	180/93	173/95	175/90	173/85	170/90	170/85	5
3	130/58	130/60	132/60	100/55	100/50	105/55	30
4	180/95	180/96	178/94	140/80	143/83	150/85	39
5	120/65	124/70	122/65	115/60	115/65	115/65	7
6	185/95	188/98	188/98	175/95	175/95	180/95	11
7	184/86	184/92	184/90	170/93	173/90	175/92	11
8	180/95	184/93	176/97	165/90	165/95	175/95	15
9	210/100	200/100	205/95	195/100	195/100	200/100	10
10	160/85	163/85	162/85	155/80	158/83	160/85	4
11	170/65	167/65	165/60	165/80	165/80	165/80	2
12	168/80	165/80	165/82	162/85	165/80	165/80	2

Appendix 21 - Postural drop in blood pressure in elderly patients 6 weeks after pneumonia .

	Supine Blood Pressure			Standing Blood Pressure			
Case No	1	2	3	1	2	3	BP drop (mmHg)
1	160/93	165/93	160/90	155/90	155/93	160/95	5
2	180/90	180/90	180/90	174/90	174/90	180/90	4
3	*	*	*	*	*	*	*
4	180/95	183/95	180/95	175/90	175/90	180/95	4
5	140/70	140/72	142/70	135/80	135/80	135/80	5
6	*	*	*	*	*	*	*
7	172/80	176/80	174/80	165/75	165/80	170/80	8
8	143/85	146/88	145/88	140/80	143/83	143/80	3
9	185/85	187/88	187/85	180/83	183/85	185/85	4
10	155/85	160/88	160/85	150/80	155/85	155/85	5
11	160/93	160/95	158/93	150/90	148/93	153/93	8
12	170/85	173/80	177/85	165/85	162/80	170/80	8

Appendix 22 - Postural drop in blood pressure in elderly patients 6 months after pneumonia .

* patient deceased

	Resting Blood Pressure (mmHg)			Blood Pressure during sustained handgrip (mm Hg)			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg)
1	193/90	191/93	195/90	200/105	210/110	210/115	24
2	175/83	175/85	173/83	190/110	200/115	190/112	31
3	160/80	161/85	158/85	180/105	185/110	183/105	28
4	150/85	158/83	156/86	170/100	172/105	160/90	20
5	165/80	160/83	163/80	200/85	190/95	190/98	17
6	160/90	155/85	157/90	170/105	180/110	185/100	21
7	185/90	189/95	190/93	200/120	205/120	200/120	27
8	155/80	160/75	158/75	180/100	195/105	180/100	30
9	163/80	158/83	162/80	170/100	173/100	180/95	19
10	145/83	150/85	147/84	160/98	153/95	160/93	14
11	190/88	190/90	188/90	190/110	195/115	198/115	26
12	165/80	165/83	165/80	170/98	165/98	170/95	17
13	145/80	145/83	150/83	155/100	150/95	150/93	18
14	150/93	153/95	160/95	160/112	160/110	150/95	18
15	143/80	143/80	145/75	150/100	150/98	153/96	22

Appendix 23 - Rise in diastolic blood pressure on sustained handgrip in normal elderly people .

	Blood Pressure at rest (mmHg)			Blood Pressure during sustained hand grip (mmHg)			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg).
1	150/85	154/853	154/85	163/102	165/100	160/100	17
2	160/84	165/85	165/85	170/94	173/98	175/100	15.4
3	173/80	173/85	175/80	180/100	190/100	192/95	18
4	160/88	158/86	158/88	165/100	163/95	166/93	12
5	140/80	144/85	142/80	160/115	155/110	150/110	33
6	145/86	148/86	148/90	145/100	152/105	158/88	20
7	163/88	165/86	165/96	172/95	176/106	176/108	22
8	153/85	153/88	155/88	163/108	165/110	170/108	9
9	156/88	158/86	158/86	163/105	165/105	160/100	18
10	168/90	170/94	168/90	175/105	183/108	185/108	16
11	150/85	153/88	153/88	170/104	173/100	160/95	17

Appendix 24 - Rise in diastolic blood pressure on sustained handgrip in elderly patients mobilizing after a fracture neck of femur .

	Resting Blood Pressure			Blood Pressure during sustained handgrip			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg)
2	160 / 84	165 / 85	165 / 85	170 / 94	173 / 98	175 / 100	15
2	***165 / 92***	***163 / 90***	***165 / 92***	***170 / 108***	***172 / 110***	***178 / 110***	***19***
3	173 / 80	173 / 85	175 / 80	180 / 100	190 / 100	192 / 95	18
3	***165 / 92***	***164 / 90***	***165 / 90***	***170 / 105***	***172 / 108***	***174 /110***	***19***
5	140 / 90	144 / 85	142 / 80	160 / 115	155 / 110	150 / 110	33
5	***145 / 83***	***146 / 85***	***148 / 80***	***154 / 98***	***156 / 100***	***158 / 100***	***17***

Appendix 25 - Rise in diastolic blood pressure on sustained handgrip in patients 2 , 3 , 5 at follow-up after 6 weeks .

Follow-up results in bold and italics .

Patient 4 declined follow-up while patient 10 was lost to follow up .

	Resting Blood Pressure (mmHg)			Blood pressure during sustained handgrip. (mmHg)			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg)
1	160/83	163/90	162/93	160/103	155/105	160/100	17
2	195/100	190/95	185/98	190/95	200/105	200/100	7
3	160/80	155/75	160/83	160/89	158/85	163/87	10
4	175/100	175/98	170/98	180/105	180/100	175/103	6
5	120/70	120/75	120/75	120/70	123/75	121/70	2
6	180/100	180/98	180/98	190/105	192/108	188/105	9
7	160/80	160/83	160/80	190/95	183/93	185/95	14
8	160/90	163/94	165/94	170/105	172/100	180/105	12
9	185/100	188/103	185/100	193/106	200/108	200/104	7
10	160/93	162/93	164/90	170/105	170/105	175/105	13
11	143/80	140/80	140/83	150/90	145/95	145/95	14
12	120/68	125/75	120/70	130/86	130/86	135/80	15

Appendix 26 - Rise in diastolic blood pressure on sustained handgrip in elderly patients immediately after pneumonia

	Resting Blood Pressure (mmHg)			Blood Pressure during sustained hand grip (mmHg)			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg)
1	130/68	135/72	130/70	145/90	138/90	140/85	20
2	180/90	173/88	175/92	180/105	180/102	185/100	15
3	130/60	130/60	130/60	132/65	133/60	133/60	5
4	178/95	180/95	180/95	190/110	190/112	185/100	17
5	120/65	124/70	122/65	125/85	125/88	125/88	22
6	185/95	188/95	185/98	190/115	185/105	185/110	19
7	185/88	190/86	186/86	190/105	195/108	190/95	21
8	180/90	180/93	180/90	190/120	190/120	190/120	29
9	200/100	195/100	195/95	200/120	195/120	195/125	27
10	163/85	160/85	163/83	170/105	173/103	173/105	21
11	170/65	175/65	170/65	180/80	190/85	186//80	20
12	165/80	165/83	165/80	170/95	175/100	175/100	19

Appendix 27 - Rise in diastolic blood pressure on sustained handgrip in elderly patients 6 weeks after pneumonia .

	Resting Blood Pressure (mmHg)			Blood Pressure during sustained handgrip (mmHg)			
Case No	1	2	3	1	2	3	Rise in diastolic BP (mmHg)
1	160/90	160/93	160/93	175/115	173/113	173/115	23
2	180/90	180/90	180/92	190/100	195/102	190/95	11
3	*	*	*	*	*	*	*
4	180/95	180/95	180/95	190/115	190/115	185/100	20
5	140/70	140/72	142/70	140/85	150/88	185/90	19
6	*	*	*	*	*	*	*
7	172/80	174/80	176/80	182/98	188/98	190/100	20
8	143/88	145/88	145/88	147/105	148/108	145/100	20
9	185/95	188/98	188/95	190/98	190/98	190/98	2
10	155/85	155/85	158/88	160/105	155/105	160/100	19
11	160/93	158/95	158/95	170/110	168/113	168/110	19
12	170/85	173/80	173/80	180/95	185/100	185/100	18

Appendix 28 - Rise in diastolic blood pressure on sustained handgrip in elderly patients six months after pneumonia .

* patient decaesed