AN ECHOCARDIOGRAPHIC SURVEY OF A RANDOM SAMPLE OF

THE POPULATION OF NORTH GLASGOW AGED 55 TO 74 YEARS

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Submitted for the degree of Doctor of Medicine

UNIVERSITY OF GLASGOW

2000

ProQuest Number: 10645961

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Acknowledgements

was always available for epidemiological advice.

The general practitioners of North Glasgow who allowed us to study their patients deserve mention as do the people of North Glasgow who came along and allowed us to study them for two hours. I hope that the results of this study will go some way to changing the face of cardiac disease for their city.

Abstract

The syndrome of chronic heart failure resulting from left ventricular dysfunction , either systolic or diastolic, is a public health problem for the Western world.

The study presented in this thesis looked at 1009 individuals aged between 55 and 74 years of age randomly selected from the population of north Glasgow - response rate 59.8%. Within the study cohort there was a significant prevalence of both hypertension (44.1%) and ischaemic heart disease (43.9%). Left ventricular (L.V.) systolic function was measured by calculating an echocardiographic left ventricular ejection fraction (L.V.E.F.) in 75% of participants. The median L.V.E.F. was 50.7% and significant left ventricular systolic dysfunction (L.V.D.) was shown to be represented by an L.V.E.F. of $\leq 35\%$; being present in 6.7% of the cohort with a measured L.V.E.F. The prevalence of L.V.D. rose with age and was higher in men than in women (9.4% v 4.0% P=0.004). The proportion which was considered symptomatic was 45.0% with no age or gender effect. The principle aetiological associate of L.V.D. was ischaemic heart disease with it accompanying 78% of all cases. Isolated hypertension was no more prevalent in individuals with L.V.D. than in the whole population. The L.V.D. was undertreated with only 16% of cases currently receiving treatment with an angiotensin converting enzyme inhibitor.

The presence of L.V.D., even when apparently asymptomatic, was associated with a reduced effort capacity on treadmill testing. Similarly it was associated with impaired quality of life scores in affected individuals, being true for both symptomatic and for treated L.V.D. (using loop diuretics), and there was possibly a small effect seen in asymptomatic L.V.D.

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Transmitral Doppler indices were used to examine L.V. diastolic filling in participants and showed diastolic filling to be affected by several biological variables including gender, age, body mass index, blood pressure and relative L.V. wall thickness. Disease states such as hypertension, ischaemic heart disease and L.V.D. were all shown to be associated with abnormal L.V. diastolic filling. Looking at a group of individuals who reported breathlessness in the absence of either airways disease or L.V.D. showed that they had a higher prevalence of ischaemic heart disease but without any evidence of abnormal diastolic filling. Removing the individuals with ischaemic heart disease from this group revealed some abnormalities of diastolic filling but also removed any objective impairment of effort capacity.

Circulating plasma concentrations of the natriuretic peptides N-terminal atrial natriuretic (N-ANP) and brain natriuretic (BNP) peptides were shown to be elevated in the presence of L.V.D.. Individuals with increased measurements of L.V. mass also had higher levels of both peptides; as did individuals with evidence, by transmitral Doppler indices, of elevated L.V. operating pressures. Examining their potential as screening blood tests for the presence of L.V.D. in the population showed that BNP fared better than N-ANP with a sensitivity of 82.0% and a specificity of 57.6% at a concentration of 15.20 pg./ml. BNP also performed better in a high risk group with ischaemic heart disease (sensitivity - 97.4%, specificity - 20.5%, concentration - 8.30 pg./ml) and had an excellent negative predictive value of 98.2% in this group. It also had a high negative predictive value in a group of breathless individuals for the presence of L.V. systolic dysfunction (97.1%). Natriuretic peptides were shown to lack some discriminatory power with reduced specificities and positive predictive values

owing to the presence of confounding factors in the population. Their future role may therefore be to exclude the presence of L.V.D. in individuals. BNP concentrations measured in unextracted plasma using the relatively simpler, and recently commercially available, Shionoria immunoradiometric assay kit also performed well as screening blood tests but not as well those obtained using a standard radioimmunoassay from extracted plasma.

1. Introduction

1.1 Chronic Heart Failure - Definition

Normal left ventricular (L.V.) function has been defined as the ability of the left ventricle to pump blood forcefully in systole and to fill adequately at low pressure in diastole (Vasan et al. 1996). Abnormalities of one, or indeed both, of these functions may cause the clinical syndrome of chronic heart failure (C.H.F.) with its own characteristic symptoms - breathlessness, either at rest or on exertion, fatigue and ankle swelling (The Task Force on Heart Failure of the European Society of Cardiology, 1995). Increasingly C.H.F. is being viewed as a multisystem disorder and Poole-Wilson defined it as "a clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamics, renal, neural and hormonal responses" (Poole-Wilson, 1985).

1.2 Chronic Heart Failure - A Public Health Problem

Heart failure has become a major public health problem in Europe and North America (Dargie and McMurray J.V., 1994; O'Connell and Bristow, 1994) with increasing levels of morbidity, mortality and health budget expenditure attributable to it.

1.2.1 The Increasing Mortality from Heart Failure

Heart failure resulting from left ventricular systolic dysfunction (L.V.D.) carries with it a terrible prognosis. Untreated New York Heart Association (N.Y.H.A.) Class IV heart failure has an average survival of just under 18 months (Swedberg et al. 1999). Medical and surgical advances which have improved survival in coronary heart disease have brought with them an "ironic failure of success" (Beamish, 1994) as the number of people who survive to develop C.H.F. has increased (Zannad et al. 1999). Both of these facts are reflected in the substantial, and possibly rising, mortality rates attributable to C.H.F. in both the U.K. and North America.

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Examination of death certification data for Scotland shows that C.H.F. is a significant contributor to both total and premature mortality (Murdoch et al. 1998). It accounted directly for 1.5% of all deaths between 1979 and 1992 and was a contributory factor in 15.6% of all deaths, including 8.3% of deaths amongst those aged below 65 years. Figures from the United States for the same period show that deaths due to heart failure rose to almost 50,000 per annum by 1995 (Centers for Disease Control and Prevention, 1998).

1.2.2 The Increasing Morbidity from Heart Failure

Chronic heart failure is associated with a substantial number of hospital admissions each year and this has increased over recent years. During the 1980's in Scotland there was a 60% increase in admissions primarily for heart failure (McMurray et al. 1993). In the United States the number of admissions related to C.H.F. has also increased since 1985 and C.H.F. now directly accounts for 871,000 admissions and is a contributory factor in at least 2.6 million admissions annually (Haldeman et al. 1999).

The burden of care extends also into the community with almost a quarter of people over the age of 65 years discharged from hospitals in the U.S. with heart failure requiring long term care in the community (Croft et al. 1997). In addition to this, annually in the United States there are reckoned to be nearly three million outpatient and primary care consultations because of heart failure (National Heart Lung and Blood Institute, 1996).

1.2.3 The Ageing Population Bear the Burden

The majority, 78%, of hospitalisations for heart failure occur in the over 65 years age group (McMurray et al. 1993) and heart failure is now the leading diagnosis for hospitalisations for individuals in this age group in the United States (Graves and Billum, 1996). Again the majority of deaths due to heart failure occur in the over 65 years age group with an annual age adjusted mortality rate of 32.2 per 1000 in the United States (Centers for Disease Control and Prevention, 1998).

1.3 The Benefits of Treatment in Left Ventricular Systolic Dysfunction

1.3.1 Treatment Improves Survival

It is now known from the results of 32 clinical trials, enrolling 7105 patients, that in individuals with C.H.F. resulting from L.V.D. treatment with angiotensin-converting enzyme (A.C.E.) inhibitors improves survival (Garg and Yusuf, 1995). It brings about an average 23% reduction in mortality with the greatest benefit being seen in those with the most severe grades of heart failure. Survival in N.Y.H.A. class IV heart failure may be increased to an average of 26 months (Swedberg et al. 1999). Mortality benefits have also been suggested from trials of treatment with angiotensin II receptor antagonists (Pitt et al. 1997).

More recently treatment with beta-adrenoreceptor blockers in addition to A.C.E. inhibitor therapy has been shown to bring about further survival benefits (Packer et al. 1996b; CIBIS-II Investigators & Committees, 1999) with treatment with bisoprolol reducing mortality by 34% (CIBIS-II Investigators & Committees, 1999).

1.3.2 Treatment Reduces Morbidity

A.C.E. inhibitor therapy in individuals with L.V.D., whether symptomatic or not, results

in fewer hospitalisations for heart failure (The SOLVD Investigators, 1991; The SOLVD Investigators, 1992) and in asymptomatic individuals treatment with enalapril reduces the progression to the overt clinical syndrome of C.H.F. (The SOLVD Investigators, 1992). Treatment with beta-blockers also appears to reduce the frequency of worsening heart failure and the need for hospital admission: by 27% in one study (Packer et al. 1996b) - even in mild classes of heart failure. Treated patients had fewer symptoms and treatment in the longer term appeared to improve L.V. systolic function (Olsen et al. 1995) and thus to be actually influencing the course of the disease.

With these available effective therapies the assessment of L.V. systolic function in patients with suspected heart failure has therefore become critical (Senni et al. 1999).

1.4 Diagnosing Left Ventricular Systolic Dysfunction

1.4.1 The Problems with Clinical Diagnosis

There is no one accepted set of criteria for making a clinical diagnosis of C.H.F. (Denolin et al. 1983) and such a clinical diagnosis lacks the ability to accurately distinguish between individuals with impaired systolic function and individuals with preserved systolic function (Cowie et al. 1997b; Remes et al. 1991). Such false positives for the diagnosis of systolic dysfunction are more common amongst women (Hlatky et al. 1986) and the elderly (Wong et al. 1989). Factors such as obesity, pulmonary disease and unrecognised myocardial ischaemia increase their occurrence (Remes et al. 1991). Even two of the best known research criteria - the Framingham and the Boston Criteria - have been shown to be relatively insensitive and non-specific for detecting the presence of L.V.D. (Marantz et al. 1988).

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Accurate clinical diagnosis is further hampered by the fact that chronic heart failure is characterised by the activation of a number of compensatory mechanisms which remove some of the classical clinical signs and symptoms (Stevenson and Perloff, 1989). Furthermore L.V.D. may exist in an asymptomatic state which cannot be detected by clinical examination (The Task Force on Heart Failure of the European Society of Cardiology, 1995).

1.4.2 The Case for Echocardiography

In view of the above, the guidelines published by the European Society of Cardiology (The Task Force on Heart Failure of the European Society of Cardiology, 1995), the American College of Cardiology and American Heart Association jointly (American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 1995), and the Agency for Health Care Policy and Research (Agency for Health Care Policy & Research, 1998) all recommend that echocardiography be performed in individuals with suspected C.H.F. since in patients with the syndrome of C.H.F. but with preserved systolic function it may provide clues to the aetiology of their cardiac dysfunction by assessing valvular function, L.V. mass, regional wall motion abnormalities and diastolic filling (Senni et al. 1999) and so may guide further investigation and treatment.

1.4.3 Measuring L.V. Systolic Function by M-mode Echocardiography

This echocardiographic modality has been extensively used since the 1970's for follow-up in the Framingham Heart Study (Savage et al. 1987). The investigators found there to be a significant learning curve for this measurement with an increase in the number

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of acceptable echocardiograms from 28% during the first part of the study to between 74 and 81% after two years. Male sex, increasing age, and a reduced forced vital capacity decreased the likelihood of having an acceptable echocardiogram. This was partly explained by the greater prevalence of emphysematous changes in the fifth through seventh decades of life which reduces the availability of the parasternal echo window.

There are a number of drawbacks to using M-mode echocardiography to derive a measure for global L.V. function (Weyman, 1998). The measurement is made from a single pair of points at the base of the heart which means that the measure of L.V. function will be influenced heavily by abnormal basal and septal wall motion as may occur in localised infarction and also in circumstances not necessarily associated with impaired L.V. function such as left bundle branch block, right ventricular pressure overload, right ventricular pacing and post cardiac surgery effects. Equally it will not take into account the effects of apical wall motion abnormalities. It has also been shown that geometric assumptions based on M-mode echocardiography do not apply if the L.V. is remodelled and dilated (Weyman, 1998).

1.4.4 Measurement of Ejection Fraction by Echocardiography

A more precise method of measuring L.V. systolic function is allowed by calculating L.V. volumes, and hence a left ventricular ejection fraction, using a biplane algorithm ("method of discs summation", Simpson's rule) (Schiller et al. 1979). Measuring cardiac volumes accurately by echocardiography is generally limited by the ability to identify and measure the entire endocardial left ventricular contour (Rumberger et al. 1997). This process also has a pronounced learning phase attached to it (Rumberger et al. 1997) and interobserver variation for the technique has been quoted as high as

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26.1% (Gopal et al. 1995).

In one study of patients following a myocardial infarction 67% of patients had suitable echocardiographic images to allow calculation of an ejection fraction by a biplane Simpson's method (Breekland et al. 1997). The correlation between this echo ejection fraction and an ejection fraction obtained by radionuclide ventriculography was good with a correlation coefficient of 0.88 (Breekland et al. 1997). In that study biplane Simpson's ejection fraction measurements were found to be accurate, sensitive and specific for identifying ejection fractions at differing levels as determined by radionuclide ventriculography. Both single plane ejection fractions and a wall motion score index fared less well at the lower range of ejection fractions. Other studies comparing the Simpson's method with radionuclide ventriculography have shown the results from both techniques to be within 19 to 21% of each other 95% of the time (Gopal et al. 1995).

Although the differences between the two methods of measuring L.V.E.F. may appear relatively small, a major problem occurs when absolute values of L.V.E.F. are used to classify patients as either normal or abnormal. Such cut-off values are often quoted in reports of clinical trials, and easily become adopted into clinical practice without necessarily making adjustment for the method of measuring L.V.E.F. used locally, and the normal distribution of L.V.E.F. by this method. A common example of this is the use of guidelines for pharmacological intervention in L.V.D. e.g. in the post myocardial infarction setting. There is no guarantee that the absolute value of L.V.E.F. quoted in a paper as the cut-off for diagnosing L.V.D. corresponds to anything similar when using the local method of measuring L.V.E.F.; whether it be echocardiography or

radionuclide ventriculography. This can lead to the misclassification of a substantial number of patients. This degree of misclassification increases with the variability of the measurement, and since the variability is greater with echocardiography, so the degree of misclassification may be greater by echocardiography. One study carried out in Glasgow amongst post myocardial infarction patients (Ray et al. 1995) showed that the proportion of patients assigned to A.C.E. inhibitor therapy for L.V.D. varied widely between different hospitals, and between methods of measuring the L.V.E.F.. The greatest variation was seen between echocardiography and radionuclide ventriculography. Therefore, when absolute values of L.V.E.F. are quoted it is important to know by which method they were obtained, and how they correlate with the results which would be obtained locally, using possibly a different method of measurement.

1.5 The Epidemiology of Heart Failure - What the Studies Tell Us

1.5.1 Prevalence

Prevalence estimates for both C.H.F. and L.V.D. vary considerably reflecting differences in methodology, timing and populations studied (Cowie et al. 1997a). Epidemiological studies have either studied the prevalence of the clinical syndrome of heart failure (including inevitably both individuals with impaired and individuals with intact L.V. systolic function) diagnosed according to various clinical and radiological criteria, or else have looked specifically at the prevalence of left ventricular systolic dysfunction by echocardiography. Studies are therefore not necessarily stating the prevalence of the same condition.

(a) Prevalence Studies Using Clinical Criteria

(i) Within the United Kingdom

Two large retrospective general practice casenote studies have been undertaken. The first carried out in London in 1988 (Parameshwar et al. 1992b) examined the records of 30,204 patients. They were only able therefore to identify symptomatic individuals who had sought medical attention and found the prevalence to be 0.4% in the whole population and 2.8% in those aged 65 years and older. The second study carried out in 1994 in Liverpool (Mair et al. 1996) searched 17,400 casenotes and found the overall prevalence to be 1.53%. In both studies less than one third of individuals with heart failure had had an echocardiogram performed.

(ii) Outside the United Kingdom

The best known of all cardiovascular epidemiology studies is the Framingham Heart Study (McKee et al. 1971) which has studied a large, unselected, geographical population since 1948 using a combination of clinical and chest radiograph findings to diagnose heart failure. Data from the 1980's (Ho et al. 1993b) showed that the prevalence of clinical heart failure was 0.7% with roughly equal proportions men and women. The prevalence rose with age from 0.8% in the sixth decade to 7.9% in the ninth decade.

Another large study in the U.S. used the same diagnostic criteria as the Framingham Heart Study to look at 14,407 individuals aged 25 to 74 years during the 1970s and reported the prevalence to be 2% (Schocken et al. 1992). Males tended to have a higher prevalence than females and the prevalence again increased with age.

"The Men Born in 1913" study based in Gothenburg, Sweden looked at men from age

50 years onwards and last reported findings at age 67 years (Eriksson et al. 1989). Again this was a clinical diagnosis of "manifest heart failure". The prevalence increased steadily up to the age of 60 years and then rose at a much greater rate. By age 67 years 13% were found to have manifest heart failure.

(b) Prevalence Studies Using Echocardiography

(i) Within the United Kingdom

Two recent studies have used echocardiography to look for the presence of L.V.D.. In a random sample of the population of North Glasgow aged between 25 and 74 years (McDonagh et al. 1997) the overall prevalence of significant L.V.D. was found to be 2.9% of which 48% was considered asymptomatic. The prevalence increased markedly from the fifth decade onwards for men and from the seventh in women mirroring the age related increase in ischaemic heart disease in that population (Tunstall-Pedoe et al. 1994). Overall there was a 2:1 ratio of men to women affected.

A more recent study from Poole, England (Morgan et al. 1999) examined an older group of patients from general practice aged between 70 and 84 years and found the overall prevalence of L.V.D. to be 7.5%. The prevalence was again higher in men than in women - more than four times higher.

(ii) Outside the United Kingdom

The Rotterdam Study (Mosterd et al. 1997) looked at 1980 individuals aged 55 years and older by means of M-mode echocardiography and found a prevalence of reduced left ventricular systolic function of 3.0%.

The Cardiovascular Health Study (Gardin et al. 1995), a large echocardiographic study

of 5201 women and men from various communities in the U.S. aged 65 years and over, reported the overall prevalence of L.V.D. to be 6.3% in men and 1.8% in women. The prevalence increased steadily with age and was higher in men.

1.5.2 Aetiology - A Changing Picture

Classification of aetiology is dependent upon the criteria used. By clinical criteria alone and without using coronary angiography and echocardiography the aetiology of heart failure is subject to misclassification.

Coronary heart disease and hypertension (either singly or together) account for the vast majority of cases of heart failure within the developed world (Cowie et al. 1997a). The relative importance of these two factors appears to have changed over the past 50 years. The Framingham Heart Study showed that hypertension carried the greatest population-attributable risk for the development of heart failure between 1960 and 1990 (Kannel et al. 1972) (Levy et al. 1996) but only because the definition of hypertension was changed during the thirty year period with a resultant increase in its prevalence. Over the same period however the relative importance of coronary artery disease showed a true increase (Ho et al. 1993a). Conversely valvular heart became a less frequent cause of heart failure. Myocardial infarction, despite its low prevalence in this particular population, carried a high population-attributable risk and amongst hypertensive individuals myocardial infarction increased the risk further.

The Men born in 1913 study concluded that in 1980 the most important risk factors for developing clinical heart failure were hypertension, smoking and obesity (Eriksson et al. 1989). However 35.8% of those who developed heart failure had suffered a

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myocardial infarction and 26.1% suffered from angina compared with only 19.1% and 7.7% respectively for the total population.

The relative importance of coronary artery disease over that of hypertension was confirmed recently on both sides of the Atlantic in the North Glasgow study (McDonagh et al. 1997) and the Cardiovascular Health Study (Gardin et al. 1995). The latter study showed the prevalence of L.V.D. to be 10.5% in people with coronary artery disease (with or without hypertension) and only 1.7% in people with isolated hypertension. McDonagh found that in Glasgow the aetiological factor conferring the greatest relative risk for L.V.D. was a clinical or electrocardiographic diagnosis of ischaemic heart disease especially in combination with hypertension.

Diabetes has been shown to be an important precursor to C.H.F.. In the Glasgow study the prevalence of L.V.D. was high amongst diabetics - 17% - but all had co-existing coronary artery disease and 75% had co-existing hypertension.

1.5.3 Aetiology - Reasons for the Changes

Preventative medicine may be playing a role in the changing aetiology of C.H.F.. Improved treatment and detection of hypertension may have reduced the population-attributable risk associated with it (Yusuf et al. 1989). Trials have shown that by treating hypertension - systolic at least - the incidence of clinical C.H.F. can be reduced (Kostis et al. 1997). The reduction appears to be higher in individuals with a history of previous myocardial infarction underscoring the apparent synergism between hypertension and coronary heart disease for the development of C.H.F. The only note of caution to be sounded is the lack of differentiation in studies between systolic and diastolic L.V. impairment. Therefore at least some of the reduction reported in the

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prevalence of C.H.F may be through a reduction in diastolic L.V. impairment (Kostis et al. 1997).

Over the past five years a case has been made for the use of cholesterol lowering therapy in individuals with established coronary artery disease. This has be shown to reduce the incidence of myocardial infarction (Scandinavian Simvastatin Survival Study Group, 1994) and with it both the risk of C.H.F. and C.H.F.-related mortality (Kjekshus et al. 1997). This adds further weight to the evidence that ischaemic damage to the left ventricle from coronary artery disease is a major factor in the development of L.V.D. at least within the population of North Europe (Coats, 1998).

1.5.4 Survival in Chronic Heart Failure

Median survival in Framingham between 1948 and 1988 after the onset of heart failure was 1.7 years in men and 3.2 years in women being worse in elderly subjects (Ho et al. 1993a). Over the period of the study there was no appreciable change in overall survival. The Olmsted County incident study of heart failure in 1991 (Senni et al. 1998) confirmed the prognosis to be poor with only 35% of patients alive at 5 years. Even when early mortality was taken out the 5 year survival was still only 41%.

1.6 The Syndrome of Heart Failure with Normal Left Ventricular Systolic Function

1.6.1 The Diagnosis of Primary Diastolic Heart Failure

When studies began to look objectively at L.V. function in people with the clinical syndrome of C.H.F. they found that some individuals, although they had signs and symptoms of raised L.V. filling pressures - pulmonary and systemic congestion, they

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had normal L.V. systolic function (Vasan et al. 1995). This led to the recognition that abnormalities of L.V. diastolic filling could lead to the clinical syndrome of C.H.F. in the absence of systolic dysfunction (Wheeldon et al. 1994) - so-called primary diastolic heart failure (Goldsmith and Dick, 1993; Shiels and MacDonald, 1998; Brutsaert et al. 1993).

Three obligatory conditions need to be simultaneously satisfied to diagnose primary diastolic heart failure (European Study Group on Diastolic Heart Failure, 1998). 1. The presence of signs or symptoms of C.H.F. attributable to raised left atrial pressure: exertional dyspnoea being frequently the earliest symptom. 2. The presence of normal or near normal L.V. systolic function. 3. Evidence of abnormal L.V. diastolic filling.

1.6.2 Prevalence of Diastolic Heart Failure

The prevalence of diastolic heart failure in the community is largely unknown (Vasan et al. 1995). In studies looking objectively at L.V. systolic function in individuals with a clinical diagnosis of C.H.F. the proportion found to have normal systolic function varies widely from 13% to 74% with an average prevalence of around 40% (Vasan et al. 1995). This prevalence is much higher amongst the older population (Wong et al. 1989; Takarada et al. 1992). In studies looking at these individuals with normal systolic function between 20% (Soufer et al. 1985) and 62% (Aguirre et al. 1989) will have echocardiographic evidence of abnormal diastolic function.

1.6.3 Aetiology of Diastolic Heart Failure

Similar to systolic dysfunction, the main diseases implicated in the aetiology of diastolic dysfunction are hypertension - in between 11% (Madsen et al. 1994) and 83% (Brogan et al. 1992) - and coronary artery disease in between 5% (Echeverria et al.

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1983) and 67% (Judge et al. 1991).

1.6.4 Prognosis of Diastolic Heart Failure

The reported annual mortality rate in heart failure with intact systolic function varies widely from 1.3% (Brogan et al. 1992) to 17.5% (Kinney and Wright, 1989). One of the best studies to look at this was the V-HeFT study (Cohn et al. 1986; Cohn et al. 1991) where the annual mortality of patients with C.H.F. and a normal ejection fraction was 8% which is substantially lower than the 15 to 20% mortality rate that was seen in those with a depressed L.V. ejection fraction (Chon and Johnson, 1990). A more recent community based study from the U.S. showed, after adjustment for the presence of coronary artery disease, similar survival rates for individuals with C.H.F. whether their L.V. systolic function was preserved or impaired (Senni et al. 1998).

The different estimates for prognosis most likely relate to differences in the prevalence and severity of coronary artery disease (Gheorghiade and Bonow, 1998). The Coronary Artery Surgery Study registry showed that for people with heart failure symptoms but normal L.V. systolic function the 6-year survival rate was 92% with no coronary artery disease, 83% with one or two-vessel coronary disease, and 68% in patients with three-vessel coronary disease (Judge et al. 1991).

1.6.5 The Pathophysiology of Diastolic Dysfunction

Abnormalities of diastolic filling may occur because of two main pathophysiological processes: impaired relaxation of the myocardium and/or reduced ventricular compliance (Devereux, 1989; Wheeldon et al. 1994; Lenihan et al. 1995; Grossman, 1991).

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(a) Impaired relaxation of the myocardium

Relaxation of the myocardium during diastole is a an active energy-dependent process involving pumping of free cytosolic calcium into the sarcoplasmic reticulum (Pouleur, 1990; Grossman, 1991); abnormalities of which will lead to impaired myocardial relaxation and to a slower decay in the atrioventricular pressure gradient in early diastole. This reduces the early phase of L.V. filling and proportionately greater filling from atrial contraction occurs as a compensatory mechanism (Taylor and Waggoner, 1992; Grossman, 1991). It also takes an increased length of time for the left atrial and L.V. pressures to equalise and so the deceleration time is prolonged.

(b) Reduced ventricular compliance.

A reduction in the compliance of the L.V. will cause a rapid increase in the left ventricular pressure after its nadir so causing a rapid deceleration of the blood flow during early filling (Nishimura and Tajik, 1997). During atrial systole there will be reduced filling of the left ventricle because of the higher L.V. pressure.

1.6.6 Echocardiographic Assessment of Diastolic Function

All ventricular filling indices by echocardiography are indirect measures of diastolic function (Vasan et al. 1996). They have largely been based on transmitral flow velocity curves measured by Doppler echocardiography (Appleton et al. 1988). At any point in time these measure the relative driving pressure across the mitral valve from the left atrium to the left ventricle (Nishimura and Tajik, 1997; Appleton, 1993).

(a) Normal Transmitral Doppler Flow

In sinus rhythm two distinct waves can be seen - Figure 1-1 - (Nishimura and Tajik, 1997; Wheeldon et al. 1994) - the early or E wave - corresponding to the period of

Figure 1-1 Patterns of Doppler Transmitral Flow Velocity Curves in Health and in Diastolic Dysfunction.
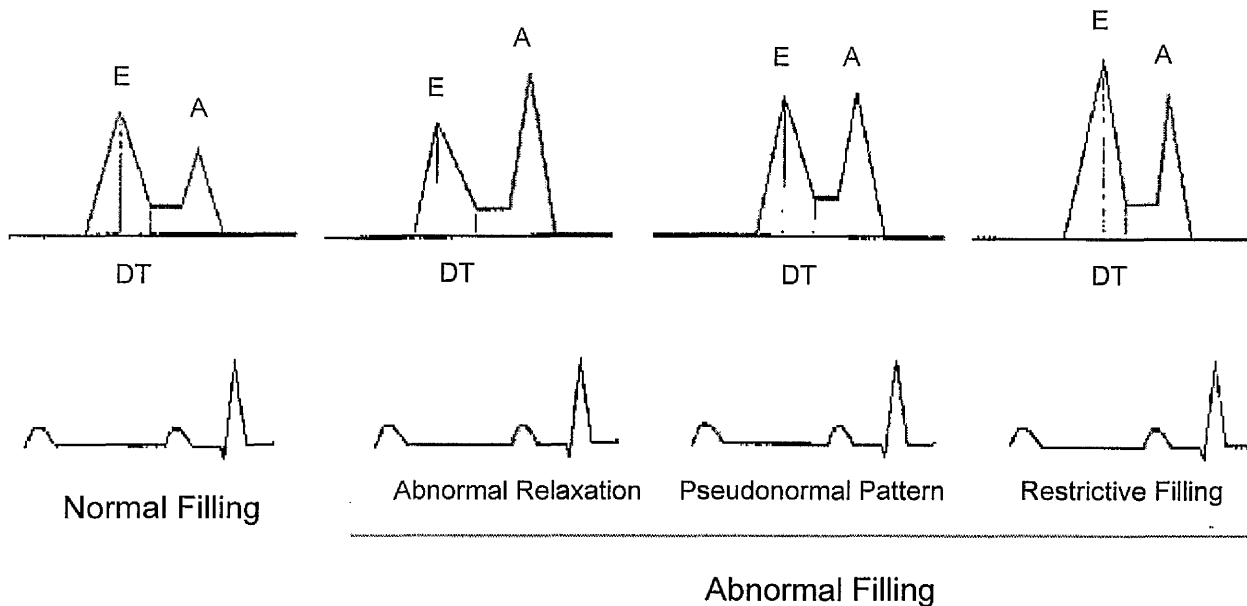
Top - Patterns of transmitral flow with various degrees of ventricular diastolic dysfunction.

Bottom - Electrocardiographic tracings corresponding to diagrams.

In healthy subjects, the transmitral flow is biphasic, consisting of an initial tall E wave followed by a shorter A wave. The deceleration time (DT) is the interval between the peak early diastolic flow velocity and the onset of diastasis; this parameter measures how rapidly left atrial and left ventricular pressures equalize in early diastole and is related inversely to ventricular compliance.

From: Vasan,R.S.: Arch Intern Med, Volume 156(2).January 22, 1996.146-157

passive early L.V. filling, and the atrial or A wave corresponding to atrial systole. Each has a peak velocity followed by an deceleration slope. The deceleration slope of the E wave is dependent mainly on the compliance of the left ventricle (Little et al. 1995; Ohno et al. 1994). In normal individuals the E wave peak velocity exceeds the A wave peak velocity indicating the relative contributions of the early and atrial phases of filling to total L.V. filling. The ratio of these two peak velocities - the E:A ratio - is therefore normally greater than one.

(b) Abnormal Patterns of Transmitral Doppler

Three main abnormal patterns of transmitral Doppler have been described (Appleton et al. 1988; Ohno et al. 1994; Nishimura and Tajik, 1997) - Figure 1-1.

1. Impaired / abnormal relaxation pattern. - Abnormal relaxation without compensatory elevation of filling pressures causes a reduction in the peak velocity of the E wave; prolongation of the deceleration time of the E wave, and an increase in the proportion of filling due to atrial contraction - leading to an increase in the peak velocity of the A wave.

2. Restrictive pattern - Abnormal compliance of the left ventricle leads to limitation of the extent of L.V. filling during atrial systole. Increases are seen in the peak velocities of both the E and A waves but with the E wave velocity increased proportionately more such that the E:A ratio increases. Because of the rapid rise in L.V. filling pressure during the early phase of filling there is a shortened deceleration time.

3. Pseudonormalisation - Experimental models of diastolic heart failure have shown that with abnormal relaxation pattern may be a compensatory rise in left atrial pressure and

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preload causing the E:A ratio and deceleration time to appear normal - so called pseudonormalisation (Iga et al. 1990; Wheeldon et al. 1994).

1.6.7 Pathological Conditions and Diastolic Dysfunction

(a) Left ventricular hypertrophy and hypertension

Left ventricular hypertrophy is a common cause of diastolic heart failure (Lenihan et al. 1995). Hypertensive individuals even in the absence of left ventricular hypertrophy have been shown to exhibit impairment of early diastolic relaxation, with a compensatory increase in atrial filling (Gardin et al. 1998; Inouye et al. 1984).

(b) Coronary Artery Disease

Some impairment of diastolic function may be present in the majority of individuals with coronary artery disease with or without previous infarction (Reduto et al. 1981; Bonow et al. 1982; Wheeldon et al. 1994). Such patients account for more than half of all the cases of heart failure with normal systolic function in studies (Vasan et al. 1995). It may be that ischaemia impairs calcium handling in the excitation-contraction-relaxation process (Pouleur, 1990).

(c) Systolic Dysfunction

Individuals with systolic dysfunction have been shown to frequently exhibit abnormalities of diastole; with echocardiography showing a restrictive pattern indicative of elevated left ventricular filling pressures (Rihal et al. 1994). This diastolic dysfunction appears to contribute to both symptoms and exercise intolerance (Packer, 1990; Xie et al. 1996; Rihal et al. 1994). In a multivariate analysis (Xie et al. 1996) the presence of a restrictive pattern of transmitral Dopplers correlated with worsening functional class and reduced exercise capacity, independent of the L.V. ejection fraction. Indices of diastolic filling may also be related to prognosis with patients who

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have short deceleration times having a poorer prognosis (Rihal et al. 1994).

(d) Diabetes Mellitus

Studies have suggested that there are small changes in diastolic filling in diabetic individuals manifest as an increase in the deceleration time of the E wave (Chen et al. 1996). Additionally, when challenged with acute preload reduction evidence of diastolic dysfunction can be unmasked suggesting that diabetics may have a preload dependence in diastolic filling (Gotzsche et al. 1993).

1.6.8 Factors Affecting Indices of Diastolic Filling in Normal Individuals

(a) Age

Ageing is associated with impaired L.V. relaxation and reduced compliance (Templeton et al. 1979). This leads to the finding of an abnormal relaxation pattern of transmitral Dopplers (Gardin et al. 1998; Benjamin et al. 1992; Kitzman et al. 1991). This effect has been shown across all age ranges and occurs in both sexes (Xie et al. 1995). In the Framingham Heart Study, looking at normal individuals, age was found to be the strongest factor determining Doppler indices (Benjamin et al. 1992).

(b) Gender

Women appear to have higher peak velocities of both the E and A waves after adjusting for other factors (Gardin et al. 1998; Xie et al. 1995). The E:A ratio does not however differ between men and women.

(c) Blood Pressure

Blood pressure appears to have effects on indices of diastolic filling but not in a consistent manner in all studies. The Cardiovascular Health Study showed that the peak velocities of both the E and A waves were positively correlated with the systolic blood

pressure and negatively correlated with the diastolic (Gardin et al. 1998). It may be therefore that there is a relationship between pulse pressure and diastolic filling velocities. Another study however showed that only systolic blood pressure exerted an independent effect and this was to increase the velocity of the A wave, so decreasing the E:A ratio (Xie et al. 1995).

(d) Left Ventricular Mass and Relative Left Ventricuiar Wall Thickness

In one study increased L.V. mass was shown to decrease the peak E wave velocity and so the E:A ratio (Gardin et al. 1998). However the Framingham Heart Study could not find any effect of L.V. mass on diastolic indices after correcting for other factors (Benjamin et al. 1992). A third study showed that the relative L.V. wall thickness correlated in women with an increased A wave velocity and a decreased E:A ratio (Xie et al. 1995).

(e) Mitral Incompetence

The presence of mitral incompetence increases the peak velocity of the E wave by increasing preload and so left atrial pressure (Gardin et al. 1998; Rokey et al. 1985).

(f) Body mass

Increased body weight appears to have a small effect, increasing the peak A wave velocity and decreasing the E:A ratio (Xie et al. 1995).

(g) Site of Doppler sampling

Sampling of the Doppler flow velocity at the mitral valve annulus rather than at the tips of the mitral valve leaflets will result in lower peak E velocities and reduced E:A ratios (Gardin et al. 1986; Xie et al. 1996).

(h) Loading conditions

Any variable describing diastolic function may change dramatically with different loading conditions on the heart (Nishimura et al. 1989; Choong et al. 1987). The peak E wave velocity is positively correlated to the degree of preload and thus left atrial pressure (Taylor and Waggoner, 1992). The deceleration time is negatively correlated to the preload probably because more rapid left ventricular filing occurs such that the atrial and ventricular pressures equalise more quickly during early filling (Taylor and Waggoner, 1992).

Increases in afterload will primarily prolong the rate of L.V. relaxation so reducing the peak E wave velocity and prolonging the deceleration time (Nishimura and Tajik, 1997).

1.6.9 Problems of Assessing Diastolic Filling by Transmitral Doppler Flow Velocities

Over the past years it has become apparent that simple Doppler indices cannot fully describe such a complex phenomenon as diastole with its interrelated factors (Cheitlin et al. 1997). The main drawbacks are: (1) The dependence on loading conditions of the common Doppler indices. (2) A normal Doppler pattern does not rule out significant diastolic dysfunction - this is because there is a continuum from abnormal (impaired relaxation) through pseudonormal to abnormal (restrictive filling) (Taylor and Waggoner, 1992). (3) The method is only applicable in the main in sinus rhythm.

Nevertheless the A.C.C. and A.H.A. guidelines (Cheitlin et al. 1997) state that echocardiographic indices of diastolic function are useful in characterising large groups of subjects. In addition "when interpreted in the context of clinical variables,

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recognising all the known potential confounding factors, they may provide valuable information in individual subjects".

1.7 Natriuretic Peptide System

1.7.1 The Biology of the Natriuretic Peptide System

Over the past twenty years a group of natriuretic peptides has been identified which plays a part in the integrated control of renal and cardiovascular homeostasis. To date three peptide hormones have been described.

Atrial natriuretic peptide (ANP) is synthesised and stored in granules in atrial myocytes (de Bold et al. 1981). It is stored as a 126 amino acid prohormone which is cleaved by a membrane bound protease into two fragments both of which enter the circulation: the 28 amino acid carboxyl-terminal (C-terminal) peptide and the 98 amino acid N-terminal-ANP (Glembotski et al. 1988). Only the C-terminal peptide is biologically active with a half-life of 13.3 minutes being cleared by both binding to a clearance receptor (Maack et al. 1987) and by enzymatic degradation by neutral endopeptidase (Struthers, 1994). The N-terminal has a much longer plasma half-life of 54.8 minutes and is probably renally cleared (Thibault et al. 1988). Circulating levels of N-terminal ANP are about ten to twenty-fold higher than those of C-terminal ANP levels (Sundsfjord et al. 1988).

Brain natriuretic peptide (BNP) is a 32 amino acid peptide which despite its name is synthesised mainly by ventricular myocardium (Sudoh et al. 1988; Mukoyama et al. 1991). It is not stored to the same degree as ANP and so increased levels of BNP must be preceded by increased mRNA concentrations (de Bold et al. 1981). It has a half-life

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in plasma of 20.7 minutes and is cleared by degradation by neutral endopeptidase (Mukoyama et al. 1991). Circulating BNP levels are normally about 20% of circulating C-terminal ANP (Mukoyama et al. 1991).

ANP and BNP have similar physiological actions. They cause natriuresis, arterial and venous vasodilatation, and antagonism of the renin-angiotensin-aldosterone system (Struthers, 1994). This has the effect of reducing the circulating volume and thus cardiac preload (Wei et al. 1993). The stimulus to their release is volume expansion and pressure overload of the heart (Wilkins et al. 1997). Experiments suggest that ANP responds to acute elevations in preload whereas BNP increases during more chronic elevations of cardiac pressures (Lang et al. 1992). BNP concentrations appear therefore to reflect long-term intravascular volume status rather than momentary volume expansion (Cheung and Kumana, 1998).

The third natriuretic peptide, C-type (Sudoh et al. 1990), differs in its biology from the other two in that it is synthesised in the vascular endothelium (Stingo et al. 1992) and has more of a paracrine effect. Despite its name it lacks any natriuretic activity (Stingo et al. 1992) and causes vasodilatation particularly on the venous side of the circulation (Struthers, 1994).

1.7.2 The Natriuretic Peptides and Chronic Heart Failure

Left ventricular systolic dysfunction, both symptomatic and asymptomatic (Francis et al. 1990; Lerman et al. 1993; McDonagh et al. 1998) has consistently been shown to be associated with increased circulating levels of both ANP (C- and N-terminal) and BNP. The increased levels of ANP are brought about both by increased synthesis and release, secondary to atrial stretch (Cody et al. 1986), and by decreased clearance by

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the liver and kidneys (Richards et al. 1986). The increase in BNP is due to increased cardiac myocyte production (Takahashi et al. 1992). The ratio of concentrations of BNP:C-terminal ANP increases in heart failure and may exceed one in the most severe cases (Mukoyama et al. 1991; Lang et al. 1992).

Levels of both ANP and BNP correlate with the degree of central haemodynamic upset in systolic dysfunction (Dickstein et al. 1995; Maeda et al. 1998). N-terminal ANP levels have been found to correlate with the L.V. ejection fraction (Lerman et al. 1993; Dickstein et al. 1995) and N.Y.H.A. functional class (Lerman et al. 1993; Dickstein et al. 1995). Dickstein found that N-ANP levels actually correlated better with functional class than did the L.V. ejection fraction, L.V. dimensions or pulmonary artery pressure (Dickstein et al. 1995).

BNP concentrations have been found to correlate more closely than N-terminal ANP with the degree of L.V.D. as measured by the L.V. ejection fraction (Lerman et al. 1993). BNP concentrations have been shown to be an independent predictor of the L.V. end diastolic pressure in patients with symptomatic L.V.D. (Maeda et al. 1998). This perhaps underscores that fact that BNP is of ventricular origin (Lerman et al. 1993) but it may also reflect the fact that ANP levels fluctuate more than BNP due to the fact that ANP is subject to both more rapid degradation (Ruskoaho, 1992) and more acute regulation (Nicholson et al. 1993).

1.7.3 Effects of Treatment on Natriuretic Peptides

A.C.E. inhibitor therapy in patients with L.V.D. produces a fall in both ANP and BNP (Maeda et al. 1998; Motwani et al. 1993) which parallels the fall in the L.V. end diastolic pressure (Maeda et al. 1998). BNP has been shown to be superior in tracking

this response to treatment (Maeda et al. 1998).

1.7.4 Diagnosing Systolic Dysfunction Using Peptides

A number of studies have studied natriuretic peptides as blood markers for the presence of L.V.D. (McDonagh et al. 1998; Lerman et al. 1993; Davis et al. 1994; Cowie et al. 1997b; Davidson et al. 1996; Omland et al. 1996a; Yamamoto et al. 1996; Friedl et al. 1996). All found to varying degrees that N-ANP and BNP were sensitive and moderately specific. In the studies that compared N-ANP with BNP, the latter was found to have a higher diagnostic value (Omland et al. 1996b; Yamamoto et al. 1996; Friedl et al. 1996; Davidson et al. 1996).

(a) Clinical Studies in Patients

In symptomatic patients suspected of having C.H.F. in primary care (Cowie et al. 1997b) measurement of BNP levels was shown to be both highly sensitive and specific. Measurement of N-terminal ANP in addition did not improve the diagnostic yield. Within a group of patients admitted to hospital with acute dyspnoea of unknown aetiology BNP, again more so than ANP, has been shown to accurately detect the presence of L.V.D. (Davis et al. 1994).

Natriuretic peptides have been studied extensively in the post myocardial infarction (M.I.) population. Elevated BNP levels have been demonstrated in L.V.D. following anterior M.I., which persist for at least six months (Motwani et al. 1993). Treatment with an A.C.E. inhibitor results in a reduction in these BNP levels (Motwani et al. 1993). Elevated levels of peptides in the subacute phase of an M.I. have been shown to be associated with both a higher risk of developing overt heart failure and mortality (Darbar et al. 1996; Omland et al. 1996a; Hall et al. 1994).

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Concentrations of natriuretic peptides have been shown to provide prognostic information in L.V.D. over and above routine measurements such as the L.V. ejection fraction (Hall et al. 1994; Rouleau et al. 1994; Darbar et al. 1996; Omland et al. 1996a). In patients with symptomatic L.V.D. BNP was shown to be a significant, independent predictor of mortality: a better predictor than L.V. ejection fraction (Tsutamoto et al. 1997). ANP was inferior to BNP in this respect.

(b) Studies in Unselected Populations

In McDonagh's large epidemiological study in North Glasgow BNP was found to be superior to N-ANP in detecting L.V.D., whether symptomatic or not (McDonagh et al. 1998). The predictive accuracy of BNP was higher in high risk groups such as the older population and individuals with a clinical diagnosis of coronary heart disease.

A smaller study based within general practice in Glasgow (McClure et al. 1998), looking at people with a previous myocardial infarction, found that neither BNP nor N-terminal ANP were useful in discriminating between normal and milder degrees of L.V.D.. The authors conclude that the diagnostic accuracy was reduced because their population was older and may have had a higher prevalence of hypertension, left ventricular hypertrophy and diastolic dysfunction all of which are known to increase levels of natriuretic peptides in the absence of systolic dysfunction (McClure et al. 1998). In addition the authors used only a semi-quantitative method for assessing L.V. systolic function.

1.7.5 Peptides and Left Ventricular Hypertrophy

In hypertensive patients with left ventricular hypertrophy (L.V.H.) plasma BNP

concentrations have been shown to be elevated (Kohno et al. 1992; Kohno et al. 1995). This appears to be related to the degree of L.V.H. rather than the level of blood pressure. BNP levels correlate with the L.V. mass index and relative wall thickness (Kohno et al. 1995) and regression of L.V.H. is associated with a fall in BNP concentrations (Kohno et al. 1995).

A meta-analysis (Hollister and Inagami, 1991) of 17 case-control studies concluded that no significant difference existed in plasma ANP levels between subjects with normal blood pressure and those with untreated hypertension in the absence of target organ damage. In non-obstructive hypertrophic cardiomyopathy (Yoshibayashi et al. 1993) and normal L.V. systolic function plasma BNP levels have been shown to be 50 times higher than in normals and about ten times higher than in people with L.V.H. secondary to pressure overload e.g. aortic stenosis. ANP was found to be three times higher than normals in non-obstructive hypertrophic cardiomyopathy

1.7.6 Peptides and Age

In a wide range of individuals from the population C-terminal ANP levels have been shown to increase with increasing age (Flickinger et al. 1995).

1.7.7 Peptides and Diastolic Dysfunction

In patients with the clinical syndrome of heart failure but normal L.V. systolic function there is a significant negative correlation between the E:A ratio and both ANP and BNP (Lang et al. 1994). The raised operating L.V. pressures which characterise diastolic dysfunction triggers both BNP release and elevates left atrial pressures so increasing left atrial stretch and hence ANP release (Lang et al. 1994). In one study (Yamamoto et al. 1996) an elevated BNP concentration was found to have a sensitivity of 0.85 and a

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specificity of 0.74 for the presence of primary left ventricular diastolic dysfunction.

In hypertensives without L.V.H. ANP levels were negatively correlated with the E:A ratio (Pontremoli et al. 1993). It is hypothesised that impaired diastolic relaxation and reduced ventricular compliance secondary to hypertension may increase the left atrial pressure and so act as a stimulus for ANP secretion (Pontremoli et al. 1993).

In patients with L.V.D. both ANP and BNP levels are significantly higher in individuals with a restrictive pattern on transmitral flow Dopplers than in those without (Yu et al. 1996).

1.7.8 Stability of Natriuretic Peptides

Both N-terminal ANP (Murdoch et al. 1997; Hall et al. 1995) and BNP (Murdoch et al. 1997) are stable in whole blood stored at room temperature for up to 72 hours with only minor changes in concentration. N-terminal ANP has also been shown to be resistant to two repeated freezing-and-thawing cycles (Hall et al. 1994).

1.7.9 Screening for Asymptomatic Systolic Dysfunction

The results of the above studies suggest that screening for asymptomatic L.V. systolic dysfunction by measuring plasma concentrations of natriuretic peptides, especially BNP, potentially fulfils the criteria for a screening test (McMurray et al. 1998). However, as a screening test, the finding of a moderate concentration of BNP in any one individual may lack specificity (McMurray et al. 1998) but a low BNP level has an excellent negative predictive value for the presence of systolic dysfunction (Cheung and Kumana, 1998). This may therefore remove the need for further investigations in certain individuals.

1.8 Effort Capacity and Heart Failure

Exercise intolerance is a cardinal feature of C.H.F. (Franciosa et al. 1979) and is one of the most common problems experienced by patients prompting them to seek medical help (Atherton et al. 1997). Patients stop exercising because of either breathlessness or fatigue depending on the form of exercise being undertaken (Atherton et al. 1997). During fast treadmill exercise this is most likely to be breathlessness, and fatigue during slower walking or cycle exercise (Atherton et al. 1997).

1.8.1 Measurement of Effort Tolerance

Effort tolerance can be measured either by duration of exercise on a treadmill or bicycle or by the distance walked in a defined time period. These two measures give different information, the latter providing information about submaximal exercise capacity (Atherton et al. 1997).

(a) Symptom-Limited Exercise Testing and Measurement of Oxygen Uptake

The measurement of gas exchange and thus peak oxygen consumption during maximal exercise testing has emerged as one of the most important prognostic variables in heart failure (Parameshwar et al. 1992a) and its reduction is a major criterion of selection for cardiac transplantation (Costanzo, 1996).

(b) Six Minute Walk Test

This form of submaximal exercise testing has the advantage of more effectively evaluating the impairment and functional status during daily activities (Brunner-La Rocca et al. 1999) and has been shown to be reproducible (Guyatt et al. 1984). The test appears to be able to predict prognosis better than both the L.V. ejection fraction

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and the N.Y.H.A. functional class of patients. In the SOLVD Registry distance walked was inversely related to subsequent mortality and rate of hospitalisation for heart failure (Bittner et al. 1993).

1.8.2 Relationship of Effort Capacity to Severity of L.V. Systolic Dysfunction

Standard measures of cardiac function such as L.V. ejection fraction, echocardiographic L.V. dimensions, and pulmonary capillary wedge pressure do not consistently predict effort tolerance in patients with heart failure (Webb-Peploe et al. 1998; Franciosa et al. 1981; Higginbotham et al. 1983). Neither does the degree of patients' symptoms on maximal exercise testing correlate with these markers of underlying L.V. systolic dysfunction and haemodynamic abnormality (Wilson et al. 1995). In particular the level of perceived dyspnoea does not correlate with the L.V. filling pressures as measured by the pulmonary capillary wedge pressure (Wilson et al. 1995). Some research suggests that echocardiographic variables such as preserved right ventricular function and the absence of a restrictive pattern on transmitral Dopplers predict improved effort tolerance (Webb-Peploe et al. 1998).

Despite the increasing functional impairment implied by the N.Y.H.A. grading of heart failure symptoms, objective exercise testing shows little difference in effort tolerance between patients in different N.Y.H.A. classes (Franciosa et al. 1979; Bittner et al. 1993)..

1.8.3 Effort Capacity in Asymptomatic L.V. Systolic Dysfunction

The SOLVD trial showed that individuals with L.V.D. who are either asymptomatic or only mildly symptomatic (defined as not requiring diuretic therapy) have lower values of peak oxygen uptake during maximal exercise than control individuals (Liang et al.

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1992; LeJemtel et al. 1994). They however have higher values than symptomatic subjects but this difference cannot be explained by differences in L.V. ejection fraction between the asymptomatic and symptomatic groups.

1.8.4 Mechanisms of Effort Intolerance

The evidence suggests that effort intolerance is not solely due to abnormalities of central haemodynamics and the inability of heart failure patients to augment their cardiac output during exercise (Wilson et al. 1995; Atherton et al. 1997). Equally important are peripheral factors in skeletal muscle and the lungs (Atherton et al. 1997). Muscle wasting occurs early in even mild heart failure (Mancini et al. 1992) and patients have weaker limbs and fatigue more easily than controls (Harrington et al. 1997). There is a reduction in muscle efficiency accompanied by both histological (Drexler et al. 1992) and physiological changes (Massie et al. 1987). This is brought about by a number of factors including deconditioning - disuse atrophy - malnutrition and the action of cytokines especially tumour necrosis factor (Atherton et al. 1997).

Changes in the lungs contribute to symptoms during exercise including increased airways resistance, decreased lung compliance and ventilation/perfusion mismatch (Atherton et al. 1997). In addition there is a subjective component to the symptom of breathlessness which can be reduced by the administration of opiates allowing improved effort capacity (Chua et al. 1997).

1.9 Chronic Heart Failure and Quality of Life

1.9.1 Measuring Quality of Life

Quality of life is inherently subjective and can be influenced by many factors including an individual's own expectations (Testa and Simonson, 1996). Questionnaires

measuring quality of life can be divided into those which are specific for a particular disease and those which are generic. The latter can be used to compare the effects of different disease states on the same or on different individuals using a common yardstick (Garratt et al. 1993; Stewart et al. 1989).

The Short Form 36 (SF36) questionnaire is a generic measure of quality of life. It is a shortened version of a battery of 149 health status questions developed and tested on a U.S. population of over 22 000 patients as part of the Medical Outcomes Study (Tarlov et al. 1989). It has subsequently undergone minor changes of wording by a team in Sheffield to make it acceptable to the British population (Brazier et al. 1992). It has been shown to be acceptable, internally consistent and to meet accepted criteria for reliability and validity (Garratt et al. 1993). It is designed to either be self administered, taking five to ten minutes to complete, or answered during an interview (Ware et al. 1993).

1.9.2 Studies of Quality of Life in Chronic Heart Failure

(a) Symptomatic Heart Failure

Comparison of the impact of a number of chronic illnesses, including C.H.F., on quality of life has been made in a couple of large epidemiological surveys in the U.S (Stewart et al. 1989; Fryback et al. 1993). The Medical Outcomes study in 1986 (Stewart et al. 1989) showed that C.H.F. had effects on each aspect of functioning - physical, role and social - and on health perceptions. Among the chronic conditions studied health perceptions were poorest for C.H.F..

The SF36 questionnaire was used as a measure in 1990 during a random survey of adults - the Beaver Dam Health Outcomes Study (Fryback et al. 1993). On the general

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health domain C.H.F. had the lowest score of all chronic conditions examined ranking lower than chronic back pain and chronic asthma. A study in 1994, from Oxford (Jenkinson et al. 1997), looked at 68 elderly patients with symptomatic heart failure and found that all dimensions of quality of life were severely reduced.

(b) Asymptomatic Left Ventricular Dysfunction

The SOLVD investigators showed that even individuals with asymptomatic L.V.D. had impaired quality of life compared to normals (Rogers et al. 1994). The impairment of quality of life was however less than that seen in symptomatic heart failure.

1.9.3 Effect of Treatment on Quality of Life in C.H.F.

In contrast to their effects on morbidity and mortality a beneficial effect of treatment with A.C.E. inhibitors on quality of life in C.H.F has not been proven. The V-HeFT II trial, using a disease specific questionnaire - the Minnesota Living with Heart Failure questionnaire, was unable to show a sustained improvement in quality of life for patients receiving treatment with A.C.E. inhibitors or other vasodilators (Rector et al. 1993). There was in fact a gradual decline over two years paralleling the decline in L.V. ejection fraction and V0$_2$ max. Smaller trials of A.C.E. inhibitors confirmed this showing either modest (Bulpitt et al. 1998) or no benefit (Jenkinson et al. 1997) in the short to medium term. The SOLVD investigators (Rogers et al. 1994) were able to show that treatment with enalapril did not improve quality of life in asymptomatic L.V.D. but there was improvement for those who were symptomatic, persisting for at least one year.

1.10 Aims of This Thesis

Given what has been said above about the importance and impact of C.H.F., whether the result of systolic or diastolic L.V. dysfunction, on both the individual and the nation

the emphasis must now be on prevention. Prevention of L.V. dysfunction in the first place (primary prevention) and prevention of progression of the dysfunction once established (secondary and tertiary prevention). To do this there is a need for epidemiological studies, such as this current one, to determine who the affected individuals in the community are, and to develop strategies for identifying them at an early stage when secondary and tertiary prevention may be of benefit. Studies also need to identify "at-risk" individuals in whom primary prevention may be beneficial.

The aims of this study were:

1. To recruit and characterise a random selection of people from a defined geographical population with a presumed high prevalence of risk factors for ischaemic heart disease and subsequent left ventricular systolic dysfunction (Chapter 3).

2. To use echocardiography to determine normal and abnormal left ventricular systolic function in this cohort and thus determine the prevalence and aetiology of left ventricular systolic dysfunction (Chapter 4).

3. To examine the effects of this left ventricular systolic dysfunction on both effort capacity, as determined by formal exercise testing, and on quality of life (Chapter 5).

4. To look at the determinants of left ventricular diastolic filling in an unselected population and to assess whether or not abnormal diastolic filling has a significant effect on individuals within the general population as opposed to patients (Chapter 6).

5. To examine the relationship between left ventricular function - systolic and diastolic - and natriuretic peptides, and to explore their use as blood screening tests for the presence of left ventricular systolic dysfunction in the community. As part of this to also compare the use of a new, commercially available, immunoradiometric assay for brain natriuretic peptide against the conventional radioimmunoassay (Chapter 7).

2. Methods

2.1 The Study Population - Sampling and Invitation Process

The theoretical population studied was defined as all persons resident within the boundary of the city of Glasgow, north of the River Clyde, born between 31/3/20 and 1/4/39 and registered with a general practitioner, serving the same geographical area. This is the same geographical population as was studied by the World Health Organisation's MONICA study (Tunstall-Pedoe et al. 1994).

The study was designed to study 1000 randomly selected individuals - 125 males and 125 females in each five year age band between 55 and 74 years. This was achieved by a two stage random sampling process. First a random 1 in 7 sample of the 210 general practitioners with practices serving the area was chosen and the agreement of all thirty general practitioners to participate in the study obtained. Next a random sample of all patients meeting the above criteria was chosen with each practice contributing a "quota" of patients within each five year sex and age band in proportion to the practice size relative to the geographical population. Where necessary oversampling took place. The G.P.s were asked to exclude any patients who they felt would not be able to participate on the grounds of severe physical or mental ill health.

The subjects chosen were invited by letter to attend the study: enclosed with the invitation was information about the study. This was followed up by a telephone reminder or a postcard reminder, if they did not have a telephone. Those who did not attend were sent a further appointment. If individuals failed to attend for a second appointment a researcher visited their address to make personal contact and to establish the accuracy of the address list.

2.2   Questionnaires and Interview

With the invitation each individual received copies of a Personal Health Record (PHR) Questionnaire and the SF-36 quality of life questionnaire (Brazier et al. 1992) – Appendix A. The PHR sought basic demographic details; family history of early heart disease; physician made diagnoses of angina, myocardial infarction, hypertension, cerebrovascular disease, and diabetes mellitus; current medication; smoking history, and alcohol consumption in the form of a diary. Within the PHR were questions composing the M.R.C. breathlessness questionnaire (Fletcher et al. 1959) which was designed to distinguish between breathlessness attributable to chronic bronchitis - defined as breathlessness associated with a cough productive of sputum occurring on most days during at least three winter months each year - and other causes.

The SF-36 questionnaire issued was the Brazier/Sheffield version (Brazier et al. 1992). The questionnaire was checked for completeness of information during the study visit and, if need be, it was administered in part or in full by interview. It was subsequently scored according to the scoring manual from the Medical Outcomes Trust (Medical Outcomes Trust, 1994). A scale score was calculated if the respondent had answered at least half of the items in a multi-item scale (or half plus one in the case of scales with an odd number of items).

The deprivation category for each attendee was assigned on the basis of the postcode sector in which they lived, grouped by health board. The category was obtained from a table supplied by the Public Health Research Unit of the University of Glasgow and was based on the 1991 Scottish Census (McLoone 2000). The categories range from Depcat 1 (the most affluent postcode sectors) to Depcat 7 (the most deprived). They are

calculated from the Carstairs score (Carstairs and Morris 1991) for each postcode sector and are based on four variables measuring: 1) overcrowding, 2) percentage male unemployment, 3) percentage low social class, and 4) car ownership. The Depcat score is thus a measure of deprivation for a postcode sector rather than for a specific individual.

2.3 *Body Mass Index*

Participants' heights and weights were measured after removal of their shoes and heavy outer garments. Weight was measured by SECA electronic scales - checked daily using a British Standard 5Kg weight - to the nearest 100 grams. Body mass index (kg/m^2) was calculated as the weight (kg) divided by the height (m) squared.

2.4 *Blood Pressure Measurement*

Blood pressure readings were obtained with the use of a random-zero sphygmomanometer (Hawksley and Sons, Ltd., West Essex, England). A cuff size appropriate for the subject's arm was chosen. Two blood pressure readings were taken at least two minutes apart after ten minutes of seated rest. The pressure at Korotkoff phase I sound was recorded as the systolic blood pressure and the diastolic blood pressure was determined at the occurrence of Korotkoff phase V sound in all participants. The average of the two readings was recorded and used in further analysis.

2.5 *Spirometry*

Standard spirometric measurements of forced vital capacity (FVC), vital capacity (VC) and the forced expired volume in one second (FEV$_1$) were made using a Microlab 3330 spirometer (Micro Medical, Kent, England). The final measurement was recorded as the highest value of three attempts. A standard demonstration of the technique was

given initially to the attendee and each was allowed two practise attempts with appropriate correction of technique if required. Uniform encouragement was given during each attempt.

2.6 Echocardiography

2.6.1 Performance of the Echocardiogram

Standard two-dimensional, colour-flow and Doppler echocardiography was recorded on an Acuson 128 ultrasound machine (Acuson Inc., Mountain View, CA, USA) with the individual reclining on a couch at 45 degrees in the left lateral position. An E.C.G. channel was recorded throughout the examination. The whole study was recorded in real time on half inch super-VHS video tape for later review with the participants identified only by a study number.

At least three single-cycle loops of both the apical 4- and 2-chamber views were digitised and transferred onto optical discs, as were frames of the M-mode measurements (at least five cardiac cycles) and the Doppler flow curves (at least five cardiac cycles) using an off-line digital image processing and analysis system (Tomtec Imaging System Inc., Boulder, Colorado, USA). Cardiac cycles that were ectopic beats, or pre- or post-ectopic beats were not analysed. Similarly only if the heart rate was 100 beats per minute or less were the echocardiograms analysed further objectively. All measurements were made during quiet respiration.

2.6.2 Measurement of Left Ventricular Ejection Fraction

The left ventricular ejection fraction was measured using a biplane algorithm "method of discs summation", Simpson's rule (Schiller et al. 1979) as an average of three cycles. To be suitable for analysis at least 80% of the endocardium had to be visible. End-

diastole was defined as the frame with the largest L.V. cavity at the initial systolic coaptation of the mitral valve, and end-systole as the subsequent frame with the smallest cavity area (Badano et al. 1996).

Previous work from our echocardiographic lab has shown the intraobserver variation for the L.V.E.F. measured by a biplane Simpsons method, expressed as a median percentage, to be 7% (McDonagh et al. 1997). For this study we assessed the interobserver variation by having a second observer analyse a subset of 90 echocardiograms, from the cohort, for determination of an L.V.E.F.. This second observer was blinded to the results obtained by the first observer. The median percentage difference in L.V.E.F. between the two sets of results was 5.6%. Using the method described by Bland and Altman (Bland and Altman, 1986) the limits of agreement between the two measurements of L.V.E.F. were found to be between –14.8 and 6.2 percentage points.

2.6.3 M-Mode Measurements and Derived Values

All M-Mode measurements were made on three consecutive cycles from the parasternal long axis view with the M-mode sector positioned using 2D echocardiography such that it was perpendicular to the interventricular septum at the level of the tips of the mitral valve leaflets. Diastole was defined as the onset of the R wave on the E.C.G. signal and systole as the point of maximal anterior excursion of the posterior L.V. wall.

Measurements were made as an average of three cycles according to the conventions established by the American Society of Echocardiography using a leading-edge-to-leading-edge method (Sahn et al. 1978) and the criteria of Schieken et al (Schieken et al. 1979) were used to determine the acceptable technical quality for M-Modes. The

measurements taken were: 1. the left ventricular end-diastolic dimension (LVEDD); 2. the left ventricle end-systolic dimension (LVESD); 3. the thickness of the interventricular septum in diastole (IVSd), and 4. the LV posterior wall thickness during diastole (LVPWd). From these the left ventricular mass was calculated using the Penn Cube formula (Devereux et al. 1986) as below:

LV Mass (g) = 1.04 [(IVSd+LVEDD+LVPWd)^3 - LVEDD3] -13.6 g

The LV mass index was calculated by divided the L.V. mass by the height in metres.

Both the L.V. mass and L.V. mass index, where appropriate, were considered seperately for males and females.

The relative L.V. wall thickness (R.Th.) was calculated in diastole as the ratio of half the sum of the interventricular septum in diastole and the LV posterior wall, to half the LV internal dimension

i.e. Relative LV Wall Thickness (R.Th.) = [(IVSd + LVPWd) ÷2] ÷ [LVEDD ÷2].

2.6.4 Doppler Echocardiographic Measurements

Doppler interrogation of the mitral valve inflow was obtained from the apical four-chamber view using pulsed wave Doppler with a 4mm sample volume placed in the mitral valve orifice close to the tips of the mitral valve leaflets. The measurements were regarded as acceptable if the angle between the Doppler beam and the mitral inflow did not exceed thirty degrees. The trans-aortic valve velocity profile was measured from the apical five-chamber view using continuous wave Doppler.

Measurements were taken as the average of five cycles and velocity curves were traced at the outer edge of the spectral envelope. Where the deceleration slope of the early transmitral velocity wave (E wave) could not be distinguished from the late transmitral velocity wave (A wave) measurements were not made. The deceleration time of the E

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wave was measured from the peak of the E wave to a point on the baseline where the E wave by extrapolation of the slope would have intersected it.

2.6.5 Subjective Assessment of Left Ventricular Function

One observer with experience of reporting echocardiograms reviewed all the anonymised video tapes to assess global left ventricular function using all the available views - parasternal long and short axis views and the apical four- and two- chamber views. Global function was graded as either impaired or normal. The definition of impairment was defined as being of clinical significance and ideally equating to an L.V. ejection fraction of 35% or less.

2.6.6 Valvular Dysfunction

The severity of any mitral incompetence seen on colour flow Doppler was graded by mapping the extent of the jet into the left atrium using pulsed wave Doppler; dividing the length of the left atrium behind the mitral valve into thirds. Mitral incompetence was considered mild if it extended less than one third, moderate if it extended between one- and two-thirds, and severe if it extended more than two-thirds of the length of the left atrium. Significant mitral incompetence was regarded as a severity greater than mild. Mitral stenosis was defined as the presence of thickened mitral valve leaflets and a pressure half-time of the transmitral E wave of greater than 100 msecs.

Aortic stenosis was regarded as a trans-aortic velocity of greater than 2.2 ms^{-1} (i.e. gradient > ~ 20mmHg). Aortic incompetence was graded subjectively according to the breadth of the jet orifice on colour flow doppler of the aortic valve on a parasternal short axis view. This was graded as either mild or significant - this being anything degree greater than mild.

The presence of prosthetic valves was noted on review of the real-time video tapes.

2.7 Twelve-Lead Electrocardiogram

This was recorded in a standard fashion at a paper speed of 25mm per second on a Siemens Sicard 440 electrocardiograph (Siemens Elema, Stockholm, Sweden) and transmitted to the E.C.G. laboratory at Glasgow Royal Infirmary for storage on a central Mingocare data base (Siemens Elema, Stockholm, Sweden). They were subsequently coded by computer algorithm (Macfarlane, 1998) according to the Minnesota ECG code (Prineas et al. 1982) for the presence of Q/QS waves (codes 1.1-1.3), left bundle branch block (7.11), ST segment depression (4.1-4.4), left ventricular hypertrophy (3.1, 3.3, 3.4) or atrial flutter/fibrillation (8.31, 8.32). All E.C.G. results were verified by visual inspection.

2.8 Treadmill Exercise Testing

Symptom limited treadmill exercise testing was carried out after the echocardiogram in the absence of standard contraindications - unstable angina, significant aortic stenosis or hypertrophic obstructive cardiomyopathy, recent myocardial infarction or a systolic blood pressure >220 mmHg or a diastolic blood pressure >110 mmHg. The Standardised Treadmill Exponential Exercise Protocol (S.T.E.E.P.) was used (Northridge et al. 1990).

A short demonstration was given by a technician and this and all further instruction was standardised for all participants. Participants were asked to continue for as long as they could and further standard encouragement was given every two minutes. A 12 lead

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E.C.G. was recorded and blood pressure measured 10 seconds before the end of each two minute stage and at 1, 3 and 5 minutes following the end of exercise. Participants were encouraged to exercise for a further 30 seconds, if they could, after they indicated that they wished to stop. The test was terminated by the technician or supervising doctor if they felt standard criteria for termination had been met (Froelicher, 1994). The participant's reasons given for asking to stop were recorded.

2.8.1 Analysis of Exercise Electrocardiographs

All exercise tests were analysed independently by two coders for the presence of ST segment depression according to the Minnesota Coding Manual (Prineas et al. 1982) with discrepancies in coding being arbitrated by a third coder. ST segment measurements were made on the resting E.C.G. and peak exercise E.C.G.s taking the measurement at 80 msecs beyond the J point.

2.9 Venous Blood Sampling

Following 20 minutes supine rest a venous blood sample was taken for the following analyses.

2.9.1 Venous Blood Glucose

This was a random sample measured in whole blood by a photometric method using Glucotide reagent strips read by a Glucometer 4 meter (Bayer Diagnostics, Newbury, England) with a range of 0.6 to 33.3 mmolL^{-1}. Quality control was maintained by monthly validation of the meter and reagent strips by the hospital's Clinical Chemistry Dept. using test standard glucose solutions (Bayer Diagnostics, Newbury England).

2.9.2 Plasma Cholesterol

A 10ml sample of venous blood was collected in a tube with a small amount of potassium-EDTA and sent to the Clinical Chemistry laboratory of the Western

Infirmary, Glasgow for measurement of plasma total cholesterol, triglycerides and the HDL fraction of cholesterol, if possible, according to standards validated by the Royal College of Pathologists.

2.9.3 Neurohormones

(a) Sample Handling and Plasma Extraction

A 10ml sample of blood was placed into a pre-chilled tube containing potassium-EDTA (1mg/ml blood) and aprotonin (50 I.U./ml blood). The sample was stored on ice and centrifuged at 3000 r.p.m. for 10 minutes at 4° C within 30 minutes of collection. The plasma was immediately frozen and stored at -70° C. until assay.

Both N-terminal atrial natriuretic peptide (N-ANP) and brain natriuretic peptides (BNP) were measured in plasma after extraction. The plasma was acidified with an equal volume of trifluoroacetic acid (T.F.A.) and then centrifuged. The supernatant was then allowed to pass slowly through a Sep-Pak C18 mini column (Waters Associates Ltd., Watford, England) which had been preconditioned with methanol (5ml), then 1% T.F.A. (5ml) and finally a further two aliquots of 1% T.F.A. (3ml). The column was then washed with 1% T.F.A. (5ml) followed by 0.1% T.F.A. (2ml). The eluted peptides were dried by rotary vacuum and redissolved in buffer for assay. Recoveries were 87% and 82% for N-ANP and BNP respectively.

(b) N-Terminal ANP Assay - Indirect

N-ANP was measured after dilution (1/100) by radioimmunoassay using an antibody - RAS 9129 (Peninsula Laboratories, Belmont, California, USA) - raised against the 1 to 30 N-terminal fragment. This antiserum has no detectable cross reaction with either C-terminal ANP or BNP and has an IC_{50} of 18 pg. per tube in the assay. The within-assay

and between-assay coefficients of variation (Cvs) for this assay were 15% (n=16) and 16% (n=48) respectively (Lang et al. 1993).

(c) BNP Assay - Indirect

BNP was measured in the extract (1/4 dilution) using a radioimmunoassay kit for human BNP - RIK 9086, (Penninsula Laboratories, Belmont, California, USA). This has an IC_{50} of 20 pg. per tube. The within-assay and between-assay Cvs were 18% (n=16) and 15% (n=46) respectively.

(d) BNP Assay - Direct

BNP was also assayed in unextracted plasma using a direct immunoradiometric assay kit (Shionoria BNP kit) supplied by Shionogi & Co, Ltd. (Osaka, Japan) (Kono et al. 1993). This uses two monoclonal antibodies which recognise the carboxyl terminal sequence and the ring structure of human BNP, respectively, and measures BNP by sandwiching it between the two antibodies without plasma extraction (Yasue et al. 1994). The minimum detectable quantity of human BNP is 2 pg./ml and the degree of cross reactivity with human ANP is less than 0.001% on a molar basis (Tsutamoto et al. 1997). The within-assay and between-assay Cvs were both <5%.

2.10 Definitions

So that comparisons could be drawn, and for consistency, the definitions used were, in the main, those used by McDonagh in her previous study of this population (McDonagh et al. 1997) and as presented in her MD thesis based on the same study (McDonagh 1998).

2.10.1 Ischaemic Heart Disease

Ischaemic heart disease was defined as the presence of one or more of: 1. a prior physician-made diagnosis of myocardial infarction or angina; 2. the current use of

nitrates; or 3. ECG evidence of ischaemic heart disease according to the Minnesota coding system (Prineas et al. 1982) using codes for pathological Q waves (codes 1.1 - 1.3), ST segment depression (4.1 - 4.4) or left bundle branch block (7.11).

2.10.2 Hypertension

Hypertension was principally defined as the presence of one or more of the following: 1. a systolic blood pressure exceeding 160 mmHg; 2. a diastolic blood pressure exceeding 95 mmHg; or 3. the current use of specific antihypertensive medication.

For comparison, hypertension was also defined using the cut-off points for blood pressure as defined in the Sixth Report of the Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure (Joint National Committee on Prevention, Evalaution and Treatment of High Blood Pressure 1997) - the JNC VI guidelines. Hypertension [JNC VI] was thus defined as the presence of one or more of the following: 1. a systolic blood pressure $\geq$ 140mmHg; 2. a diastolic blood pressure $\geq$90mmHg; or 3. the use of specific antihypertensive medication.

2.10.3 Diabetes Mellitus

Diabetes mellitus was defined as the presence of one or more of the following: 1. a prior physician-made diagnosis of diabetes mellitus; 2. the current use of either insulin or oral hypoglycaemic agents, or 3. a random venous blood glucose $\geq$ 11.1 mmolL^{-1}.

2.10.4 Excessive Alcohol Intake

This was assessed from the alcohol diary and was defined as a typical alcohol intake of greater than the 95th percentile for the population which was 56 units per week.

2.11 Statistical Analysis

Statistical analyses were performed using Minitab for Windows (Minitab Inc, Pennsylvania, U.S.A.) . Variables with normal distributions are described by the mean and the standard deviation (SD) and means were compared using a two sample t test. Variables with a skewed distribution which could not be transformed easily were described by the median value and interquartile range. The median values for two groups were compared using the Mann-Whitney U test. The proportions of individuals in two or more groups were compared by the Chi-square test or where appropriate Fisher's exact test . Univariate and multivariate linear regression analyses were used to determine the relationship between a variable or a set of variables and a single outcome. A P value of <0.05 was taken to be significant.

2.12 Ethics

The study was approved by the West Glasgow Ethics Committee. All participants gave their written consent to each part of the study visit after having been given prior written information with the invitation and a verbal explanation at the time of their visit.

3. Characteristics of Study Population and Risk Factors for Ischaemic Heart Disease.

3.1 Introduction

The MONICA population of North Glasgow (Tunstall-Pedoe et al. 1994) is an inner-city population with a high degree of both social and material deprivation (Tunstall-Pedoe et al. 1996), having a socioeconomic status well below that for the rest of Scotland (Morrison et al. 1997). It is characterised by a high event rate for myocardial infarction and coronary death in both males and females (Tunstall-Pedoe et al. 1996). Since the majority of left ventricular (L.V.) dysfunction, both systolic and diastolic, in the Western world today can be attributed to the effects, either singularly or in combination, of ischaemic heart disease (I.H.D.) and hypertension (Cowie et al. 1997a; Madsen et al. 1994; Brogan et al. 1992; Judge et al. 1991; Echeverria et al. 1983) this population was chosen in which to define the prevalence, causes and characteristics of both abnormal systolic and diastolic L.V. function.

A previous study looking at L.V. systolic dysfunction in this population had been carried out some three years prior (McDonagh et al. 1997) and looked at a wide age range - 25 to 75 years. It showed, as have other studies (Schocken et al. 1992; Ho et al. 1993a; Ho et al. 1993b), that the prevalence of L.V. systolic dysfunction rises with age, and particularly steeply so after the age of 55 years. Therefore this current study concentrated on the older age range of 55 to 74 year olds recognising that morbidity and mortality in this group is both premature and still impacts greatly on the individual and community, since individuals at this point in life, being increasingly freed from the ties of employment and family, expect to enjoy a good quality of life.

It was the aim of this study to recruit and study a well characterised random sample of this high risk population. This chapter describes in detail the study population

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characteristics with particular emphasis on established coronary risk factors

3.2 *Methods*

These are described in detail in Chapter 2 but briefly the theoretical population was all men and women resident within the city of Glasgow, north of the River Clyde aged between 55 and 74 years.   By means of a two stage, stratified, random sampling process, and by over sampling where required,   125 males and females within each five year age band were studied.   Each attendee completed questionnaires regarding demographics, past medical history and current medication.   Both height and weight were measured and body mass index was calculated as weight (kg) ÷ height^2 (m). Blood pressure was measured as the average of two readings using a random-zero sphygmomanometer (Hawksley and Sons, Ltd., West Essex, England) after ten minutes seated rest.   A random, non-fasting, blood sample was taken for measurement of total serum cholesterol and blood glucose by a photometric method using Glucotide reagent strips read by a Glucometer 4 meter (Bayer Diagnsotics, Newbury, England) with a range of 0.6 to 33.3 mmolL^{-1}.   Finally a 12 lead resting ECG was recorded and Minnesota coded (Prineas et al. 1982).

3.2.1 Definitions

Hypertension: current treatment with antihypertensive medication and/or a systolic blood pressure >160 mmHg and/or a diastolic blood pressure >95 mmHg.

Hypertension [JNC VI]: current treatment with antihypertensive medication and/or a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg. Hypertension is further subdivided into Stage 1:   BP 140-159/90-99 and Stage 2:

≥160/≥100 mmHg.

Ischaemic Heart Disease: the presence of one or more of: (a) a prior physician-made diagnosis of myocardial infarction or angina; (b) the current use of nitrates; (c) ECG evidence of possible I.H.D. - pathological Q waves (codes 1.1 - 1.3) , ST segment depression (4.1 - 4.4) or left bundle branch block (7.11).

Diabetes Mellitus (D.M.): either (a) a prior physician-made diagnosis of diabetes mellitus or (b) the current use of either insulin or oral hypoglycaemic agents or (c) a random venous blood glucose ≥ 11.1 mmolL^{-1}.

3.2.2 Statistical Analysis

Values with a normal distribution are quoted as the mean ± standard deviation (S.D.). Other values are quoted as the median and interquartile range (I.Q.R.). Student's t test (two-tailed) was uséd to compare means, the Mann Whitney U test to compare medians and the Chi-squared test or Fisher's exact test, where appropriate, was used to compare the proportions of individuals within two or more groups. A P value of <0.05 was taken to be significant.

3.3 Results

3.3.1 Response Rates and Non-Attenders

From the general practice lists 2404 individuals were selected of which 285 (11.9%) were excluded by their G.P. and a further 139 (5.8%) were found subsequently to have moved out of the area. Of the 1688 people invited 1009 (59.8%) finally attended - the age and sex breakdown of which is shown in Table 3-1. The response was greater in men than in women - 63.1% v 56.8%, P=0.008 - and fell with increasing age; being greater in the first ten compared to the second ten years of the age range -

Table 3-1 - Age and Sex Distribution of Attendees

AGE GROUP	MALE	FEMALE	TOTAL
55 - 59 yrs	123	131	254
60 - 64 yrs	128	133	261
65 - 69 yrs	122	124	246
70 - 74 yrs	127	121	248
Totals	500	509	**1009**

Table 3-2 - Response Rate by Age and Sex

N=1009

AGE GROUP	MALE	FEMALE	TOTAL
55 - 59 yrs	65.1%	64.2%	64.6%
60 - 64 yrs	69.9%	60.5%	64.8%
65 - 69 yrs	64.2%	53.4%	58.3%
70 - 74 yrs	55.2%	50.4%	52.8%
	63.1%	**56.8%**	**59.8%**

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64.7% v 55.4%, P<0.001 - Table 3-2 & Figure 3-1. The poorest response was seen in the oldest age group of females - 50.4%. A detailed summary of the characteristics of the attendees is presented in Table 3-3. The deprivation categories for the entire study cohort, based on the postcode sectors for the attendees' addresses, are shown in Table 3-3, and are compared to those of the entire Scottish population in a frequency distribution histogram – Figure 3-2 . Over half the cohort (52.7%) were in the most deprived categories – Depcat 6 or 7 – compared to just 15% of the whole Scottish population.

General practice casenotes for 462 (56.5%) of the non-attenders were made available for study. In 27 (5.8%) individuals a hospital diagnosis of heart failure was recorded of which six had echocardiographic evidence of L.V. systolic dysfunction.

3.3.2 Risk Factors For Ischaemic Heart Disease Within The Population

Overall there was a high prevalence of risk factors for ischaemic heart disease within the study population - Tables 3-4a to 3-4c.

(a) Blood pressure and Hypertension

The mean systolic and diastolic blood pressures in participants were 147.0 ± 24.9 mmHg and 80.5 ± 12.9 mmHg respectively, with males having a higher mean diastolic pressure than females - 81.5 ± 13.4 mmHg v 79.5 ± 12.3 mmHg, P=0.014. The frequency distributions of systolic and diastolic blood pressures within the population are shown in Figure 3-3. The prevalence of hypertension, as defined by our definition, was 44.1%, being equal in males and females, but showed a significant age gradient with it being higher in the second ten years of the age range compared with the first ten - 36.5% v 52.0% (P<0.001).
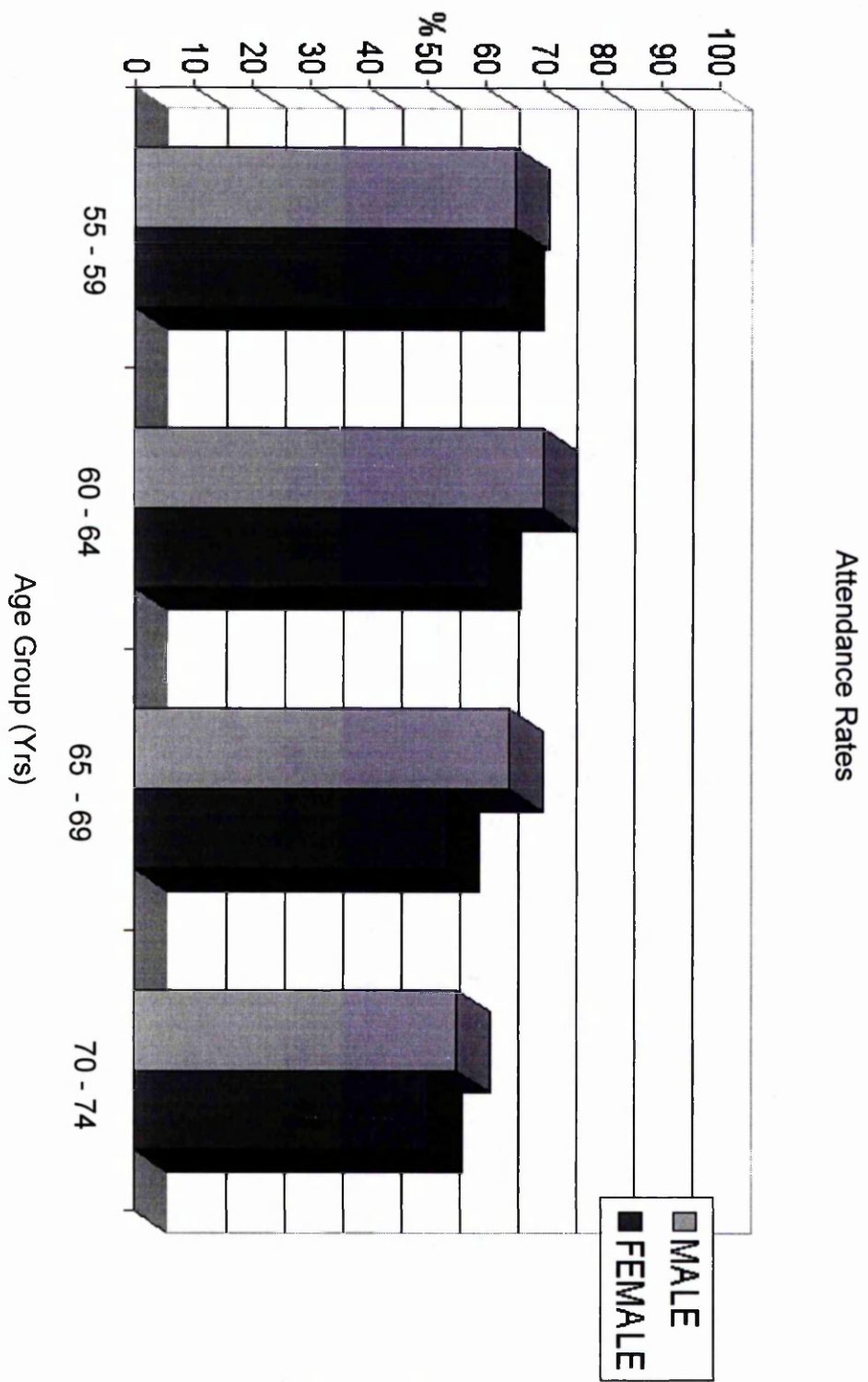
Figure 3-1 - Attendance Rates by Age and Sex

Table 3-3 - Characteristics of Participants

(n=1009)

Body Mass Index	26.9 ± 4.4	Kg/m^2
Systolic Blood Pressure	147.0 ± 24.9	mmHg
Diastolic Blood Pressure	80.5 ± 12.9	mmHg
Total Cholesterol	5.99 ± 1.12	mmolL^{-1}

	Number	**%**
• Diabetes Mellitus	67	6.6%
Diet controlled	24	2.4%
Oral hypoglycaemic agents	26	2.6%
Insulin	6	0.6%
New diagnosis	11	10.9%
• Hypertension	445	44.1%
Currently on medication	240	23.8%
• Hypertension (JNC VI)	677	67.1%
Currently on medication	240	23.8%
• Ischaemic Heart Disease	443	43.9%
Self Reported M.I.	108	10.7%
Self Reported Angina	165	16.4%
Nitrate Use	100	9.9%
Q/QS pattern	67	6.6%
Major E.C.G. Ischaemia	266	26.4%
• Cigarette Smoking		
Current	91	9.0%
Ex-smoker	604	59.9%
Never	306	30.3%
Not known	8	0.8%
• Alcohol Consumption		
$\leq$ 21 units / week	654	64.8%
> 21 units / week	95	9.4%
Not known	260	25.8%
• Current Medication		
Aspirin $\leq$ 300mg /day	182	18.0%
Beta Blockers	126	12.5%
Calcium Channel Blockers	114	11.3%
Nitrates incl. S/L GTN	100	9.9%
ACE inhibitors	46	4.6%
Loop diuretics	58	5.7%
Warfarin	15	1.5%
Digoxin	20	2.0%

Table 3-3 - (Cont.)

	Number	%
Highest Level of Education Attained		
University degree	20	2.0%
Professional / Technical Diploma	120	11.9%
Secondary School	804	79.7%
Primary School	44	4.4%
Not Known	21	2.1%

	Number	%
Housing Tenure		
Owner Occupier (Private Sale)	208	20.6%
Owner Occupier (former Local Authority)	246	24.4%
Local Authority Leasing	512	50.7%
Private Renting	24	2.4%
Not Known	17	1.7%

- Current Employment Status

	Males (n=500)		Females (509)	
	n	%	n	%
Full-time	77	15.4%	26	5.1%
Part-time	11	2.2%	49	9.6%
Unemployed	37	7.4%	9	1.8%
Long-term sick	86	17.2%	36	7.1%
Retired	280	56.0%	310	60.9%
Housewife	N/A		71	13.9%
Unknown	9	1.8%	8	1.6%

- Deprivation Category – By postcode sector

	n	%
Cat. 1	119	11.8%
Cat. 2	89	8.8%
Cat. 3	67	6.6%
Cat. 4	156	15.5%
Cat. 5	44	4.4%
Cat. 6	329	32.6%
Cat. 7	203	20.1%
Not Known	2	0.2%

Frequency Distribution of Deprivation Categories in Scotland (1991) and Study Cohort
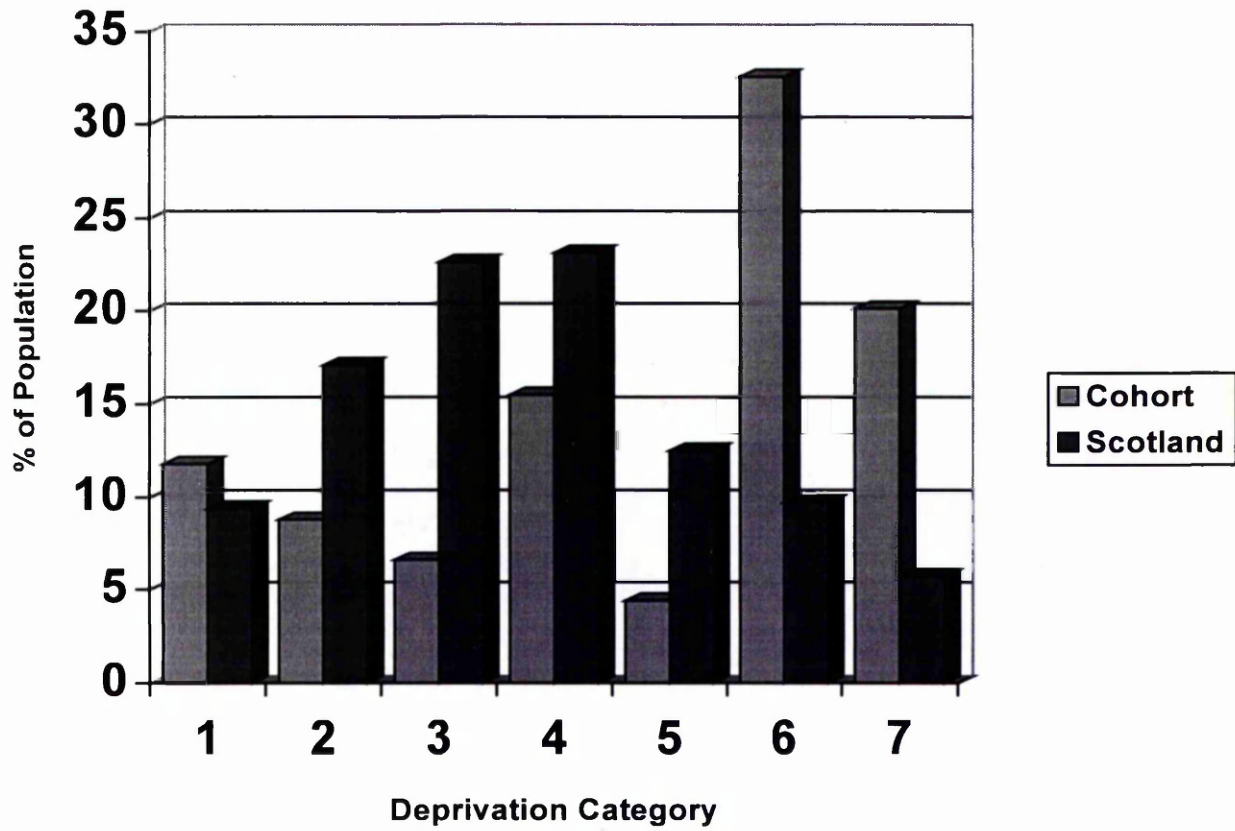
Notes:

Category 1 - Most affluent to   Category 7 – Greatest deprivation

Table 3-4a - Prevalence of Risk Factors for Ischaemic Heart Disease in Whole Cohort

Risk Factor	No.	Prevalence	
Hypertension	445	44.1%	
Hypertension [JNC VI]	677	67.1%	
Diabetes Mellitus	56	5.6%	
Cholesterol $\geq$ 6.5 mmolL^{-1}	291	28.8%	
Smoker - Ex	604	60.4%	
Current	91	9.1%	
Family History	199	19.7%	(N=1009)

Table 3-4b - Risk Factors in Male and Female Attendees

	Males n=500	Females n=509
BMI (kg/m^2)	26.7 (23.9 - 28.9)	26.6 (23.7- 29.8)
Cholesterol (mmolL^{-1})	5.65 $\pm$ 1.04	6.34 $\pm$ 1.09 **
Systolic BP (mmHg)	148.2 $\pm$ 24.2	145.5 $\pm$ 26.4
Diastolic BP (mmHg)	81.5 $\pm$ 13.4	79.4 $\pm$ 12.8 **
Alcohol (units / week)	8.0 (0 - 21.0)	2.0 (0 - 5.0) **
Hypertension	44.0%	44.2%
Hypertension [JNC VI]	69.0%	65.2%
Diabetes Mellitus	7.8%	5.5%
Cigarette Smoking		
-Ex	70.2%	49.5% **
Current	8.2%	10.0%
Cholesterol $\geq$ 6.5 mmolL^{-1}	18.0%	39.5% **
Lipid Lowering Therapy	1.4%	2.9%
Family History of I.H.D.	15.8%	23.6% **

* P<0.05   ** P<0.01

Table 3-4c - Risk Factors for Ischaemic Heart Disease by Age Group

Age Group	Diabetes	Prevalence Hypertension	Hypertension [JNC VI]
55- 59 yrs	6.7%	33.9%	54.3%
60 - 64 yrs	6.5%	39.1%	62.1%
65 - 69 yrs	9.8%	51.6%	79.7%
70 - 75 yrs	3.6%	52.4%	73.0%

Change in prevalence with age: Diabetes - not significant, P=0.06

Hypertension - P<0.001

Age Group (yrs)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Total Cholesterol $(mmolL^{-1})$
55 - 59 yrs	140.4 ± 21.6	81.1 ± 11.8	6.14 ± 1.08
60 - 64 yrs	142.8 ± 24.3	80.2 ± 13.0	5.95 ± 1.03 *
65 - 69 yrs	152.3 ± 24.4**	81.6 ± 12.9	6.00 ± 1.17
70 - 75 yrs	153.0 ± 26.7**	79.2 ± 13.7*	5.88 ± 1.19 *

* P<0.05 ** P<0.01 compared to the 55 - 59 years age group

Figure 3-3 - Distribution of Systolic and Diastolic Blood Pressure in Study Population

Distribution of Systolic Blood Pressure in Study Population

N=1009
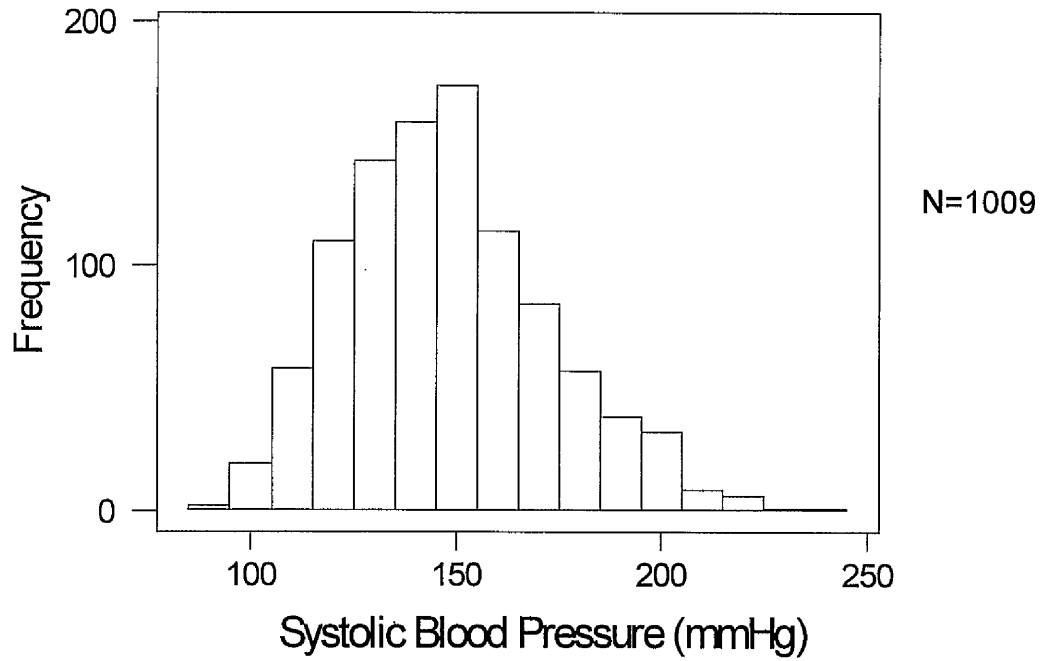
Distribution of Diastolic Blood Pressure in Study Population

N=1009
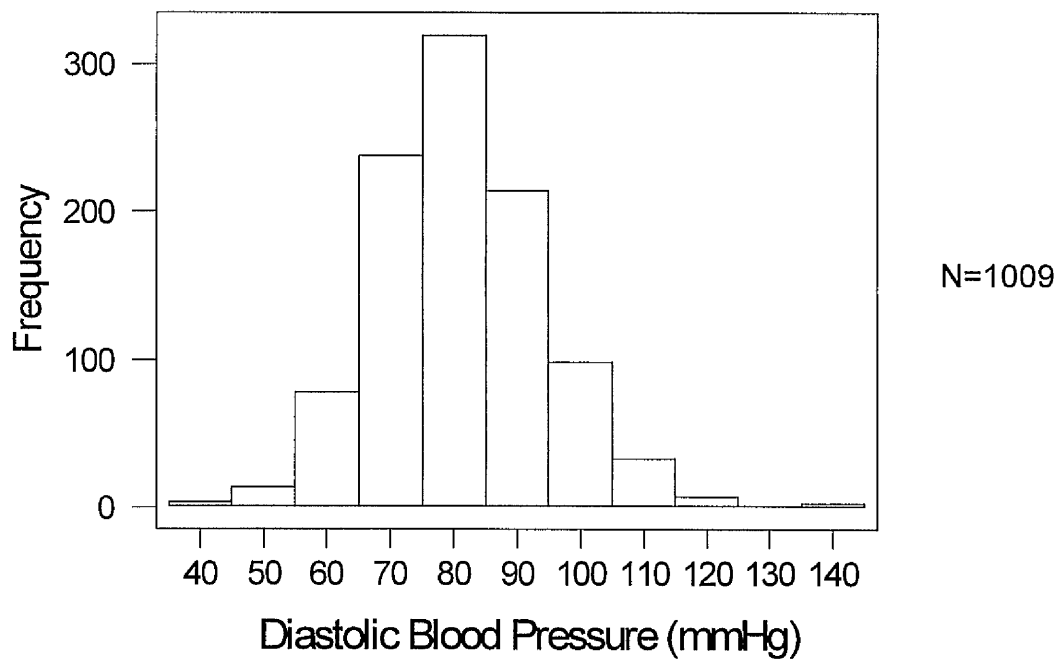
Antihypertensive medication was currently being taken by 240 individuals (23.8%) i.e. treated hypertension - Figure 3-4. A further 205 (20.3%) individuals in the absence of antihypertensive medication had a systolic blood pressure in excess of 160 mmHg and/or a diastolic blood pressure in excess of 95 mmHg - i.e. untreated hypertension. Of those who were already treated 125 (52.1%) had both a systolic blood pressure <160 mmHg and a diastolic blood pressure <90 mmHg - i.e. had treated and controlled hypertension. Of the untreated hypertensives 45 (22.0%) reported having been told by a physician at some point that they had hypertension i.e. detected but untreated hypertension.

Amongst those with hypertension the mean cholesterol was 6.05 ± 1.16 mmolL^{-1} with a range of 2.89 to 9.85 mmolL^{-1} and lipid lowering agents were being taken by 14 individuals. Diabetes mellitus was present in 38 (8.5%) individuals. Current cigarette smoking was reported by 34 (7.6%) individuals and 277 (62.2%) were former smokers.

(b) Hypertension – JNC VI based Definition

Using the blood pressure limits for normality as set out in the JNC VI guidelines 677 (67.7%) people were considered to be hypertensive.- Tables 3-4a to 3-4c and 3-5. Of these, 437 persons were not currently receiving antihypertensive treatment; 242 of whom were defined as having stage 1 hypertension (BP 140-159 / 90-99 mmHg) and 195 of whom were defined as having stage 2 (BP ≥ 160/100 mmHg). A further 119 individuals had a high/normal blood pressure (BP 130-139 / 85-89 mmHg) in the absence of antihypertensive therapy. Of the 240 individuals receiving antihypertensive treatment 176 (73.3%) still had a blood pressure ≥140/90 i.e. were not adequately controlled according to the JNC VI guidelines – although these had not been published

Hypertensives Within Population
N=445
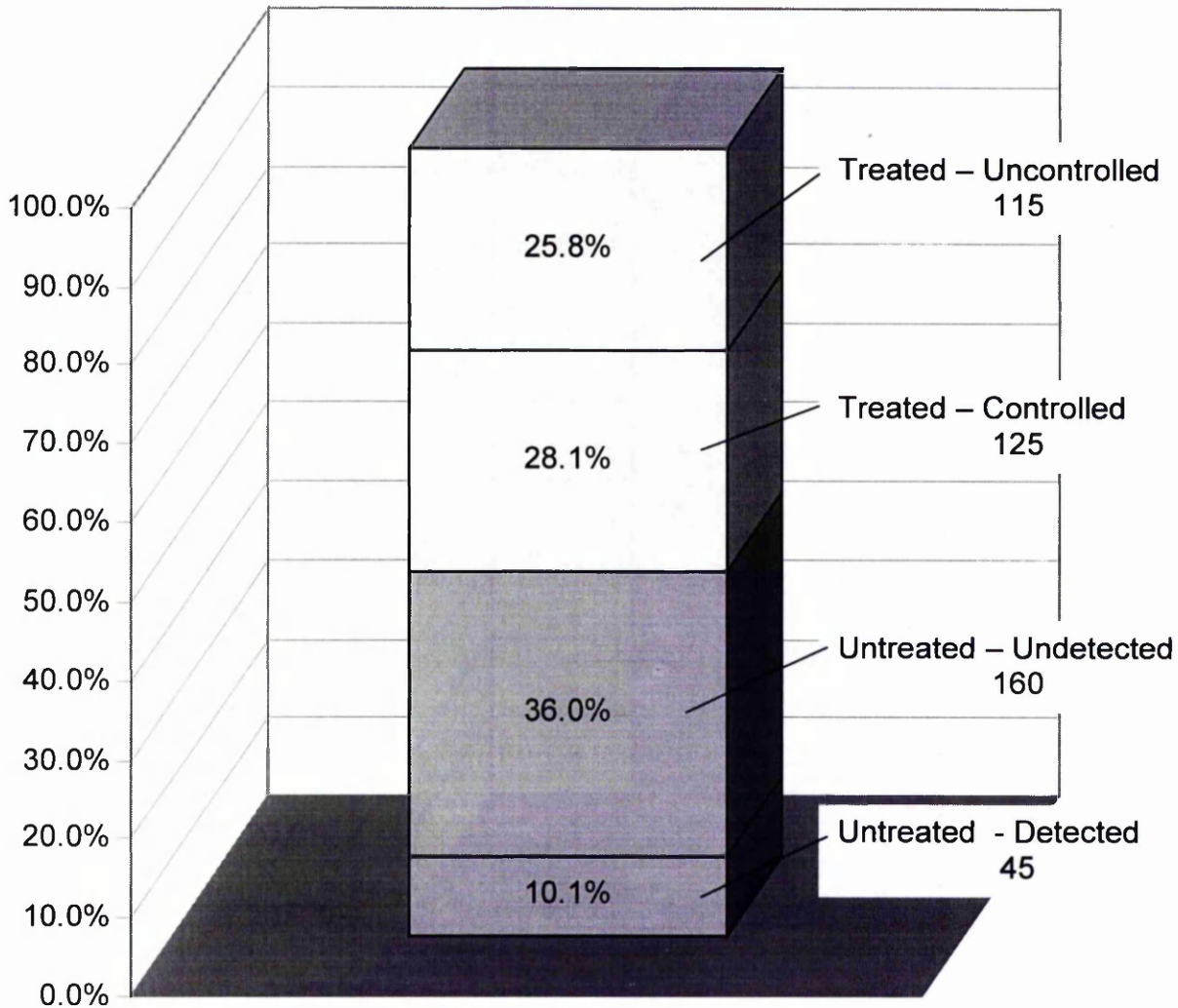
Definitions

Hypertension- Systolic BP >160 mmHg and / or
              Diastolic BP >95 mmHg and / or
              Currently on antihypertensive medication.

Controlled -   Systolic BP <160 mmHg - on treatment
               Diastolic BP <90 mmHg - on treatment

Detected -   Previous physician diagnosis

Table 3-5 - Prevalence of Hypertension by JNC VI Guidelines

Blood Pressure Category	All	Antihypertensive Therapy	
		Current	None
Normal <130/85	249 (24.7%)	36 (3.6%)	213 (21.1%)
High Normal 130-139 / 85-89	147 (14.6%)	28 (2.8%)	119 (11.8%)
Stage 1 140-159 / 90-99	321 (31.8%)	79 (7.8%)	242 (24.0%)
Stage 2 ≥160 / ≥100	292 (28.9%)	97 (9.6%)	195 (19.3%)
Total	1009	240 (23.8%)	769 (76.2%)

N (% of entire cohort)

at the time this study was performed.

(c) Diabetes Mellitus

The prevalence of diabetes was 6.6% in this study with no gender difference. A previous physician-made diagnosis was reported by 56 people (5.6%) and this was being treated by diet alone in 24 individuals, oral hypoglycaemic agents in 26 and insulin therapy in six. In addition 11 (1.1%) individuals had a random venous blood glucose of ≥ 11.1 mmolL^{-1} without a prior diagnosis of diabetes.

Of those with diabetes 38 (56.7%) were hypertensive, and the mean cholesterol was 5.61 $\pm$ 0.88 mmolL-^{1}; range 3.51 to 8.46 mmolL-^{1}. Four were currently taking lipid lowering drugs. Only one individual still smoked regularly but 49 were former regular cigarette smokers.

(d) Cholesterol Levels

A plasma cholesterol level was measured in 989 people and the mean was 5.99 $\pm$ 1.12 mmolL^{-1}; range 2.68 to 9.88 mmolL^{-1}. The frequency distribution of total cholesterol in the study population is shown in Figure 3-5. Males had a lower mean cholesterol than females - 5.65 $\pm$ 1.04 mmolL^{-1} v 6.34 $\pm$ 1.09 mmolL^{-1}, P<0.001. A level of ≥ 6.5 mmolL^{-1} was taken to indicate significant hypercholesterolaemia and was found in 291 (28.8%) of the cohort. Lipid lowering drugs were being taken by 22 individuals whose mean cholesterol was 6.16 $\pm$ 0.87 mmolL^{-1}, which was not significantly different from the mean level for the cohort as a whole.

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Figure 3-5 - Distribution of Total Cholesterol In Study Population

Distribution of Total Cholesterol in Study Population
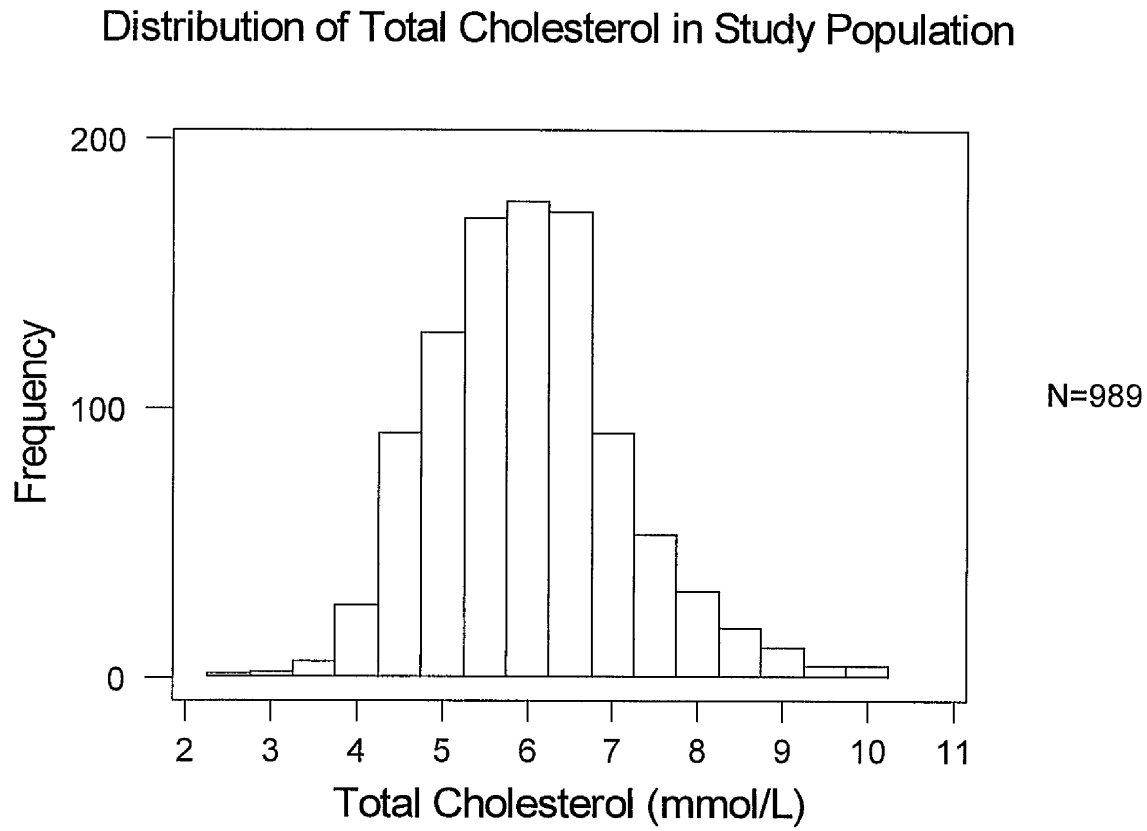
(e) Cigarette Smoking

Of the 1001 people who answered the smoking questionnaire 306 (30.6%) had never smoked cigarettes regularly.   Of the remainder 91 (9.1%) were current smokers - smoking a median of fifteen cigarettes a day - and 604 (60.4%) were former regular smokers.

(f) Family History

As to whether or not they had a parent or sibling suffer from heart disease before the age of 60 years 199 people (19.7%) answered in the affirmative.

(g) Multiple Risk Factors

Two or more of the above risk factors for ischaemic heart disease were present in 57.3% of the population - Table 3-6.

3.3.3 Ischaemic Heart Disease Within the Population

The overall prevalence of ischaemic heart disease (I.H.D.) within the study population was 43.9% and rose with age from 37.8% in the 55 to 59 years age group to 51.6% in the 70 to 75 years age group (P=0.002) - Table 3-7.   There was no significant gender difference.

Clinical I.H.D. - i.e. either self-reported or treated with nitrates - was present in 212 individuals (21.0%) - Table 3-8 - of whom 101 (47.6%) reported a diagnosis of angina, 44 (20.8%) a previous M.I. and 64 (30.2%) both.   A further three individuals were

Table 3-6 - Prevalence of Two or More Risk Factors for Ischaemic Heart Disease Within the Study Population

Diabetes				
38 (3.8%)	Hypertension			
50 (5.0%)	311 (30.8%)	Smoker Current/ Ex		
6 (0.6%)	135 (13.4%)	186 (18.4%)	Cholesterol ≥ 6.5mmolL^{-1}	
14 (13.9%)	77 (7.6%)	123 (12.2%)	59 (5.8%)	Family History

N=1009

Table 3-7 - Prevalence of Ischaemic Heart Disease by Age and Sex

N=1009

AGE GROUP	MALE	FEMALE	TOTAL
55 - 59 yrs	35.0%	40.5%	37.8%
60 - 64 yrs	45.3%	35.3%	40.2%
65 - 69 yrs	50.0%	42.7%	46.3%
70 - 74 yrs	49.6%	53.7%	51.6%
	45.0%	**42.8%**	**43.9%**

Table 3-8 - Proportion of Ischaemic Heart Disease Which Is Clinical

N=1009

AGE GROUP	MALE	FEMALE	TOTAL
55 - 59 yrs	41.9%	43.4%	42.7%
60 - 64 yrs	51.7%	40.4%	46.7%
65 - 69 yrs	52.5%	37.7%	45.6%
70 - 74 yrs	63.5%	46.2%	54.7%
	63.5%	**46.2%**	**54.7%**

Male v Female P=0.164

Clinical I.H.D. - Reported physician diagnosis of ischaemic heart disease or myocardial infarction or current use of nitrates.

currently using nitrates but did not report a prior physician diagnosis of I.H.D. The difference between the proportion of males and females who were symptomatic did not reach statistical significance nor did the difference across the age ranges. Of the 67 individuals with E.C.G. evidence of previous M.I. only 22 (32.8%) reported clinical I.H.D. and of the 266 with major ischaemia only 80 (30.0%) reported clinical I.H.D.

Diabetes mellitus and hypertension were both more prevalent amongst those with I.H.D. than amongst those without: diabetes 9.0% v 4.8% (P<0.01) and hypertension 53.1% v 37.1% (P<0.001). Smoking, both current and previous, was no more prevalent amongst those with I.H.D. (69.1%) than those without (68.7%). The mean cholesterol for individuals with I.H.D. was 5.99 ± 1.20 mmolL^{-1} which is not significantly different to the mean for individuals without I.H.D - 5.99 ±1.06 mmolL^{-1}.

Diabetic individuals compared to non-diabetic individuals had a higher prevalence of both ischaemic heart disease (59.7% v 42.9%, P<0.01) and hypertension (56.7% v 43.2%, P<0.05). Hypertensive individuals compared with those considered normotensive had a higher prevalence of both diabetes (8.5% v 5.1%, P<0.05) and ischaemic heart disease (52.8% v 36.9%, P<0.001).

3.4 Discussion

This study succeeded in its primary aim of assembling and studying a cohort of individuals from the community. The overall response rate was lower than might have been expected. The previous study undertaken in the same population (McDonagh et al. 1997) achieved a response rate of 83% but this was both amongst second time responders and across a wider age range including younger individuals who were shown, in that study and in this present one, to be more likely to attend. A community

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based study looking at an older age group (Morgan et al. 1999) achieved a response rate of 77.4% but found, like this study, that non-attenders were more likely to be older and female.

There are several factors which are likely to have influenced attendance. The major one may have been the need, because of the size of echocardiographic equipment, to use a single study site to cover what is a wide geographical area. Although travel costs were reimbursed, individuals from several of the furthest areas are likely to have been deterred from attending by distance. This might have explained the especially low percentage response amongst older females - a group least likely to travel far. Newer, more portable, echocardiographic equipment should allow future studies to be conducted in local communities.

There is the potential that those who did not attend suffered from more cardiovascular disease than those who did. Whether it was this that deterred them from attending or whether it was some other disease, possibly with an aetiology common also to cardiovascular disease such as smoking related airflow obstruction or diabetes, we do not know. The attempt to quantify this by looking at the general practice casenotes of non-attenders proved too difficult an exercise. Being an addendum to the original study protocol it ran into problems regarding consent and confidentiality. What it did suggest however was that there was at least as high a prevalence of heart failure in the non-attenders and so it is likely that any prevalence estimate in the study cohort will not be an overestimate for the whole population.

In this current study we set out to replicate the methods (apart from the

echocardiographic equipment) and definitions used by McDonagh in her previous study of this population (McDonagh et al. 1997; McDonagh 1998). Undoubtedly how one chooses to define a condition will influence its prevalence. Equally a condition whose signs may change on a daily basis, such as hypertension or diabetes mellitus, may be difficult to obtain a true prevalence for, based on a single clinical visit. In this study the aim was that the definitions used should be more exclusive than inclusive to avoid overestimating prevalences. Considerable importance was therefore attributed to previous physician-made diagnoses in view of the single clinical visit. Clearly there was no way of validating such prior diagnoses; however future programmes set up to screen for the presence of L.V. dysfunction are likely to have to use similar criteria and definitions for identifying individuals at risk and so this current study's methods seem appropriate.

The definition of hypertension used in this current study was the same as used in the 1994 Health Survey for England (Colhoun et al. 1998) and was based on the 1993 British Hypertension Society Guidelines (Sever et al. 1993) which were in force at the time of this study and which recommended, on the basis of three separate readings, treating a systolic blood pressure in excess of 160 mmHg and a diastolic blood pressure in excess of 90 to 100 mmHg depending on the presence of other factors. Once treated, the guidelines recommended a target systolic blood pressure of 160 mmHg or less and a diastolic blood pressure of 90 mmHg. The latest guidelines from the British Hypertension Society (Ramsay et al. 1999) are broadly similar with a threshold of $\geq$160/100 mmHg taken for the initiation of antihypertensive drug therapy except in the presence of cardiovascular complications, target organ damage (L.V.H., proteinuria etc), or a calculated ten-year coronary heart disease risk of $\geq$15%, when a level of

≥140/90mmHg is advised as the threshold for pharmacological intervention.

Using the definition of hypertension as set out in the JNC VI guidelines (Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure 1997) gives an even greater prevalence of hypertension in our cohort. Undoubtedly on the basis of a single visit we are likely to over estimate the true prevalence of hypertension, and this proportion of false positive diagnoses will increase as we lower the cut-off values of blood pressure, in untreated individuals, for the diagnosis of hypertension. This is because, in spite of our study protocols, we are likely to see some "white coat" effect on blood pressure. Hence the reason why, for the major part, we have taken 160/95 as our cut-off for the diagnosis of hypertension in the untreated individual. In doing so we ackowledge that lower levels of blood pressure may not necessarily be normal, and that there is a continuum of risk for coronary heart disease across an increasing range of blood pressure from high-normal to clearly abnormal (Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure 1997).

Hypertension was common in the study group although it was no more common than that found in the 1994 Health Survey for England (Colhoun et al. 1998) which showed the prevalence in the age group 55 to 64 years to be ~ 34%, with a slight excess in males compared to females, rising to 52.4% for men and 57.0% for women in the age group 65 top 74 years. The prevalence in this study was 36.5% in the age group 55 to 64 years and 52.0% in the 65 to 74 years olds.

In 1972 the "Rule of Halves" with regard to hypertension in the community was

conceived (Wilber and Barrow, 1972). This states that half of hypertension is undetected; half of those detected are untreated and in half of those treated hypertension is not controlled. This rule was shown to hold for Scotland between 1984 and 1986 (Smith et al. 1990) using the same definition as this current study. This present study showed that in 1994/1996 only 36% of the hypertension was undetected which may reflect the greater emphasis placed in primary care on screening and primary prevention. Of those treated 47.9%, however, were not controlled, based on a single visit, suggesting that whilst detection has improved follow-up may not have.

The prevalence of diabetes mellitus was lower than would be expected from previous studies in Caucasian populations: 6% in the 45 to 65 years age group and 11% in the over 65 years group (Harris, 1998). The definition of diabetes mellitus, incorporating a non-fasting blood glucose concentration, will almost certainly have underestimated its true prevalence. Depending on the interval elapsed since, and the nature of, the last meal the blood glucose in a diabetic individual may be less than or equal to 11.0 $mmolL^{-1}$. The recognition that, not only in epidemilogic studies, but also in clinical practice there is a potential to under-diagnose the condition, especially in its milder forms, has led to a recent change in the diagnostic criteria for diabetes mellitus contained within the most recent guidelines (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2000). These guidelines recommend that the diagnosis should be based on the results of a fasting plasma glucose; with the condition being diagnosed if the glucose is $\geq$ 7.0 $mmolL^{-1}$. They also recommend that this measurement, in the absence of clear metabolic upset attributable to diabetes, should be repeated before a definite diagnosis is made. The guidelines do allow the diagnosis to be made when a non-fasting plasma glucose is $\geq$11.1 $mmolL^{-1}$ but only in association

with the symptoms of diabetes. The same diagnostic criteria, the guidelines state, should be used in epidemiologic studies. Clearly not having measured a fasting plasma glucose in this study does not allow us to comply with these guidelines, which were published subsequent to the completion of this study. We have therefore had to use the available data collected to make some form of estimation of prevalence. The decision to use a non-fasting glucose of ≥ 11.1 mmolL^{-1} was in accordance with what was accepted clinical practice at the time this study was performed, and is in general agreement with the latest guidelines with regard to non-fasting levels, although we did not take into account the presence or absence of symptoms.

Population studies of diabetic patients in Finland, Framingham and Wisconsin, USA have shown that coronary heart disease increases with increasing levels of glycaemia (Kuusisto et al. 1994; Wilson et al. 1991; Klein, 1995). In this present study no assessment was made of glycaemic control in diabetic individuals nor of duration of disease. In future studies the measurement of glycosylated haemoglobin levels in blood might go part way to both detecting diabetes in the context of a normal random blood glucose and yielding information on glycaemic control in the medium term.

The level of total cholesterol which was taken to represent hypercholesterolaemia was based on the level of 6.5 mmolL^{-1} required for inclusion in the first stages of the WOSCOPS study (Shepherd et al. 1995; The WOSCOPS Study Group, 1995). In the Scottish Heart Health Study the mean cholesterol in men aged 45 to 59 years was 6.4 mmolL^{-1}. A decade later the finding of a mean cholesterol of 5.99 mmolL^{-1} in this study's population may have more than one explanation. One is selection bias: the more health conscious are likely to attend for a study, such as this one, with a perceived

benefit to the individual. Although, this does not seem to have been evident in other risk factors. The other is that individuals with high cholesterol levels may have already died from their premature coronary event.

The diagnosis of the presence of ischaemic heart disease without recourse to coronary angiography can never be totally accurate and any method used, whether it be questionnaires or electrocardiographs, is but a screening test with its own sensitivity and specificity. Our definition of I.H.D. is therefore, to a greater or lesser extent, flawed; as is that used by most epidemiologic studies. E.C.G. findings, with possibly the exception of large q waves, are not completely specific for ischaemia; the same finding may result from other myocardial diseases or simply the extremes of physiological variation (Rose et al. 1978). This is particularly true of left bundle branch block and ST segment depression, both of which may accompany left ventricular hypertrophy rather than I.H.D. As an isolated feature the Framingham study found that T wave inversion was of no significance (Higgins et al. 1965). The decision to exclude T wave inversion as a marker of I.H.D. will have undoubtedly lowered the overall prevalence of the condition and have led to an unspecified number of false negative diagnoses. Equally the inclusion of ST segment depression and left bundle branch block will have led to a number of false positive diagnoses being made. Relying upon patient recall of previous physician-made diagnoses is also inherently flawed. Firstly the diagnosis may not be correct, and there is no way of corroborating it, and secondly the recall may be inaccurate. In one study only one in five men with evidence on questionnaire or on E.C.G. criteria of I.H.D. recalled having been told by a physician that they had angina (Shaper et al. 1984). Other studies have used a chest pain questionnaire (the Rose questionnaire (Rose et al. 1977)) to diagnose ischaemic

heart disease (Bainton et al. 1988). The use of this in this present study would have improved the sensitivity of the definition used for diagnosing ischaemic heart disease. In future studies this should be included and its exclusion from this analysis was perhaps an oversight. In any study, however, the definition of I.H.D. based on simple clinical and electrocardiographic criteria will always be arbitary.

Accepting that the definition of I.H.D. in this study has at least impaired sensitivity, the prevalence of I.H.D. was still relatively high and agrees with what we know about the high coronary event rate in this population. It shows a rise with age in both sexes as would be expected. Previous studies using the Rose questionnaire and wider E.C.G. criteria have shown the prevalence to be lower in other populations. The Caerphilly and Speedwell studies (Bainton et al. 1988) in 1978, looking only at men, showed a prevalence of I.H.D. in the age group 55-59 years of between 24.4 - 29.9% compared with a prevalence of 35.0% in this present study. The prevalence in these published studies was higher amongst the unemployed suggesting a effect of socioeconomic status. In this north Glasgow geographical population it has been shown previously, for both men and women, that the risk of myocardial infarction increases with increasing deprivation (Morrison et al. 1997). This "socioeconomic gradient" is acting within a population which is already skewed towards the lower end of the socioeconomic scale. We demonstrated in this study that the cohort studied certainly had an overall socioeconomic status which was heavily skewed towards deprivation.

Therefore this study's well characterised population not only has a high, and possibly underestimated, prevalence of I.H.D., and its recognised risk factors, but is also socioeconomically disadvantaged - an additional risk factor in its own right.

4. Prevalence and Aetiology of Left Ventricular Systolic Dysfunction

4.1 Introduction

Much work has been carried out to establish the epidemiology of the clinical syndrome of chronic heart failure (C.H.F.) in the U.K., Europe and perhaps most famously in the U.S.A.   Less has been done to determine the epidemiology of the major contributor to the syndrome namely left ventricular systolic dysfunction (L.V.D.).   To date only two such studies have been carried out in the U.K.   McDonagh et al showed that in 1992 the prevalence of L.V.D. within the population of north Glasgow, aged between 25 and 74 years, by echocardiography was 2.9% although it was higher in the older decades. A more recent study from Dorset showed the prevalence to be 7.5% within an older age group of 70 to 84 year olds.   In both studies L.V.D. was mainly attributable to ischaemic heart disease (I.H.D.).

Following on from McDonagh's study, and seeking to replicate its methods but using more advanced echocardiographic equipment, this study aimed to establish the prevalence, aetiology and characteristics of L.V.D. within a larger random sample of 1000 individuals resident within the population of north Glasgow aged between 55 and 74 years. The characteristics of the study cohort are described in detail in Chapter 3.

4.2 Methods

These are described in detail in Chapter 2 but briefly each individual attended the study centre for one visit during which they completed questionnaires regarding past medical history, medication and the M.R.C. breathlessness questionnaire (Fletcher et al. 1959); which distinguishes dyspnoea possibly due to chronic bronchitis from that possibly cardiac in origin.   Their seated blood pressure was taken as the average of two readings after 10 minutes rest using a random zero sphygmomanometer (Hawksley and Sons,

Ltd., West Essex, England). A random venous blood sample was taken for measurement of glucose concentrations in whole blood by a photometric method using Glucotide reagent strips read by a Glucometer 4 meter (Bayer Diagnsotics, Newbury, England) with a range of 0.6 to 33.3 $mmolL^{-1}$.

A full two-dimensional echocardiogram was performed using an Acuson 128 ultrasound machine (Acuson Inc., Mountain View, CA, USA). At least three single-cycle loops of both the apical 4- and 2-chamber views were digitised and transferred onto optical discs using an off-line digital image processing and analysis system (Tomtec Imaging System Inc., Boulder, Colorado, USA). The left ventricular ejection fraction (L.V.E.F.) was measured using a biplane algorithm ("method of discs summation") - Simpson's rule (Schiller et al. 1979) - as an average of three cycles. To be suitable for analysis at least 80% of the endocardium had to be visible. End-diastole was defined as the frame with the largest L.V. cavity at the initial systolic coaptation of the mitral valve, and end-systole as the subsequent frame with the smallest cavity area (Badano et al. 1996).

A 12 lead electrocardiograph was recorded in a standard fashion at a paper speed of 25mm per second on a Siemens Sicard 440 electrocardiograph (Siemens Elema, Stockholm, Sweden) and subsequently coded by computer algorithm (Macfarlane, 1998) according to the Minnesota E.C.G. code (Prineas et al. 1982) for the presence of Q/QS waves (codes 1.1-1.3), left bundle branch block (7.11), ST segment depression (4.1-4.4), left ventricular hypertrophy (3.1, 3.3, 3.4) or atrial flutter/fibrillation (8.31, 8.32). All ECG results were verified by visual inspection.

4.2.1 Definitions

Hypertension: current treatment with antihypertensive medication and/or a systolic blood pressure >160 mmHg and/or a diastolic blood pressure >95 mmHg.

Hypertension [JNC VI]: current treatment with antihypertensive medication a systolic blood pressure ≥ 140mmHg; 2. a diastolic blood pressure ≥90mmHg; or 3. the use of specific antihypertensive medication.

Ischaemic Heart Disease: the presence of one or more of: (a) a prior physician-made diagnosis of myocardial infarction or angina; (b) the current use of nitrates; (c) ECG evidence of possible I.H.D. - pathological Q waves (codes 1.1 - 1.3) , ST segment depression (4.1 - 4.4) or left bundle branch block (7.11).

Diabetes Mellitus (D.M.): either (a) a prior physician-made diagnosis of diabetes mellitus or (b) the current use of either insulin or oral hypoglycaemic agents or (c) a random venous blood glucose ≥ 11.1 mmolL^{-1}.

Cardiac-type dyspnoea: Breathlessness reported on the M.R.C. questionnaire in the absence of symptoms of chronic bronchitis.

Abnormal E.C.G.: the presence of at least one of: Q/QS waves, ST segment depression, left bundle branch block or atrial flutter/fibrillation.

4.2.2 Statistical Analysis

Values with a normal distribution are quoted as the mean ± standard deviation (S.D.). Other values are quoted as the median and interquartile range (I.Q.R.). Student's t test (two-tailed) was used to compare means, the Mann Whitney U test to compare medians and the Chi-squared test or Fisher's Exact test where appropriate, the proportions of individuals within two or more groups. A P value of <0.05 was taken to be significant.

4.3 Results

4.3.1 Availability of the L.V. Ejection Fraction Within the Population

Of the 1009 participants 750 (74.3%) had an echocardiogram suitable for calculation of an L.V. ejection fraction - Table 4-1. The availability of a measured L.V.E.F. fell with age being greater in the 55 to 64 years age range than in the 65 to 75 years age range (77.3% v 71.3%, P=0.029). Compared to the group with a measured L.V.E.F., the group without an L.V.E.F. had a greater prevalence of both I.H.D. (54.8% v 40.1% P<0.01) and diabetes mellitus (10.8% v 5.2% P<0.01) but not hypertension which was equally prevalent in both groups - Table 4-2.

4.3.2 Definition of Left Ventricular Systolic Dysfunction

The distribution of L.V.E.F. for the whole population was skewed to the right with a median value of 50.7% (45.0 - 54.7%) and a range of 12.0% to 67.7%; mean 49.0 $\pm$ 8.1% - Figure 4-1. A subgroup of 144 individuals from the cohort with no evidence of cardiovascular disease, or its major risk factors (except for smoking) - the "normal" subgroup was identified. The L.V.E.F. in this group was also slightly positively skewed with a median of 51.8% (47.8 - 55.7%) - Figure 4-2 - and with females having a higher median L.V.E.F. than males - 53.7% (49.7 - 56.7%) v 50.0% (45.5 - 54.5%), P<0.01. Mean values were: females - 50.7 $\pm$ 7.3%, males 47.3 $\pm$ 8.5%. There was no significant effect of age.

The normal range of values for the L.V.E.F. was defined as the range from the 2.5[th] to the 97.5[th] percentiles inclusive for the normal subgroup: 37.2% to 61.6%. An L.V.E.F. of $\leq$ 35% was therefore taken to represent significant left ventricular systolic dysfunction (L.V.D.).

Table 4-1 - Availability of Simpson's Left Ventricular Ejection Fraction by Age and Sex

AGE GROUP	MALE	FEMALE	TOTAL
55 – 59	75.6%	77.9%	76.8%
60 – 64	82.0%	73.7%	77.8%
65 – 69	69.7%	81.5%	75.6%
70 – 74	70.1%	63.6%	66.9%
	74.4%	**74.3%**	**74.3%**

N=1009

Table 4-2 - Comparison Of Individuals With and Without a Measured L.V.E.F.

Parameter	LVEF (n=750)	No LVEF (n=259)
Age (yrs)	65.0 (60.0 - 69.0)	66.0 (61.0 - 71.0)
Sex - Male	49.6%	50.8%
Diastolic B.P. (mmHg)	80.6 ± 12.9	79.9 ± 13.7
Systolic B.P. (mmHg)	147.2 ± 25.0	146.1 ± 26.2
B.M.I. (Kg/m^2)	26.3 ± 4.0	28.7 ± 5.1 **
Cholesterol (mmolL^{-1})	6.00 ± 1.1	5.96 ± 1.1
% I.H.D.	40.1%	54.8% *
% Hypertension	42.8%	47.9%
% Hypertension [JNC VI]	66.5%	68.7%
% Diabetic	5.2%	10.8% *
Previous M.I.	10.0%	12.4%
Smoker	68.5%	69.9%

* - P<0.05   ** - P <0.001

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Figure 4-1 - Distribution of Left Ventricular Ejection Fraction Within Whole Population

N=750
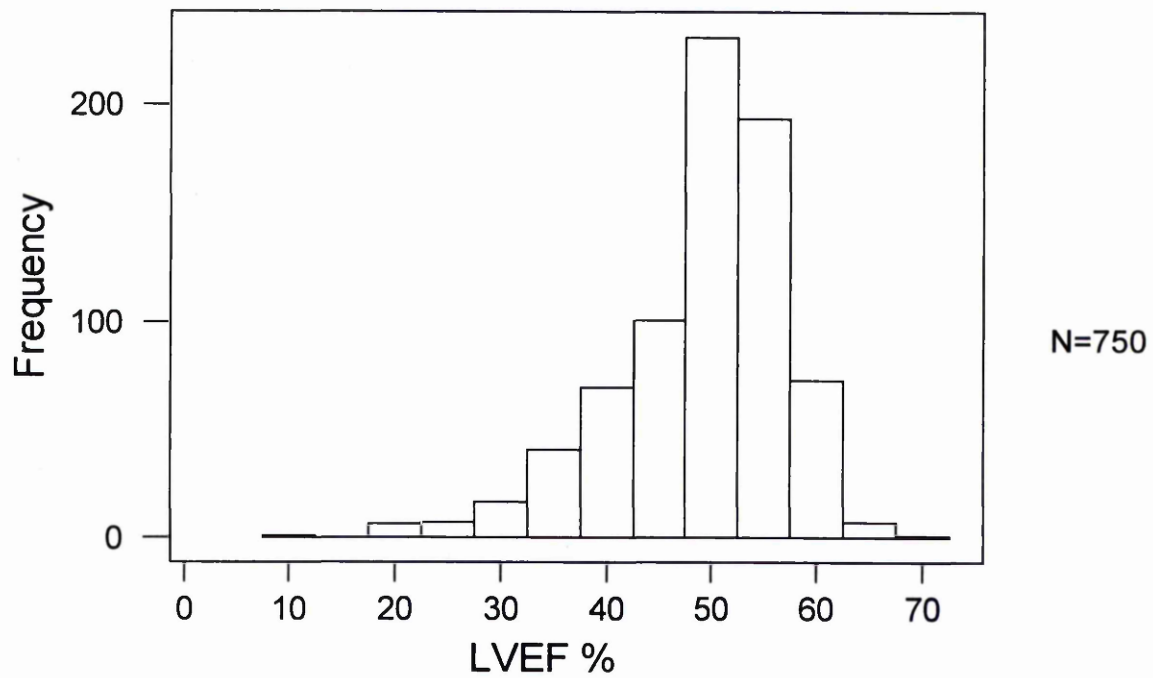
Figure 4-2 - Distribution of Left Ventricular Function in Normal Subgroup

N=144
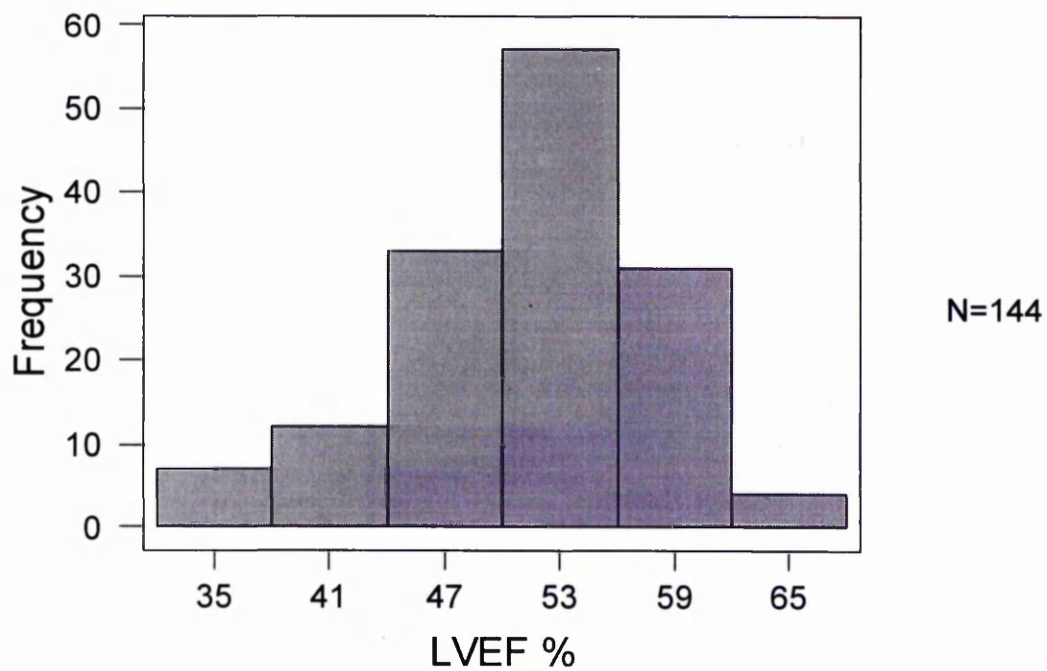
4.3.3 Prevalence of Left Ventricular Systolic Dysfunction

The prevalence of L.V.D. was 6.7% within the population with an L.V.E.F. measured; being greater in males than in females - 9.4% v 4.0%, P=0.004, and rising with age - Table 4-3 & Figure 4-3. The median age for those with L.V. dysfunction was higher than for those with normal L.V. function - 69.0 years v 65.0 years , P=0.017. There was no difference in terms of blood pressure, body mass index, plasma cholesterol or alcohol consumption between those with L.V.D. and those without - Table 4-4.

4.3.4 Symptomatic and Asymptomatic L.V. Systolic Dysfunction

L.V.D. was defined as being symptomatic if there was a need for loop diuretic therapy and/or reported cardiac-type dyspnoea on the breathlessness questionnaire. Of those with L.V.D. 45.0% were considered to be symptomatic and this proportion did not differ significantly between the age groups - Table 4-5 & Figure 4-4 . The median L.V.E.F. for the symptomatic group was lower than for the asymptomatic group - 28.0 (28.7-34.7%) % v 33.0 (18.7-35.0%) %, P=0.003.

4.3.5 Aetiology of L.V. Dysfunction

The commonest underlying disease was I.H.D. with it accompanying 78.0% (P<0.001) of cases of L.V.D. - Tables 4-4 and 4-6. Both a previous physician-made diagnosis of myocardial infarction and angina were strongly associated with the presence of L.V.D. - being present in 46.0% (P<0.001) and 44.0% (P<0.001) of cases respectively. L.V.D. was common amongst individuals reporting a previous M.I. with 30% having L.V.D. - Table 4-6. Approximately one person out of every eight with I.H.D. had L.V.D. In the absence of I.H.D., hypertension − both definitions, valvular heart disease and diabetes were all no more prevalent in individuals with L.V.D. than in those without. In fact the prevalence of L.V.D. in isolated hypertension [JNC VI] - in the absence of

Table 4-3 - Prevalence of Left Ventricular Systolic Dysfunction by Age and Sex

Age / Sex	MALE	FEMALE	TOTAL
55 – 59 yrs	5 / 93 5.4%	4 / 102 3.9%	9 / 195 4.6%
60 – 64 yrs	8 / 105 7.6%	3 / 98 3.1%	11 / 203 5.4%
65 – 69 yrs	6 / 85 7.1%	4 / 101 4.0%	10 / 186 5.4%
70 – 74 yrs	16 / 89 18.0%	4 / 77 5.2%	20 / 166 12.0%
	35 / 372 9.4%	15 / 378 4.0%	50 / 750 6.7%
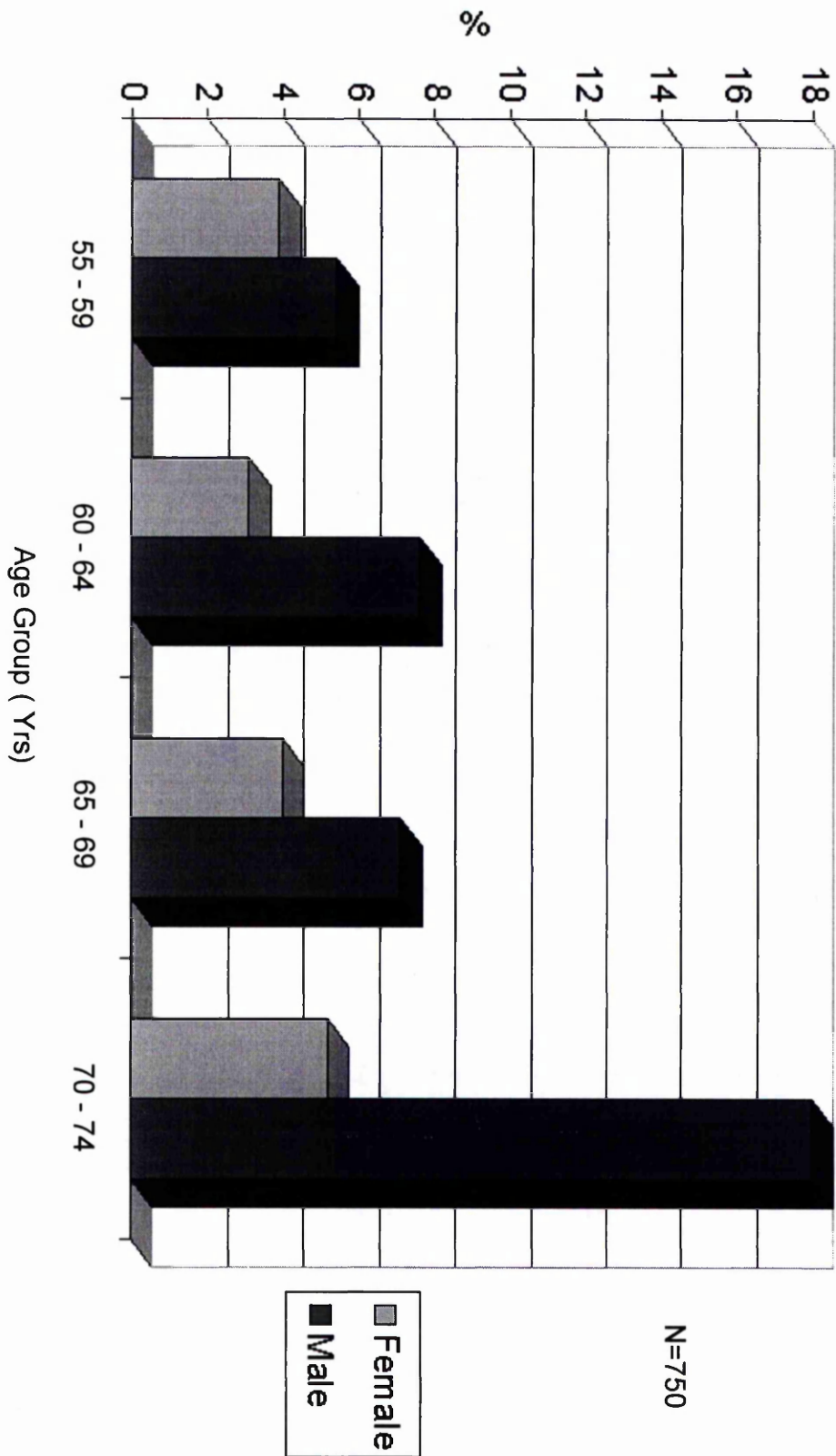
Figure 4-3 - Prevalence of Left Ventricular Systolic Dysfunction by Age and Sex

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*Table 4-4 - Comparison Between Participants With and Without L.V.
Dysfunction*

Parameter	No LV Dysfunction (n=700)	LV Dysfunction (n=50)
Age (yrs)	65.0 (60.0 - 69.0)	69.0 (61.0 - 71.0) *
Sex - Male	48.3%	70.0% *
Diastolic B.P. (mmHg)	80.4 ± 12.7	84.1 ± 15.7
Systolic B.P. (mmHg)	147.0 ± 25.1	150.3 ± 25.0
B.M.I. (Kg/m^2)	26.22 ± 5.6	26.78 ± 3.8
Cholesterol $(mmolL^{-1})$	5.96 ± 1.3	6.13 ± 1.1
Alcohol Intake (Units/wk)	3.0 (0 - 11.0)	8.0 (0 - 14.0)
Diabetes	5.1%	6.0%
Previous M.I.	7.6%	46.0% **
Angina	12.0%	44.0% **
I.H.D.	37.4%	78.0% **
Hypertension	42.1%	52.0%
Hypertension [JNC VI]	66.0%	74.0%
Valve Defects	9.7%	34.0% **
I.H.D. & Hypertension	19.9%	40.0% *
Isolated Hypertension	22.3%	12.0%
Isolated HBP [JNC VI]	37.9%	18.0%*
Isolated I.H.D.	17.4%	38.0% *
Isolated valve defects	3.6%	0%

* P <0.05   ** P<0.001

Table 4-5 - Asymptomatic and Symptomatic L.V. Dysfunction By Age Group

Age Group	L.V. Dysfunction	
	Asymptomatic (%)	Symptomatic (%)
55-59 yrs	5 (55.6%)	4 (44.4%)
60-64 yrs	6 (54.5%)	5 (45.5%)
65-69 yrs	5 (50.0%)	5 (50.0%)
70-75 yrs	11 (55.0%)	9 (45.0%)
	27 (54.0%)	**23 (46.0%)**

Notes:

Symptomatic - Need for loop diuretic therapy and/or reported cardiac-type dyspnoea on questionnaire (excludes symptoms of chronic bronchitis).
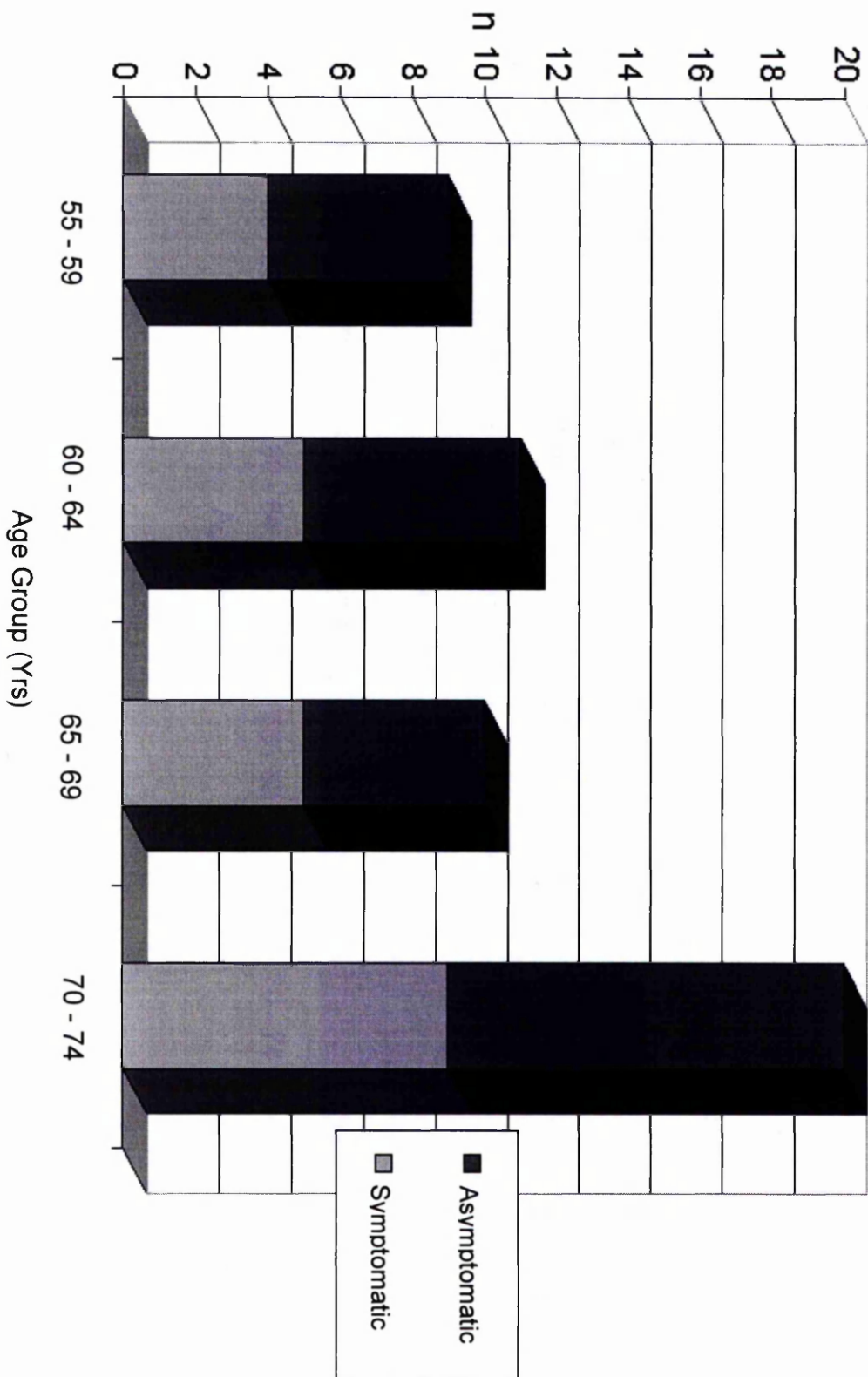
Figure 4-4 - Asymptomatic and Symptomatic Left Ventricular Systolic Dysfunction

Table 4-6 - Prevalence of Left Ventricular Dysfunction in Various Conditions.

Condition	Number with an L.V.E.F.	Prevalence of L.V. Dysfunction
I.H.D. - All	301	13.0% **
Hypertension - All	321	8.1%
Hypertension [JNC VI]	499	7.4%
Isolated I.H.D.	173	14.6% **
Isolated Hypertension	162	3.7%
Isolated Hypert.[JNC VI]	274	3.3%**
I.H.D. & Hypertension	159	12.6% **
Diabetes	39	7.7%
Reported M.I.	76	30.3% **
Reported Angina	106	20.8% **
E.C.G. M.I.[1]	46	8.7%
E.C.G. Major Ischaemia[2]	183	14.8% **
E.C.G. Any Ischaemia[3]	198	16.2% **

   * P<0.05   ** P<0.001
Compared to remainder of population without the condition.

Notes
[1] Presence of Q/QS waves.
[2] Presence of ST segment depression or left bundle branch block.
[3] Presence of Q/QS waves, ST segment depression or left bundle branch block.

I.H.D. - was only 3.3% and this was significantly less than the prevalence in the remainder of the population.

4.3.6 Electrocardiographic Findings and L.V. Dysfunction

An abnormal E.C.G. was present in 78% of people with L.V.D. compared with 37.7% of people with normal L.V. function (P<0.001). Both significant E.C.G. evidence of I.H.D. (54.0% v 22.3% - P<0.001) and atrial fibrillation (10.0% v 1.3% - P=0.003) were more common in the L.V.D. group but pathological Q waves were no more common (8.3% v 6.1%, P=0.710).

4.4 Discussion

This current study has shown that in individuals in whom an L.V.E.F. could be calculated L.V.D. was relatively common and was more common than previous studies have suggested. Like other studies the prevalence increased with age and was higher in men than in women. The principle aetiological associate of L.V.D. in this population was I.H.D. and L.V.D. was common in individuals with I.H.D.

4.4.1 Availability of Echocardiographic Ejection Fraction

Only one published study has described the epidemiology of L.V.D. within a population by calculating an echocardiographic L.V. ejection fraction (McDonagh et al. 1997). Other large studies such as the Cardiovascular Health Study (Gardin et al. 1995) have relied upon a qualitative assessment of L.V. systolic function. This latter approach whilst allowing an assessment of L.V. systolic function in a greater proportion of the population may introduce a subjective component which makes it difficult to define a standard for L.V.D. Calculating an L.V.E.F. reduces the availability of a measure of

L.V. systolic function but does allow a population to be objectively and clearly divided into individuals with normal and individuals with impaired L.V. systolic function.

In this study its was possible to calculate an L.V.E.F. in 75% of individuals and, in some age and sex groups, fewer. This is a lower figure than reported in studies by McDonagh et al. (89.5%) (McDonagh et al. 1997) and Morgan et al. (82%) (Morgan et al. 1999), although higher than in a study of post-M.I. patients (67%) (Breekland et al. 1997). In McDonagh's study the group with the lowest availability (86.2%) of a measured L.V.E.F. - males aged 65 to 74 years - still had a higher availability than any age/sex group in this study.

The main limiting factors to calculating a biplane L.V.E.F. in this study were the ability to trace the endocardium over at least 80% of the L.V. contour and the availability of a suitable apical two-chamber view. These limitations are not peculiar to this study being well recognised drawbacks of the technique (Rumberger et al. 1997) and have been shown in other studies (Breekland et al. 1997). It had been hoped that with improved echocardiographic equipment there would be greater endocardial definition and so an increased availability of an L.V.E.F. compared to McDonagh et al. To that end this study did not succeed. It may have been a product of chance and the nature of the subjects who attended or else we were not as skilled in acquiring images as McDonagh's group.

Compared with the group of individuals in whom an L.V.E.F. was able to be measured the group of people without a measured L.V.E.F. had a higher body mass index, were twice as likely to suffer from diabetes and had higher prevalences of both I.H.D. and treated hypertension. This mirrors findings by McDonagh et al. The implication of

this being that the true prevalence of L.V.D may have been underestimated in the entire cohort.

4.4.2 Definition of L.V. Systolic Dysfunction

Both McDonagh's study and this study chose to define a normal range for L.V.E.F. based on our study population and a subgroup of "normal" individuals from within it. This statistical approach to defining abnormal allows for systematic differences in methodology and technique between research groups. Such a difference in technique may explain why an L.V.E.F. of $\leq 30\%$ defined L.V.D. in McDonagh's study and an L.V.E.F. $\leq 35\%$ in this study.

Comparing the distribution of L.V.E.F. in the "normal" subgroups for the two studies shows differences between the studies which are unlikely to be due to methodology alone. In McDonagh's study the L.V.E.F. was normally distributed in the "normal" subgroup whereas in this study it was slightly skewed to the right with a longer tail extending towards the lower range of L.V.E.F. The reason for this may be that all individuals with slightly impaired L.V. systolic function as a result of subclinical I.H.D. were not able to be removed from the "normal" subgroup. Previous autopsy studies have suggested that, especially in the older population, the prevalence of clinical I.H.D. is about one third of the true prevalence at determined post mortem (Elveback and Lie, 1984). Had wider criteria for the definition of I.H.D. been used - by using the Rose chest pain questionnaire (Rose et al. 1977) and by including T wave inversion as an electrocardiographic sign of ischaemia (Minnesota codes 5.1-5.3) - a greater proportion of subclinical I.H.D. might have been excluded. In McDonagh's study whilst they used the same criteria as this study did by which to select the "normal" subgroup it was

a much larger and younger group and is likely therefore to have had fewer people with subclinical I.H.D. and a mildly reduced L.V.E.F.

The decision to take an L.V.E.F. of ≤ 35% to represent L.V.D. was justified both statistically, as it lies below the 2.5[th] percentile for the "normal" subgroup, and from previous studies which have shown that L.V.D. defined by this cut-off point for the L.V.E.F. is associated with morbidity and mortality, and benefits from pharmacological treatment (The SOLVD Investigators, 1991; The SOLVD Investigators, 1992). Whether this range of L.V.D. represents biologically important L.V.D., accompanied by increased morbidity and mortality, will only be revealed in follow-up studies. Similarly whether the value of 35% corresponds to the value quoted in outcome and treatment studies is unclear but this problem of standardisation for L.V.E.F. exists within every clinical department quoting an echocardiographic L.V.E.F. and yet most cardiologists are willing to act upon such a figure.

4.4.3 Prevalence of Systolic Dysfunction

The prevalence of L.V.D. in this cohort was higher than previously found in McDonagh's study of this population. In men the prevalence in this study was 6.6% in the 55 to 64 yrs age group and 12.6% in the 65 to 74 yrs age group. This compares to 5.7% and 6.4% for the similar age groups in McDonagh's study. For women the prevalence was 3.5% and 4.4% for the two 10 year age bands compared with a prevalence of 2.0% and 4.9% in McDonagh's study. Why these two studies in the same geographical population should have arrived at such differing results is not clear. McDonagh's study used a lower L.V.E.F. to represent L.V.D. so there is the potential that that study missed a proportion of L.V.D or else that the definition of L.V.D. in this

present study was not rigorous enough. Again only follow-up data will reveal the significant level of L.V.E.F. in each study. There could have been a selection bias in favour of individuals with L.V.D. in this present population given both the lower response rate and availability of L.V.E.F. This would however require both the presence of volunteer bias in favour of individuals with cardiovascular disease and the presence of a higher prevalence of I.H.D. in the group with an L.V.E.F. measured. The first of these assumptions seem unlikely and the second is not supported by the data.

The prevalence was higher than that found in other populations. Morgan et al in Dorset found the prevalence to be 9.4% in males and 2.2% in females aged 70 to 74 yrs (Morgan et al. 1999). The Cardiovascular Health Study found a prevalence of 2.3% in 65 to 69 yrs olds and 3.6% in 70 to 74 yrs olds (Gardin et al. 1995). It is difficult to make direct comparisons with these studies since the methods of assessing L.V. systolic function were fundamentally different. In addition, one would expect the prevalence to vary considerably between populations studied reflecting the difference in the prevalence of I.H.D. and in particular myocardial infarction - both of which are likely to be higher in North Glasgow than in the populations of rural Dorset and California.

Like other echocardiographic studies there was a clear sex difference in the prevalence of L.V.D. with it being much greater in men - more than twice as great. This is a similar sex difference to that quoted by McDonagh although Morgan found that the prevalence was four times higher in males than in females. The sex difference in the prevalence of L.V.D. is likely to reflect the sex difference in myocardial infarction with reported previous myocardial infarction being over twice as common in males as in females in this study; although no difference was evident in the rates of either reported

angina or E.C.G. evidence of I.H.D.

4.4.4 Asymptomatic L.V. Dysfunction

It is known that asymptomatic L.V.D. may be the precursor to overt chronic heart failure (Pfeffer and Braunwald, 1990; Gaudron et al. 1993). In both this study and McDonagh's study approximately half of L.V.D. was asymptomatic and so not readily detected without screening tests. In this current study, unlike McDonagh's study, the proportion of L.V.D. which was symptomatic did not rise with age. McDonagh's data suggests that there may be a transition within individuals over time from asymptomatic to symptomatic L.V.D. In this present study's older population this transition may not be so evident because of an equilibrium reached between the generation of new cases of asymptomatic L.V.D., the transition from asymptomatic to symptomatic L.V.D. and the death of cases of symptomatic L.V.D. Longitudinal follow-up should provide data on incidence, mortality and the transition between asymptomatic and symptomatic L.V.D.

4.4.5 Aetiology of L.V. Dysfunction

In this study I.H.D. was common in people with L.V.D., with a reported previous myocardial infarction being six times more prevalent and angina almost four times more prevalent in those with L.V.D. compared to those without. Hypertension, not accompanied by I.H.D. and as defined by both definitions, was no more common in individuals with L.V.D., and infact, in the case of hypertension, as defined by the JNC VI criteria, it was substantially less common. Diabetes mellitus was similarly no more prevalent in the group with L.V.D.. If hypertension and diabetes are exerting an effect is therefore likely to be through an increased risk, and hence prevalence, of I.H.D. within the population. We must, however, also consider the effect that L.V.D. and its

treatment may have on blood pressure. An individual previously hypertensive once they develop L.V.D. may have a blood pressure which falls to within the normal range; whether as a result of the reduced cardiac output, or as result of the medication used. Therefore, we may have underestimated the true prevalence of hypertension in the group with L.V.D., and may have understated its importance as a aetiological factor for L.V.D. in its own right, separate from being a risk factor for I.H.D..

Our findings underscore what previous studies have shown about the aetiology of L.V.D. at the end of the twentieth century. McDonagh showed that in the north Glasgow population the independent predictors of the presence of L.V.D., besides male sex, were a reported history of angina, E.C.G. evidence of ischaemia or infarction, and hypertension. In Morgan's older cohort the predictors were a history of M.I. or angina (Morgan et al. 1999) and the Cardiovascular Health Study showed that both clinical I.H.D. and hypertension were independent predictors of L.V.D. (Gardin et al. 1995). Over the past forty years there has been a shift in the aetiology of C.H.F. from hypertension as was reported by the Framingham Heart Study in the 1950's and 1960's (Kannel et al. 1972) to I.H.D (Kannel et al. 1994). It is likely that this change in aetiology has occurred as a result of the improved detection and treatment of hypertension and the increase in the number of patients who survive their myocardial infarction but do so at the expense of having L.V.D.

5. Treatment and Effects of Left Ventricular Systolic Dysfunction

5.1 Introduction

Whilst doctors are often primarily concerned with the high mortality and the large number of hospital admissions in chronic heart failure (C.H.F.), the patient may be more concerned about the impact that the syndrome has on their quality of life (Q.O.L.), including their ability to perform daily activities and conduct a normal social life. Previous research has shown that both clinical C.H.F. and left ventricular systolic dysfunction (L.V.D.) have significant deleterious effects on Q.O.L. (Stewart et al. 1989; Fryback et al. 1993; Rogers et al. 1994; Jenkinson et al. 1997). Quality of life may be assessed by means of questionnaires which can either be specific for a disease or generic; the latter allowing comparison of Q.O.L. in different disease states. The Short Form 36 (SF-36) questionnaire is a generic measure of Q.O.L. which was developed as an instrument for evaluating the impact of different illnesses upon functioning and well-being (Garratt et al. 1993) (Ware et al. 1993).

A major contributor to this impaired Q.O.L. is effort intolerance which is one of the commonest problems experienced by patients (Franciosa et al. 1979) and will be one of the main prompts for them to seek medical help (Franciosa et al. 1979). It is not due solely to cardiac dysfunction but rather due to peripheral factors, particularly changes in skeletal muscle (Wilson et al. 1995; Franciosa et al. 1979; Mancini et al. 1992; Harrington et al. 1997). Effort capacity may be measured either by symptom-limited exercise testing or by submaximal walking tests such as the six-minute walk test.

Treatment with angiotensin-converting enzyme (A.C.E.) inhibitors in L.V.D. has been shown to reduce mortality, if symptoms are present, and the need for hospitalisation even if the condition is asymptomatic (Garg and Yusuf, 1995); as well as being cost-

effective (McMurray and Davie, 1996). However it has been suggested previously that they are being underused in both L.V.D. and C.H.F.

This present study looked at the effects of L.V.D. on exercise capacity as measured by symptom-limited, maximal treadmill exercise testing, and on Q.O.L. using the SF-36 questionnaire. It also examined whether individuals with L.V.D. were being treated according to the trial evidence.

5.2 Methods

These are described in detail in Chapter 2 but briefly 1009 individuals, aged between 55 and 74 years, from the population were randomly selected (response rate 59.8%). Each individual completed a questionnaire regarding demography; past medical diagnoses, drug therapy, and the M.R.C. Breathlessness Questionnaire (Fletcher et al. 1959). Their height and weight were measured and the body mass index (B.M.I.) calculated as weight (Kg) divided by height (m) squared. A left ventricular ejection fraction (L.V.E.F.) was calculated by echocardiography using a biplane algorithm ("method of discs summation"), Simpson's rule (Schiller et al. 1979). A standard graded treadmill exercise test was performed using the Standardised Treadmill Exponential Exercise Protocol (S.T.E.E.P.) (Northridge et al. 1990).

The SF-36 questionnaire - the Brazier/Sheffield version (Brazier et al. 1992) - was issued, checked for completeness of information during the study visit and if need be it was administered in part or in full by interview. It was subsequently scored according to the scoring manual from the Medical Outcomes Trust (Medical Outcomes Trust, 1994). A scale score was calculated if the respondent had answered at least half of the items in a multi-item scale (or half plus one in the case of scales with an odd number of

items).

5.2.1 Definitions:

Left ventricular systolic dysfunction - an L.V.E.F. measured as ≤ 35%.

Cardiac-type dyspnoea - the presence of dyspnoea in the absence of symptoms suggestive of chronic bronchitis as assessed by the M.R.C. questionnaire.

Asymptomatic L.V.D. - the absence of both reported cardiac-type dyspnoea and current treatment with loop diuretics.

Symptomatic L.V.D - either reported cardiac-type dyspnoea or current treatment with loop diuretics.

5.2.2 Statistical Analysis

Values with a normal distribution are quoted as the mean ± standard deviation (S.D.). Other values are quoted as the median and interquartile range (I.Q.R.). Student's t test (two-tailed) was used to compare means, the Mann Whitney U test to compare medians and the Chi-squared or Fisher's exact test where appropriate was used to compare the proportions of individuals within two or more groups. Univariate and multivariate analysis was performed using Minitab for Windows. A P value of <0.05 was taken to be significant.

5.3 Results

5.3.1 Medication Use in Left Ventricular Systolic Dysfunction

The use of cardioactive medication including A.C.E. inhibitors, beta-blockers, loop diuretics and nitrates was higher in the group of fifty individuals with L.V.D. than in the group with normal L.V. systolic function - Table 5-1a. Overall only 16% of people with L.V.D. were currently being treated with an A.C.E. inhibitor and of the fifteen

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Table 5-1 - Medication Use in Left Ventricular Systolic Dysfunction

Table 5-1a - Comparison Between Normal and Impaired L.V. Function

	L.V. Systolic Dysfunction (n=50)	Normal L.V. Function (n=700)
Loop Diuretic	30.0% **	4.0%
ACE inhibitor	16.0% **	3.4%
Digoxin	10.0% **	1.0%
Nitrate	36.0% **	7.3%
Beta-blocker	22.0% *	9.9%

Table 5-1b - Medication and Breathlessness in L.V. Dysfunction

	Breathless# (n=15)	Not Breathless (n=35)
Loop Diuretic	46.7%	22.9%
ACE inhibitor	26.7%	11.4%
Digoxin	13.3%	8.6%
Nitrate	26.7%	40.0%
Beta-blocker	13.3%	8.6%

Reported on M.R.C Breathlessness questionnaire, excluding symptoms of chronic bronchitis

Table 5-1c - Medication and Symptomatic L.V. Dysfunction

	Symptomatic (n=23)	Asymptomatic (n=27)
ACE inhibitor	30.4% *	3.7%
Digoxin	17.4%	3.7%
Nitrate	43.5%	29.6%
Beta-blocker	17.4%	25.9%

Symptomatic - includes reported breathlessness and/or current use of loop diuretics

* P<0.05   ** P<0.001

people who were currently treated with a loop diuretic only seven (46.7%) were also receiving treatment with an A.C.E. inhibitor. A greater proportion of people with L.V.D. who reported cardiac-type dyspnoea were currently being treated with a loop diuretic or A.C.E. inhibitor than people who did not report dyspnoea, but this did not reach statistical significance; and still more than half of breathless individuals with L.V.D. were not receiving treatment with a loop diuretic - Table 5-1b. The use of A.C.E. inhibitors amongst people with asymptomatic L.V.D. was very low at only 3.7% and even in symptomatic L.V.D. they were being taken by only 30% - Table 5-1c.

5.3.2 Exercise Capacity and Left Ventricular Systolic Dysfunction

The treadmill exercise test was attempted by 605 participants of whom 32 had L.V.D. - 25 males and 7 females. Of the individuals with L.V.D. 11 were considered to be symptomatic and 21 asymptomatic. The median exercise time for those with L.V.D. was lower than for those with normal L.V. function - 467.5 (279.0 - 631.0) secs v 627.0 (490.5 - 729.5) secs , $P<0.001$ - Figure 5-1. This was true for both females 324.0 (197.0 - 491.0) secs v 608.0 (438.0 - 679.0) secs, $P<0.05$, and for males 498.0 (361.5 - 637.5) secs v 665.5 (553.8 - 772.5) secs, $P<0.001$. Median exercise times for those with symptomatic and asymptomatic L.V.D. were not significantly different 435.0 (264.0 - 619.0) secs v 474.0 (295.5 - 650.0) secs, $P=0.648$. Compared to individuals with normal L.V. systolic function, individuals with asymptomatic L.V.D. had a lower exercise capacity 474.0 (295.5 - 650.0) secs v 627.0 (490.5 - 729.5) secs, $P=0.007$.

5.3.3 Limiting Symptoms on Treadmill Exercise Testing

There was no difference between the group of people with L.V.D. and the group with normal L.V. function with regard to the proportion who gave breathlessness as their primary reason for stopping exercising on the treadmill - Table 5-2. Similarly there

Figure 5-1 - Left Ventricular Systolic Dysfunction and Exercise Time

EFFECT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION ON EXERCISE TIME
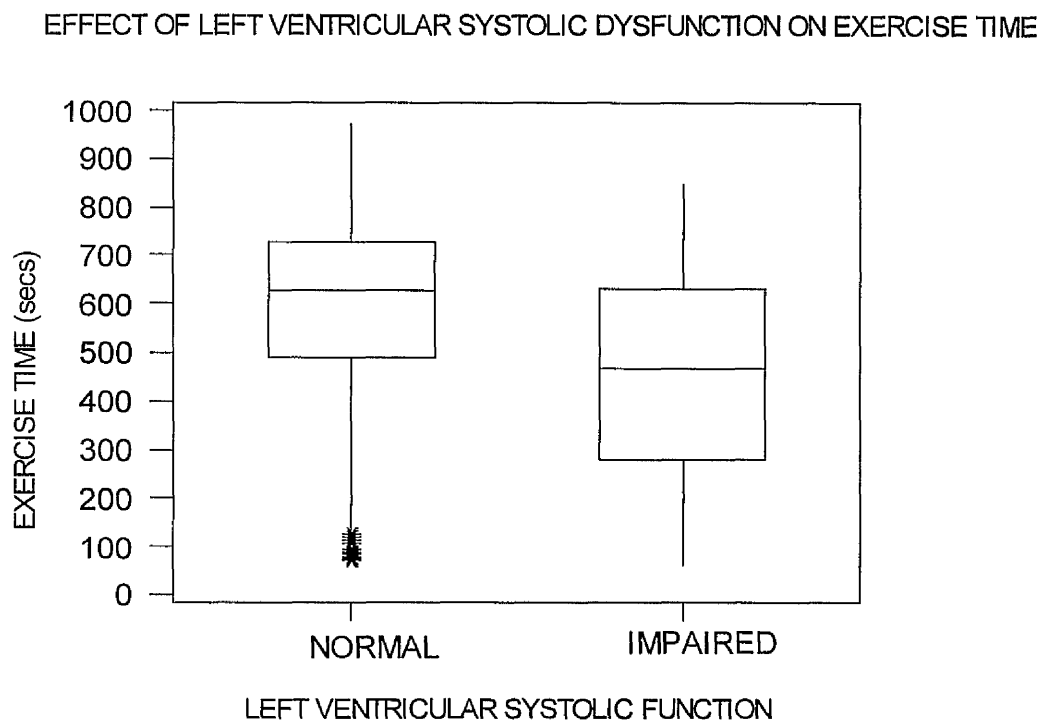
Impaired left ventricular systolic function = ejection fraction $\leq$ 35%

Table 5-2 - Principle Reason Given by Participant for Stopping Exercise Test

Reason	L.V. Systolic Dysfunction		Normal L.V. Function	
	n	%	n	%
Chest Pain	2	6.3%	5	0.9%
Breathlessness	9	28.1%	145	25.3%
Fatigue	4	12.5%	133	23.2%
Leg Pain / Fatigue	10	31.3%	163	28.4%
Other*	7	21.9%	127	22.2%
TOTAL	32		573	

* Includes those cases where the test was stopped primarily on the decision of the supervising technician.

was no difference in the proportion of individuals with symptomatic L.V.D. who stopped because of breathlessness compared to those with asymptomatic L.V.D.

5.3.4 Determinants of Effort Capacity Within the Population

In both males and females univariate linear regression analysis - Table 5-3 - showed that the L.V.E.F. was positively correlated with total exercise time whereas both age and the B.M.I. were negatively correlated. In females when these three variables were put in a multivariate analysis - Table 5-3 - all remained as significant predictors of effort capacity but described only 14% of the variation in exercise time. For males only age and the L.V.E.F. remain significant independent predictors of effort capacity in multivariate analysis describing only 11% of the variation. The correlation between the L.V.E.F. and exercise time in the population was poor, however, - for males 0.26 and females 0.17 - Figure 5-2.

5.3.5 Left Ventricular Dysfunction and Quality of Life

Satisfactory completion of the SF-36 questionnaire to allow computation of scores for six of the dimensions - Table 5-4 - was achieved in 48 participants with L.V.D. and in 684 with normal L.V. function. The median scores for these six dimensions in both groups are shown in Table 5-5 and in Figure 5-3. The group of people with L.V.D. had significantly lower scores in the dimensions measuring physical functioning - 52.5 (20.0 - 75.0) v 75.0 (50.0 - 90.0) P<0.001 - , role physical - 37.5 (0.0 - 100.0) v 100.0 (25.0 - 100.0), P<0.05 - , general health - 47.5 (30.0 - 75.0) v 65.0 (50.0 - 80.0), P<0.01 - and social functioning 78.7 (60.6 - 100.0) v 100.0 (67.5 - 100.0), P<0.05. The degree of systolic dysfunction did not have a major effect on the Q.O.L. scores. Dividing the L.V.D. group in two based on the L.V.E.F. (< or > 30.8%) showed that the only significant difference in scores between those in the upper and lower halves was in the

Table 5-3 - Determinants of Exercise Time - Regression Analyses

Females

Variable	Univariate P value	Multivariate P value	R^2 (adj)
L.V.E.F.(%)	0.004 +	0.001	14.3%
B.M.I. (Kg/m^2)	0.008 -	0.006	
Age (Yrs)	<0.001 -	0.001	

Males

Variable	Univariate P value	Multivariate P value	R^2 (adj)
L.V.E.F (%)	<0.001 +	0.001	10.9%
B.M.I. (Kg/m^2)	0.028 -	0.067	
Age (Yrs)	<0.001 -	0.001	

Notes:

+ Positive association
- Negative association

R^2(adj) = the square of the multivariate correlation coefficient adjusted for the expected chance prediction when the null hypothesis is true. It indicates how much of the variation is explained by the factors in the model.

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*Figure 5-2 - Correlation Between Effort Capacity and Left Ventricular Systolic
Function*

Females

r=0.17

Males

r=0.26
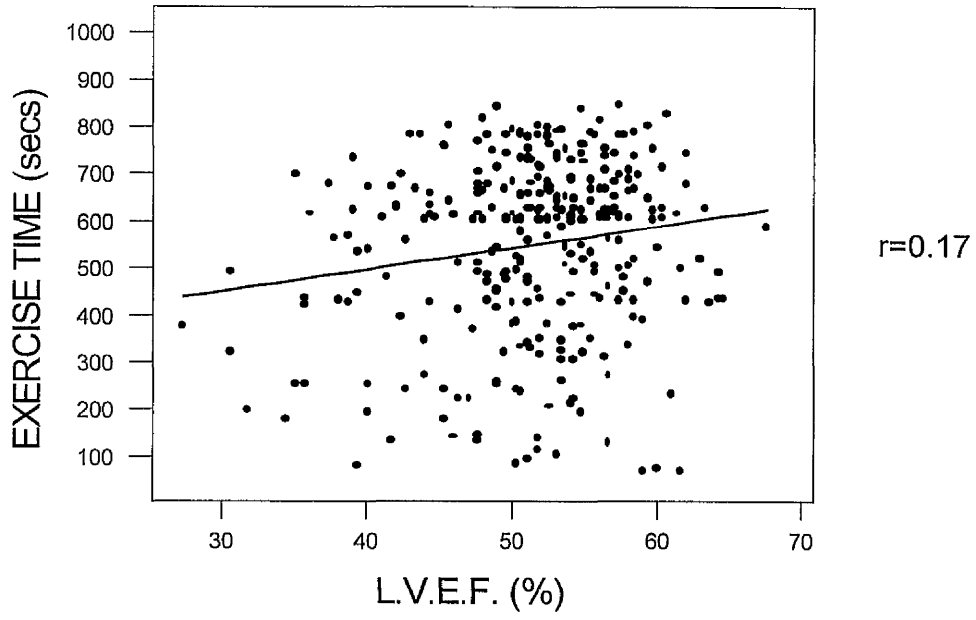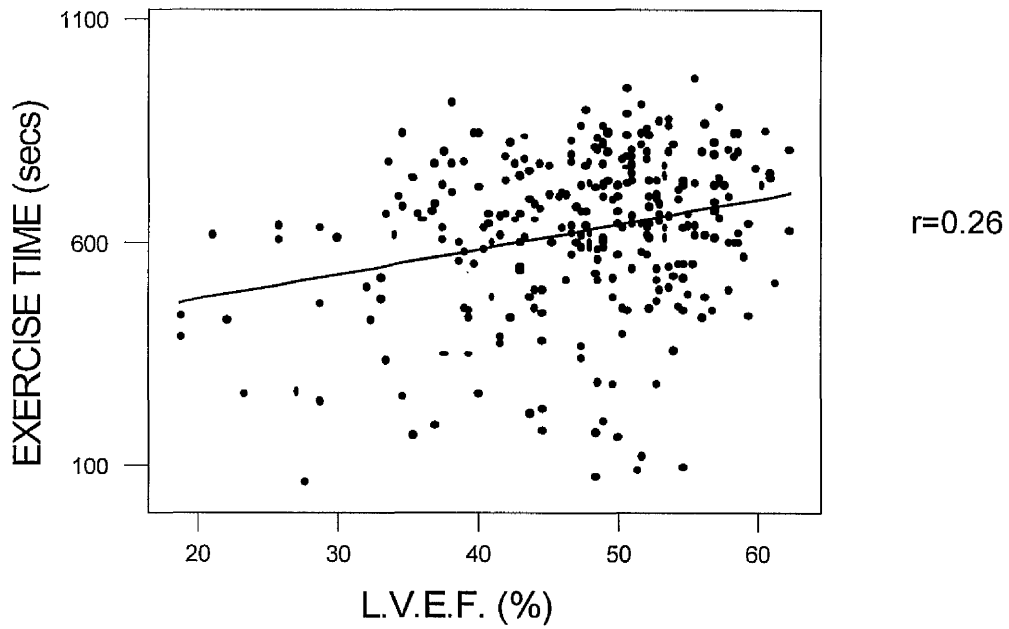
Table 5-4 - Health concepts measured by six SF-36 scales

Concept	Summary of Content
Physical Functioning	Extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting, and moderate and vigorous exercises.
Role Functioning - Physical	Extent to which physical health interferes with work or other daily activities, including accomplishing less than wanted, limitations in the kind of activities, or difficulty in performing activities.
General Health	Personal evaluation of health, including current health, health outlook, and resistance to illness.
Vitality	Feeling energetic and full of life versus feeling tired and worn out.
Social Functioning	Extent to which physical health or emotional problems interfere with normal social activities.
Role Functioning - Emotional	Extent to which emotional problems interfere with work or other daily activities, including decreased time spent on activities, accomplishing less, and not working as carefully as usual.

Table 5-5 - Median Quality of Life Scores in Normal and in Impaired L.V. Function

	Normal LV Function n=684	Impaired LV Function n=48
Physical Functioning	75.0 (50.0 - 90.0)	52.5 ** (20.0 - 75.0)
Role Physical	100.0 (25.0 - 100.0)	37.5 * (0.0 - 100.0)
General Health	65.0 (50.0 - 80.0)	47.5 * (30.0 - 75.0)
Vitality	60.0 (45.0 - 75.0)	51.7 (40.0 - 70.0)
Social Functioning	100.0 (67.5 - 100.0)	78.7 * (60.6 - 100.0)
Role Emotional	100.0 (33.3 - 100.0)	100.0 (33.3 - 100.0)

* P <0.05   ** P<0.001
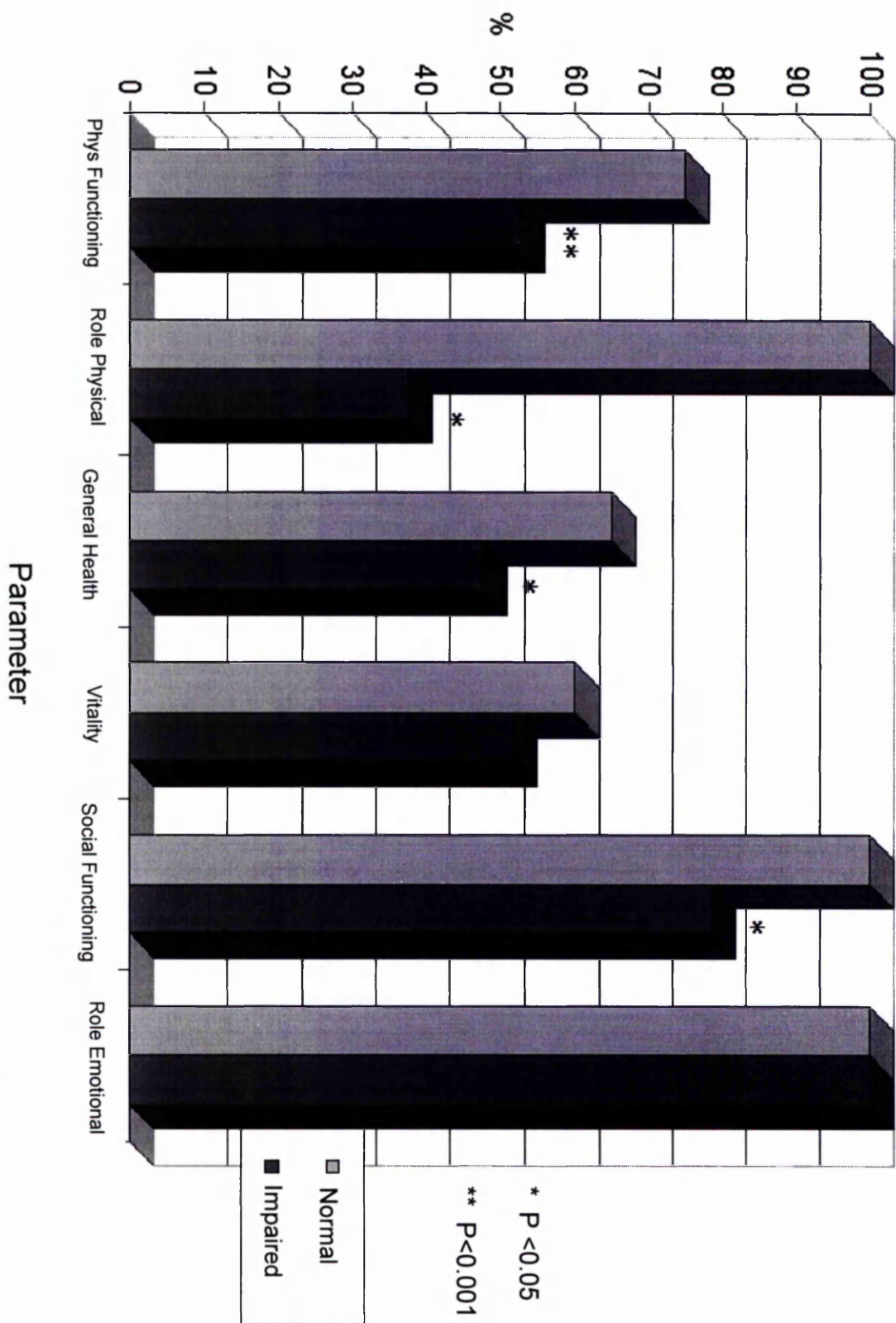
Figure 5-3 - Quality of Life Scores in Left Ventricular Systolic Dysfunction

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dimension measuring role physical - 0.0 (0.0 - 93.8) v 100.0 (6.3 - 100.0), P=0.03.

5.3.6 Effect of Breathlessness on Quality of Life in L.V. Dysfunction

Of the individuals with L.V.D. 14 reported symptoms of cardiac-type dyspnoea. Compared to the individuals without dyspnoea (whether as a result of being rendered symptom free by diuretic therapy or not) these individuals had a lower median score for vitality - 42.5 (23.8 - 55.0) v 55.0 (45.0 - 75.0), P<0.05 - Table 5-6. They also tended to have lower scores in other dimensions but none reached statistical significance.

Comparing the group with L.V.D. who had no dyspnoea with the group with normal L.V. function revealed a reduction in the dimension measuring physical functioning - 57.5 (20.0 - 86.3) v 75.0 (50.0 - 90.0) , P<0.05 - Table 5-6. Furthermore compared to a group with both normal L.V. function and no dyspnoea they had not only significantly lower scores in the dimension measuring physical functioning 57.5 (20.0 - 86.3) v 80.0 (55.0 - 90.0), P<0.05 but also in the dimensions measuring role physical 75.0 (0 - 100.0) v 100.0 (50.0 - 100.0), P<0.05 and general health 47.5 (33.8 - 80.0) v 70.0 (50.0 - 80.0), P<0.05.

5.3.7 Effect of Treated L.V. Dysfunction on Quality of Life

The need for treatment with a loop diuretic in 15 people with L.V.D. was associated with a greater degree of impairment of Q.O.L. compared to those not requiring diuretic therapy - Table 5-6. Median scores were lower for dimensions measuring role physical 0.0 (0 - 75.0) v 100.0 (0- 100.0), P=0.04 and general health 35.0 (20.0 - 60.0) v 55.0 (35.0 - 80.0), P=0.025. The median L.V.E.F. for those on diuretic therapy was lower than for those not on diuretics 27.7% (21.0 - 32.0%) v 32.3% (28.7 - 34.2%), P=0.008.

Impaired L.V. Function

Dimension	Normal LV	All	Symptomatic	Asymptomatic	Diuretic Rx	Breathless	Not Breathless
Physical Functioning	75.0 (50.0 - 90.0)	52.5 ** (20.0 - 75.0)	42.5 ** (15.0 - 62.5)	60.6 (23.8 - 91.3)	33.3 (10.0 - 60.0)	42.5 (15.0 - 62.5)	57.5* (20.0 – 86.3)
Role Physical	100.0 (25.0 - 100.0)	37.5 * (0.0 - 100.0)	12.5 * (0.0 - 81.3)	100.0 (0.0 - 100.0)	0.0 (0.0 - 75.0)	12.5 (0 - 81.3)	75.0 (0.0 - 100.0)
General Health	65.0 (50.0 - 80.0)	47.5 * (30.3 - 75.0)	42.5 * (23.8 - 61.3)	60.0 (35.0 - 81.3)	35.0 (35.0 - 80.0)	42.5 (23.8 - 61.3)	47.5 (33.8 - 80.0)
Vitality	60.0 (45.0 - 75.0)	51.7 (40.0 - 70.0)	50.0 (38.8 - 58.8)	55.0 (43.8 - 75.0)	50.0 (42.5 - 72.5)	50.0 (38.8 - 58.8)	55.0 (45.0 - 75.0)
Social Functioning	100.0 (67.5 - 100.0)	78.7 * (60.6 - 100.0)	70.0 * (55.0 - 100.0)	80.0 (64.4 - 100.0)	70.0 (63.8 - 100.0)	70.0 (55.0 - 100.0)	80.0 (64.6 - 100.0)
Role Emotional	100.0 (33.3 - 100.0)	100.0 (33.3 - 100.0)	100.0 (33.3 - 100.0)	100.0 (0.0 - 100.0)	100.0 (16.7 - 100.0)	100.0 (33.3 - 100.0)	100.0 (0 - 100.0)

Notes: Asymptomatic - Absence of cardiac-type dyspnoea and loop diuretic therapy.

Symptomatic - Presence of cardiac type dyspnoea or current loop diuretic therapy.

Breathless - presence of cardiac-type dyspnoea on MRC questionnaire.

* P <0.05 ** P<0.001

Compared to normal L.V. function

Table 5-6 - Quality of Life Scores for Subgroups of L.V. Dysfunction Group

5.3.8 Comparison of L.V. Dysfunction with Other Chronic Diseases

The median scores for individuals with L.V.D. who reported breathlessness were compared to the scores for individuals identified from the study cohort with normal measured L.V. function but with either a previous physician diagnosis of asthma or angina (the two conditions were taken to be mutually exclusive) - Table 5-7. Compared to the group with asthma the L.V.D. group had a lower median score for the dimension measuring physical functioning 36.7 (15.0 - 58.8) v 65.0 (32.5 - 85.0), P=0.03 but there was no significant difference between the two groups in the other dimensions. The group with angina did not differ significantly from the L.V.D. group with breathlessness with respect to any dimension.

Table 5-7 - Median Quality of Life Scores for Three Chronic Conditions

Dimension	L.V. Dysfunction Breathless N=14	Angina (Normal LV) N=75	Asthma (Normal LV) N=54
Physical Functioning	36.7 (15.0 - 58.8)	50.0 (30.0 - 70.0)	65.0* (32.5 - 85.0)
Role Physical	12.5 (0.0 - 81.2)	25.0 (0.0 - 100.0)	50.0 (0.0 - 100.0)
General Health	45.0 (23.8 - 62.5)	50.0 (35.0 - 70.0)	52.5 (38.8 - 70.0)
Vitality	42.5 (23.8 - 55.0)	45.0 (30.0 - 65.0)	55.0 (35.0 - 70.0)
Social Functioning	70.0 (50.6 - 100.0)	67.5 (35.0 - 100.0)	90.0 (58.8 - 100.0)
Role Emotional	100.0 (91.7 - 100.0)	66.7 (0.0 - 100.0)	100.0 (0.0 - 100.0)

*P=0.03 for difference compared to breathless L.V. dysfunction.

5.4 Discussion

5.4.1 Medication Use in Left Ventricular Systolic Dysfunction

This study confirms the findings of other investigators showing that L.V.D. and heart failure is undertreated (O'Connell and Bristow, 1994; McMurray, 1998). Although this study was carried out between 1994 and 1996 the results of the large trials of A.C.E. inhibitor treatment in L.V.D. had been known for at least three years prior to its commencement (The CONSENSUS Trial Study Group, 1987; Cohn et al. 1991; The SOLVD Investigators, 1991; The SOLVD Investigators, 1992). By definition it is impossible to ensure appropriate treatment in asymptomatic L.V.D. without screening programmes being in place, but in this study less than half of patients with treated heart failure (L.V.D. and loop diuretic treatment) were receiving treatment with an A.C.E. inhibitor. This proportion fell to less than one third if those who were either breathless and/or being treated with a loop diuretic were included. Whilst the picture will have improved since 1996 with respect to treating overt heart failure, as yet there is no screening programme for asymptomatic L.V.D. therefore undertreatment must be continuing. These results underscore the need for screening programmes - both to identify asymptomatic L.V.D. and also to identify patients being treated with loop diuretics so that it can be established whether or not they have systolic dysfunction and so determine the need for A.C.E. inhibitors.

5.4.2 Exercise Testing

This study showed that, compared to individuals with normal L.V. systolic function, individuals with L.V.D., whether apparently symptomatic or not, have a poorer effort capacity as measured by treadmill exercise testing. By dichotomising the range of exercise times based on the L.V.E.F. (35% in this case) an effect of L.V. systolic

function on effort capacity was shown. In multivariate analysis the L.V.E.F. was still shown to be an independent factor in determining effort capacity for both males and females. The amount of interindividual variation in effort capacity attributable to the L.V.E.F. was however small - by univariate analysis 2.4% in females and 6.4% in males - and the correlation between L.V.E.F. and exercise time was extremely poor.

The fact that the L.V.E.F. has relatively little influence on effort capacity within the whole population does not come as a surprise. It is only one factor in a complex interplay of variables which contribute to effort capacity including respiratory, cardiac, peripheral vascular and musculoskeletal function; as well as body habitus and psychological factors including motivation and tolerance of discomfort. Individuals who are obese are more likely to experience symptoms than patients who are not obese (Wilson et al. 1995) and in this study both body mass index and age were significant independent determinants of effort capacity. Even in C.H.F. effort capacity does not correlate with indices of cardiac function and central haemodynamics (Franciosa et al. 1981; Higginbotham et al. 1983; Lipkin et al. 1986). The mechanism for effort intolerance may be related to changes in skeletal muscle mass, structure (Mancini et al. 1992) and function (Harrington et al. 1997).

A significant finding was that asymptomatic L.V.D. was associated with a reduced effort capacity. The number of individuals in this group was small and it is difficult to be sure that this was not the effect of other factors such as physical deconditioning, ischaemic heart disease or peripheral vascular disease, all of which may affect patients with an ischaemic aetiology for their L.V.D. (Clark et al. 1997). However one other study has shown that asymptomatic L.V.D. was associated with a reduced peak aerobic

capacity (LeJemtel et al. 1994). Therefore patients whilst reportedly asymptomatic during the course of their normal daily activities show abnormalities on objective testing. It has been hypothesised that in such patients the impairment is secondary to cardiac dysfunction rather than peripheral factors (LeJemtel et al. 1994).

The fact that breathlessness was as common a limiting symptom in the normal group as in the L.V.D. group demonstrates how non-specific the symptom is. It is not a particularly good measure on maximal exercise testing as it will be heavily influenced by physical conditioning in both groups. Heart failure patients have been shown to report similar levels of dyspnoea across various classes of haemodynamic severity (Wilson et al. 1995). Patients with I.H.D. - and this will include many in the asymptomatic L.V.D. group - regardless of their L.V. function, may complain of breathlessness on exercise as a manifestation of coronary ischaemia even in the absence of chest pain or ECG changes of ischaemia (Cook and Shaper, 1989; Clark et al. 1997).

A major limitation of this study was the small number of individuals with L.V.D. and the even smaller number who exercised, which was not altogether surprising given the age range being studied. This prevented control for confounding factors. Had a six-minute walk test been used more people in whom the limiting factor was not cardiac, but for example musculoskeletal disability, might have been able to exercise. In addition using a form of submaximal testing such as the six-minute walk test may have more effectively evaluated the impairment and functional status during daily activities (Brunner-La Rocca et al. 1999).

5.4.3 Quality of Life

This study showed that, compared with the remainder of the population, and over and

above the effects of any concomitant chronic illnesses, the presence of L.V.D. was associated with poorer Q.O.L. scores in dimensions measuring physical functioning and activity, perception of general health, and social functioning. The presence of breathlessness caused an additional impairment in vitality. Even in the individuals who did not currently report breathlessness, whether this was the result of treatment or not, there was still a measurable reduction in physical functioning suggesting that breathlessness is not the only mechanism for impairment of physical functioning. The degree of impairment was even greater if one controlled for the presence of breathlessness and compared this group to individuals with both normal L.V. function and no breathlessness. Treated heart failure resulted in the greatest impact on quality of life probably because the need for treatment is a marker of a greater severity of symptoms and poorer functional class.

Previous epidemiological studies have assessed the impact of clinical chronic heart failure rather than L.V.D. on Q.O.L.. Two of the largest and earliest were carried out in North America - the Medical Outcomes Study (M.O.S.) in 1986 (Stewart et al. 1989) and the Beaver Dam Health Outcomes Study (B.D.H.O.S.) (Fryback et al. 1993) in 1990. The B.D.H.O.S. used the SF-36 questionnaire and the M.O.S. used its forerunner. Both studies showed that C.H.F. resulted in the greatest impairment of Q.O.L. of all the chronic conditions studied. In terms of the dimensions affected by C.H.F. they showed similar results to this current study; with the M.O.S. showing impairment in scores for physical functioning, role physical and social functioning, and the B.D.H.O.S. showing an effect also on general health. These findings have been confirmed more recently in the U.K. using the SF-36 questionnaire in C.H.F. patients aged 60 years or over (Jenkinson et al. 1997). Symptomatic C.H.F. impacted greatly

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upon all eight dimensions and had an additive effect over and above the presence of other chronic illnesses.

This present study and these previous studies are not directly comparable as both previous studies looked at the syndrome of C.H.F. which by its very definition causes symptoms. The individuals in these published studies are probably best compared to the group with both L.V.D. and breathlessness in this present study. None of the published studies assessed the severity of heart failure or indeed confirmed that it was the result of systolic dysfunction.

The S.O.L.V.D. investigators, as part of their treatment trials (The SOLVD Investigators, 1991; The SOLVD Investigators, 1992), looked at the impact of both symptomatic and asymptomatic L.V.D. (Rogers et al. 1994) on Q.O.L.. They found that asymptomatic L.V.D. was associated with impaired Q.O.L. although the degree of impairment was not as great as that seen in symptomatic. This present study was able to show some impairment attributable to L.V.D. in the absence of reported breathlessness; although some of these individuals may have only been asymptomatic as the result of diuretics and are therefore not directly comparable to the S.O.L.V.D. asymptomatic group. These results suggest that although, by current clinical definition, L.V.D. may exist in an "asymptomatic" form, this may only be because we do not include impairment of Q.O.L. in our definition of symptomatic.

With a small number of individuals with L.V.D. it was not possible in this study to control for the presence of concomitant disease which explains why comparisons with other disease groups showed only a minor difference. The impact of L.V.D. on Q.O.L.

in this study will have been diminished somewhat by the presence of concomitant chronic diseases in both the L.V.D group and the whole population. One might expect this to be the case in a group of 55 to 74 year olds from a socially deprived population. In fact this may be a strength of the present study as, by using the background population as a control group rather than a control set of normative data from another study as Jenkinson et al used (Jenkinson et al. 1997), it was able to show an additive effect of L.V.D.; that is over and above any background impairment of Q.O.L. in the population.

6. Left Ventricular Diastolic Filling and Left Ventricular Mass

6.1 Introduction

It is now recognised that the syndrome of chronic heart failure may arise in the absence of any abnormality of left ventricular (L.V.) systolic function (Grossman, 1991; Brutsaert et al. 1993; Goldsmith and Dick, 1993; Gaasch, 1994). In such patients abnormalities of L.V. diastolic filling may have a major role in producing signs and symptoms (Nishimura and Tajik, 1997) and this has led to use of the term "diastolic heart failure" (Brutsaert et al. 1993). Diastolic filling is a complex phenomenon determined by numerous factors both physiological and pathological acting either in isolation or in a complex interplay (Vasan et al. 1996; European Study Group on Diastolic Heart Failure, 1998; Taylor and Waggoner, 1992).

Doppler echocardiography has become well accepted as a reliable, reproducible and practical non-invasive method for the diagnosis and longitudinal follow-up of patients with diastolic dysfunction (Nishimura and Tajik, 1997). All ventricular filling indices by echocardiography are however indirect measures of diastolic function (Vasan et al. 1996) and have largely have been based on transmitral flow velocity curves (Appleton et al. 1988). Two main patterns of abnormal flow velocity curves have been described (Appleton et al. 1988; Ohno et al. 1994; Nishimura and Tajik, 1997). An abnormal / impaired L.V. relaxation pattern is characterised by a reduction in the peak velocity of early diastolic filling (the E wave), an increase in the peak velocity of late diastolic filling (the A wave), resulting in a reduction in the ratio of these velocities (E:A ratio), and accompanied by an increase in the deceleration time of the peak E wave velocity curve (M.V.D.T.). A pattern of restrictive L.V. filling is shown by an increase in the peak E velocity, a decrease in the peak A velocity, an increase in the E:A ratio and a reduction in the M.V.D.T.

The determinants and correlates of L.V. diastolic filling were assessed by transmitral Doppler flow velocity curves both in the entire cohort attending this study and in subgroups with cardiovascular pathology. The hypothesis that individuals reporting cardiac-type dyspnoea in the absence of L.V. systolic dysfunction (L.V.D.) and pulmonary disease would have evidence of abnormal L.V. diastolic filling on Doppler echocardiography was also tested.

6.2 Methods

These are described in detail in Chapter 2 but briefly each individual completed a questionnaire regarding demography; past medical diagnoses, drug therapy, and the M.R.C. breathlessness questionnaire (Fletcher et al. 1959). Their blood pressure was measured as was their height and weight. The body mass index (kg/m^2) was calculated as the weight (kg) divided by the height (m) squared. Spirometry was performed and a blood sample was taken for a random blood glucose level. A twelve-lead ECG was recorded and coded according to the Minnesota ECG code (Prineas et al. 1982) and a treadmill exercise test was performed using the Standardised Treadmill Exponential Exercise Protocol (Northridge et al. 1990) with manual ST segment analysis carried out on the 12 lead E.C.G. during exercise and the recovery period according to the Minnesota Coding Manual - (Prineas et al. 1982).

A full two-dimensional and Doppler echocardiogram was performed with an L.V. ejection fraction (L.V.E.F.) calculated from a biplane algorithm (Simpson's rule) (Schiller et al. 1979). M-mode measurements were taken as the average of three cycles and were made according to the conventions established by the American Society of Echocardiography using a leading-edge-to-leading-edge method (Sahn et al. 1978) and

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the criteria of Schieken et al (Schieken et al. 1979) were used to determine the acceptable technical quality for M-Modes. The left ventricular mass was calculated using the Penn Cube formula (Devereux et al. 1986) as:

LV Mass (g) = 1.04 $[(IVSd+LVEDD+LVPWd)^3 - LVEDD^3]$ -13.6 g . IVSd - Interventricular septum in diastole; LVEDD - LV end diastolic dimension; LVPW - LV posterior wall.

The L.V. mass index (g/m) was calculated by dividing the L.V. mass by the height (m). The relative L.V. wall thickness (R.Th.) expresses the proportion of the L.V. radius in diastole which is L.V. wall: $[(IVSd + LVPWd)/2] \div [LVEDD/2]$.

Transmitral Doppler flow velocity curves were measured as the average of five cycles and traced at the outer edge of the spectral envelope. Where the deceleration slope of the E wave could not be distinguished from the A wave measurements were not made. The M.V.D.T. was measured from the peak of the E wave to a point on the baseline where by extrapolation the slope would have intersected it.

6.2.1 Definitions:

Hypertension - a systolic blood pressure >160mmHg systolic or a diastolic > 95 mmHg (Korotkoff phase V) or the current use of antihypertensive medication.

Hypertension [JNC VI]: as above, but using the cut-off points for blood pressure as defined in JNC VI guidelines (Joint National Committee on Prevention, Evalaution and Treatment of High Blood Pressure 1997) which are a systolic blood pressure of ≥140mmHg and/or a diastolic blood pressure ≥ 90mmHg.

Diabetes mellitus - previous physician-made diagnosis or the current use of insulin or oral hypoglycaemic agents or a random venous glucose ≥ 11.1 $mmolL^{-1}$.

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Ischaemic heart disease - at least one of 1) a previous physician diagnosis of angina

pectoris or myocardial infarction 2) an ECG showing myocardial infarction or major

ischaemia 3) current use of nitrates including sublingual glyceryl trinitrate.

Cardiac dyspnoea - reported breathlessness on the M.R.C. Breathlessness questionnaire

in the absence of symptoms of chronic bronchitis.

Left ventricular systolic dysfunction (L.V.D.) - an L.V.E.F. $\leq 35\%$.

6.2.2 Statistical Analysis

Statistical analyses were performed using Minitab for Windows (Minitab Inc,

Pennsylvania, U.S.A.). Where variables such as the transmitral Doppler indices were

not normally distributed the median value and interquartile range is used for descriptive

purposes and non-parametric tests - the Mann Whitney U test and the Kruskal Wallis

test - were used to compare medians. The proportions of individuals in two groups

were compared by the Chi-square test or Fisher's Exact test where appropriate.

Univariate and multivariate linear regression analyses were used to determine the

independent relationships between a set of variables and a single outcome. A P value of

<0.05 was taken to be significant.

6.3 Results

6.3.1 Transmitral Doppler Indices in the Whole Population

Transmitral Doppler indices were suitable for analysis in 910 individuals - 468 female

and 442 males - Table 6-1. The median values for the peak velocities of both the E

wave and the A wave were higher in females than in males - peak E: 0.60 (0.52 - 0.69)

ms^{-1} v 0.58 (0.48 - 0.67) ms^{-1}, P=0.003; peak A: 0.71 (0.62 - 0.83) ms^{-1} v 0.69 (0.60 -

0.79) ms-^{1}, P=0.021. There was no gender difference seen in either the M.V.D.T. or the

E:A ratio.

Table 6-1 - Transmitral Doppler Indices for Whole Cohort

Index	Males (n=442)	Females (n=468)
Peak E Wave (ms^{-1})	0.58 (0.48 - 0.67)	0.60* (0.52 - 0.69)
Peak A Wave (ms^{-1})	0.69 (0.60 - 0.79)	0.71* (0.62 - 0.83)
E:A Ratio	0.83 (0.71 - 0.97)	0.84 (0.70 - 0.98)
M.V. Dec.Time. (msecs)	218.0 (185.0 - 259.0)	214.5 (185.3 - 249.8)

All values expressed as median (interquartile range).

* $P<0.05$

6.3.2 Establishing Normal Ranges for the Population

A subgroup of 138 "healthy" participants were identified who were considered free of cardiovascular disease and its major risk factors, had no L.V.D. and had analysable transmitral Dopplers. The median values for the transmitral doppler indices in this group are shown in Table 6-2. The normal range for the whole population was defined as encompassing and including the 2.5th and 97.5th percentiles for this subgroup.

6.3.3 Characteristics of Individuals with Abnormal Mitral Valve Doppler Indices

The 52 individuals with an abnormally low E:A ratio (<0.56) compared to the remainder of the population were older, had a higher body mass index, a higher systolic and diastolic blood pressure, a lower L.V.E.F., a higher relative L.V. wall thickness and were more likely to suffer from ischaemic heart disease and L.V. systolic dysfunction - Table 6-3.

The 40 individuals with a higher than normal E:A ratio (>1.28) had compared to the remainder of the population a higher prevalence of both L.V.D. and I.H.D - Table 6-3. The same was true of the 33 people with an abnormally prolonged mitral valve deceleration time (>328.6 msecs) in whom the prevalence of I.H.D. was 50% higher than in the remainder of the population - Table 6-4. This group were also older, had a higher systolic blood pressure and had a greater proportion of individuals with hypertension (using 160/95 as a cut-off) than the remainder of the population.

6.3.4 Mitral Valve Doppler Indices in Disease States

From the 701 individuals with both a measured L.V.E.F. and transmitral Doppler indices four groups with cardiovascular disease were identified as follows:

Table 6-2 - Transmitral Doppler Indices for Normal Subgroup with Normal Left Ventricular Systolic Function

Index	Median (I.Q.R.)	Percentiles 2.5th	97.5th
Peak E Wave (ms^{-1})	0.57 (0.51 - 0.66)	0.38	0.87
Peak A wave (ms^{-1})	0.67 (0.59 - 0.75)	0.47	0.91
E:A Ratio	0.86 (0.76 - 1.00)	0.56	1.28
M.V. Dec.Time. (msecs)	211.0 (181.0 - 243.8)	128.3	328.6

N=138

Table 6-3 - Characteristics of Individuals with An Abnormal E:A Ratio

	Low E:A Ratio (<0.56)		High E:A Ratio (>1.28)	
	No N=840	Yes N=52	No N=852	Yes N=40
Age (yrs)	65.0 (60.0 - 69.0)	70.0 ** (65.3 - 72.8)	65.0 (60.0 - 70.0)	64.5 (59.0 - 71.0)
B.M.I. (Kg/m^2)	26.6 (23.7 - 29.2)	27.4 * (25.2 - 30.5)	26.6 (23.9 - 29.4)	25.1 (22.6 - 28.8)
Diastolic B.P. (mmHg)	80.0 (71.0 - 87.0)	84.5 * (75.3 - 92.0)	80.0 (72.0 - 88.0)	73.0 * (64.3 - 82.0)
Systolic B.P. (mmHg)	144.0 (129.0 - 160.0)	154.0 * (135.8 - 179.3)	145.0 (129.0 - 161.0)	145.5 (128.8 - 159.0)
L.V.E.F. (%)	51.0 (46.3 - 54.7)	48.0 * (39.3 - 51.3)	51.0 (46.3 - 54.7)	49.0 (41.0 - 53.7)
L.V. Mass Index (g/m)	122.0 (97.0 - 156.0)	149.0 (113.0 - 183.0)	123.0 (97.3 - 156.0)	140.5 (102.8 - 174.7)
R.Th.	0.42 (0.35 - 0.50)	0.48 * (0.45 - 0.56)	0.43 (0.34 - 0.51)	0.42 (0.28 - 0.47)
I.H.D	41.7%	55.8% *	41.7%	60.0% *
H.B.P.	42.6%	51.9%	42.8%	50.0%
HBP [JNCVI]	65.6%	78.8%	66.2%	70.0%
ECG L.V.H.	14.4%	23.1%	14.7%	20.0%
Diabetic	5.8%	11.5%	6.2%	5.0%
L.V.D.	3.5%	9.6% *	3.4%	12.5% *

Measurements expressed as median (interquartile range).

* P<0.05   **P<0.001

Table 6-4 - Characteristics of Individuals with An Abnormal Mitral Valve Deceleration Time

	Short MV Dec Time (<128.3)		Long M.V. Dec.Time (>328.6)	
	No N=876	Yes N=16	No N=861	Yes N=31
Age (yrs)	65.0 (60.0 - 70.0)	64.0 (59.0 - 68.8)	65.0 (60.0 - 70.0)	70.0 ** (66.0 - 72.0)
B.M.I. (Kg/m²)	26.6 (23.9 - 29.3)	23.9 * (21.1 - 27.1)	26.6 (23.8 - 29.3)	25.7 (23.3 - 28.7)
Diastolic B.P. (mmHg)	80.0 (71.0 - 88.0)	80.0 (75.0 - 82.8)	80.0 (72.0 - 87.0)	77.5 (66.8 - 90.3)
Systolic B.P. (mmHg)	145.0 (129.0 - 161.0)	141.5 (121.0 - 158.3)	144.0 (129.0 - 160.0)	150.5 * (139.5 - 173.3)
L.V.E.F. (%)	123.0 (98.0 - 157.0)	121.0 (94.0 - 177.0)	123.0 (98.0 - 156.5)	160.5 (96.0 - 190.0)
L.V. Mass Index (g/m)	0.43 (0.35 - 0.51)	0.38 (0.35 - 0.55)	0.43 (0.35 - 0.51)	0.44 (0.30 - 0.64)
R.Th.	50.7 (46.3 - 54.7)	42.7 (39.3 - 56.3)	50.7 (46.3 - 54.7)	50.3 (41.7 - 54.3)
I.H.D	42.6%	50.0%	42.0%	63.6% *
H.B.P.	42.8%	45.0%	42.2%	60.6% *
HBP[JNCVI]	67.2%	75.0%	66.9%	80.6%
ECG L.V.H.	15.3%	15.0%	15.1%	21.2%
Diabetic	6.2%	5.0%	6.0%	9.1%
L.V.D.	4.0%	15.0%	4.5%	0.0%

Measurements expressed as median (interquartile range).

* P<0.05   **P<0.001

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(1) Evidence of I.H.D. but without hypertension (Isolated I.H.D.) - 128 individuals.

(2) Hypertension but without I.H.D. - Isolated hypertension (160/95 cut-off) - 138 individuals; and isolated hypertension [JNC VI] (140/90 cut-off) – 239 individuals.

(3) Both hypertension and I.H.D. - 111 individuals.

(4) L.V. systolic dysfunction - 39 individuals.

Individuals with either L.V.D. and/or significant valve defects were excluded from the first three categories.

Comparing the median values for the transmitral Dopplers for the four disease categories with the "healthy" group - Table 6-5 - shows that individuals with isolated I.H.D. have a longer M.V.D.T. - 224.5 (196.5 - 252.8) msecs v 211.0 (181.0 - 243.8) msecs (P<0.05). The group with isolated hypertension have both a higher peak A wave velocity - 0.71 (0.62 - 0.83) ms^{-1} v 0.67 (0.59 - 0.75) ms^{-1}, P<0.01 and a longer M.V.D.T. - 226.0 (194.8 - 259.5) msecs v 211.0 (181.0 - 243.8) msecs, P<0.05 although the effect on the M.V.D.T. was not significant if hypertension was defined using the JNC VI criteria. Individuals with both hypertension and I.H.D. show the greatest increase in both the M.V.D.T. - 228.0 (195.0 - 264.0) msecs v 211.0 (181.0 - 243.8) msecs, P<0.05 - and the peak A wave velocity - 0.74 (0.65 - 0.87) ms^{-1} v 0.67 (0.59 - 0.75) ms^{-1}, P<0.01. This has the effect of producing a significant reduction in the E:A ratio - 0.78 (0.67 - 0.96) v 0.86 (0.76 - 1.00), P<0.01. The only significant difference shown in the group with L.V.D. was an increase in the peak A wave velocity to 0.75 (0.61 - 0.87) ms^{-1} P<0.05, and although there was a trend for the median M.V.D.T. to be shorter and the peak velocity of the E wave to be higher neither of these reached significance.

Table 6-5 - Median Values for Transmitral Flow Dopplers In Various Disease States

	Peak E ms^{-1}	Peak A ms^{-1}	E:A Ratio	M.V.D.T. msecs
Normals[1] **N=138**	0.57 (0.51 - 0.66)	0.67 (0.59 - 0.75)	0.86 (0.76 - 1.00)	211.0 (181.0 - 243.8)
All **N=910**	0.59 (0.51 - 0.68)	0.70 * (0.61 - 0.82)	0.83 (0.70 - 0.97)	216.0 (185.0 - 254.0)
IHD Only[1] **N=128**	0.59 (0.49 - 0.67)	0.68 (0.61 - 0.79)	0.84 (0.73 - 0.98)	224.5 * (196.5 - 252.8)
HBP Only[1] **N=138**	0.61 (0.52 - 0.67)	0.71 ** (0.62 - 0.83)	0.83 (0.70 - 0.98)	226.0* (194.8 - 259.5)
HBP[JNC VI][1] **Only N=239**	0.59 (0.51 – 0.67)	0.70** (0.62 – 0.82)	0.82 (0.71 – 0.98)	220.0 (190.0 – 254.0)
IHD and HBP[1] **N=111**	0.61 (0.51 - 0.71)	0.74 ** (0.65 - 0.87)	0.78 ** (0.67 - 0.96)	228.0 * (195.0 - 264.0)
L.V.D **N=39**	0.67 (0.46 - 0.78)	0.75 * (0.61 - 0.87)	0.81 (0.61 - 0.98)	188.0 (170.0 - 227.0)

* P<0.05   ** P<0.01 compared to normals

[1] Excluding those with an L.V. ejection fraction of $\leq$ 35% and/ or significant valvular disease.

6.3.5 Determinants of Transmitral Doppler Indices in The Population

The possible effects of several clinical variables on transmitral Doppler indices were analysed by univariate regression analyses - Table 6-6.   Age was positively associated with both the M.V.D.T. and the peak A velocity and negatively with the E:A ratio.   The B.M.I. similarly increased the peak A wave velocity and so decreased the E:A ratio.

The different blood pressure variables showed differing effects on transmitral Doppler indices. The systolic, diastolic and mean blood pressures all exert similar effects; increasing the M.V.D.T. and the A wave, and so decreasing the E:A ratio. The diastolic pressure and the mean pressure additionally decrease the E wave. The pulse pressure although it increases the peak A wave velocity also increases the peak E velocity and so has no significant effect on the E:A ratio.   It does however like the other variables increase the M.V.D.T..

Neither the L.V. mass nor L.V. mass index exerted a significant effect on the Doppler indices but the relative L.V. wall thickness was positively associated with the peak A velocity and so negatively with the E:A ratio. The relative wall thickness also acts to increase the M.V.D.T.   The L.V.E.F. was not associated with any of the mitral valve Doppler indices.

When the variables which were significant by univariate analyses were combined into a multivariate analysis - Table 6-7 - it was shown that both the diastolic blood pressure and the pulse pressure remained significantly associated with the peak E wave velocity. Inclusion of both the systolic and diastolic blood pressures in a model looking at the determinants of the peak A velocity shows that the diastolic blood pressure no longer exerts a significant effect.   The model which describes the greatest variation

Table 6-6 - Determinants of Transmitral Doppler Indices - Univariate Regression Analysis

P values

	Peak E (ms^{-1})	Peak A (ms^{-1})	E:A	M.V.D.T. (msecs)
Age (yrs)	0.871	**<0.001 +**	**<0.001 -**	**<0.001 +**
B.M.I. (Kg/m^2)	0.315	**0.004 +**	**0.005 -**	0.635
S.B.P. (mmHg)	0.276	**<0.001 +**	**<0.001 -**	**<0.001 +**
D.B.P. (mmHg)	**0.001 -**	**<0.001 +**	**<0.001 -**	**0.005 +**
M.A.P. (mmHg)	0.191	**<0.001 +**	**<0.001 -**	**<0.001 +**
Pulse P. (mmHg)	**<0.001 +**	**<0.001 +**	0.214	**<0.004 +**
L.V. Mass (g) Male	0.425	0.555	0.438	0.570
L.V. Mass (g) Female	0.184	0.586	0.154	0.589
Mass Index (g/m) Male	0.579	0.839	0.570	0.621
Mass index (g/m) Female	0.144	0.415	0.194	0.662
R.Th.	0.846	**<0.001 +**	**0.002 -**	**0.003 +**
L.V.E.F. (%)	0.680	0.103	0.880	0.840

+ Positive association
- Negative association

S.B.P. - Systolic blood pressure   D.B.P. - Diastolic blood pressure
M.A.P. - Mean blood pressure   Pulse P. - Pulse pressure

Table 6-7 - Determinants of Transmitral Doppler Indices - Multivariate Analysis.

	P values			
	Peak E	**Peak A**	**E:A**	**M.V.D.T.**
Age		<0.001	0.016	0.001
B.M.I.		n.s.	0.014	0.031
S.B.P.			n.s.	n.s.
D.B.P.	<0.001		n.s.	n.s.
Pulse Press.	<0.001			
M.A.P.		0.019		
R.Th.		0.047	0.027	n.s.
R^2 (adj)	2.8%	10.6%	5.4%	6.3%

Notes:

R^2(adj)= the square of the multivariate correlation coefficient adjusted for the expected chance prediction when the null hypothesis is true. It indicates how much of the variation that is explained by the factors in the model.

S.B.P. - Systolic blood pressure   D.B.P. - Diastolic blood pressure
M.A.P. - Mean blood pressure   Pulse Press. – Pulse Pressure

(10.6%) in the peak A velocity is the one which includes age, mean blood pressure and the relative wall thickness; which were all positively associated. The model looking at the E:A ratio shows that none of the blood pressure variables remain significant when combined with other variables. The factors which are significantly associated, all negatively, with the E:A ratio are age, B.M.I. and the relative L.V. wall thickness. The main determinants of the M.V.D.T. were age and B.M.I.. As with the E:A ratio, none of the blood pressure variables remain significant when combined in a multivariate analysis looking at the M.V.D.T. and neither does the relative L.V. wall thickness.

6.3.6 Left Ventricular Mass within The Population

A satisfactory M-mode echocardiogram was obtained in 374 (37.1%) people with the availability reducing with age from 44.9% in individuals aged 55 to 59 years to 34.7% in those aged 70 to 74 years ,P=0.02. A gender difference was also seen with fewer males – 167/500 (33.4%) having an M-mode measured than females - 207/509 (40.7%), P=0.017.

In the healthy subgroup 63 individuals - 28 males and 35 females - had their L.V. mass measured by Mmode. In the males the median L.V. mass was 222.7 (194.2 to 267.7)g, and the median L.V. mass index was 132.5 (113.5 to 157.0)g/m. In the females the median L.V. mass and L.V. mass index were both significantly less than in the males: 148.4 (130.4 to 188.6)g, P<0.05, and 92.0 (82.0 to 115.0) g/m, P<0.05, respectively. Increased L.V. mass was defined as that exceeding the 97.5[th] percentile for this subgroup i.e. an L.V. mass > 364.0g in males and an L.V. mass > 242.8g in females; and an L.V. mass index > 210.6g/m in males and an L.V. mass index >151.8g/m in

females.

The relative wall thickness did not show a gender difference (males:0.41 v females: 0.40) and the median RTh for the normal subgroup was 0.40 (0.34 to 0.45) with an abnormally high RTh being taken to be greater than the 97.5[th] percentile: 0.67.

The relative L.V. wall thickness was increased in the group with hypertension - 0.47 (0.35 – 0.48) v 0.42 (0.36 – 0.55), P=0.002 , although the difference is small. In males with hypertension the L.V. mass and L.V. mass index both tended to be higher than in non-hypertensive males but the differences did not reach significance: 257.1 (211.8 – 313.5)g v 240.0 (202.5 – 285.6)g:, P= 0.148 and 153.5 (123.5 – 183.5)g/m v 143.0 (119.0 – 169.0)g/m, P=0.135. In hypertensive females, however, both the L.V. mass and L.V. mass index were significantly higher than in the non-hypertensive females: 187.9 (155.7 – 244.4)g v 160.2 (131.1 – 195.4)g, P<0.001 and 120.5 (97.5 – 157.0)g/m v 99.0 (83.5 – 122.5)g/m, P<0.001.

6.3.7   Characteristics of Individuals with Increased L.V. Mass

There was no significant difference in any of the transmitral Doppler indices of L.V. diastolic filling between either the group of 42 people (11.2%) with an increased L.V. mass or the group of 44 people (11.8%) with an increased L.V. mass index, and the remainder of the cohort - Table 6-8.   The prevalence of both hypertension and E.C.G. evidence of L.V.H. were greater in the groups of individuals with an increased L.V. mass or L.V. mass index – table 6-9.   The prevalence of hypertension [JNC VI definition] was however not significantly higher in these groups.

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	Age yrs	BMI Kg/m²	S.B.P. mmHg	D.B.P. mmHg	Peak E ms⁻¹	Peak A ms⁻¹	E:A	M.V.D.T. msecs
High LV Mass	67.0 (60.5 - 71.0)	28.7** (25.6 - 31.9)	159.1* (33.5)	84.1* (16.3)	0.57 (0.48 – 0.70)	0.69 (0.56 – 0.82)	0.78 (0.65 – 0.98)	219.5 (163.7 - 262.5)
Normal LV Mass	64.0 (59.0 – 69.0)	25.8 (23.5 - 28.4)	144.2 (23.0)	78.8 (11.0)	0.60 (0.51 – 0.68)	0.68 (0.59 – 0.79)	0.87 (0.75 – 1.00)	208.0 (179.0 – 237.0)
High Mass Index	67.5* (62.0 – 71.0)	29.4** (26.0 – 32.2)	160.6* (32.8)	78.9 (16.4)	0.59 (0.49 – 0.74)	0.72 (0.60 – 0.86)	0.78 (0.69 – 0.98)	212.0 (167.3 – 265.8)
Normal Mass Index	64.0 (59.0 – 69.0)	25.7 (23.5 - 28.4)	143.9 (22.8)	83.4 (11.0)	0.60 (0.51 – 0.68)	0.68 (0.59 – 0.79)	0.87 (0.75 – 1.00)	208.0 (179.0 – 238.0)
High R.Th	71.0 * (63.5 - 72.0)	26.3 (21.7 - 29.9)	166.6 * (30.3)	88.0 * (15.2)	0.55 (0.48 - 0.66)	0.75 * (0.67 - 0.98)	0.71 ** (0.57- 0.81)	237.0 * (206.5 - 281.0)
Normal R.Th	64.0 (60.0 - 69.0)	26.3 (23.8 - 28.7)	145.0 (24.0)	79.0 (11.9)	0.60 (0.51 - 0.68)	0.67 (0.59 - 0.79)	0.89 (0.75 - 1.01)	207.5 (177.0 - 238.0)

Values expressed as median (I.Q.R.) except for blood pressure - mean (S.D.)

* - P<0.05, ** - P<0.001 compared to group with corresponding normal index of LV mass.

Table 6-8 - Characteristics of Individuals with Abnormal Indices of L.V. Mass

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Table 6-9 - The Relationship between L.V. Mass and Hypertension

L.V. Mass

	Increased n=42	Normal n=332
Hypertension	61.9%	40.4%*
Hypertension [JNC VI]	66.7%	62.3%
E.C.G. L.V.H.	33.3%	14.5%*

L.V. Mass Index

	Increased n=44	Normal =329
Hypertension	61.4%	40.4%*
Hypertension [JNC VI]	70.5%	62.0%
E.C.G. L.V.H.	34.1%	14.3%*

L.V. Wall Thickness

	Increased n=21	Normal n=353
Hypertension	71.4%	40.9%*
Hypertension [JNC VI]	62.0%	76.2%
E.C.G. L.V.H.	33.3%	15.6%*

* $P<0.05$ ** $P<0.001$

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An increased relative L.V. wall thickness was found in 21 individuals (6.3%) who compared with the remainder of the population, were older 71 (63.5 - 72.0) v 64 (60.0-69.0) yrs, P=0.006, and had a higher prevalence of both hypertension (71.4% v 40.9%, P<0.01) and E.C.G. evidence of L.V.H. (33.3% v 15.6%, P<0.05), but not hypertension [JNC VI criteria] (76.2% v 62.0%, P=0.245). They had a higher mean diastolic and systolic blood pressure - systolic 166.6 ± 30.3 v 145.0 ± 24.0 mmHg (P=0.004) and diastolic 88.0 ± 15.2 v 78.9 ± 11.9 mmHg (P=0.015). Their median peak A wave velocity was increased - 0.75 (0.67 - 0.98) ms^{-1} v 0.67 (0.59 - 0.79) ms^{-1}, P=0.004, but the peak E wave velocity was not different. This had the effect of reducing the median E:A ratio to 0.71 (0.57 - 0.81) v 0.89 (0.75 - 1.01), P<0.001. The median M.V.D.T. was increased 237.0 (206.5 - 281.0) msecs v 208.0 (177.0 - 238.0) msecs P=0.009.

6.3.8 Breathlessness Without L.V. Systolic Dysfunction

A group of 449 individuals were identified in whom L.V.D. had been excluded by demonstrating an L.V.E.F. >35% and normal L.V. systolic function verified on visual assessment. Significant airflow obstruction was excluded by spirometry by showing an $F.E.V_1$ ≥75% of the predicted value based on age, sex and height. None was receiving treatment with respiratory medication and none had significant valvular abnormalities. Within this group 54 people (12.0%) either reported cardiac-type dyspnoea or were in receipt of treatment with a loop diuretic. Comparing this symptomatic group with the remainder - Table 6-10 - showed that there were no significant differences between the two groups with respect to any of the transmitral Doppler indices. A greater proportion of symptomatic than asymptomatic people had evidence of I.H.D. (59.3% v 32.7%, P<0.001) but there was no difference in the proportions with hypertension. During treadmill exercise testing the symptomatic individuals exercised for a shorter median

Table 6-10 - Comparison between breathless and asymptomatic individuals with normal L.V. systolic function and no airflow obstruction.

Variable	Asymptomatic N=395	Breathless N=54
Age (yrs)	64.0 (60.0 - 68.0)	62.0 (58.8 - 68.0)
B.M.I. (Kg/m²)	26.0 (23.7 - 28.5)	28.1 ** (25.5 - 31.2)
Exercise Time (secs)	653.0 (549.5 - 746.3)	561.0 ** (444.0 - 653.0)
Peak E (ms⁻¹)	0.59 (0.51 - 0.67)	0.55 (0.48 - 0.66)
Peak A (ms⁻¹)	0.69 (0.60 - 0.80)	0.68 (0.61 - 0.77)
E:A Ratio	0.85 (0.73 - 1.00)	0.84 (0.72 - 0.93)
M.V. Dec Time (msecs)	216.5 (188.0 - 252.8)	226.0 (188.0 - 261.0)
L.V.E.F. %	51.7% (47.7 - 55.7)	49.7% (46.1 - 53.0)
Systolic B.P. (mmHg)	147.0 (131.0 - 164.0)	134.0 (122.3 - 154.5)
Diastolic B.P. (mmHg)	81.0 (73.0 - 89.0)	79.5 (70.8 -86.0)
I.H.D.	32.7%	59.3% **
Hypertension	43.0%	42.6%
I.H.D. Only	19.2%	35.2% *
Hypertension Only	25.3%	16.7%
ST segment Shift on exercise (mm)	-0.4 (-0.9 - 0.0)	-0.5 (-1.0 - -0.1)

  * P<0.05   **P<0.001

Notes
Includes only those with measured normal L.V. systolic function and excludes all taking respiratory medication or with an $F.E.V_1$ of <75% predicted value, or with valvular disease.

time - 561.0 (444.0 - 653.0) secs v 653.0 (549.5 - 746.3) secs, P=0.001 - but the median level of electrocardiographic ST segment shift was not significantly different between the two groups .   The symptomatic group had a higher median B.M.I. 28.1 (25.5 - 31.2) Kg/m^2 v 26.0 (23.7 - 28.5) Kg/m^2, P<0.001.

Removing individuals with I.H.D. from the analysis left 288 people - Table 6-11.   The symptomatic proportion of these, 22 people, now had a lower median peak velocity of the E wave 0.51 (0.45 - 0.63) ms^{-1} v 0.58 (0.51 - 0.67) ms^{-1} , P=0.038 with no change in the peak A wave velocity and so they had a significantly lower E:A ratio 0.77 (0.71 - 0.87) v 0.87 (0.74 - 1.00) P<0.05. Both the proportion with hypertension and the mean age did not differ between groups. The difference in median exercise times was no longer present once individuals with I.H.D. had been removed.

6.4 Discussion

This study looking at 55 to 74 year olds from the general population confirms the results of previous studies showing that transmitral Doppler indices of L.V. diastolic filling are affected by several biological variables and disease states including gender, age, body mass index, blood pressure, relative L.V. wall thickness, hypertension, ischaemic heart disease and L.V. systolic dysfunction.

An increased L.V. mass and relative wall thickness were shown to be associated with a higher prevalence of E.C.G. evidence of L.V.H. and hypertension. The association with hypertension was only seen with hypertension defined by a 160/95 mmHg cut-off. This may be because the stricter 140/90 mmHg criteria, when applied to a single observation, includes a number of people with spuriously raised blood pressure – the

Table 6-11 - Comparison between breathless and asymptomatic individuals with normal L.V. systolic function, no evidence of I.H.D. and no airflow obstruction

Variable	Asymptomatic N=266	Breathless N=22
Age (yrs)	64.0 (60.0 - 68.0)	64.0 (59.0 - 68.5)
B.M.I. (Kg/m^2)	25.4 (23.6 - 28.1)	27.2 (24.7 - 29.9)
Exercise Time (secs)	668.0 (596.5 - 773.0)	638.5 508.5 - 694.5)
Peak E (ms^{-1})	0.58 (0.51 - 0.67)	0.51 * (0.45 - 0.63)
Peak A (ms^{-1})	0.68 (0.60 - 0.79)	0.68 (0.59 - 0.75)
E:A Ratio	0.87 (0.74 -1.00)	0.77 * (0.71 - 0.87)
M.V. Dec Time (msecs)	214.0 (186.0 - 247.8)	227.0 (179.0 - 258.0)
L.V.E.F. %	51.7% (47.7 - 55.7)	51.0% (44.1 - 53.9)
Systolic B.P. (mmHg)	144.0 (129.0 - 161.3)	137.5 (118.5 - 165.3)
Diastolic B.P. (mmHg)	81.0 (72.0 - 89.0)	83.0 (75.0 - 87.0)
I.H.D.	37.6%	40.9%
Max ST segment Shift on Ex. ECG (mm)	-0.30 (-0.8 - 0.0)	-0.35 (-1.1 - -0.1)

* P<0.05   **P<0.001

Notes
Includes only those with measured normal L.V. systolic function and excludes all taking respiratory medication or with an $F.E.V_1$ of <75% predicted value, or with valvular disease, or with evidence of I.H.D.

"White Coat" effect. Equally it may well be that lower levels of blood pressure, as included in the JNC VI definition, are not sufficient to cause a demonstrable increase in L.V. mass; large enough to be detected in our study using echocardiography. Ultimately the biological importance of a certain level of blood pressure is only shown by its longterm effects, not only on the myocardium but on the wider cardiovascular system; which this study cannot demonstrate.

6.4.1 Effect of Biological Variables

Looking at the whole cohort with measured transmitral Dopplers in this study showed that females had higher median values for both the peak E and A wave velocities with no difference in the E:A ratio. The magnitude of the difference was small - ~3% greater than median values for males. A similar gender effect has been found in other larger studies looking at both people in the third and fourth decades (Xie et al. 1995) and aged 65 years and over (Gardin et al. 1998). The explanation for this observation is unclear. It may be due to females having smaller mitral valve orifices and hence a lower valve orifice to cardiac output ratio although the Cardiovascular Health Study showed that females actually had lower stroke volumes than men (Gardin et al. 1998). It remains a possibility that there are fundamental differences in the physiology of diastole between men and women.

A consistent finding in epidemiological studies is that age affects transmitral Doppler indices. In this study multivariate analysis showed age to be positively associated with the peak A velocity and the M.V.D.T. and negatively associated with the E:A ratio. The Framingham Heart Study over a sixty year age range found age to be the strongest

determinant of transmitral Doppler indices (Benjamin et al. 1992) and even the C.A.R.D.I.A. study looking at an age range of only ten years found the same associations with age as this study found (Kronmal et al. 1996). Logistic Regression Analysis in the large Cardiovascular Health Study showed, that with all other factors held equal, for each ten year increase in age there was an increase in the peak A velocity of $0.065ms^{-1}$ (Gardin et al. 1998).

These results suggest that with age there is progressive impairment of early left ventricular diastolic relaxation and a shift to a greater reliance upon left atrial systole for L.V. filling. This is in keeping with experimental evidence that ageing is associated with greater stiffness of the L.V. and impaired relaxation (Templeton et al. 1979; Kitzman et al. 1991). This may explain why the elderly do not tolerate as well the loss of atrial function as occurs with the onset of atrial fibrillation.

Body mass index in other studies has been shown to be associated with abnormalities of L.V. diastolic filling. Xie et al. looking at body weight found, like as this study did, that it was associated with the peak A velocity although in that study it also affected the E:A ratio (Xie et al. 1995). Kangro looking at 50 yr. old women found that the B.M.I. was negatively associated with the E:A ratio (Kangro et al. 1996). In this present study this effect was independent of blood pressure. It may be that the effect is as a result of increased pericardial fat reducing the compliance of the myocardium.

6.4.2 Blood pressure, L.V. Mass and Hypertension

The blood pressure variables studied in this study population have different, independent, effects on the various transmitral Doppler indices but the general picture

is that increasing levels of blood pressure - both systolic and diastolic - are associated with changes in transmitral Doppler indices indicating increasing impairment of L.V. diastolic filling. These effects were independent of both the L.V. mass and the relative L.V. wall thickness.

Previous studies have also shown blood pressure variables to have differing effects on transmitral Dopplers but have found, as this study did, that the trend is for increasing levels of blood pressure to be associated with impairment of L.V. diastolic filling. The C.A.R.D.I.A. study found, as this study did, that the systolic blood pressure was positively associated with the peak A velocity (Xie et al. 1995). The Cardiovascular Health Study postulated that the effect of blood pressure might be due to the pulse pressure since, in that study, both the systolic and diastolic blood pressures had equal but opposite effects on both the peak E and peak A wave; with the systolic positively related to them and the diastolic inversely (Gardin et al. 1998). Whilst a study by Kangro could find no association with systolic blood pressure it did find that the diastolic blood pressure was inversely related to the E:A ratio (Kangro et al. 1996).

A diagnosis of isolated hypertension (using a 160/95 cut-off) in this study was associated with both a higher peak A velocity and a longer deceleration time suggesting impaired L.V. diastolic filling. Similar changes were shown in the Cardiovascular Health Study where hypertension was associated with an increased A wave and a decreased E:A ratio (Gardin et al. 1998). This has been shown to be true for people with borderline hypertension even in the absence of L.V. mass changes (Kapuku et al. 1993). This suggests that the effect of hypertension may be at least at first related to loading conditions on the left ventricle or to microscopic changes in the

myocardium such as increased fibrosis (Kapuku et al. 1993; Chen et al. 1996)

Neither the L.V.. mass nor the L.V. mass index appeared to exert an effect on transmitral Dopplers in this population. This lack of effect by L.V. mass has been noted in other studies (Benjamin et al. 1992; Voutilainen et al. 1991; Graettinger et al. 1987). This study did find, however, that the relative L.V. wall thickness by univariate analysis was significantly associated with the peak A velocity, the E:A ratio and the M.V.D.T.; and in multivariate analysis it was independently associated with the peak A velocity and the E:A ratio. Other studies have found the L.V. wall thickness to correlate with markers of diastolic filling. Kangro found that, in normal individuals, it influenced L.V. filling whereas the L.V. mass did not (Kangro et al. 1996). The Cardiovascular Health Study found that the L.V. wall thickness was associated with an increased A wave velocity (Gardin et al. 1998) and Xie found in females not only this but also that it was associated with a decreased E:A ratio (Xie et al. 1995).

It appears, therefore, that rather than the total mass of the left ventricle influencing diastolic filling it is the relative degree to which the L.V. wall is hypertrophied or not. This may be a more accurate reflection of pathophysiology as it both makes allowance for small hearts which may not have a high total mass but which are relatively hypertrophied, and it takes into account the degree to which the left ventricular cavity is encroached upon and restricted by any myocardial hypertrophy.

6.4.3 Ischaemic Heart Disease

Individuals with I.H.D. with or without concomitant hypertension were shown to have changes in the transmitral Dopplers suggesting impaired relaxation with longer deceleration times and increased peak A velocities compared to normals.

Abnormalities of L.V. diastolic filling have been shown previously in individuals with I.H.D. whether or not they have had a previous myocardial infarction (Grossman, 1991; Hirota, 1980). This may be due, in part, to ischaemia impairing calcium handling and the energy-dependent process of diastolic relaxation and, in part due, to replacement of infarcted myocardium by inelastic fibrous tissue (Grossman, 1991).

6.4.4 L.V. Systolic Dysfunction

The number of individuals with L.V.D. and measurable transmitral Doppler indices in this cohort was small. Looking at them as a group they displayed evidence of impaired diastolic relaxation with higher median peak A wave velocities. There was also a trend, although not significant, for the deceleration time to be shorter and for the peak E velocity to be higher suggesting a higher prevalence of a restrictive pattern of transmitral Doppler indices. Looking at the group of individuals with a restrictive pattern of transmitral Doppler indices there was a higher prevalence of L.V.D. compared to people with a non-restrictive pattern. Therefore there is a suggestion that L.V.D. in this small group can be associated with either pattern.

The mechanisms responsible for impaired diastolic function, particularly in ischaemic cardiomyopathy, are multifactorial (Brutsaert et al. 1993) and includes the effects of ischaemia, abnormal calcium handling at cellular level (Gwathmey et al. 1987), left ventricular remodelling (Pfeffer and Braunwald, 1990) and elevated filling pressures (Brutsaert et al. 1993). Individuals with L.V.D. and a restrictive pattern of transmitral Doppler indices have been shown to have elevated L.V. filling pressures (Pozzoli et al. 1996) whereas individuals with a non-restrictive pattern or a pattern of abnormal relaxation usually have normal or near-normal L.V. filling pressures at rest (Appleton et al. 1988). The presence of a restrictive pattern is associated with greater symptoms and

effort intolerance (Xie et al. 1996).

One limitation of this current study, which will be clarified by follow-up, was the inability to differentiate between a normal and a pseudonormal pattern of transmitral Doppler indices. The latter is a transition state between an abnormal relaxation pattern and a restrictive filling pattern and is associated with increased L.V. filling pressures (Iga et al. 1990; Nishimura and Tajik, 1997). This transition may occur as a disease involving the myocardium progresses from being initially associated with impaired relaxation to later reducing the effective chamber compliance and so increasing the left ventricular and then left atrial pressures (Nishimura and Tajik, 1997). Therefore it is likely that the group with L.V.D. was composed of a mix of individuals with all three patterns of transmitral Dopplers depending on the stage of the disease process. The only way that normal and pseudonormal patterns could have been differentiated would have been to have recorded Doppler signals from the pulmonary veins (Nishimura and Tajik, 1997).

6.4.5 Breathlessness With Normal Systolic Function

Exertional breathlessness is a common complaint made by patients attending both cardiology and respiratory clinics and is one of the cardinal symptoms of the syndrome of heart failure; whether due to systolic or diastolic dysfunction (The Task Force on Heart Failure of the European Society of Cardiology, 1995). Looking at individuals with both normal L.V. systolic function and spirometry, and using the M.R.C. breathlessness questionnaire to detect exertional dyspnoea, this study was unable to find a difference in transmitral Doppler indices between those who reported breathlessness and those who did not. Those who reported breathlessness did show a poorer effort capacity when this was tested formally by treadmill testing; with them

exercising for a median of 1½ minutes less than those who were asymptomatic. Thus one can be sure that the questionnaire did detect a real symptom with real consequences in term of objective effort intolerance.

There are a number of possible reasons as to why this study did not detect any difference in L.V. diastolic filling. The most obvious is that the dyspnoea was not due to diastolic dysfunction and may not even have been due to cardiac causes at all. Dyspnoea is a non specific symptom and can be produced by a number of other cardiac and non-cardiac conditions (Vasan et al. 1996). Although spirometry was measured and individuals taking bronchodilators and theophyllines were excluded this does not rule out the possibility of untreated episodic bronchospasm. This study showed a higher median B.M.I. for the breathless group suggesting that obesity may have at least been a contributory factor. The dyspnoea in the study group was accompanied by a higher prevalence of I.H.D. raising the possibility that the questionnaire was actually detecting symptomatic angina presenting with exertional dyspnoea whether accompanied by chest pain or not. Equally individuals with I.H.D., who have reversible myocardial ischaemia on exertion, may as a result of this on exertion have reversible systolic and/or diastolic myocardial dysfunction (Vasan et al. 1996). Such people may show no abnormalities of either L.V. systolic or diastolic function at rest.

These findings support previous research which has suggested that the high false-positive rate for the diagnosis of heart failure in primary care may be related to obesity, pulmonary disease or unrecognised ischaemia (Remes et al. 1991). A review of published studies looking for diastolic filling abnormalities in patients with C.H.F. and normal systolic function (Vasan et al. 1995) found them to be present in between only

20% (Soufer et al. 1985) and 62% (Aguirre et al. 1989). Equally the prevalence of coronary artery disease in this condition has been reported as being as high as 67% (Judge et al. 1991).

After removing individuals with I.H.D. from the analysis a small difference in the E:A ratio was evident between those with and those without reported dyspnoea. One cannot automatically assume that this study had identified a group of individuals with diastolic dysfunction since the other major aetiological factor besides I.H.D. for this condition, namely hypertension, was no more prevalent in the symptomatic group. Equally if a real condition had been found, an objective impact upon effort capacity could not be demonstrated; although numbers were small.

In conclusion abnormalities of L.V. diastolic filling can be demonstrated in the population but their impact upon the individual and their contribution to symptoms is not clear.

7. Natriuretic Peptides and Their Relationship to Left Ventricular Function and Mass

7.1 Introduction

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are circulating cardiac hormones which are secreted predominantly by atrial and ventricular myocardium, respectively, in response to volume expansion and cardiac pressure overload (Yasue et al. 1994). They have similar physiological actions - natriuresis, arterial and venous vasodilatation, and antagonism of the renin-angiotensin-aldosterone system (Struthers, 1994). This has the effect of reducing the circulating volume and thus cardiac preload (Wei et al. 1993). ANP is synthesised and stored in granules in atrial myocytes (de Bold et al. 1981) as a 126 amino acid prohormone which is cleaved into two fragments: the 28 amino acid carboxyl-terminal (C-terminal) peptide and the 98 amino acid N-terminal-ANP (N-ANP) (Glembotski et al. 1988). The N-terminal has a much longer plasma half-life than the C-terminal (Thibault et al. 1988) and so circulating levels are about ten to twenty-fold higher than those of C-terminal ANP (Sundsfjord et al. 1988).

Both N-ANP and BNP have been shown to be elevated in L.V. systolic dysfunction (L.V.D.) (Wei et al. 1993; Burnett et al. 1986; Cody et al. 1986; McDonagh et al. 1998; Dickstein et al. 1995; Lerman et al. 1993; Davidson et al. 1996; Friedl et al. 1996) and several studies have looked at the possibility of using them as screening blood tests for its presence within the general population (McDonagh et al. 1998; Cowie et al. 1997b; McClure et al. 1998; Davidson et al. 1996; Friedl et al. 1996). They have also been shown to be elevated to differing degrees in other conditions such as diastolic dysfunction (Pontremoli et al. 1993; Wilkins et al. 1997; Lang et al. 1994) and left ventricular hypertrophy (Kohno et al. 1992; Kohno et al. 1995; Yoshibayashi et al. 1993).

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The aims of this study were to investigate the determinants of levels of N-ANP and BNP within an unselected population; to examine the effects of L.V. systolic and diastolic dysfunction on peptide levels and to explore the possibility of using either N-ANP or BNP as screening blood tests for the presence of L.V.D. Recently a direct immunoradiometric assay (I.R.M.A.) kit (Shionoria BNP kit, Shionogi &Co, Ltd, Osaka, Japan) for detecting BNP levels in unextracted plasma (Kono et al. 1993) has become available and it was decided to compare the results for BNP levels obtained by this method with those obtained from extracted plasma using a radioimmunoassay kit for human BNP - RIK 9086, (Penninsula Laboratories).

7.2 Methods

Each person completed questionnaires regarding demographics, past medical history, current medication, and the presence of breathlessness - M.R.C. questionnaire. Their height, weight, blood pressure and spirometry were measured and a 12-lead E.C.G. was recorded and Minnesota coded (Prineas et al. 1982). Next a full two-dimensional and Doppler echocardiogram was performed using an Acuson 128 ultrasound machine (Acuson Inc., Mountain View, CA, USA) with calculation of a left ventricular ejection fraction (L.V.E.F.) using a biplane algorithm ("method of discs summation", Simpson's rule) (Schiller et al. 1979), and transmitral Doppler signals recorded and analysed.

The left ventricular mass was calculated from M-mode using the Penn Cube formula (Devereux et al. 1986). The L.V. mass index was calculated by dividing the L.V. mass by the height (m). The relative L.V. wall thickness (R.Th.) expresses the proportion of the L.V. radius in diastole which is L.V. wall.

A 10ml blood sample was taken, after 20 minutes of supine rest, and placed into a pre-chilled tube containing potassium-EDTA (1mg/ml blood) and aprotonin (50 I.U./ml blood) for measurement of natriuretic peptides. The sample was stored on ice and centrifuged at 3000 r.p.m. for 10 minutes at 4° C within 30 minutes of collection. The plasma was immediately frozen and stored at -70° C. until assay. Both N-ANP and BNP were measured in plasma after extraction. N-ANP was measured after dilution (1/100) by radioimmunoassay using an antibody - RAS 9129 (Peninsula Laboratories, Belmont, California, USA) - raised against the 1 to 30 N-terminal fragment. BNP was measured in the extract (1/4 dilution) using a radioimmunoassay kit for human BNP - RIK 9086, (Penninsula Laboratories). BNP was also assayed in unextracted plasma using a direct immunoradiometric assay kit (Shionoria BNP kit) supplied by Shionogi & Co, Ltd. (Osaka, Japan) (Kono et al. 1993). This uses two monoclonal antibodies which recognise the carboxyl terminal sequence and the ring structure of human BNP, respectively and measures BNP by sandwiching it between the two antibodies without the need for prior plasma extraction (Yasue et al. 1994).

7.2.1 Definitions

Hypertension: current treatment with antihypertensive medication and/or a systolic blood pressure >160 mmHg and/or a diastolic blood pressure >95 mmHg.

Hypertension [JNC VI]: as above, but using the cut-off points for blood pressure as defined in JNC VI guidelines (Joint National Committee on Prevention, Evalaution and Treatment of High Blood Pressure 1997) which are a systolic blood pressure of $\geq$140mmHg and/or a diastolic blood pressure $\geq$ 90mmHg.

Ischaemic Heart Disease: the presence of one or more of: (1) a prior physician-made diagnosis of myocardial infarction or angina; (2) the current use of nitrates; (3) ECG

evidence of possible ischaemic heart disease according to the Minnesota coding system using codes for pathological Q waves (1.1, 1.2, 1.3) , ST segment depression (4.1, 4.2, 4.3, 4.4), or left bundle branch block (7.11).

Abnormal E.C.G. – defined as the presence of atrial fibrillation or atrial flutter (8.31,8.32), or Q waves (1.1, 1.2, 1.3), or ST segment depression (4.1, 4.2, 4.3, 4.4), or left bundle branch block (7.11) , or left ventricular hypertrophy (3.1, 3.3, 3.4) or T wave inversion (5.1, 5.2, 5.3).

Cardiac breathlessness - reported as breathlessness on the M.R.C. questionnaire (Fletcher et al. 1959) in the absence of symptoms of chronic bronchitis - defined as breathlessness associated with a cough occurring on most days during at least three winter months each year.

Left Ventricular Systolic Dysfunction: a measurable L.V.E.F. of 35% or less.

Symptomatic L.V. Systolic Dysfunction: a measurable L.V.E.F. of 35% or less and either reported cardiac breathlessness or current treatment with a loop diuretic.

Asymptomatic L.V. systolic Dysfunction: a measurable L.V.E.F. of 35% or less in the absence of both reported cardiac breathlessness and current treatment with a loop diuretic.

Increased L.V. mass, mass index and relative L.V. wall thickness (R.Th.) : >97.5[th] percentile for each measurement in a healthy subgroup - an L.V. mass >364.0g in males, and >242.8g in females; an L.V. mass index > 210.6g/m in males, and >151.8g/m in females; and a R.Th. >0.67 in both sexes.

7.2.2 Statistical Analysis

Statistical analyses were performed using Minitab for Windows (Minitab Inc, Pennsylvania, U.S.A.) . Variables with normal distributions are described by the mean and the standard deviation (S.D.) and means were compared using a two sample t test.

Variables with a skewed distribution which could not be transformed easily were described by the median value and interquartile range. Medians were compared using the Mann-Whitney U test. The proportions of individuals in two groups were compared by the Chi-square test or where appropriate Fisher's exact test. Univariate and multivariate linear regression analyses were used to determine the relationship between a variable or a set of variables and a single outcome.

A P value of <0.05 was taken to be significant.

7.3 Results

7.3.1 Natriuretic peptides in the whole population

Median peptide levels and ranges for the whole population are shown in Table 7-1. BNP measured by the Shionoria I.R.M.A. method (Sh-BNP) showed the greatest spread with values ranging from 1.0 to 750.0 pg./ml. The correlation between N-ANP and BNP and between N-ANP and Sh-BNP was only moderate; r= 0.59 and 0.63 respectively - Figure 7-1. The two methods of measuring BNP correlated reasonably well (r= 0.81) - but the Sh-BNP tended to yield higher results in the same individual with the regression equation being Sh-BNP = 2.41(BNP) - 4.61. However, a plot of the agreement between paired BNP measurements – Figure 7-2 , using the method described by Bland and Altman (Bland and Altman, 1986), shows that the difference in results obtained by the two assays increases linearly with increasing concentrations of BNP. Logarithmic transformation does not alter this linear relationship and so the limits of agreement between the assays cannot be meaningfully calculated (Bland and Altman, 1986).

There was no difference in median values for the three natriuretic peptide

Table 7-1 - Natriuretic Peptide Measurements in the Population According to Presence or Absence of Left Ventricular Systolic Dysfunction

N-ANP (ng/ml)

	Median	Interquartile Range	Range
All	2.27	1.50 - 3.76	0.20 - 20.51
No L.V.D.	2.24	1.49 - 3.53	0.32 - 12.59
L.V.D.	3.89**	1.82 - 7.64	0.70 - 16.40

BNP (pg.ml)

	Median	Interquartile Range	Range
All	13.60	8.90 - 22.33	1.00 - 247.40
No L.V.D.	13.30	8.50 - 20.98	1.00 - 247.40
L.V.D.	39.35**	16.97 - 68.37	2.80 - 224.00

Sh-BNP (pg./ml)

	Median	Interquartile Range	Range
All	23.0	12.0 - 45.0	1.0 - 750.0
No L.V.D.	22.0	12.0 - 41.0	1.0 - 586.0
L.V.D.	69.0**	4.0 - 226.0	2.0 - 750.0

* P<0.05   ** P<0.001 compared with No L.V.D. group

Figure 7-1 - Correlation Between N-ANP and BNP Levels in Whole Population
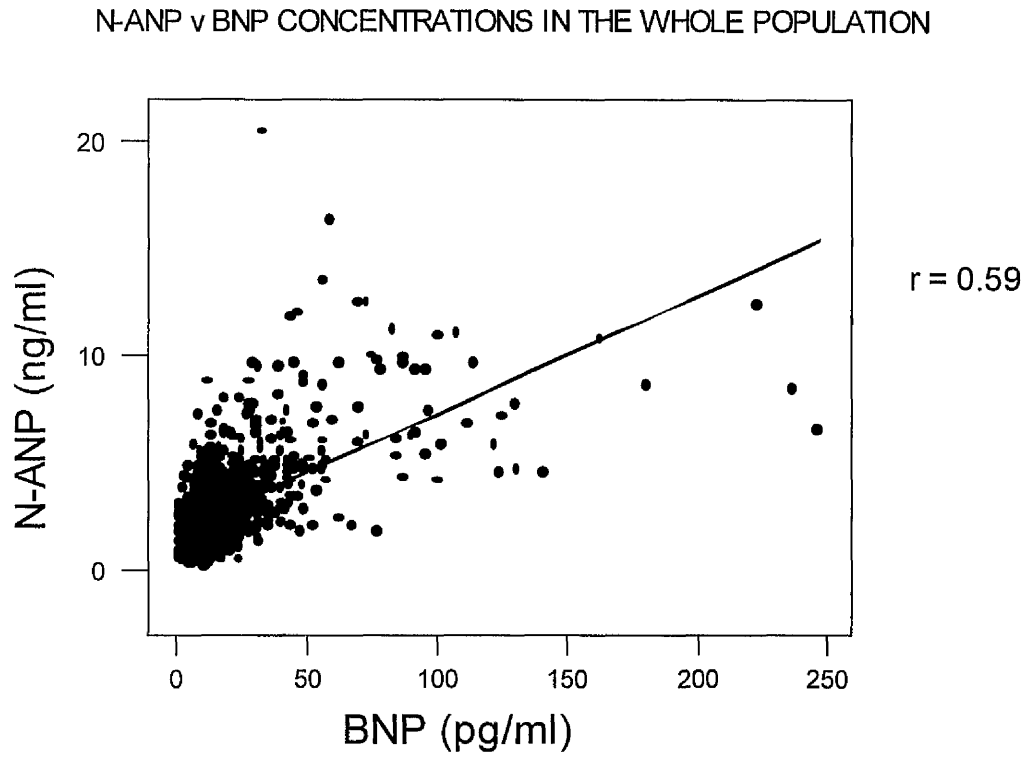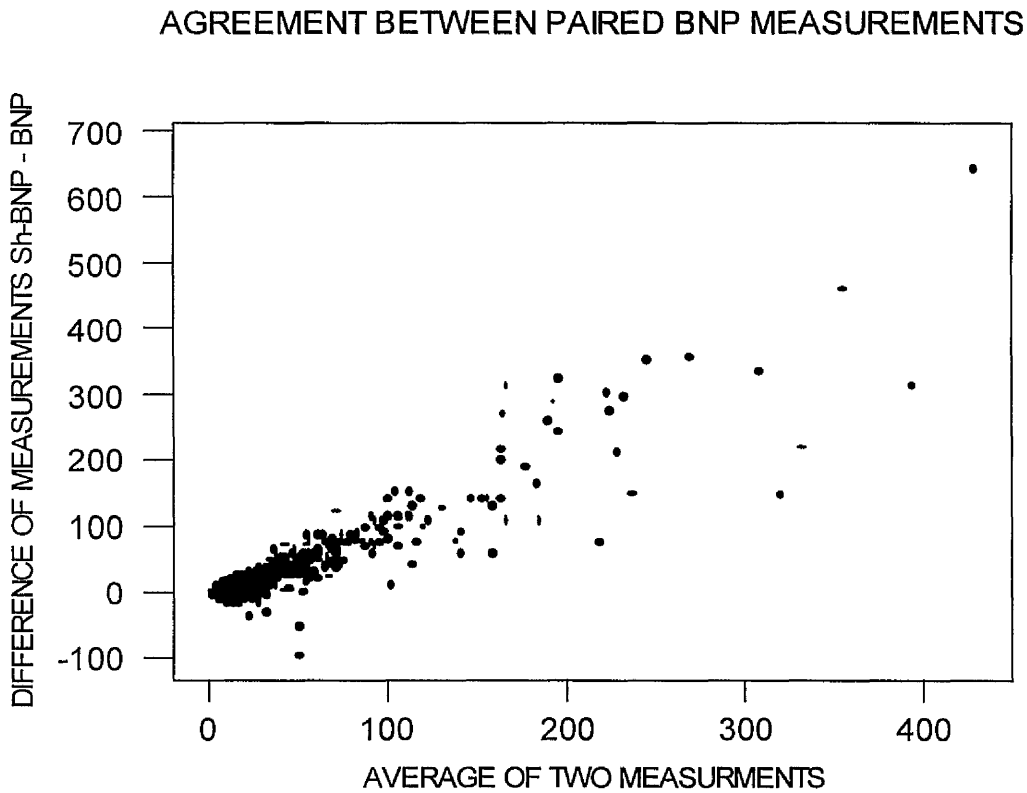
N-ANP v BNP CONCENTRATIONS IN THE WHOLE POPULATION

Figure 7-2 – Plot of Agreement Between Paired BNP Measurements by Penninsula (BNP) and Shionoria (Sh-BNP) Assays

AGREEMENT BETWEEN PAIRED BNP MEASUREMENTS

measurements between individuals with and without a measured L.V. ejection fraction.

7.3.2 L.V. Systolic Dysfunction and Natriuretic Peptides

The presence of L.V.D. was associated with significantly higher levels of all three peptide measurements - Table 7-1 & Figure 7-3. Of the 50 people with systolic dysfunction 23 were by definition symptomatic and their median L.V.E.F. was lower than those who were asymptomatic - 28.0% (24.0 - 32.0) v 33.0% (28.7 - 34.7), P=0.003 - but there was no significant difference in the median levels of the three peptides - Table 7-2.

The need for treatment with loop diuretics in fifteen individuals with L.V.D. was associated with a lower median L.V.E.F. than in those not receiving such treatment - 27.7% (21.0 - 32.0) v 32.3% (28.7 - 34.3) , P=0.009. Higher levels of circulating N-ANP were found in the treated group - 6.20 (3.10 - 10.80) ng/ml v 3.37 (1.66 - 4.72) ng/ml, P=0.03 - but whilst the levels of BNP and Sh-BNP also tended to be higher these differences did not reach statistical significance.

7.3.3 Using Natriuretic Peptides As A Screening Blood Test to Detect the Presence of L.V. Systolic Dysfunction

Receiver operating characteristic (R.O.C.) curves - Figure 7-4 - show that as a screening test for the presence of L.V.D. within the whole population a BNP at a concentration of 15.2 pg./ml performs best of the three peptides with a sensitivity of 82.0% and a specificity of 57.6% - Table 7-3. N-ANP proved to be the worst. The negative predictive value of BNP was high (97.8%) but the positive predictive value was very low (12.3%).

Figure 7-3 - B.N.P. Concentrations in Normal and in Impaired L.V. Systolic Function.

BNP CONCENTRATIONS IN NORMAL AND IMPAIRED LV FUNCTION
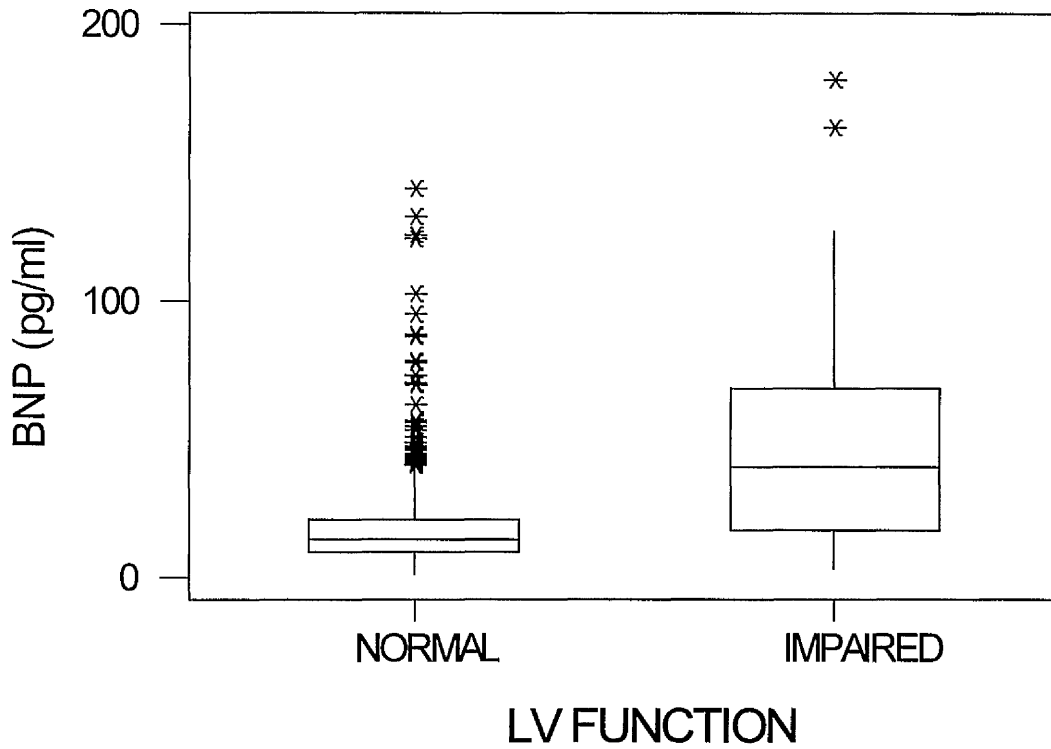
Notes: Impaired L.V. Function = L.V. Ejection Fraction ≤ 35%.

Table 7-2 - Natriuretic Peptide Levels in Left Ventricular Systolic Dysfunction

Symptomatic L.V. Systolic Dysfunction

	Median	I.Q. Range	Range
L.V.E.F (%)	28.0	24.0 - 32.0	12.0 - 34.0
N-ANP (ng/ml)	4.73	2.37 - 9.78	1.09 - 16.40
BNP (pg./ml)	43.0	21.3 - 84.3	7.8 - 180.5
Sh-BNP (pg./ml)	113.0	40.0 - 323.4	2.5 - 750.5

Asymptomatic L.V Systolic Dysfunction

	Median	I.Q. Range	Range
L.V.E.F. (%)	33.0	28.7 - 34.7	18.7 - 35.0
N-ANP (ng/ml)	3.37	1.66 - 4.72	0.70 - 12.50
BNP (pg./ml)	29.8	14.3 - 53.0	2.8 - 224.0
Sh-BNP (pg./ml)	51.9	21.9 - 155.5	3.4 - 445.6

L.V. Systolic Dysfunction Treated with Loop Diuretics

	Median	I.Q. Range	Range
L.V.E.F. (%)	27.7	21.0 - 32.0	12.0 - 34.0
N-ANP (ng/ml)	6.20	3.10 - 10.80	1.09 - 12.60
BNP (pg./ml)	49.3	31.0 - 100.7	11.3 - 162.6
Sh-BNP (pg./ml)	145.8	51.0 - 333.5	2.5 - 750.5

Figure 7-4 - Receiver Operator Characteristic Curves for Natriuretic Peptides to Detect L.V. Dysfunction in Whole Population

N-ANP v BNP TO DETECT LEFT VENTRICULAR DYSFUNCTION
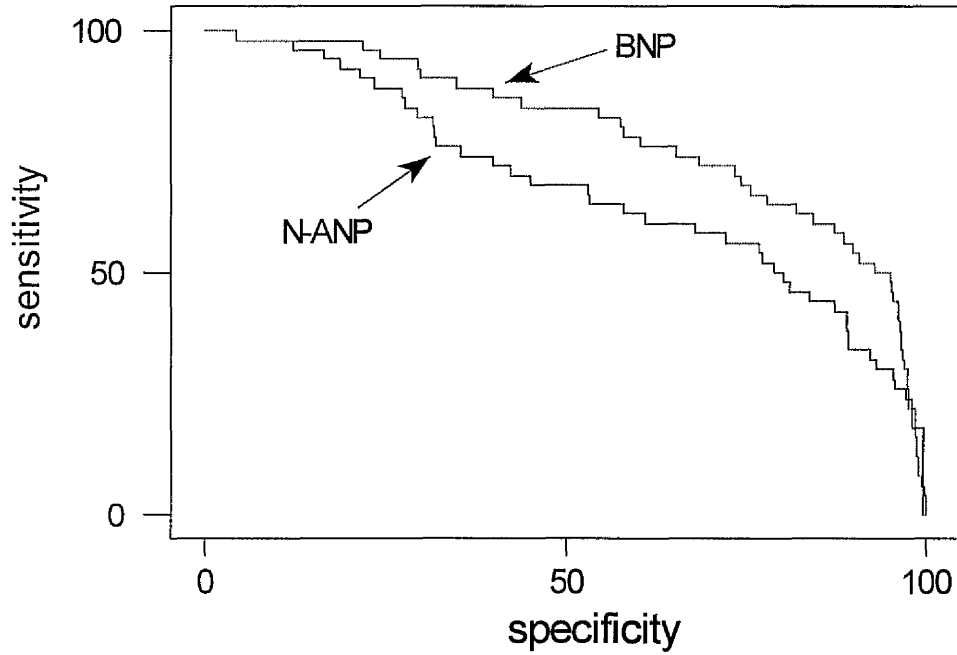
BNP v Sh-BNP TO DETECT LEFT VENTRICULAR DYSFUNCTION

Table 7-3 - Concentrations of Natriuretic Peptides for Screening for L.V. Dysfunction Within the Population

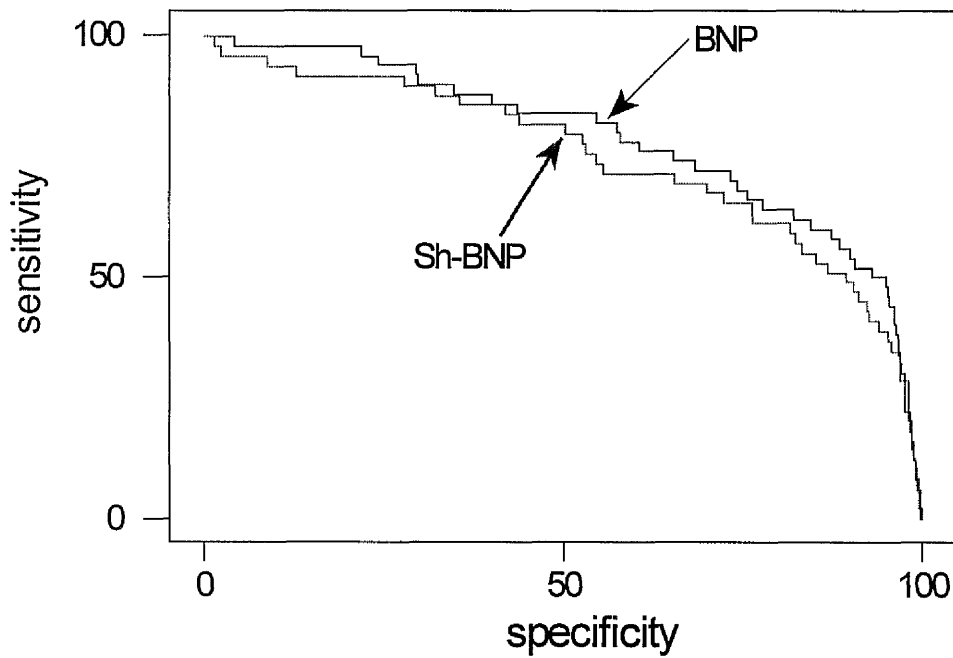| Peptide	Conc.	Sensitivity	Specificity	P.P.V.	N.P.V.
N-ANP	1.73 ng/ml	80.0%	31.8%	7.8%	95.6%
BNP	15.20 pg./ml	82.0%	57.6%	12.3%	97.8%
Sh-BNP	22.0 pg./ml	81.6%	50.2%	10.6%	97.4%

Table 7-4 - Concentrations of Natriuretic Peptides for Screening for L.V. Dysfunction Within Breathless Individuals

Peptide	Conc.	Sensitivity	Specificity	P.P.V	N.P.V.
N-ANP	1.84 ng/ml	84.0%	38.3%	16.0%	94.5%
BNP	16.0 pg./ml	88.0%	56.9%	22.2%	97.1%
Sh-BNP	24.0 pg./ml	79.2%	51.8%	18.7%	94.7%

Table 7-5 - Concentrations of Natriuretic Peptides for Screening for L.V. Dysfunction In Individuals With Evidence of Ischaemic Heart Disease

Peptide	Conc.	Sensitivity	Specificity	P.P.V.	N.P.V.
N-ANP	1.45 ng/ml	94.9%	16.6%	14.5%	95.6%
BNP	8.30 pg./ml	97.4%	20.5%	15.5%	98.2%
Sh-BNP	20.0 pg./ml	92.1%	36.9%	17.9%	96.9%

Table 7-6 - Concentrations of Natriuretic Peptides for Screening for L.V. Dysfunction In Individuals With A Previous Myocardial Infarction

Peptide	Conc.	Sensitivity	Specificity	P.P.V.	N.P.V.
N-ANP	2.04 ng/ml	91.3%	30.8%	36.4%	89.1%
BNP	11.0 pg./ml	100.0%	21.2%	35.5%	100.0%
Sh-BNP	18.0 pg./ml	100.0%	30.6%	38.5%	100.0%

Notes:
P.P.V. - Positive Predictive Value   N.P.V. - Negative Predictive Value

The three peptide measurements were examined in a group of 204 individuals with breathlessness, whether of cardiac or respiratory origin, all of whom had a measured L.V.E.F.. L.V.D. was present in 25 people (12.4%). Once again BNP, at a level of 16.0 pg./ml, performed best as a screening test with a sensitivity of 88.0% and a specificity of 56.9% and N-ANP fared worst - Table 7-4 & Figure 7-5.

The three peptides were also examined in a high risk group for L.V.D. namely the 301 individuals with evidence of I.H.D. and a measured L.V.E.F.; a subgroup of which reported a previous myocardial infarction (76 people). The prevalence of L.V.D. was 13.0% in the I.H.D. group as a whole and 30.3% in the subgroup with a previous M.I.. The sensitivity of BNP at a concentration of 8.3 pg./ml to detect L.V.D. rose to 97.4% although the specificity was only 20.5% - Table 7-5 & Figure 7-6. The negative predictive value was high at 98.2%. The sensitivity and the negative predictive value were both higher in the previous M.I. subgroup - both 100% for a BNP of 11.0 pg./ml - Table 7-6 & Figure 7-7. In the previous M.I. subgroup Sh-BNP performed even better than BNP with a higher specificity and positive predictive value - 30.6% and 38.5% respectively. N-ANP was inferior to BNP and Sh-BNP in all respects.

7.3.4 Additional Information from E.C.G. Findings For Screening

Figures 7 – 8 and 7 - 9 show possible strategies for screening for the presence of L.V. systolic dysfunction in our cohort; including only the 738 indivdiuals with both a measured L.V.E.F. and a BNP. These strategies would involve everyone having both a BNP measured and an ECG recorded. By only measuring BNP, and echoing individuals found to have a level >15.2 pg/ml, one would miss nine of the 50 cases of L.V.D.. By only performing an E.C.G. and echoing the individuals with an abnormal

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*Figure 7-5 - Receiver Operator Curves For BNP and Sh-BNP to Detect L.V.
Dysfunction in Breathless Individuals*

BNP v Sh-BNP TO DETECT L.V. DYSFUNCTION IN UNSPECIFIED DYSPNOEA
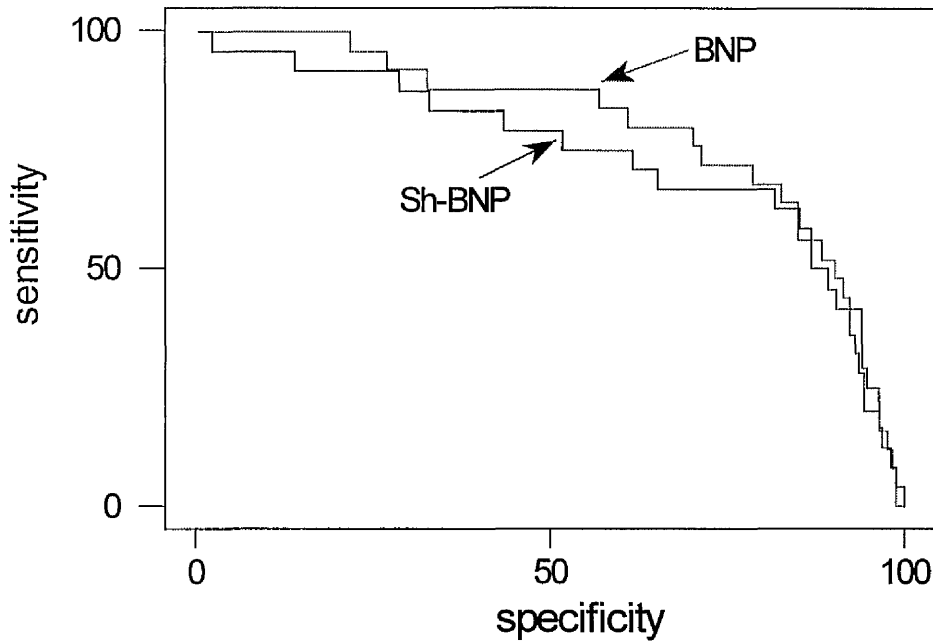
*Figure 7-6 - Receiver Operator Characteristic Curves for BNP and Sh-BNP to
Detect L.V. Dysfunction in Ischaemic Heart Disease*

BNP v Sh-BNP TO DETECT LV DYSFUNCTION IN I.H.D.

Figure 7-7 - Receiver Operator Curves for BNP and Sh-BNP to Detect L.V. Dysfunction in Individuals With Previous M.I.

BNP v Sh-BNP TO DETECT L.V. DYSFUNCTION IN SELF-REPORTED PREVIOUS MI.
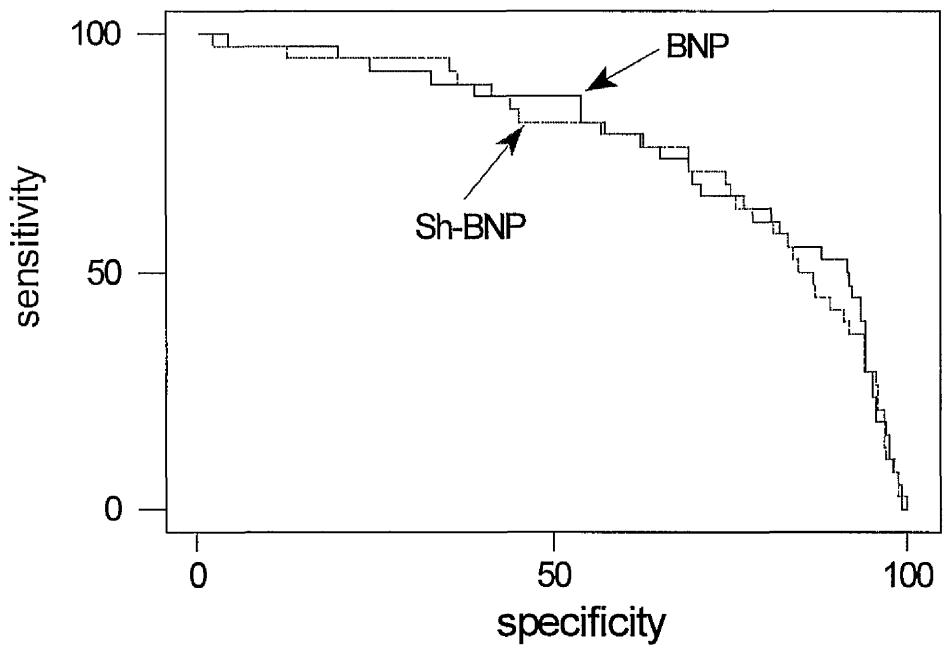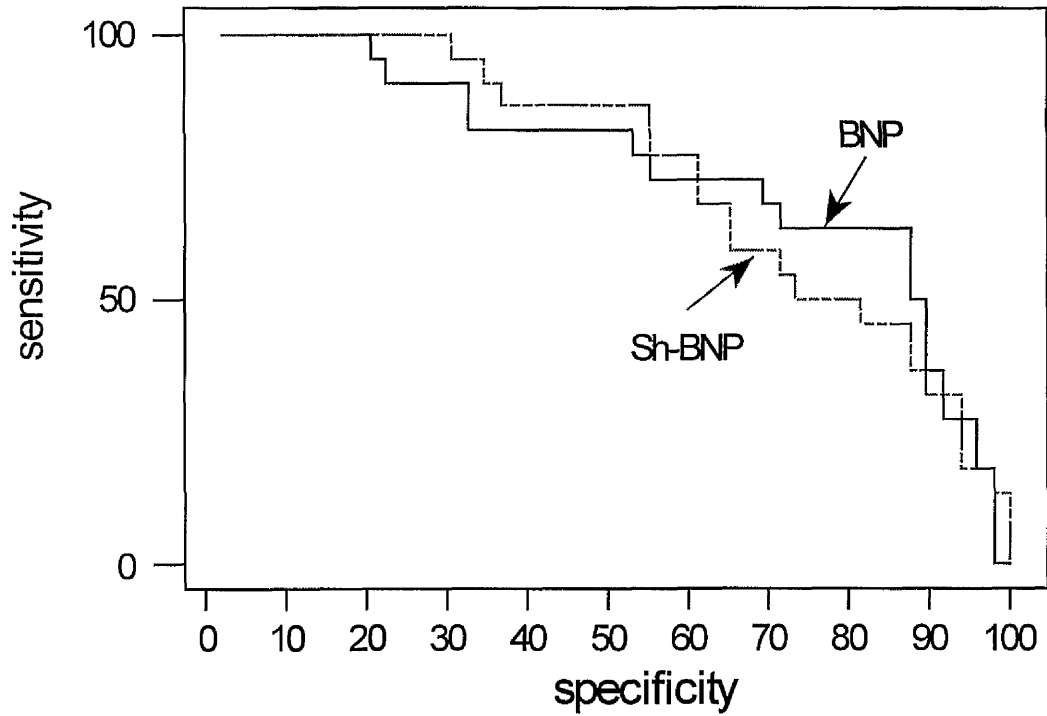
Figure 7-8 Possible strategy for screening the population for L.V. systolic dysfunction using BNP and an E.C.G
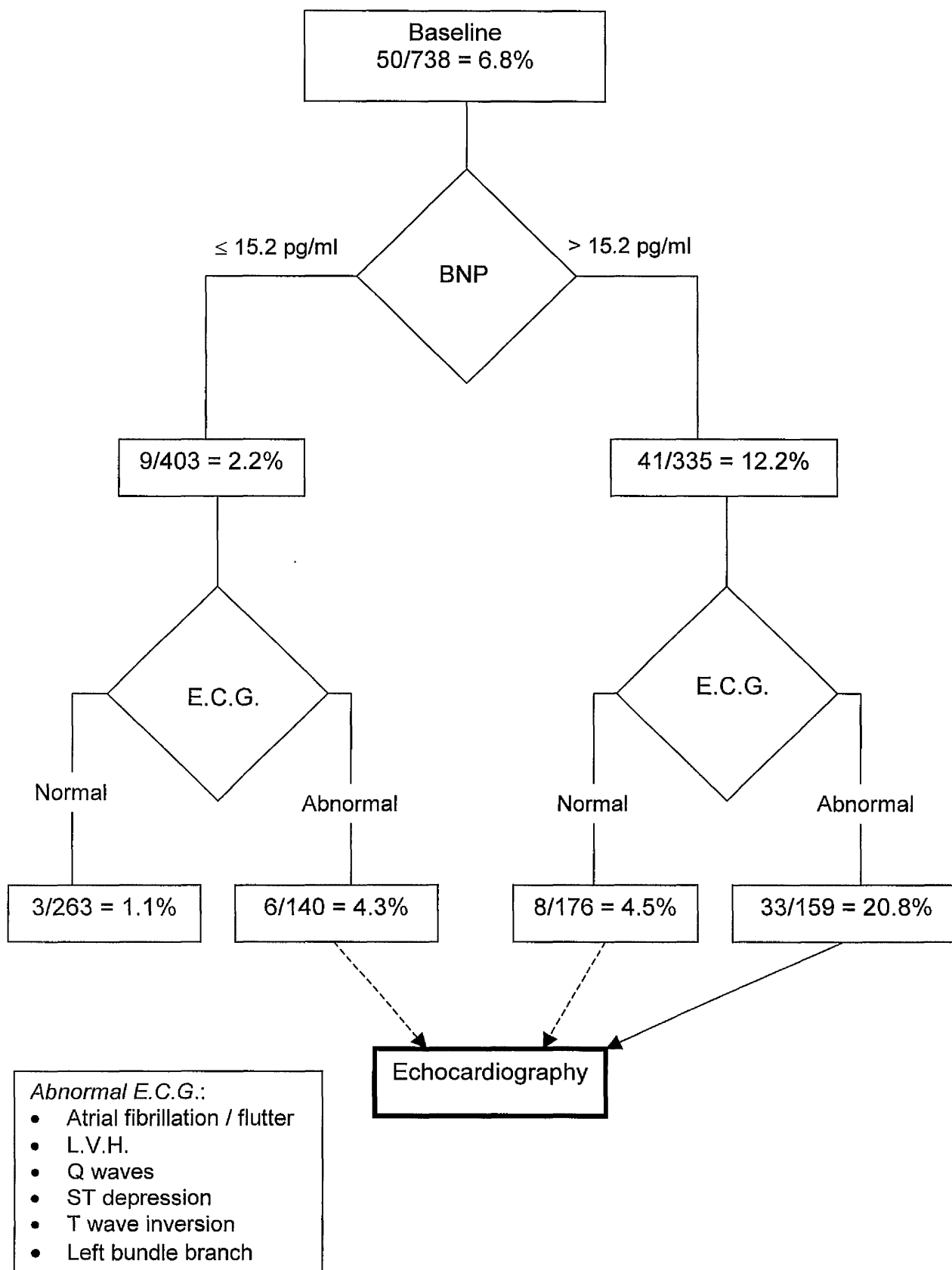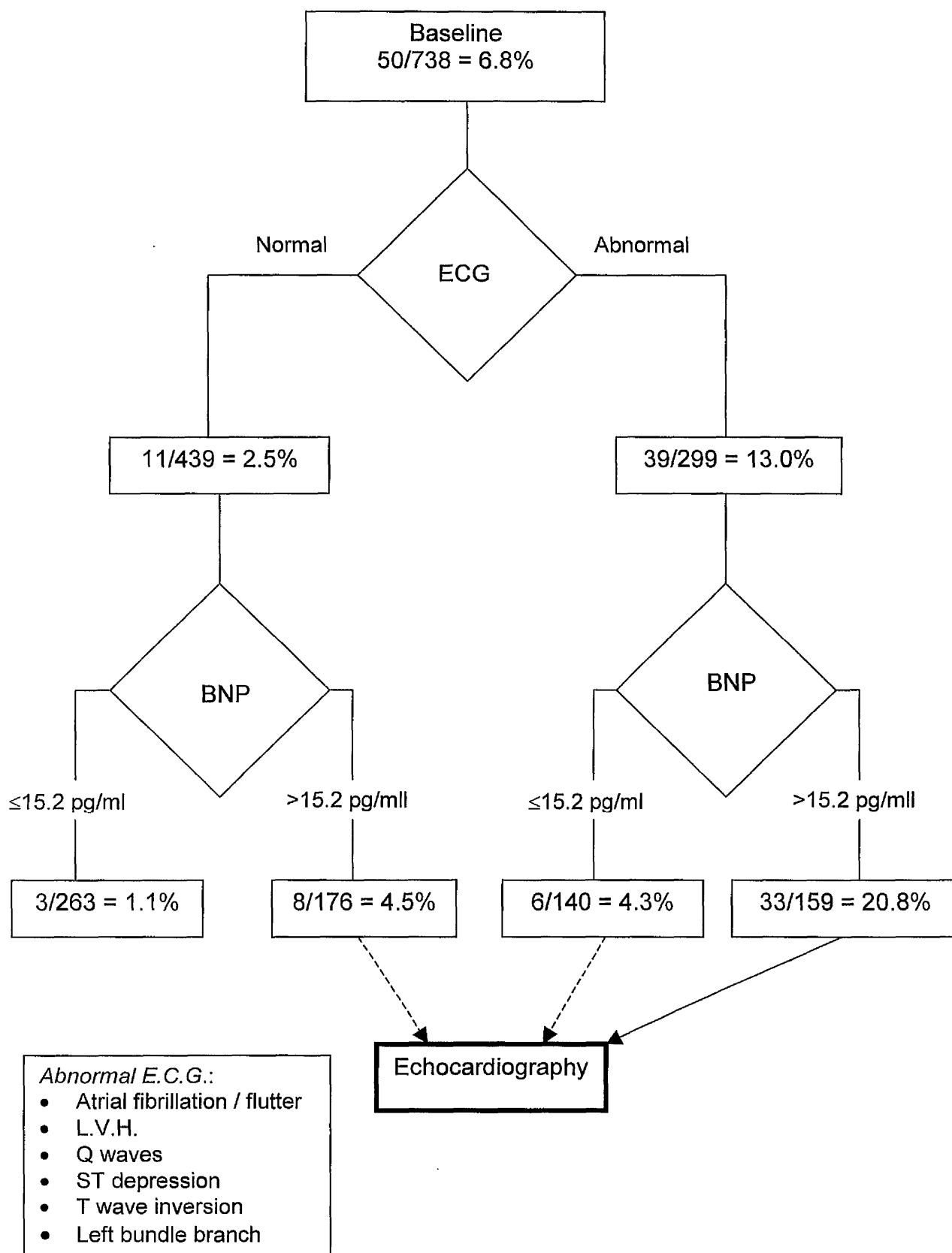
Figure 7-9 Possible strategy for screening the population for L.V. systolic dysfunction using BNP and an E.C.G

E.C.G. (as defined above) we would miss eleven of the cases of L.V.D.. If however we performed both, and did not refer for echocardiography individuals with both a normal E.C.G. and a BNP level ≤ 15.2pg/ml, this would detect 47 of the 50 cases (94%) of L.V.D, but at a saving of 263 fewer (35.6% fewer) echocardiograms.

7.3.5 Effects of Increased L.V. Mass

Compared with the remainder of the cohort the 42 people, with an increased L.V. mass had higher median plasma levels of all three peptide measurements Table 7-7: N-ANP 3.04 (2.01 − 6.16) ng/ml v 2.25 (1.52 - 3.38) ng/ml, P=0.002 ; BNP 18.60 (11.40 - 54.10) pg./ml v 13.60 (98.50 - 21.80) pg./ml, P=0.004 and Sh-BNP 32.0 (16.5 − 168.0) pg/ml v 21.0 (11.0 − 43.3) pg/ml. An increased L.V. mass index was found in 44 people and they had higher median levels of both N-ANP 2.88 (1.88 − 4.97) ng/ml v 2.26 (1.51 - 3.60) ng/ml, P=0.011 and Sh-BNP 28.0 (16.0 − 167.0) pg./ml v 21.0 (11.0 - 42.5) pg./ml, P=0.010. An increased relative L.V. wall thickness was found in 21 individuals but they did not show any difference in the levels of any of the natriuretic peptides.

7.3.6 Determinants of Natriuretic Peptide Levels Within the Population

The effect of a number of clinical variables on natriuretic peptide levels within the population was analysed by univariate regression analyses - Table 7-8. For all three peptide measurements age, systolic blood pressure, pulse pressure, L.V. mass, L.V. mass index, peak E wave velocity and E:A ratio were positively associated and the L.V.E.F. negatively associated. In addition mean blood pressure was positively associated with both N-ANP and BNP levels, and the mitral valve deceleration time was positively associated with N-ANP levels. Combining those variables which were significant in univariate analysis into a multivariate analysis - Table 7-9 - showed that

Table 7-7 - Natriuretic Peptide Levels in Normal And Increased Left Ventricular Mass

	N-ANP (ng/ml)	BNP (pg/ml)	Sh-BNP (pg/ml)
Normal L.V. Mass	2.25 (1.52 – 3.38)	13.60 (8.50 – 21.80)	21.0 (11.0 – 43.3)
High L.V. Mass	3.04* (2.01 – 6.16)	18.60* (11.40 – 54.10)	32.0* (16.5 – 168.0)
Normal L.V. Mass Index	2.26 (1.51 – 3.60)	13.80 (8.80 – 22.22)	21.0 (11.0 – 42.5)
High L.V. Mass Index	2.88* (1.88 – 4.97)	14.00 (11.10 – 49.30)	28.0* (16.0 – 167.0)
Normal R.Th.	2.27 (1.57 - 3.80)	13.80 (9.10 - 22.95)	21.0 (11.4 - 46.1)
High R.Th.	2.62 (1.71 - 3.02)	15.00 (11.30 - 25.00)	23.4 (18.1 - 74.7)

* $P<0.05$ ** $P<0.001$

Table 7-8 - Determinants of Natriuretic Peptides Within the Population. Univariate Analysis

	N-ANP		BNP		Sh-BNP	
	P	R² %	P	R² %	P	R² %
Age (Yrs)	<0.001 +	7.8	<0.001 +	4.7	<0.001 +	4.1
L.V.E.F. (%)	<0.001 -	5.3	<0.001 -	10.8	<0.001 -	11.8
SBP (mmHg)	<0.001 +	1.3	<0.001 +	1.9	0.002 +	1.2
DBP (mmHg)	0.486		0.568		0.670	
MAP (mmHg)	0.041 +	0.3	0.032 +	0.5	0.140	
Pulse P (mmHg)	<0.001+	2.2	<0.001 +	3.1	<0.001 +	1.8
LV Mass (g) Male	0.028 +	2.5	0.001 +	5.9	<0.001 +	12.0
Female	<0.001 +	11.3	<0.001 +	10.2	<0.001 +	16.9
LV Mass Ind. Male	0.044 +	2.0	0.007 +	4.1	<0.001 +	9.9
(g/m) Female	<0.001 +	10.6	<0.001 +	11.0	<0.001 +	16.7
R.Th.	0.984		0.915		0.741	
Peak E (ms⁻¹)	<0.001 +	6.8	<0.001 +	4.2	<0.001 +	4.6
Peak A (ms⁻¹)	0.401		0.177		0.286	
E:A	<0.001 +	2.7	<0.001 +	7.9	<0.001 +	8.0
M.V.D.T. (msecs)	0.010 +	0.6	0.342		0.052	

+ Positive association

- Negative association

Notes:

SBP - Systolic Blood Pressure   DBP - Diastolic Blood Pressure

MAP - Mean Arterial Pressure   Pulse P - Pulse Pressure

LV Mass Ind. - L.V. Mass Index   R.Th. - L.V. Relative Wall Thickness

R^2 (adj) = the square of the multivariate correlation coefficient adjusted for the expected chance prediction when the null hypothesis is true. It indicates how much of the variation is explained by the factors in the model.

Table 7-9 - Determinants of Natriuretic Peptides Within the Population Multivariate Analysis

Males

	P Values		
	N-ANP	**BNP**	**Sh-BNP**
Age (Yrs)	0.001 +	0.019 +	0.005 +
LVEF (%)	0.495	0.001 -	0.035 -
LV Mass Ind. (g/m)	0.051	0.033 +	<0.001 +
E:A Ratio	0.012 +	<0.001 +	<0.001 +
R^2(adj)	12.1%	25.2%	33.2%

Females

	P Values		
	N-ANP	**BNP**	**Sh-BNP**
Age (Yrs)	<0.001 +	0.001 +	<0.001 +
LVEF (%)	0.004 -	<0.001 +	<0.001 +
LV Mass Ind. (g/m)	0.003 +	0.001 +	<0.001 +
E:A Ratio	<0.001 +	<0.001 +	<0.001 +
R^2(adj)	36.4%	33.8%	56.4%

Notes:

+ Positive association
 - Negative association

R^2 (adj) = the square of the multivariate correlation coefficient adjusted for the expected chance prediction when the null hypothesis is true. It indicates how much of the variation is explained by the factors in the model.

for all three peptides age and E:A ratio were positively associated and L.V.E.F. was negatively associated. The L.V. mass index was positively associated with the three peptides in females but in males it just failed to reach a significant association with N-ANP but was significantly associated with BNP by both assays. The degree to which these four variables described variation in the three peptide measurements varied. In females they described a greater degree of the individual variation than in males.

None of the blood pressure variables remained significant in multivariate analysis. The peak velocity of the transmitral Doppler E wave remained significant in multivariate analysis but the inclusion instead of the E:A ratio explained a greater degree of the variation in peptide levels.

7.4 Discussion

This present study shows that concentrations of peptides in the population are affected independently by age, L.V. systolic function, L.V. mass and transmitral Doppler indices of L.V. diastolic filling.

With regard to the effect of age on peptide levels these results agree with the results of previous studies showing that levels of ANP increase with age independent of any changes in L.V. mass or blood pressure (Flickinger et al. 1995; Pontremoli et al. 1993; Dutka et al. 1996). By univariate analysis age appeared to explain a greater degree of variation in levels of N-ANP (R^2=7.8%) than BNP (R^2=4.7%) or Sh-BNP (R^2=4.1%). In one study over a wider age range, approximately 55 years, age accounted for ~ 12 to 13% of the interindividual variation in plasma ANP (Flickinger et al. 1995). It has also been shown that the ANP response to saline loading is exaggerated in older

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individuals (Tan et al. 1990) and taken together these results support the theory that as ventricular compliance decreases with age both atrial and ventricular pressures rise acting as a stimulus for the release of natriuretic peptides.

7.4.1 Left Ventricular Systolic Dysfunction

Elevated levels of both N-ANP and BNP in L.V.D. have been shown by other studies (Wei et al. 1993; Burnett et al. 1986; Cody et al. 1986; McDonagh et al. 1998; Dickstein et al. 1995; Lerman et al. 1993; Davidson et al. 1996; Friedl et al. 1996). There were however certain differences between the findings of these studies and this current study. Firstly there was no difference in peptide levels between individuals with symptomatic and asymptomatic L.V.D. even although the symptomatic group had a lower median ejection fraction. Other studies have shown that N-ANP levels are higher in symptomatic individuals (Lerman et al. 1993) and correlate with the severity of symptoms (Dickstein et al. 1995; Wei et al. 1993; Lerman et al. 1993). The reason for the lack of any difference in this current study is likely to be in part due to the small number of individuals with L.V.D. within each group and the wide spread of peptide levels. In addition the severity of symptoms were not quantified and so it could have been that all the symptomatic group were in N.Y.H.A. class II i.e. only mildly symptomatic. When the subgroup currently treated with loop diuretics were specifically looked at higher levels of N-ANP were found compared with the untreated group. The treated group had a lower median L.V.E.F. although the magnitude of this difference is no greater than that seen between the symptomatic and asymptomatic groups. It is likely that, regardless of the L.V.E.F., the need for treatment with a loop diuretic is a marker of greater symptoms and higher L.V. filling and pulmonary artery pressures, both of which have been shown to correlate with higher N-ANP levels (Mathisen et al. 1993; Dickstein et al. 1995).

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7.4.2 Use of Peptides as Screening Tools for L.V. dysfunction

Like previous studies (McDonagh et al. 1998; Cowie et al. 1997b; McClure et al. 1998; Davidson et al. 1996; Friedl et al. 1996) this study has shown that BNP was a better marker for the presence of L.V.D. than N-ANP within the whole population, within breathless individuals, and within a high risk group. Comparing the two BNP assays, the results obtained by the Shionoria I.R.M.A. assay were inferior to the radioimmunometric assay (R.I.A.). The I.R.M.A. gave a much wider spread of values particularly in the higher range of values compared to the R.I.A.. The plot of agreement between the two measurements showed that the difference between the two assays increases with increasing levels of BNP; with the I.R.M.A. consistently giving higher measurements. One possible reason for this difference would be if the Shionoria I.R.M.A. had a certain amount of cross reactivity either a second part of the BNP molecule or with another molecule released along with BNP such as N-terminal pro-BNP (Hunt et al. 1995).

An ideal screening blood test should have distributions of values for normals and abnormals which are distinct from each other since the degree of any overlap will inversely correlate with the diagnostic accuracy. The ranges of peptide concentrations in this study population for those with and without L.V.D. show considerable overlap. In particular the group with no L.V.D. had several high levels of peptides. This will undoubtedly have reduced the discriminatory power of peptides.

There are a number of possible explanations for why there was such an overlap between the L.V.D. and no L.V.D. groups but the main reason is likely to be the fact that the "no L.V.D." group is not the same as a group of "normals" - free from cardiovascular

disease. A number of other cardiac conditions are known to be associated with elevated levels of both N-ANP and BNP including left ventricular hypertrophy - secondary to hypertension (Kohno et al. 1992; Kohno et al. 1995; Pontremoli et al. 1993), hypertrophic cardiomyopathy (Yoshibayashi et al. 1993), or aortic stenosis (Yoshibayashi et al. 1993) - diastolic dysfunction (Lang et al. 1994) and mitral incompetence. Non cardiac conditions including renal impairment and chronic obstructive pulmonary disease (Cheung and Kumana, 1998) as well a drugs including beta-blockers (Sanderson et al. 1995) may all cause elevations in BNP (Cheung and Kumana, 1998). All of these factors could not be adjusted for in this study.

Compared with other studies BNP did not perform as well in this current study cohort as a screening test for L.V.D. In a previous study within the same geographical area and age group (McDonagh et al. 1998) we found BNP to have a sensitivity of 89% and a specificity of 71% compared with 82.0% and 57.6% respectively in this study. The corresponding values for the negative and positive predictive accuracies in the earlier study were 99.2% and 18.0%, respectively, compared to 97.8% and 12.3% in this study. In the previous study there was a narrower range of values for the peptides in the L.V.D. and no L.V.D. groups and hence possibly the greater diagnostic accuracy. Other studies have achieved even better results than either of these studies but within selected populations e.g. from referrals to heart failure clinics (Cowie et al. 1997b) or from referrals for radionuclide ventriculography (Davidson et al. 1996). They have looked at symptomatic individuals who have sought medical attention and are therefore likely to have greater haemodynamic compromise, higher L.V. filling pressures and consequently higher peptide levels.

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Within a high risk population, individuals with I.H.D., BNP performed much better although the specificity was lower because cut-off values were chosen which gave greater sensitivity assuming that within a high risk population sensitivity was more important than specificity. Compared with our previous study (McDonagh et al. 1998) looking at a high risk group the negative predictive values were similar in this current study (98.2% v 98.5%) but the positive predictive value was lower (15.5% v 32.0%).

In symptomatic individuals BNP performed reasonably well with a high negative predictive value of 98.2% although again the positive predictive value was poorer. In acute dyspnoea an elevated BNP has been shown to have a sensitivity and specificity both in excess of 90% for detecting the presence of L.V.D. (Davis et al. 1994). However such acute left heart failure is likely to be characterised by much greater haemodynamic upset and neuroendocrine activation than the chronic, treated phase. This possibly explains the greater diagnostic accuracy of peptides in the acute setting.

In this present study, therefore, natriuretic peptides did not discriminate sufficiently between those with and without L.V.D. probably because of the high prevalence of other conditions which raise levels of one or both of the natriuretic peptides. This does not permit a diagnosis of L.V.D. to be based on the BNP result alone but in the context of screening within the general population it may identify those who need further investigation for possible cardiac dysfunction. In symptomatic patients and in high risk groups a BNP measurement has a very high negative predictive value and does therefore allow one to at least exclude the presence of L.V.D.. It is likely that if peptides are to be used then different cut-off levels will need to be used in different patient groups depending on the level of risk and whether individuals are symptomatic

or not.

The combination of E.C.G. findings and the BNP measurement in this cohort allows us to categorise people into three groups, and this may be useful in a strategy for screening the whole population. There is a group with a very low probability of L.V.D. (1.1%) and this is the group with both a normal E.C.G. and a BNP measurement less than the cut-off value (15.2 pg/ml). One could suggest that it would not be worthwhile performing routine echocardiography in this group. In this study that would mean performing 263 fewer echocardiograms at the expense of performing 439 E.C.G.s. There is a second group with a high probability (20.8%) of having L.V.D.; the group of individuals with both an abnormal E.C.G. and a BNP above the cut-off value. This group almost certainly merits echocardiography with one in five having L.V. systolic dysfunction. Finally there is the largest of the three groups; that is the group of individuals with one or other of the tests abnormal, which has an intermediate probability of having L.V.D. (4.3 to 4.5%). One could simply echo all of this intermediate group but that would still be a relatively expensive process. It is therefore this group that poses us with the challenge of further refining our screening algorithm.

Although we presented a strategy with everyone having both an E.C.G. and a BNP measurement performed, if we accept that we can only exclude the low prevalence group from echocardiography (normal E.C.G. and BNP ≤ 15.2 pg.ml), then there would only be a need to perform both tests in individuals where the first test, whether that be the E.C.G. or the BNP, is abnormal. If one found either one of the tests abnormal the individual could simply be referred for echocardiography. Performing an E.C.G. intially would mean peforming 738 E.C.G.s and subsequently 299 BNP measurements.

Measuring the BNP first would mean carrying out 738 assays and subsequently 403 E.C.G.s. Both strategies would involve performing 475 echocardiograms. The order in which tests were performed would depend largely on the relative costs of a BNP assay and an E.C.G., and the ease and availability of these tests in primary care.

7.4.3 Effects of Increased L.V. Mass and Hypertension

This study demonstrated that individuals with an increased L.V. mass or L.V. mass index (based on normal ranges for our cohort) have higher concentrations of both N-ANP and BNP. Multivariate analysis shows that the L.V. mass index is independently and positively associated with BNP levels in both sexes and with N-ANP in females.

Researchers have shown varying results regarding the relationship of L.V.H. to BNP and ANP. Most studies have shown, as has this one, that BNP is elevated in L.V.H. as evidenced by an increased L.V. mass or mass index (Kohno et al. 1992; Kohno et al. 1995; Yoshibayashi et al. 1993), and in one study, increased relative L.V. wall thickness. Treatment with angiotensin converting enzyme inhibitors has been shown to cause regression of this L.V.H. which is accompanied by a parallel reduction in BNP levels (Kohno et al. 1995). There is less agreement regarding the effects of L.V.H. on ANP. One study showed that unlike BNP there was no relationship between ANP and L.V. mass but found rather that in hypertensives it correlated with the degree of blood pressure elevation (Kohno et al. 1995). In another study ANP levels were elevated in L.V.H. correlating directly with the L.V. mass index and inversely with the relative L.V. wall thickness (Pontremoli et al. 1993). The effect of blood pressure on peptide levels in individual studies is even less clear but a meta-analysis of 17 case-control studies (Hollister and Inagami, 1991) concluded that there was no significant difference

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between normotensives and untreated hypertensives in the absence of target-organ damage and controlling for salt intake.

BNP appears, therefore, to be related to the severity of L.V.H. This is not a surprise in view of the ventricular origin of BNP. Since the stimulus to release of ANP is atrial stretch (Yasue et al. 1994) the mechanism for elevated levels in L.V.H. may be an increase in left atrial pressures secondary to reduced compliance and relaxation of the left ventricle. Although it has been shown already in this study (Chapter 6) that no difference could be found in transmitral Doppler indices between individuals with and without increased L.V. mass this does not rule out the presence of elevated left atrial pressures in L.V.H. since it was not possible in this study to differentiate between normal and pseudonormal Doppler patterns; the latter being associated with elevated left atrial pressures (Iga et al. 1990; Nishimura and Tajik, 1997).

In this study within the whole cohort the E:A ratio was independently and positively correlated with both BNP and N-ANP suggesting that as L.V. filling pressures increase the pressure overload stimulates release of both hormones. This has been shown to be true for individuals with L.V.D. where the presence of a restrictive pattern of transmitral Doppler indices is associated with a much greater elevation of both ANP and BNP than if absent (Yu et al. 1996). Other studies have shown that abnormalities of L.V. diastolic filling outside the context of systolic dysfunction and in the absence of L.V.H. are associated with elevations of ANP (Pontremoli et al. 1993; Wilkins et al. 1997) and BNP (Wilkins et al. 1997). In "pure" diastolic heart failure the levels of both correlate inversely with the E:A ratio (Lang et al. 1994). The possible explanation being that diastolic abnormalities stimulate release of ANP by increased atrial stretch as

a result of the left atrium contracting against a non-compliant ventricle and they stimulate BNP release by pressure overload of the heart because the left ventricular diastolic pressure is greater for any given volume (Lang et al. 1994).

8. General Discussion

8.1 Principle Findings of Study

This study showed that the prevalence of left ventricular systolic dysfunction (L.V.D.) in this geographical population was higher than previously shown (McDonagh et al. 1997) and higher than that found in other populations (Gardin et al. 1995; Morgan et al. 1999). It is likely that this is a real finding as the L.V.D. was associated with objective effort intolerance, impaired quality of life and with neuroendocrine activation.

The aetiological associate of the L.V.D. appears to be predominantly ischaemic heart disease (I.H.D.) as reported to be the case in the majority of studies performed in recent years (McDonagh et al. 1997; Kannel et al. 1994; Morgan et al. 1999; Gardin et al. 1995). Once again it has been shown that in as many as half of all cases this L.V.D. may be asymptomatic; although this is based on the subjective reporting of one symptom. More objective testing of effort capacity and possibly also quality of life reveals that this so-called asymptomatic dysfunction may actually be exerting a demonstrable effect on an individual's physical performance. Whilst diastolic dysfunction may be an important contributor to the clinical syndrome of heart failure this study was unable, using transmitral Doppler indices in an unselected population, to show a substantial effect. Neuroendocrine activation whilst being a feature of L.V.D. also appears to accompany other cardiovascular and non-cardiovascular conditions which limits the use of natriuretic peptide levels as a discriminatory blood screening test for L.V.D..

What do the two studies performed in this population - McDonagh's previous study (McDonagh et al. 1997) - and this current one tell us about the prevalence of L.V.D. in North Glasgow? If we ignore absolute values of L.V. ejection fraction used to define

L.V.D. and assume that systolic dysfunction in both studies was the same biological entity, then combining the L.V. function data gives a total study population of 1376 within the age range 55 to 74 years. The averaged prevalence of L.V.D. from the combined data is 4.5% in the 55 to 64 yrs age group and 7.2% in the 65 to 74 yrs age range with the corresponding prevalences for males being 6.2% and 9.7% and for females 2.9% and 4.7%.

8.2 Strengths of this study

This study was one of the largest echocardiographic studies of L.V. systolic function performed in this important age range and certainly the largest conducted in this age range in the U.K. Rather than resorting to a subjective or semi-quantitative assessment of L.V. systolic function by calculating an L.V. ejection fraction this study has been able to present an objective measurement which is universally understood. This has been done in an entirely random sample drawn from a well defined population which has been studied previously (McDonagh et al. 1997; Tunstall-Pedoe et al. 1994; Morrison et al. 1997; Smith et al. 1987) such that a large amount of background information is known about it. This study was able to present data on a well characterised cohort which like the background population had a high prevalence of risk factors for I.H.D. and subsequent L.V.D.. This study has been able to study L.V.D. as it presents in the community rather than in hospital series or clinical trials with a few surprises regarding its higher than expected prevalence.

The strength of such an epidemiological study is not only in reporting point prevalences but also in its ability to follow up. A cohort has been recruited, and study methods have been used which will allow follow-up studies to be carried out for a number of years. The Framingham Heart Study (Dawber et al. 1951) is successful because it has

continued to follow-up the same population using the same methods over a number of years. Follow-up studies will hopefully report on issues such as what was prognostically important rather than statistically important L.V.D.; what is the incidence of L.V.D. is this population; what factors determine outcome in L.V.D. and what factors predict its development in the first place?

8.3 Limitations of this study.

The power of this study was limited by two factors: the suboptimal response rate and reduced availability of a measured L.V. ejection fraction. The first of these factors could be improved only by use of community venues for the study rather than one central point. This is now becoming a reality with the advent of portable echocardiographic equipment. The second is partly dependent on the skill and training of the echocardiographer and partly on the age and body habitus of the respondents. Through a process of supervision and training it was felt that the first issue had been covered but perhaps the number of suitable images obtained should have been reviewed periodically during the course of the study with quality and training issues addressed then.

The ability of this study to make statements about L.V.D. is limited by the size of the group with L.V.D.. This is true in any epidemiology study as opposed to a clinical study. McDonagh's study identified only 43 cases of L.V.D. from a screened population of 1640 (McDonagh et al. 1997) and the Cardiovascular Health Study after studying 5201 participants had only 195 cases with L.V. ejection fraction abnormalities (Gardin et al. 1995).

Were this study to be repeated then changes which should be considered would include

changing the definition of ischaemic heart disease to incorporate responses obtained from the administration of the Rose Chest pain questionnaire (Rose et al. 1977) and wider electrocardiographic criteria including the presence of T wave inversion. The likely effect of this would be to increase the prevalence of I.H.D. in the community and to possibly provide an aetiology for a greater proportion of the L.V.D. found.

The ability to study diastolic L.V. function in this study was limited by not having recorded Doppler signals from pulmonary vein flow and as stated elsewhere this may have caused the misclassification as normal of an unknown number of people with actually pseudonormal transmitral Doppler flows.

The use of symptom-limited treadmill testing limited the ability to determine effort capacity in a proportion of the individuals with L.V.D. and this could be avoided in future studies by use of the six-minute walk test.

8.4 Implications of The Study

The clinical syndrome of heart failure is a major public health problem in the Western world. It is associated with a significant morbidity and mortality and places a significant burden on the resources of an healthcare budget costing an estimated $10 billion to treat annually in the U.S. alone (Bennett et al. 1999). The syndrome is set to become more common as the population of the Western world ages and as more people survive following myocardial infarction (McMurray and Davie, 1996). We also know that treatment of L.V.D., the commonest cause of the syndrome, with angiotensin-converting enzyme (A.C.E.) inhibitors reduces the morbidity and mortality (Garg and Yusuf, 1995) whilst being cost-effective (McMurray and Davie, 1996). It is estimated

that some 60,000 deaths and 100,000 hospital admissions would be saved per year in the U.S. alone if all eligible patients were to receive A.C.E. inhibitor therapy (Packer, 1996a). This study and others have shown that at present not all eligible patients are being treated (O'Connell and Bristow, 1994; McMurray, 1998).

There is therefore a gap between available effective therapy and potential recipients. It is this gap that epidemiological studies such as this one, by identifying these recipients within the community, should be filling. Ideally one would wish to screen the whole population for L.V.D. by means of a blood test and treat them in primary care on the basis of the result. The results from this study would suggest that the use of BNP in such a setting lacks sufficient discriminatory power to allow treatment to be based on this result alone. Therefore, at present, we would still have to examine each individual by means of echocardiography to be able to make a confident diagnosis of L.V.D.. It is unlikely to be economically viable or practical to echo all of the community but using BNP, possibly in combination with E.CG., would reduce the number of individuals requiring to be echoed. Additionally we already know who the majority of people with L.V.D. within the community are. This study showed a gradient of risk for having L.V.D., from having had an M.I. diagnosed with a 30% chance, to having been diagnosed as having angina - 20% chance, to having any evidence of I.H.D. - 13% chance. All of the individuals with clinical I.H.D. were already known to primary care physicians. Further work is therefore required to refine the algorithms for screening to possibly take into account the presence of risk factors for L.V.D..

Finally we should come full circle in this thesis and say that if we know that the majority of L.V.D. is the result of I.H.D. then we must continue to put effort into

primary prevention with regard to I.H.D. In this inner city population that will not only

require education and perhaps pharmacological intervention but also a clear social and

economic policy.

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Appendix - Data Collection Forms

| PHR 01 | | Please affix sticker here |

PERSONAL HEALTH RECORD

(All information is confidential)

Please answer the questions in this record as far as you are able and bring it with you when you attend the examination. Please answer every question, as far as you can, (except those you are told to skip) and circle the box which applies to you. We cannot use those questions that you leave completely blank. If the answer in your case is 'No' or 'I don't know' you still need to show this on the paper. If you need any help, or have any questions, please ask when you come to the examination. Our nurses are there to help you, and one will check through the record with you.

Personal history

1.   (a)   Please circle the appropriate box   Male | 1 | Female | 2 |

     (b)   Date of birth   day | | | month | | | year | | |

     (c)   How many years have you lived in this town or within 10 miles of this town? | | | years

     (d)   Where were you born? Town/place   ....

                       County   ....

                       Country   ....

2.   Please circle the box showing your present marital status

| 1 | married | 4 | widowed

| 2 | cohabiting | 5 | divorced

| 3 | single | 6 | separated

3.   (a)   What is the highest level of education you have completed?

| 1 | university degree

| 2 | other professional or technical qualification or diploma after leaving school

| 3 | secondary school

| 4 | primary school

3. (b) How many years altogether have you gone to school or studied full-time from the age of 5 years? ☐☐ years

4. (a) Please circle the appropriate box about your employment situation.

☐ 1 in a full-time job

☐ 2 in a part-time job

☐ 3 unemployed, seeking work   if **unemployed and seeking work,** for how long have you been unemployed?

☐☐ years ☐☐ months

☐ 4 unemployed because sick or disabled

☐ 5 housewife/homemaker

☐ 6 wholly retired from employment

☐ 7 full-time student

(b) Please give full and precise details of your and your husband/wife's occupation (if unemployed now, give details of last job).

Your occupation .... _ _ _ _

Description of your work ....

Husband/wife's occupation .... _ _ _ _

Description of his/her work ....

(c) What is your and your partner's employment status? (If unemployed now, give details of last job.)

You   Husband/Wife

☐ 1   ☐ 1   employee not supervising other employees

☐ 2   ☐ 2   employee supervising other employees

☐ 3   ☐ 3   self-employed not employing others

☐ 4   ☐ 4   self-employed employing others

2

5. (a) How do you and your household occupy your accommodation?

    | 1 | as an owner-occupier (including purchase by mortgage)

    | 2 | by renting, or rent-free, or by lease from a local authority (council or New Town) or from a housing association

    | 3 | by renting or rent-free, from a private landlord or in some other way

    (b) If you are **owner-occupier**, is your house one which **you** previously rented from a local authority?

    | 1 | yes | 2 | no

Family history

6. Did your mother or father have heart disease before they were 60 years old?

    | 1 | yes | 2 | no | 3 | don't know

7. How many brothers and sisters did you have in your family (not counting yourself)? | | | brothers and sisters

8. Did any of your brothers and sisters have heart disease before they were 60 years old?

    | 1 | yes | 2 | no | 3 | don't know

9. How many children have you had (including any who died at birth or in childhood)?

    | | | children

3

Medical history

10. Have you ever been told by a doctor that you have, or have had any of the following? Circle **Yes** or **No** for each condition.

Yes	No	
1	2	angina
1	2	heart attack (coronary thrombosis, myocardial infarction)
1	2	high blood pressure
1	2	stroke
1	2	diabetes
1	2	high cholesterol

11. Are you now taking any medication for high blood pressure?

   1 yes   2 no

   If yes, please write the names of the medicine(s) you are taking:

   ....

   ....

12. Are you now taking any medication for high cholesterol?

   1 yes   2 no

   If yes, please write the name of the medicine you are taking:

   ....

13. Are you now taking aspirin regularly?

   1 yes   2 no   If **no**, go to question 14.

   If **yes**, is it for your heart?

   1 yes   2 no   3 don't know

If it is for your heart, why did you start taking it?

| 1 | the doctor told you to take it

| 2 | you decided for yourself

| 3 | other reason, please give details ....

14. (a) Are you regularly taking any other medication at present?

| 1 | yes | 2 | no

If **yes**, write the name of the medicine(s) and what you are taking them for (if you know). Please include all pills, bottles, tablets, inhalers (puffers), injections, etc.

....

....

....

....

(b) Are you regularly taking any vitamins, minerals or food supplements at present?

| 1 | yes | 2 | no

If **yes**, give the type of supplement, brand name and how often you take each one.

Type	Brand (and strength)	Frequency
....	....	....
....	....	....
....	....	....
....	....	....
....	....	....
....	....	....

Men miss out the next page and go to question 18

5

WOMEN ONLY
(men go to question 18 on next page)

15. (a) Are you pregnant now?

| 1 | yes | 2 | no

If no, have you ever been pregnant?

| 1 | yes | 2 | no   If **no**, go to question 16.

(b) How old were you when you had your first pregnancy? | | | years old

16. (a) Have you ever been on the contraceptive pill?

| 1 | yes   If **yes**, for how many years? | | | years

| 2 | no   If **no**, go to question 17.

(b) Are you on the contraceptive pill now?

| 1 | yes | 2 | no   If **no**, how long ago did you stop?

| | | years | | | months ago

17. (a) Are you still having periods (menstruating)?

| 1 | yes, as usual

| 2 | yes, but irregularly

| 3 | no   If **no**, how old were you when you stopped?

| | | years old

Was this because of a hysterectomy (surgical removal of the womb)?

| 1 | yes | 2 | no

(b) Have you ever taken hormone replacement therapy (HRT)?

| 1 | yes | 2 | no   If **yes**, for how many years? | | | years

If **no**, go to question 18.

(c) Are you on hormone replacement therapy (HRT) now?

| 1 | yes | 2 | no   If **no**, how long ago did you stop taking it?

[|] years   [|] months

Chest Pain

18. (a) Have you ever had any pain or discomfort in your chest?

| 1 | yes | 2 | no   If **no**, go to question 20

(b) Do you get this pain or discomfort when you walk uphill or hurry?

| 1 | yes | 2 | no

(c) Do you get it when you walk at an ordinary pace on the level?

| 1 | yes | 2 | no

(d) When you get any pain or discomfort in your chest, what do you do?

| 1 | stop

| 2 | slow down

| 3 | continue at the same pace

(e) Does it go away when you stand still?

| 1 | yes | 2 | no   If **no**, go to question 18(g)

(f) How soon?

| 1 | 10 minutes or less

| 2 | more than 10 minutes

(g) Where do you get this pain or discomfort?

Mark the place(s) with **X** on the diagram.
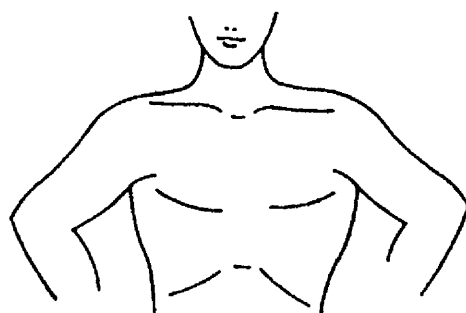
19. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

| 1 | yes | 2 | no |

Leg problems

20. (a) Do you get a pain or discomfort in your leg(s) when you walk?

| 1 | yes |

| 2 | no | If **no**, go to question 22.

| 3 | I am unable to walk | If **unable to walk**, go to question 22.

21. (a) Does this pain ever begin when you are standing still or sitting?

| 1 | yes | 2 | no |

(b) Do you get it if you walk uphill or hurry?

| 1 | yes | 2 | no |

(c) Do you get it when you walk at an ordinary pace on the level?

| 1 | yes | 2 | no |

(d) What happens to it if you stand still?

| 1 | Usually continues more than 10 minutes |

| 2 | Usually disappears in 10 minutes or less |

(e) Where do you get this pain or discomfort?

Mark the place(s) with **X** on the diagram below.

Front   Back
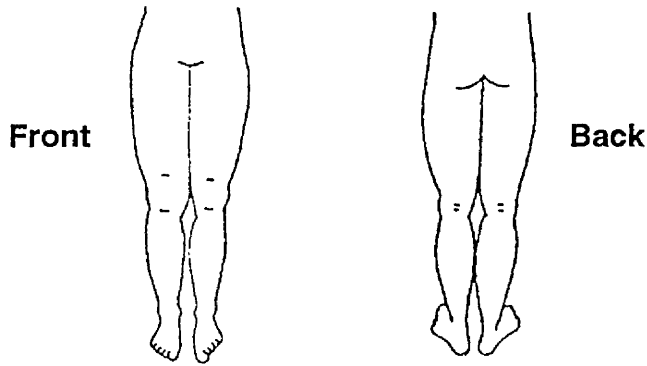
Cough

22. (a) Do you usually cough first thing in the morning in the winter?

| 1 | yes | 2 | no

(b) Do you usually cough during the day, or at night, in the winter?

| 1 | yes | 2 | no

(c) Do you cough like this on most days for as much as three months each year?

| 1 | yes | 2 | no | 8 | does not apply

Phlegm

23. (a) Do you usually bring up any phlegm from your chest first thing in the morning in the winter?

| 1 | yes | 2 | no

(b) Do you usually bring up any phlegm from your chest during the day, or at night, in the winter?

| 1 | yes | 2 | no

(c) Do you bring up phlegm like this on most days for as much as three months each year?

| 1 | yes | 2 | no | 8 | does not apply

Breathlessness

24. (a) Do you get short of breath when hurrying on level ground or walking up a slight hill?

| 1 | yes | | 2 | no |

(b) Do you get short of breath walking with other people of your own age on level ground?

| 1 | yes | | 2 | no |

(c) Do you have to stop for breath when walking at your own pace on level ground?

| 1 | yes | | 2 | no |

(d) Do you get short of breath when washing or dressing?

| 1 | yes | | 2 | no |

(e) Are you ever wakened from sleep by breathlessness?

| 1 | yes | | 2 | no |

Cigarette smoking

25. (a) Do you smoke cigarettes now?

| 1 | yes, regularly

| 2 | no   If **no**, go to question 26.

| 3 | occasionally (usually less than one a day)

(b) On average, about how many cigarettes do you smoke a day?

cigarettes a day

(c) On average, on how many days a week do you smoke cigarettes?

days a week

(d) How old were you when you began to smoke cigarettes?

years old

26. Did you ever smoke cigarettes?

| 1 | yes, regularly

| 2 | no, never

| 3 | occasionally (usually less than one a day)

Cigar smoking

27. (a) Have you ever smoked cigars?

| 1 | no   If **no**, go to question 28.

| 2 | used to, but not now   If **used to**, go to question 28.

| 3 | yes, now smoke occasionally (usually less than one a day)

| 4 | yes, now smoke regularly

(b) About how many cigars do you smoke a week? [|] cigars a week

Pipe smoking

28. (a) Have you ever smoked a pipe?

| 1 | no   If **no**, go to question 29.

| 2 | used to, but not now   If **used to**, go to question 29.

| 3 | yes, now smoke a pipe occasionally (less than one a day)

| 4 | yes, now smoke a pipe regularly

(b) About how many ounces of tobacco do you smoke a week?

[|] ozs a week

Alcoholic drinks

29. (a) Have you ever taken alcoholic drinks?

| 1 | yes | 2 | no   If **no**, go to question 31.

(b) Do you take alcoholic drinks at present

| 1 | yes | 2 | no | 3 | seldom   If **no**, go to question 30.

(c) Think back carefully over the last seven days. Please write in exactly what alcoholic drinks you have consumed on each day during the past week. Try to remember where you were and who you were with on each day. This may help you remember what you have had to drink. For each day, write in how much you have drunk:

(i) the number of pints of low-alcohol (or non-alcoholic) beer, lager, etc.
(ii) the number of pints of beer, lager, shandy, cider, stout, etc.
(iii) the number of single glasses of whisky, vodka, gin, rum, etc.
(iv) the number of single glasses of wine, sherry, Martini, port, etc.

	Pints of low-alcohol beer, etc.	Pints of beer, etc.	Single glasses of spirits	Single glasses of wine, etc.
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

(d) Would you say that last week was fairly typical of what you usually have to drink in one week?

| 1 | yes | 2 | no

(e) If last week was **not** typical, would you normally drink more or less in a week?

| 1 | more | 2 | less

30. (a) How long ago did you give up alcohol .... years ago

    (b) Why did you give up alcohol?

    | 1 | because the doctor advised me to

    | 2 | other reasons, please give details ....

Physical activity

31. Which of the following four activity classes best describes your present activity outside of your job? Please consider going to and from work, sporting activity and other physical effort during your leisure time, like gardening or dancing. (please circle one box only.)

    | 1 | No physical activity weekly

    | 2 | Only light physical activity in most weeks

    | 3 | Vigorous physical activity at least 20 minutes once or twice a week (Vigorous activity causes shortness of breath, a rapid heart rate and sweating)

    | 4 | Vigorous physical activity for at least 20 minutes three or more times a week.

THANK YOU for completing this questionnaire.

Please bring it with you to your appointment.

Office use only	
Date of visit	
Pat Init.	
Date of birth	
CRI Number	CRI- -1-
Checked by	

| SFQ 01 |

HEALTH STATUS QUESTIONNAIRE

We would be grateful if you could complete this questionnaire and bring it with you when you attend the examination. If you have any questions, please ask when you come to the examination. Our nurses are there to help you, and one will check through the record with you.

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after question 10.

Please circle one:

1. In general, would you say your health is

    | 1 | excellent |
    | 2 | very good |
    | 3 | good |
    | 4 | fair |
    | 5 | poor |

2. Compared to one year ago, how would you rate your health in general now:

    | 1 | Much better now than one year ago |
    | 2 | Somewhat better now than one year ago |
    | 3 | About the same |
    | 4 | Somewhat worse now than one year ago |
    | 5 | Much worse now than one year ago |

Health and Daily Activities

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please circle one on each line.

	Yes limited a lot	Yes limited a little	No, not, limited at all
a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c) Lifting or carrying groceries	1	2	3
d) Climbing several flights of stairs	1	2	3
e) Climbing one flight of stairs	1	2	3
f) Bending, kneeling or stooping	1	2	3
g) Walking more than a mile	1	2	3
h) Walking half a mile	1	2	3
i) Walking 100 yards	1	2	3
j) Bathing and dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Answer Yes or No to each question.

	Yes	No
a) Cut down on the amount of time you spent on work or other activities	1	2
b) Accomplished less than you would like	1	2
c) Were limited in the kind of work or other activities	1	2
d) Had difficulty performing the work or other activities (e.g. it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

   Answer Yes or No to each question.

	Yes	No
a) Cut down on the amount of time you spent on work or other activities	1	2
b) Accomplished less than you would like	1	2
c) Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups:

   Please circle one.

1	Not at all
2	Slightly
3	Moderately
4	Quite a bit
5	Extremely

7. How much bodily pain have you had during the past 4 weeks?

1	None
2	Very mild
3	Mild
4	Moderate
5	Severe
6	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

| 1 | Not at all |

| 2 | A little bit |

| 3 | Moderately |

| 4 | Quite a bit |

| 5 | Extremely |

Your Feelings

9. These questions are about how you feel and how things have been with you during the past month. (For each question, please indicate the one answer that comes closest to the way you have been feeling.)

How much time during the past month	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) did you feel full of life?	1	2	3	4	5	6
b) have you been a very nervous person?	1	2	3	4	5	6
c) have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d) have you felt calm and peaceful?	1	2	3	4	5	6
e) did you have a lot of energy?	1	2	3	4	5	6
f) have you felt downhearted and low?	1	2	3	4	5	6
g) did you feel worn out?	1	2	3	4	5	6
h) have you been a happy person?	1	2	3	4	5	6
i) did you feel tired?	1	2	3	4	5	6
j) has your health limited your social activities (like visiting friends or close relatives)?	1	2	3	4	5	6

Health In General

10. Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you.

    Please circle one box on each line

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a)	I seem to get ill more easily than other people	1	2	3	4	5
b)	I am as healthy as anybody I know	1	2	3	4	5
c)	I expect my health to get worse	1	2	3	4	5
d)	My health is excellent	1	2	3	4	5

Thank you very much for your assistance.

Please bring the questionnaire with you to your appointment.

Office use only	
Date of visit	└──┴──┴──┴──┴──┴──┘
Pat Init.	┌────┬────┐
Date of birth	└──┴──┴──┴──┴──┴──┘
CRI Number	CRI- ┌──┐ -1- ┌─┬─┬─┬─┬─┬─┐
Checked by	_____

ECHO DATA FORM 1

CRI No.: | **9** | **4** | – | **1** | – | | | | | |

Study Date: ☐☐ / ☐☐ / ☐☐   Analysis By: ☐☐

L.V. VOLUMES AND SIMPSON'S EJECTION FRACTION

1. **Echo Quality :**   4C ☐   2C ☐

4 CHAMBER	1	2	3
2. LVED Vol (ml)	☐☐☐	☐☐☐	☐☐☐
3. LVES Vol (ml)	☐☐☐	☐☐☐	☐☐☐

2 CHAMBER	1	2	3
4. LVED Vol (ml)	☐☐☐	☐☐☐	☐☐☐
5. LVES Vol (ml)	☐☐☐	☐☐☐	☐☐☐

BIPLANE	1	2	3
6. LVED Vol (ml)	☐☐☐	☐☐☐	☐☐☐
7. LVES Vol (ml)	☐☐☐	☐☐☐	☐☐☐
8. LVEF %	☐☐	☐☐	☐☐

M MODE

8. AOd ☐.☐

9. LAs ☐.☐

10. IVSd ☐.☐

11. LVEDD ☐.☐

12. LVPWd ☐.☐

13. IVSs ☐.☐

14. LVESD ☐.☐

15. LVPWs ☐.☐

University of Glasgow
CRI

CRI No.:	9	4	-	1	-	0	0				

Study Date: ☐☐ / ☐☐ / ☐☐   Analysis By: ☐☐

DOPPLER

MEAN

1. MV Peak E   ☐.☐☐   10. MV Quality   ☐

2. MV Peak A   ☐.☐☐

3. MV E VTI   ☐.☐☐

4. MV A VTI   ☐.☐☐

5. MV Dec. Time   ☐☐☐

6. MV PHT   ☐☐☐

7. AV Peak Vel.   ☐.☐☐   11. AV Quality   ☐

8. AV VTI   ☐.☐☐

9. TR Peak Vel.   ☐.☐☐   12. TV Quality   ☐

University of Glasgow
CRI

2.