EXERCISE LIMITATION IN AORTIC STENOSIS.

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Abstract

Symptomatic (Sy) aortic stenosis (AS) is a malignant condition with a five year survival of <50% but the prognosis in Asymptomatic (Asy) AS is relatively good. Aortic valve replacement (AVR) is virtually a curative procedure for those who survive the peri-operative period. AVR is recommended for symptomatic patients but the timing of surgery is critical to optimise outcome. Mechanisms underlying exercise intolerance and symptom generation in AS are poorly understood. This study investigated non-invasive predictors of exercise capacity in 37 patients with significant AS (peak PG >25mmHg) and 20 matched controls. **Methods**: Full echocardiography, cardiopulmonary exercise testing, skeletal muscle strength and endurance, arm and leg ergoreflex activation, brain natriuretic peptide (BNP) and endothelin-1 (ET-1) before and after maximal exercise, were measured. AS was classified by both disease (mild/severe) severity and symptomatic (Sy/Asy) status. Echocardiographic, anthropometric and exercise variables were examined as predictors of aerobic exercise capacity by univariate and multivariate regression analysis. **Results:** AS and control subjects were well matched for age, body size and sex. Sy patients (67.9±11, n=19) were older than Asy AS (47.6±19, n=18) and controls (50.4±17 years), p=0.001. Exercise capacity (% predicted) was reduced in Sy AS (52±27%) compared to Asy AS (86±28%) and controls (126±17%), p<0.0001. Exercise V_E/V_{CO_2} was increased in severe (34.5±8) and Sy AS (35.1±7) v mild (30.2±5), Asy AS (29.8±5) and controls (28.6±4) p≤0.01. SBP response to exercise was reduced in severe and Sy AS v controls and Asy/mild AS (P<0.001). Isometric quadriceps strength (Sym 470±169N v Asy AS 564±251N v controls 567±199N) and isokinetic endurance (Sym 83.4±16% v Asy AS 71.9±14% v controls 76.1±7%) were not significantly different between AS and controls. Arm ergoreflex activation was not significantly increased in AS. Leg ergoreflex activation (ventilation, % peak) was enhanced in Sym AS (67±50) v Asy AS (20±46) and controls (17±48), p=0.01 but did not predict exercise capacity or V_E/V_{CO_2}. BNP was increased in severe and Sym AS v mild/Asy AS and controls, p<0.0001. ET-1 was comparable at rest and after exercise in AS and controls. LV mass/mass index and BNP were independent predictors of exercise capacity in AS. **Conclusions**: Several variables have been identified which differ in symptomatic and asymptomatic AS. These (BNP, exercise capacity and SBP response) should be assessed for prognostic value in a prospective study of AS.

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Author's declaration

I declare that the work has been done and the thesis composed by myself, and that the books and papers cited were all consulted by me personally, unless it is otherwise stated.

Dr. Gerald P. McCann

Presentations and publications

The work in this thesis has been presented at the following scientific meetings:

Presentations

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Definitions and abbreviations

AS:	Aortic stenosis
AVA	Aortic valve area
VTI	Velocity Time Integral
BP:	Blood pressure
SBP	Systolic blood pressure
V_{O_2}:	Oxygen consumption
$V_{O_{2max}}$:	Maximal or peak oxygen consumption
CHF:	Chronic heart failure
V_E/V_{CO_2}:	The slope of exercise ventilation versus expired carbon dioxide
Ergoreflex	A work (or metabolic) sensitive reflex arising in skeletal muscle and involved in the control of ventilation and blood pressure.
RCO:	Regional circulatory occlusion
BNP:	Brain natriuretic peptide
NT-BNP	Amino-terminal pro-BNP
ET-1:	Endothelin-1
LBM:	Lean body mass
MI:	Myocardial infarction
CABG:	Coronary artery bypass grafting
RER	Respiratory exchange ratio
ECG	Electrocardiography
AR	Aortic regurgitation

1. INTRODUCTION

1.1 Aortic Stenosis (AS)

1.1.1 The normal aortic valve

The normal aortic valve has three cusps that are thin, flexible structures, which are covered by endothelium on both ventricular and aortic surfaces(1,2). Each leaflet is composed of three layers. The strength of the leaflets is provided by the fibrosa, a dense layer of collagen fibres arranged parallel to the leaflet edges. The flexibility is provided by the ventricularis layer of elastic fibres arranged perpendicular to the leaflets. The spongiosa is an area of loose connective tissue located in the basal third of each leaflet. The normal aortic valve has an area between $2.5cm^2$-$4.0cm^2$(3,4).

AS is defined as a reduction in the area of the aortic valve orifice.

1.1.2 Aetiology

In adults there are three main causes of AS(5-7):

i. Post-Inflammatory (rheumatic)

ii. Primary degenerative (calcific/senile)

iii. Secondary calcification of a congenital bicuspid aortic valve

Other rare causes include: unicommisural and hypoplastic valves.

Inflammatory AS develops 20-30 years after acute rheumatic fever. The disease process is initiated by thrombotic deposits affecting the free edges of valve cusps, which subsequently lead to early commisural fusion. Usually all commisures are affected and after the age of 40 years, calcification is also found within the valve cusps.

Calcific – this term is usually reserved for primary degenerative/senile AS but can also be used to describe calcification occurring in a bicuspid valve during adulthood. In congenital bicuspid AS, the calcification develops at the free edges of the cusps and progresses towards the base. Degenerative (senile) AS is

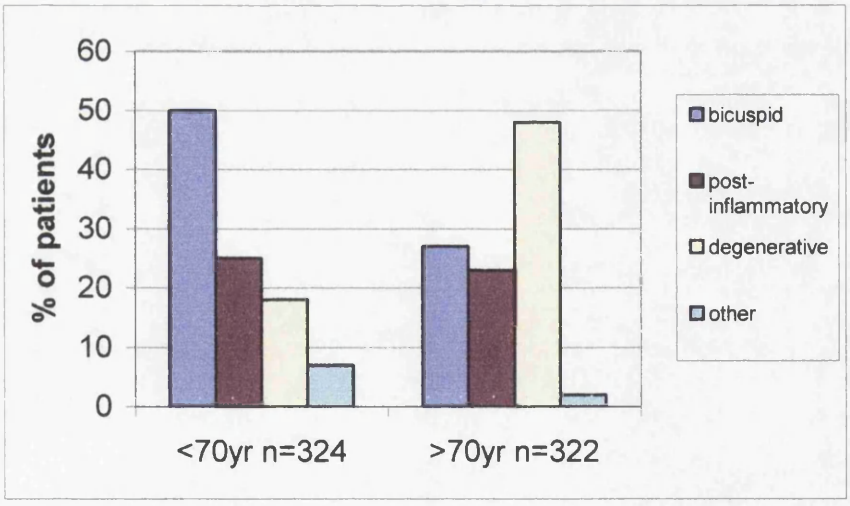
commonly found in the eighth and ninth decades of life. Calcification progresses from the base of the valve leaflets towards the cusp edges, contrary to that in congenital and inflammatory AS.

As can be seen from the above description, nearly all adults with significant AS have calcified cusps(7). The significance of this finding is that those with rheumatic and bicuspid aetiologies have commisural fusion, whereas in those with degenerative AS, the cusps open up to the aortic ring, but their mobility is limited by the presence of calcification.

1.1.2.1 Interaction of age and aetiology of AS.

There is a marked difference in the aetiology of AS depending on the age of subjects at the time of operation(5). There is a preponderance of bicuspid aortic valves in those patients under 70 years of age and degenerative valves in those older than 70 years(5) (figure 1-1). Patients with bicuspid AS are typically operated on 10 years earlier (mean age 64 years) than those with degenerative disease (74 years)(5,6).

Figure 1-1: Effect of age on aetiology of AS requiring surgery.



Adapted from (5).

1.1.2.2 Aetiological factors in development of degenerative AS

The development of senile/calcific AS has traditionally been considered to be a purely degenerative condition occurring with advancing age. More recently, it has become apparent that the inflammatory response may play an important aetiological role(8-11). Case control studies have demonstrated elevated levels of soluble adhesion molecules in patients with AS(9) and the presence of chlamydia

pneumoniae in early lesions of AS(8). There are also histological similarities to atherosclerosis, with oxidised low density lipoprotein deposition, lymphocyte and macrophage infiltration as well as basement membrane disruption(10-12). Patients with degenerative AS are twice as likely to require coronary artery bypass grafts compared to those with bicuspid valves, even when differences in age are taken in to consideration(6). Several risk factors for the development of AS are shared with coronary artery disease(1): Hypercholesterolaemia(13,14), male gender, hypertension, body mass index, smoking and diabetes mellitus. It has been proposed that degenerative AS may in fact be an atherosclerotic disease(15).

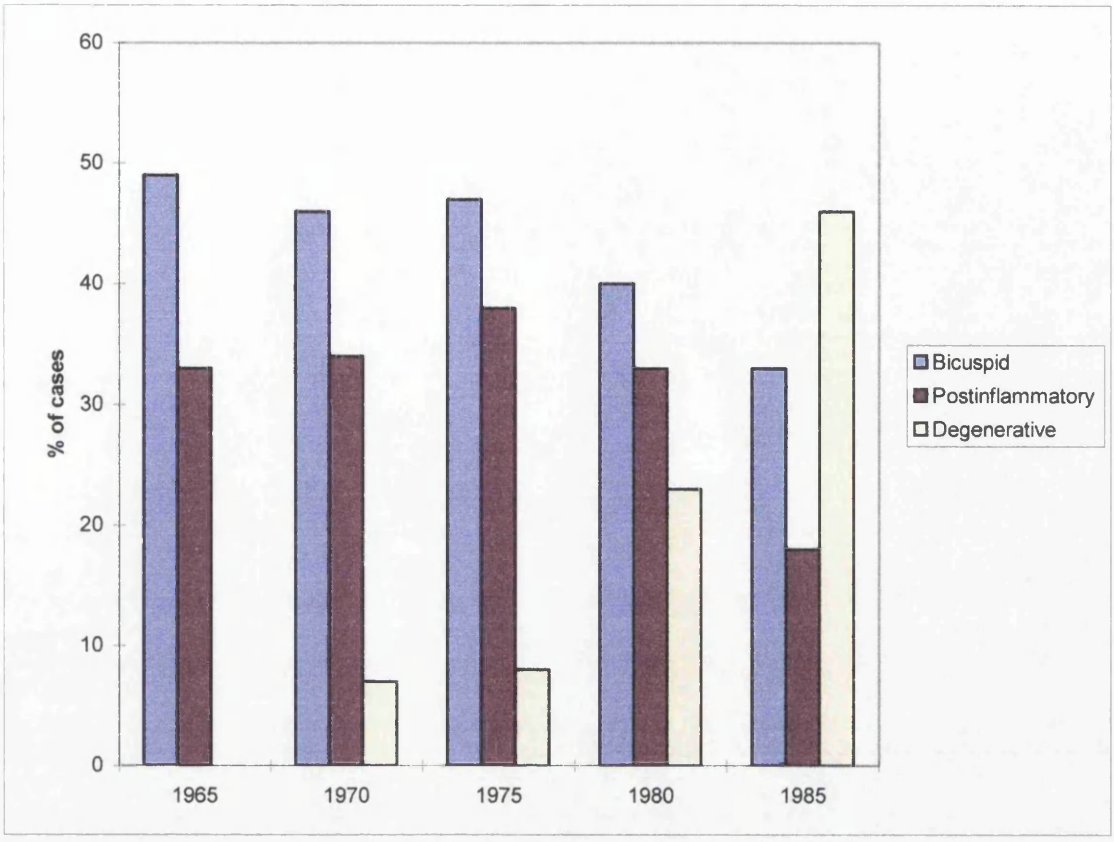
Diseases associated with hypercalcaemia (chronic renal failure, Paget's disease, hyperparathyroidism) are also risk factors(6).

1.1.2.3 Temporal changes in the aetiology of AS.

There has been a dramatic shift in the contribution of each the three main causes of AS in the last 30-40 years(5). As can be seen from figure1-2, based on 656 consecutive surgical specimens from a single centre in the USA, the proportion of patients requiring aortic valve replacement for degenerative AS has steadily increased(5).

This increase is likely to reflect both the ageing population and the willingness of cardiac surgeons to operate on older patients(3,5). The frequency of rheumatic AS has decreased throughout this period and in a recent British report accounted for only 5% of 465 consecutively excised valves, reflecting the virtual disappearance of rheumatic fever in Western societies(6).

Figure 1-2: Temporal change in aetiology of AS.



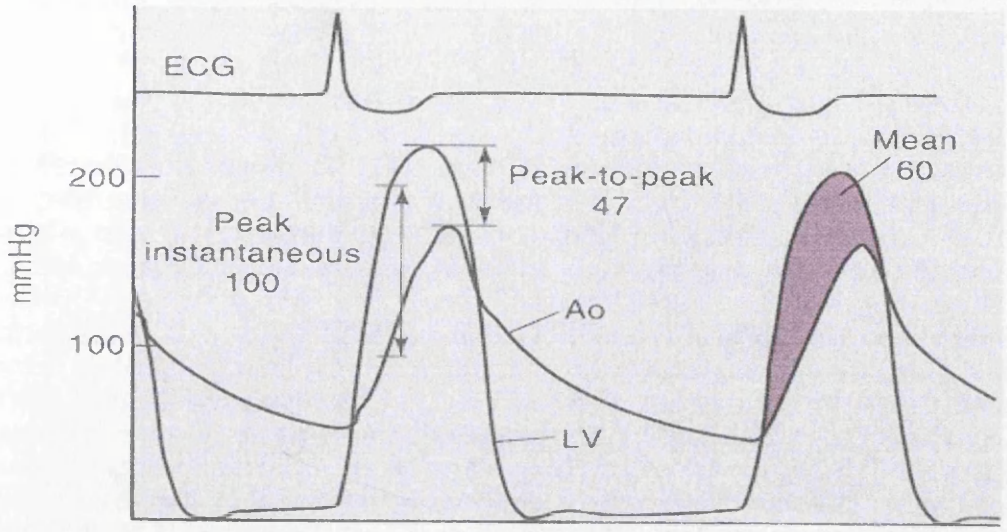
Adapted from (5).

1.2 Pathophysiology

1.2.1 Pressure differences

The reduction in aortic valve area results in a measurable difference in pressure between the left ventricle and the aorta. This pressure difference (pressure gradient or pressure drop) can be expressed in one of three ways, which are illustrated in figure 1-3 below.

Figure 1-3: Methods of quantifying transvalvular aortic pressure gradient.



Adapted from Braunwald(16).

1. The peak instantaneous pressure difference. This can be calculated by overlaying the pressure traces obtained in the left ventricle and aorta and corresponds to the peak pressure gradient measured by maximal aortic velocity on Doppler echocardiography.

2. The peak-to-peak pressure gradient. Usually measured by pullback of a catheter from the left ventricle into the aorta.

3. Mean pressure gradient. Calculated by overlaying simultaneous left ventricular and aortic pressure traces and the area of difference is calculated by planimetry.

The pressure gradient is directly related to flow, i.e. the cardiac output and especially stroke volume, but in a non-linear fashion. Flow is correlated to the square root of pressure gradient; therefore small increases in cardiac output lead to large increases in pressure gradient(see equations 2 and 4 below). Since aortic pressure is generally stable, controlled by peripheral vascular resistance, it is left ventricular systolic pressure that changes with increasing cardiac output.

1.2.2 Left ventricular hypertrophy and systolic function

Pressure overload leads to compensatory left ventricular hypertrophy to maintain wall stress, according to the law of La Place.

Equation 1: the law of Laplace

$$\text{LV wall stress} = \frac{\text{Radius x Pressure}}{\text{2 x wall thickness}}$$

Most patients (approximately 70%) develop concentric left ventricular hypertrophy, where there are increases in left ventricular wall thickness, left ventricular mass index and an increase in the relative wall thickness(17,18). In such cases the left ventricular end diastolic diameter is usually within normal limits. Over time both end diastolic and end systolic left ventricular diameters increase slowly, although this may not be apparent in those with marked concentric left ventricular hypertrophy(17). A smaller percentage of patients tend to develop eccentric hypertrophy where there are increases in left ventricular end diastolic diameter and left ventricular mass index, but the relative wall thickness is within normal limits(17). Whereas concentric left ventricular hypertrophy is regarded as a compensatory adaptation, eccentric hypertrophy is thought to be a decompensated response to the pressure overload and is associated with more severe valvular stenosis and left ventricular systolic dysfunction(17-21). As left ventricular systolic function is normal in the vast majority of patients(4,22-25), it is possible that those patients with eccentric hypertrophy and impairment of left ventricular contraction represent a more advanced stage in the disease progression(26).

1.2.3 Left ventricular hypertrophy and diastolic function

Diastolic dysfunction is directly related to increases in left ventricular mass(21,27) and occurs in approximately 50% of all patients with AS(27). Diastolic dysfunction is also present in virtually all patients who have objective evidence of reduced systolic function(27). In marked left ventricular hypertrophy, there may be evidence of subendocardial ischaemia, which contributes to both systolic and diastolic dysfunction(28). Increased end diastolic pressure requires a forceful atrial contraction to maintain optimal ventricular filling. The development of atrial fibrillation in such a situation is often followed by serious clinical deterioration(18).

1.2.3.1 Gender differences in left ventricular geometry and function

Recent echocardiographic and catheterisation studies have highlighted differences in geometric patterns and function of the left ventricle in females compared to

males(29-31). In elderly women especially, there is excessive left ventricular wall thickening, with generally lower wall stresses and preservation of systolic function despite similar degrees of stenosis severity(29-31). The mechanisms underlying these gender differences are not clearly understood, but may be related to cellular changes in the structure and deposition of collagen fibres, which occur more frequently in males(31).

1.2.3.2 Left ventricular hypertrophy and altered repolarisation

QT dispersion, which has been shown to predict the occurrence of fatal ventricular arrhythmias, is increased in patients with AS prior to valve replacement(32,33). This inhomogeneity of repolarisation is most likely related to the presence of left ventricular hypertrophy(33).

1.2.4 Haemodynamics

Cardiac output at rest is reduced in up to 50% of patients, particularly in those with severe AS(4,22,34). In the vast majority of patients, systolic function will be normal as measured by ejection fraction(22-24), although the systolic ejection period will be prolonged(22,34). The end diastolic left ventricular pressure is often elevated at rest(35) and the time constant for ventricular relaxation or the isovolumetric relaxation time are often lengthened(22,36) and may be related to increases in left ventricular mass(22).

1.2.4.1 Exercise haemodynamics

The cardiac output response to exercise is usually abnormal, with either no increase or blunting of the expected increase(34-36). Increased cardiac output is achieved primarily by an increase in heart rate, since stroke volume tends to be either static, or decreased(23,24,34). Stroke volume increases are directly proportional to changes in end diastolic volume and inversely proportional to left ventricular mass(23,24). At the beginning of exercise there are marked increases in end diastolic pressure(22,34,35) which also tend to be related to left ventricular hypertrophy(35) and rapid increases in both left atrial and pulmonary capillary wedge pressure(22). The isovolumetric relaxation time and systolic ejection periods may decrease on exercise, but typically do not reach control values(34-36). Mitral valve opening time is prolonged(36) but peak filling rates of the left

ventricle during diastole are decreased(24,36). These studies indicate the important contribution of diastolic dysfunction to exercise limitation in patients with AS and left ventricular hypertrophy. Females, who have more evidence of left ventricular hypertrophy, tend to have greater reductions in predicted aerobic exercise capacity compared to males(37).

1.3 Classification of severity

The severity of AS can be classified by one of two means; aortic valve area or measurement of transvalvular pressure gradient. These indices can be measured either invasively or non-invasively.

1.3.1 Invasive assessment of AS

1.3.1.1 The Gorlin equation.

It has long been recognised that clinical signs, particularly in the elderly, may not adequately differentiate between mild and severe AS. Prior to echocardiography, the mainstay of assessment was by cardiac catheterisation and calculation of aortic valve area by the Gorlin equation(38):

Equation 2: the Gorlin formula for aortic valve area (AVA)

$$\mathbf{AVA} = \frac{\text{Cardiac output}}{(44.3 \times \text{SEP} \times \text{HR} \times \sqrt{\text{mean PG}})}$$

where: 44.3 is a constant
SEP = systolic ejection period
PG = pressure gradient.
HR= heart rate in beats per minute

This method of assessment has several limitations. Firstly, it requires an invasive procedure with left heart catheterisation by either retrograde crossing of the aortic valve or by the transeptal technique. Secondly, as the formula uses the square root of the mean pressure gradient it is more prone to errors measuring cardiac output than pressure gradient. For this reason cardiac output should be measured by the Fick method since both the thermodilution and dye-dilution techniques can lead to overestimation, particularly in low output states(39). Thirdly, the assumptions in the equation have been questioned in recent years, particularly since the formula was only validated in patients with mitral stenosis. It has been

demonstrated that the constant varies in low and high cardiac output states, although this may actually reflect changes in the effective aortic valve area with alterations in pressure gradient(35,40-42). The equation is also invalidated in the presence of significant valvular regurgitation because the cardiac output is increased without any change in aortic valve area(39).

1.3.1.2 Hakki formula

Hakki observed that for most subjects with AS the product of HR x SEP X 44.3 was approximately 1000 and proposed a simplified equation for determination of aortic valve area(43):

Equation 3: the Hakki formula

$$\text{AVA} = \frac{\text{CO}}{\sqrt{\text{mean PG}}}$$

Where: AVA=aortic valve area
CO=cardiac output in L/min
√mean PG= square root of the mean pressure gradient

This simplified formula, like the Gorlin equation, has not been adequately validated in patient populations(39).

1.4 Echocardiographic assessment

The development of echocardiographic technology has transformed the assessment of AS. Echocardiography is the investigation of choice in the diagnosis and quantification of native and prosthetic valve disease(44).

1.4.1 M-Mode and two dimensional echocardiography

As early as 1975 M-mode echocardiography was proposed as a reliable means of assessing the severity of AS(45). The authors of this paper were able to show statistical differences in the degree of aortic valve leaflet separation in 28 adults with either mild, moderate or severe AS. This technique is limited by the degree of overlap between individuals in different groups and the problems of underestimating the degree of leaflet separation in calcific disease and overestimating separation in congenital AS(45).

Two-dimensional cross-sectional (M-Mode) echocardiography has also been shown to successfully differentiate between normal and stenotic aortic valves(46). However, the degree of aortic leaflet separation was not able to distinguish between severe (<0.75cm^2) and moderate AS (>0.75cm^2) as measured invasively by the Gorlin formula(46).

1.4.2 Doppler ultrasound measurement of transaortic pressure gradient

Doppler ultrasound allows measurement of the velocity of blood in the left ventricular outflow tract and distal to the aortic valve. The pressure gradient (pressure in the left ventricle minus pressure in the aorta) across the aortic valve can be calculated by the Bernouilli equation(47):

Equation 4: the Bernouilli equation

$$PG = 4 \times (V_2^2 - V_1^2)$$

where: PG is pressure gradient in mmHg
V2= maximal velocity across aortic valve
V1= is the velocity in the left ventricular outflow tract.

Since V_1 is usually small, (0.6-0.7 ms^{-1}) in comparison to V_2 in AS, it can be discarded giving the simplified or modified Bernouilli equation:(47)

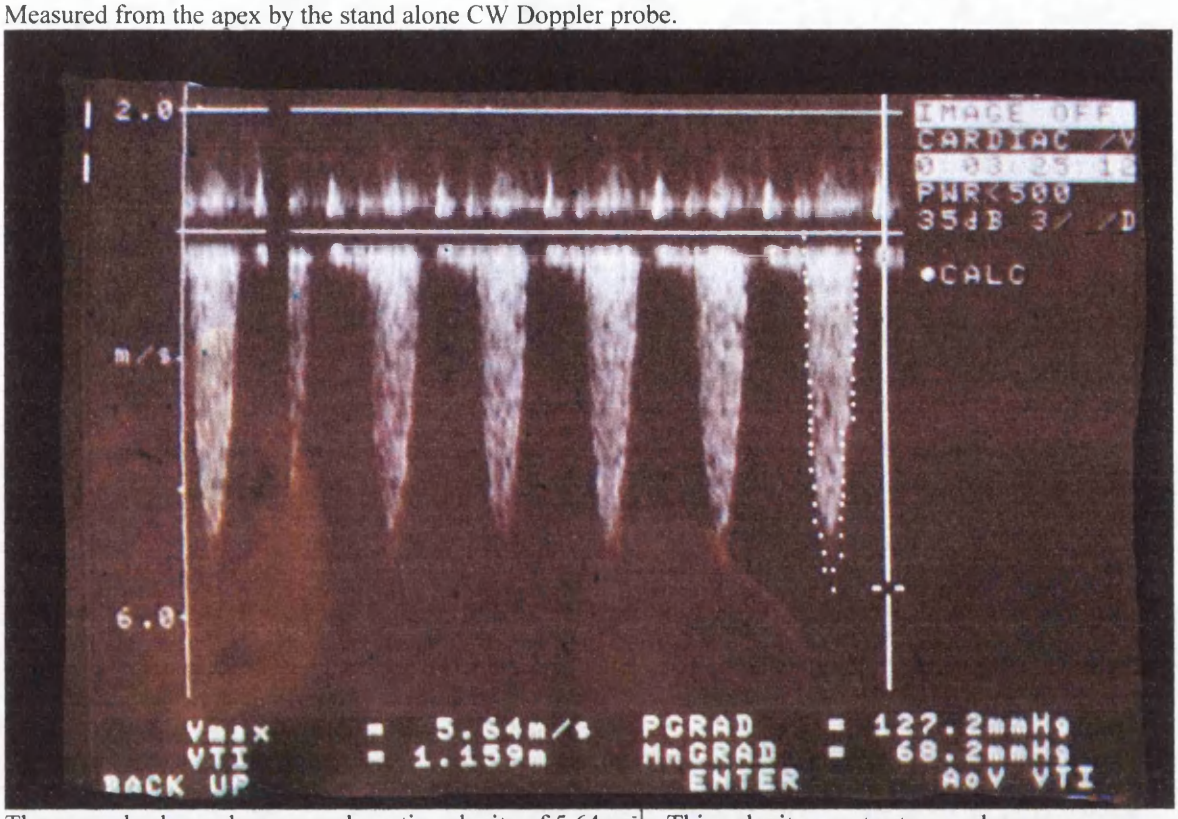
Equation 5: the modified or simplified Bernouilli equation(47)

$$PG = 4V^2$$

where: V is the maximal aortic velocity in ms^{-1}.

For accurate quantification, it is assumed that the angle between the ultrasound beam and the jet of blood is small, so that the cosine of the angle approaches 1.0 (true for angles < 20^0). The mean velocity across the aortic valve during systole can be calculated by planimetry of the spectral display of the Doppler tracing of the maximal aortic velocity and this is often known as the velocity time integral (VTI). This allows calculation of peak and mean pressure gradients as shown in figure 1-4.

Figure 1-4: VTI of aortic valve maximal velocity
Measured from the apex by the stand alone CW Doppler probe.



The example above shows a peak aortic velocity of 5.64ms^{-1}. This velocity equates to a peak pressure gradient of 127.2mmHg employing the modified Bernouilli equation. The mean gradient is derived from the VTI (average velocity divided by the systolic ejection period) and equals 68.2 mmHg.

Warth et al applied this technique to the Gorlin equation, which meant that left heart catheterisation could be omitted using the following equation:(48)

Equation 6: aortic valve area calculation by semi-invasive method(48)

AVA = cardiac output
SEP X velocity.

Where: SEP is the systolic ejection period
velocity is mean transvalvular aortic velocity

This semi-invasive approach gave an excellent correlation (r = 0.99) with the aortic valve area obtained by the formal Gorlin equation in 16 patients with AS(48). Limits of agreement for the two methods, however, were not reported.

Numerous studies have confirmed that Doppler ultrasound can give accurate assessment of transaortic peak and mean pressure gradients, provided that multiple echocardiographic windows (apical, suprasternal, sub-diaphragmatic and right intercostal) are searched and maximal velocities are used(49-53). The single best study compared catheter measured gradients with simultaneously obtained

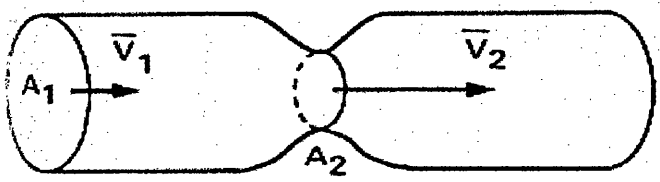
Doppler gradients in 100 adults aged over 50 years of age with AS(49). The correlation coefficients for instantaneous (catheter) gradient and maximal pressure gradients (Doppler) were 0.92, and 0.93 for mean gradient. The correlation between peak gradient (Doppler) and peak-to-peak pressure was still good (r=0.91) but the Doppler value over-estimated the invasive measure by a large proportion and should not be compared directly to peak-to-peak gradient(49). The overestimation of Doppler compared to catheter derived gradients may be explained, at least in part, by the phenomenon of aortic pressure recovery(54-57). Pressure recovery is a manifestation of the transfer of kinetic energy into potential energy seen downstream from a stenosis; that is as the velocity of blood flow decreases so does the kinetic energy and therefore the potential energy must increase(54). A significant degree of pressure recovery, and therefore probable overestimation of Doppler pressure gradient, can be expected in patients with small aortic root diameters(54,55).

Despite excellent correlations for Doppler derived and catheter measured gradients, the pressure gradient is not always a reliable measure of AS severity. According to the modified Bernouilli equation, (equation 5) small increases in flow velocity (cardiac output) will result in large increases in measured pressure gradient without a change in aortic valve area and this has been demonstrated in vivo(58). The opposite applies for low output states, e.g. significant left ventricular dysfunction with reduced cardiac output, in the presence of AS. This limitation in the assessment of pressure gradient for the severity of AS led to a totally non-invasive echocardiographic technique for calculating aortic valve area.

1.4.3 The continuity equation.

The equation of continuity, which governs flow in cylinders, was first proposed as a method of calculating aortic valve area (AVA) in 1985(50). The haemodynamic principles are outlined below.

Figure 1-5: The continuity equation for determination of aortic valve area.



Adapted from ref(59)

Equation 7: The continuity equation

$$Q = A1 \times V1 = A2 \times V2$$

$$\text{Therefore} \quad \frac{A1}{A2} = \frac{V2}{V1}$$

$$A2 = \frac{A1 \times V1}{V2}$$

where: Q= flow or cardiac output
A1 = the cross-sectional area of the left ventricular outflow tract immediately below the aortic valve,
A2 is the area of the stenotic valve.
V1 is the velocity of blood in the left ventricular outflow tract and
V2 is the velocity of blood in the ascending aorta immediately above the aortic valve.

Theoretically, this equation should be affected by neither left ventricular dysfunction nor by increased flow, as occurs in aortic incompetence. Depending on whether peak velocity or mean velocity is used in the equation, either maximal aortic valve area or effective aortic valve area respectively will be calculated(50). The validity of the continuity equation as a measure of aortic valve area was confirmed in 16 AS patients, some of whom had significant aortic incompetence, with a correlation coefficient of 0.89 with values determined by the Gorlin equation(50). Subsequent studies have reported even higher correlation coefficients (r=0.93-0.95) with subject numbers ranging from 39-100(55,59,60). Despite very high correlation coefficients, the limits of agreement may be wide (-0.56 - 0.38cm^2) for predicting the aortic valve area in any given individual and it is suggested that area should be used in conjunction with pressure gradient(55). Two studies reported that using only non-invasive indices to determine severe AS resulted in very high sensitivities and specificities for appropriate recommendation of aortic valve replacement(59,60). Otto and Pearlman have suggested that using the continuity equation to assess the severity of AS, instead of cardiac catheterisation, would result in significant cost savings, even if coronary angiography had to be undertaken prior to aortic valve replacement(60).

The major limitation in this technique is that accurate measurement of the left ventricular outflow tract may be impossible in a small number of patients, particularly those with poor two dimensional images and heavily calcified valves(50,59,60).

1.4.3.1 Flow dependence of aortic valve area.

Theoretically, blood flow should not be a confounding factor in the determination of aortic valve area, calculated by the continuity equation. Recent investigations however have shown this not to be the case(61-66). Most studies have used dobutamine stress echocardiography(62-64,66) but Otto's group have used maximal exercise testing to increase flow in asymptomatic patients with significant AS to determine the effect on calculated aortic valve area(61,65). In 66 patients, the aortic valve area increased significantly post-exercise from 1.38 to 1.58 cm^2 (14%) with mean cardiac output increasing by 25%(61). The increase in mean pressure gradient was relatively higher (39%) and there were also significant increases in valve resistance and percent stroke work loss, both measures of severity that do not have empiric constants in equations to calculate their value.

It has been suggested that tricuspid aortic valves of degenerative aetiology are more likely to demonstrate a flow dependent increase in aortic valve area than bicuspid or rheumatic valves(62). This observation seems logical since, typically, the commisures of degenerative aortic valves are not fused(7). This study was probably biased by the low numbers of subjects with definite rheumatic aetiology (n=3) and the exclusion of subjects who did not increase cardiac output in response to dobutamine infusion, thereby increasing the likelihood of excluding those with more severe disease or left ventricular dysfunction(62).

1.4.3.2 Time dependence of calculated aortic valve area.

The calculated aortic valve area by the continuity equation will also vary depending at which time point during systole velocity measurements are made. Badano et al measured left ventricular outflow tract velocity at peak, mid-acceleration and mid-deceleration in 26 AS subjects (AVA< 1.5 cm^2) and 14 healthy controls(64). They demonstrated that in the patient group the aortic valve opened slowly and continued to open throughout systole, whereas in the control subjects the aortic valve opened rapidly and maximally(64). There was no

correlation between echocardiographic measures of severity and the degree of aortic valve opening during systole(64). The weakness of this study is that it is assumed that left ventricular outflow tract area is unchanged throughout systole.

1.4.4 Other echocardiographic methods to determine stenosis severity

Several other methods for assessing AS have been proposed but none of those outlined below have yet to be used widely in clinical practice. These include: pulsed wave Doppler flow mapping(67,68), valve area by planimetry with transoesophageal echocardiography(69) and valve resistance(41). These techniques have few, if any, advantages over the continuity equation and the usefulness of resistance as a predictor of clinical outcome or recommendation for surgery has yet to be tested(70).

1.4.5 Doppler derived pressure gradients and aortic valve area

There is not absolute agreement amongst authors regarding the grading of severity of AS(16,18,71-73). A simplified classification system equating pressure gradients and aortic valve areas is outlined in the table below.

Severity	Aortic Valve Area	Transvalvular Peak Pressure Gradient	Transvalvular Mean Pressure Gradient
Mild	> 1.1 cm^2	< 40 mmHg	<20mmHg
Moderate	$0.7 - 1.09$ cm^2	40 -69 mmHg	21-39mmHg
Severe	< 0.7 cm^2	> 70 mmHg	>40mmHg

Table 1-1: Approximate equivalent values for determining severity of AS.

It must be emphasised that the above system is simplistic, since all of the above values are arbitrary cut-offs and the limitations of each method of assessment must be borne in mind. It is also possible to have severe AS with a low pressure gradient, particularly in left ventricular dysfunction, and mild AS with a high pressure gradient(74). Therefore pressure gradients should be interpreted in combination with aortic valve areas. Confusion in this area is not helped by the fact that the American College of Cardiology / American Heart Association (ACC/AHA) task force on management uses aortic valve area for sports participation(18), peak pressure gradient in congenital AS but mean pressure

gradient in acquired AS(71). Another complicating factor is that some suggest that aortic valve area should be corrected for body surface area, in the same way that cardiac output is corrected(18).

Otto has taken simplification to the extreme by suggesting that all patients with a peak velocity >4ms^{-1} should be classified as having severe AS(73). We have pointed out that the this conclusion is flawed since the study is based on asymptomatic patients in the modern era(75), many of whom underwent aortic valve replacement because of reduced exercise capacity which has not been shown to predict outcome(76).

1.5 Epidemiology

1.5.1 Prevalence

The exact prevalence of AS in the general population is unknown, however abnormalities of the aortic valve are common in the elderly. Thickened aortic valve leaflets occur as part of the ageing process and echocardiographic studies have estimated that calcification occurs in up to 40% of subjects over 75 years of age(77). The prevalence of AS (measured by increased pressure gradient) in subjects aged over 60 years of age has been estimated to be between 18%(78) and 26%(77). Severe AS (peak pressure gradient >50mmHg or aortic valve area <0.8cm^2) is found in approximately 2-3% of all elderly subjects(77,78). AS is the commonest reason for valve replacement in the USA with over 28,000 operations being performed in 1994(1). In the UK, 70 aortic valve replacements are performed each year per million population(79). The proportion of elderly patients over 70 years having surgery has increased dramatically: from 12% in 1986 to 36.6% in 1997(79).

1.6 Presentation

The condition is more prevalent in men with an approximate male to female ratio of 70:30(4,80-84). The male to female ratio for congenitally bicuspid aortic valves is higher, approaching 4:1(85,86). Symptomatic patients typically present in later life, usually in the 6th, 7th, and 8th decades(4,80,81,87). The development of AS following rheumatic fever typically occurs up to 30 years after the initial illness,

much later than for mitral stenosis(81). There is usually a long latent or presymptomatic stage with systolic murmurs often being present for more than 10 years prior to presentation(4,80).

1.6.1 Physical signs.

The physical signs in AS are: systolic thrill in the aortic area: a long or harsh systolic murmur in the aortic area; absence or diminished second heart sound, cardiac hypertrophy; a slow rising plateau pulse and a forceful and sustained apex beat(4,81,82,84,87). Other signs may be apparent with the development of chronic heart failure (CHF). The presence of the above physical signs are not present in all cases and even the systolic murmur may be inaudible in elderly subjects(4,78,87). The narrow pulse pressure described in many textbooks is uncommon(4); in one early series of 180 adult patients with definite AS, the average blood pressure (BP) was 145/84(81). The vast majority remain in sinus rhythm with less than 10% in atrial fibrillation(75,81). Although a reduced carotid pulse upstroke correlates with the echocardiographically derived pressure gradient, clinical examination is not a reliable method for differentiating mild disease from severe AS(84).

1.7 Natural history

Since the ability to accurately assess AS, by cardiac catheterisation, occurred almost simultaneously with the introduction of surgical correction one must look largely to studies prior to this era to determine the natural history of the disease(80-82). Unfortunately these early reports do not, and could not, classify the patients according to severity of AS. In addition many of these reports do not conform to the standards expected in the modern scientific journals. Several, more recent retrospective studies, have attempted to characterise the natural course of the disease by following patients who have not undergone surgical intervention(72,83,88,89) or initially were not referred for surgery(90,91).

1.7.1 Symptoms

Classically, there are three cardinal symptoms described in AS(80). These are:

Angina

Syncope

Symptoms of heart failure (marked dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and peripheral oedema).

The age at first presentation of symptoms was documented at 48 years in the Ross and Braunwald study(80) but had risen to 61 years in Lombard and Selzer's large series published in 1987(4). This trend is also likely to be a reflection of the changes seen in the aetiology of AS over the last 30 years.

1.7.1.1 Angina pectoris

Angina is a common symptom in AS occurring in approximately 30-50% of all patients at the time of assessment(4,81,83). Angina may not be indicative of underlying coronary artery disease since many patients (30-40%) experience classical angina despite having angiographically normal coronary arteries(4,83,92,93). Conversely, the absence of angina does not imply that the major epicardial coronary arteries are free of atherosclerosis, since this symptom will be absent as often as present in those with significant coronary artery disease(4,94). The overall prevalence of significant coronary artery disease in patients with AS is 40-60%(4,75,90,94,95). With such a high prevalence of atherosclerosis, it is therefore necessary that most patients who undergo aortic valve replacement will require coronary angiography before surgery. (The inability of exercise testing to reliably distinguish CAD is discussed in section 1.8.8) The mechanism causing angina pectoris in patients with AS and normal coronary arteries remains controversial(96), although is likely to involve reduced coronary flow reserve associated with elevated myocardial wall stress(97).

1.7.1.2 Syncope

Syncope occurs as a first symptom in AS in approximately 15% of patients. The average time to death from the development of syncope has been reported as varying from 9 months(81) to 3 yrs(80). Several theories have been proposed for the mechanism of syncope in AS including: carotid sinus reflex hyperactivity(98), abrupt left ventricular failure(99), arrhythmias(100), and the currently accepted theory of inappropriate left ventricular baroreceptor activity first proposed by Johnson in 1971(101). Johnson suggested that baroreceptors in the left

ventricular wall respond to severe rises in left ventricular systolic pressure occurring during exercise in patients with AS(101). The initiated vagal depressor reflex produces peripheral systemic vasodilatation, with possible dilatation of the splanchnic bed, and bradycardia. Diminished venous return with decreased cardiac output, together with decreased systemic vascular resistance leads to severe hypotension and syncope. Coronary arterial blood flow falls abruptly in the face of heavy left ventricular work and either causes syncope or, potentially, ventricular arrhythmias leading to circulatory arrest and death. Indirect support for Johnson's theory comes from the observation that patients with left ventricular systolic pressures >200mmHG are more likely to experience syncope(4). There is good experimental evidence from both human and animal models to support Johnson's theory(102-104).

1.7.1.3 Dyspnoea and heart failure

Congestive heart failure is manifested late in the course of AS and in the vast majority of patients left ventricular systolic function is preserved(4,22-24). Once heart failure develops, the prognosis is very poor with average times to death of 1-2.0 years(80,81). Although dyspnoea is often regarded as the main symptom of heart failure, it occurs early in many cases of AS(4,90) and may represent diastolic dysfunction. Dyspnoea may be present in up to 62% of all symptomatic patients(4,90). Patients who develop clinical or radiological heart failure have higher left ventricular wall stress and the majority will have an ejection fraction within the normal range although cardiac index is reduced(105).

1.7.2 Prognosis

1.7.2.1 Prognosis in symptomatic patients in the pre-surgical era

In Ross and Braunwald's classic description(80) of the natural history of AS in the era before operative intervention, average survival from onset of first symptom was as follows:

i. Angina – 3-5 years

ii. Syncope – 3 years

iii. Dyspnoea and signs of heart failure– 1.5-2 years

Angina and syncope have generally been regarded as early symptoms and dyspnoea/heart failure as a late symptom(4,80). However, dyspnoea is often the first symptom to develop(4,106) and in one early series of 180 patients with AS the average survival after the development of syncope was only nine months(81). The commonest causes of death in the pre-surgical era were progressive cardiac failure (approximately 65%), bacterial endocarditis (approximately 15%) and sudden cardiac death (approximately 20%)(80).

1.7.2.2 Prognosis in the modern era

Interpretation of the prognosis in patients in the modern era is more difficult. The relevant studies either try to assess the prognosis retrospectively or use data from patients who did not undergo surgery, either because they refused or aortic valve replacement was not offered. Such studies are likely to suffer from selection bias since these subjects are likely to represent groups of older patients or those with significant co-morbid conditions. The data are further confused by reports containing small numbers of patients with varying degrees of disease severity and those with and without symptoms. The major studies regarding the prognosis in the modern era are listed in table 1-2.

Symptomatic patients usually have moderate to severe AS, although some of those with severe AS may be entirely asymptomatic(3,72,82-84,90,91). Severe AS is associated with significant morbidity and mortality: the five and 10-year mortality for symptomatic patients are approximately 60-80% and 90% respectively(72,83). The prognosis for moderate symptomatic disease approaches that of severe AS(90). CHF is associated with increased risk: mean survival is less than I year compared to 4.6 years for angina and 2.6 years for syncope(88). The majority of deaths are secondary to progressive CHF and approximately 25% of deaths are regarded as sudden(25,72,75,106).

Author	Year	No. of subjects	Symptoms	Severity	Mean Follow-Up	Prognosis: Mortality/ Morbidity*
Frank(83)	1973	15	12 Sy 3 Asy	Mod-severe	2 years	66%
Chizner(72)	1980	42	32 Sy 10 Asy	Mod-severe	5 years	2yr 48% 5yr 64% 10yr 90%
Horskotte(88)	1988	35	Mixed	Severe	?>10years	2yr 50% 5yr 18%
VA Coop(89)	1988	106	>50%Sym	Mild-severe	5 years	5yr 57%
Kelly(106)	1988	90	39 Sy 51 Asy	Mod-severe	1.2 years	sym 38% asy 16%
Pellika(91)	1990	113	Asy	Mod-severe	1.7 years	1yr 14%* 2yr 38%*
Kennedy(90)	1991	66	58 Sy 8 Asy	Severe	3 years	21% asy 0%
Otto(75)	1997	123	Asy	Mild-severe	2.5 years	1yr 7%* 3yr 38%* 5yr 74%*
Rosenhek(25)	2000	126	Asy	Severe	1.8 years	1yr 33%* 2yr 44%* 4yr 67%*

Table 1-2: Prognosis in the modern era.
VA Coop= Veterans Cooperative study, Sy=symptomatic, Asy=Asymptomatic. *Denotes studies in which the end point was either death or aortic valve replacement.

Left ventricular systolic impairment, elevated end diastolic pressure and aortic valve area index(90), mean pressure gradient, CHF and the presence of disease in the proximal LAD have been shown to confer a worse prognosis. Even mildly symptomatic patients have a high mortality (44%) at 5 years(72).

In the elderly, AS is an independent risk factor for new cardiac events including myocardial infarction and sudden cardiac death(107, 108). Even aortic sclerosis, which was previously regarded as a benign condition, has recently been shown to confer a relative risk of 1.5 for subsequent cardiac death, even when corrected for the presence of symptomatic coronary artery disease(108).

1.7.2.3 Prognosis in asymptomatic patients

In assessing the natural history in asymptomatic patients most reports include large proportions of patients who have undergone aortic valve replacement, either

because of reduced exercise capacity or progression of haemodynamic severity(25,75,90,91). Such studies often use the combined end-point of cardiac events (defined as either sudden cardiac death or aortic valve replacement) in assessing predictors of prognosis. The use of such end-points must be questioned, since in all of these reports many patients (20-40%) have undergone aortic valve replacement even though they were asymptomatic at the time of operation(25,75,90,91). With these points in mind, the prognosis in such studies is discussed below.

The prognosis in asymptomatic AS is generally regarded as very good(3,4,25,80,109,110). In one study of eight asymptomatic patients, all of whom were less than 30 years of age, with moderate to severe disease there were no deaths during at least five years of follow-up, although five patients subsequently underwent aortic valve replacement(72). Further evidence of the excellent prognosis in young adults comes from the second natural history of congenital AS(111). For subjects with a peak pressure gradient <25mmHg the 25 year survival was 92.4% compared to the average population survival of 96% for the same age group(111). Otto's group have also demonstrated that age is an independent predictor of future events as is increasing pressure gradient measured by Doppler echocardiography(75). In the small study by Frank and Johnson one of three asymptomatic patients with moderate to severe disease died during follow-up over a period of at least two years(83). However, in patients with severe AS recommended surgery three of 35 (8.6%) died whilst still asymptomatic(88).

Pellikka et al compared the prognosis in 30 patients who underwent aortic valve replacement within three months of assessment with 113 who were managed medically(91). The one and two year event free survival was 90% for the group operated on compared to 86% and 62% for the non-operated group(91). The authors concluded that asymptomatic patients should be managed conservatively because there was a low incidence of sudden cardiac death(2%), despite the poorer prognosis in the conservatively managed group. Independent predictors of outcome were peak velocity and ejection fraction(91).

In a large series of asymptomatic subjects (defined as the absence of chest pain, syncope and dyspnoea on moderate exertion), with severe AS (velocity>4ms^{-1}) the outcome in 22 patients who had early aortic valve replacement was compared to

that in 106 who were initially managed medically(25). There were six cardiac deaths in the 106 managed conservatively, five of whom had developed symptoms, with an estimated rate of sudden cardiac death of <1%(25). The outcomes for the two groups were similar with mortality figures close to that for the general population. This study highlights the methodological difficulties with such reports. The surgical group were older (71 v 57 years) and had more severe disease (peak velocity 5.0 v 4.5ms^{-1}) than those managed medically. Furthermore, 59 patients in the medically managed group subsequently had aortic valve replacement, all apparently because of the development of symptoms. This is rather surprising considering that 22 of the original cohort had surgery whilst still asymptomatic. The true incidence of sudden death in all asymptomatic subjects is likely therefore to be higher than that reported in the modern literature since many patients, presumably those with the severest disease and therefore highest risk, undergo aortic valve replacement whilst still asymptomatic.

In summary, moderate and severe AS, which is symptomatic, confers a high risk of complications in a short follow up period. Those with reduced ejection fraction and increased symptomatology are at higher risk. The prognosis for asymptomatic AS, particularly in young adults, is significantly better than for symptomatic disease but is not neglible. For all degrees of severity the outlook is worse with evidence of left ventricular dysfunction and increased pressure gradient, particularly in elderly subjects.

1.7.3 Progression of AS

Many reports have addressed the rate of haemodynamic progression in AS (see Table 1-3).

The peak pressure gradient increases by approximately 7mmHg per year and the aortic valve area decreases approximately 0.1 cm^2 per year. Isolated cases of rapidly progressive AS have been reported(122).

First Author	Year	No.	Case Mix	Cath/ Echo	Peak PG	↑PG year	↓AVA/ year (cm^2)	Faster progression
Wagner(112)	1982	50	-	C	38	5.4	-	↑Age, Calc
Nitta(113)	1987	11	-	C	23	7.7	-	↑Age
Turina(114)	1987	29	-	C	50	3.4	-	None
Otto(115)	1989	42	-	D	54	12	0.1	↑Symptoms
Roger(116)	1990	112	-	D	35	4.8	-	↑Symptoms
Davies(117)	1991	65	-	C	10	6.5	-	Calc
Faggiano(118)	1992	45	-	D	64	15	0.1	LVSD
Peter(119)	1993	49	-	D	38	7.2	-	↑CAD
Beppu(120)	1993	75	Con	D	NA	1.8	-	Eccentric
Brener(19)	1995	394	-	D	NA	8.3	0.14	MR
Otto(75)	1997	123	Asy	D	29(x)	7	0.12	None
Palta(121)	2000	170	-	D	29		0.10	AVA, Chol, Smoking
Rosenhek(25)	2000	126	Asy	D	125	-	-	Cardiac events, Calc

Table 1-3: Echocardiographic progression in AS.
Adapted from ref(110). Con=congenital, Asy=asymptomatic, AVA=aortic valve area D= Doppler, C= cardiac catheterisation, (x)=mean PG, LVSD=left ventricular systolic dysfunction, calc=calcification, MR=mitral regurgitation. NA=not available, Chol= elevated serum cholesterol, Calc=calcification of valve

Several factors have been associated with increased rates of progression. These are: age(112,113), calcification in the valve(25,112,117), smoking, increased aortic valve area and hypercholesterolaemia(121), increased NYHA functional class(115,116), left ventricular systolic dysfunction(118), coronary artery disease(119), eccentric cusps(120) and cardiac events(25). Recently, a slow rate of change in aortic valve area during a cardiac cycle has been implicated in faster progression in mild asymptomatic AS(123). In the single largest study on progression, in 394 adult patients, Brener et al demonstrated that hypertrophy protected against left ventricular dilatation but worsening mitral regurgitation seemed to be a maladaptive response to increasing AS severity(19).

1.8 Exercise testing in AS

Traditionally moderate to severe AS has been regarded as either a relative or absolute contraindication to exercise testing(18,124-126). The rationale for excluding patients with AS from exercise testing is based on the already documented occurrence of syncope and sudden death (neither of which occur exclusively on exertion) and isolated case reports of deaths during exercise or exercise testing(100,127,128). As early as 1969 exercise haemodynamics were suggested as a useful indicator of when to recommend aortic valve replacement(129). More recently several authors have advocated the use of exercise testing in AS, particularly in the assessment of asymptomatic patients prior to aortic valve replacement(18,126,130,131).

1.8.1 Safety of exercise testing in AS

Exercise testing in AS is performed routinely in some countries, particularly in Sweden(132). Table 1-4 lists the major studies of exercise tolerance testing in adults with AS.

First Author	Year	No. of Subjects	Status	Type of exercise	Exercise endpoint	Complications
Atterhog(133)	1979	?AS >50,000	Pre-cath	Bicycle	Symptom	1 Death 3 VT
Almendral(135)	1982	16	Pre-AVR	Treadmill	85%max pred HR	1 VT 1 AF
Niemela(136)	1983	19	Pre-AVR	Bicycle	Symptom	None
Linderholm(92)	1985	35 (+500)*	Pre-AVR	Bicycle	Symptom	None
Nylander(93)	1986	76	Sym	Bicycle	Symptom	None
Clyne(24)	1991	14	Asy	Treadmill	Symptom	None
Driscoll(86)	1993	134	Adult cong.	Treadmill	Symptom	2 Arrhythmia 1 Syncope
Otto(75)	1997	123	Asy	Treadmill	Symptom	None
Gencbay(137)	1999	42	Asy	Treadmill	Max pred HR	None

Table 1-4: Studies demonstrating the safety of exercise testing in AS.
Sym = symptomatic; Asy = asymptomatic; cath = cardiac catheterisation; AVR = aortic valve replacement; TM = treadmill; Adult cong. = adult congenital AS. *Detailed results given for 35 patients but authors comment that over 500 tests carried out in AS without a fatality.

Many studies, in addition to those examining exercise haemodynamics, have demonstrated the safety of exercise testing in a controlled hospital environment with careful attention to BP response.

Only one death has been reported in the literature(133). Unfortunately, although AS was said to confer a higher risk of complications during this very large prospective study of over 10,000 exercise tests, the number of patients with AS and the frequency of adverse events were not reported(133).

Most studies have reported infrequent and self-limiting complications and used similar criteria for termination of the test: fall in systolic BP(SBP), >5mm ST depression and persistent arrhythmia. Atwood has estimated that the mortality for exercise testing in AS is approximately one fifth of that for coronary artery disease(134).

Exercise is usually performed on an electrically braked bicycle or motorised treadmill and a wide range of protocols have been employed. A fall in systolic BP, which may indicate left ventricular baroreceptor activation, is an indication for termination of the test but is sometimes reported as a complication(75,133). All of the studies have continuously monitored the electrocardiogram and BP has been recorded at three minute intervals or more frequently.

1.8.2 Exercise capacity in AS

1.8.2.1 Maximal aerobic capacity

There has only been one reported study, which directly compares exercise capacity with age, and sex matched controls(24). (See table 1-5). Clyne et al exercised 14 asymptomatic adults with moderate to severe AS and 14 healthy control subjects(24). The patient group had normal left ventricular systolic but abnormal diastolic function. The aortic patients had significantly reduced maximum oxygen consumption, maximum SBP and a borderline significant reduction in exercise duration. There were no significant differences in resting heart rate, systolic BP or maximum heart rate. Four patients in whom exercise ejection fraction was reduced had significantly impaired VO_{2max} compared to those with normal left ventricular function (20 v 29ml/kg/min)(24).

	Controls	AS	P Value
Age	46	42	ns
M/F	12/2	12/2	ns
Resting Heart Rate (bpm)	79	73	ns
Resting SBP (mmHg)	136	141	ns
Peak Exercise HR (bpm)	171	177	ns
Peak Exercise SBP (mmHg)	192	167	< 0.001
VO_2max (ml/kg/min)	36.3	26.7	0.004
Exercise duration (min)	13.3	10.7	0.06

Table 1-5: Exercise capacity in AS compared to matched controls.
ns= non-significant

Several studies have compared exercise capacity with predicted values for normal populations using standardised protocols(75,86,93,135), whilst others have simply reported results pre and post-surgery(136). In a large series of 123 adults with asymptomatic AS, exercise capacity was reduced by only 10%(75) in contrast to the 26% reduction in measured VO_{2max} seen in Clyne's study(24). Similarly, in the NHS II study of congenital AS, many of whom had undergone aortic surgery, exercise capacity was on average 86.5% of that predicted(86). On the other hand, in elderly subjects with severe AS, 95% will have an exercise capacity < 80% of that predicted for age(93).

The majority of AS patients will achieve close to their predicted maximum heart rate(34,75,86,93). Those patients with severe AS will tend to have an attenuated increase in systolic BP on exercise(135) and may have a greater amount of ST segment depression during exercise testing(86).

1.8.3 Symptoms limiting exercise capacity

Most patients with untreated AS are symptom-limited on exercise tolerance testing(75,93,136). Those with severe disease are more likely to develop symptoms than those with mild to moderate AS(34). Dyspnoea and fatigue account for 60% of test terminations due to symptoms. Other less frequently occurring symptoms requiring test termination are angina (3-25%) and dizziness, approximately 1%(75,93). Medical termination of exercise tests is uncommon (approximately 8%) with the most frequent indications being a reduction in

SBP(93), and rarely, either sustained ventricular arrhythmias or ST segment depression > 5 mm(93).

1.8.4 NYHA functional class and exercise capacity

Interestingly, symptomatic status, as judged by NYHA functional class, is a poor predictor of exercise capacity in AS. In Nylander's elderly symptomatic group, many patients in NYHA class II had < 50% of their predicted exercise capacity, whereas some in class III only had a moderate restriction(93). There was a large overlap between the groups of patients in each functional class(93). In a smaller study, there was no correlation between NYHA class and exercise duration(135). In completely asymptomatic individuals, i.e. NYHA class I, predicted exercise capacity was reduced by 10% $\pm$ 33%(75). In 14 asymptomatic patients with moderate-severe disease VO_{2max} was reduced by 26%(24). This discrepancy between symptomatic status and objective measurement of exercise capacity suggests that as the degree of AS severity increases, patients may become more sedentary, perhaps subconsciously avoiding activities which make them feel unwell or attribute their reduced exercise tolerance to the ageing process.

1.8.5 Predictors of exercise capacity

Resting haemodynamic measurements such as pressure gradient(135) ejection fraction, cardiac index and pulmonary artery pressure(136) do not correlate significantly with aerobic exercise capacity. In Clyne's small study of 14 patients, exercise capacity was correlated with increasing cardiac output, measured by radionuclide ventriculography(24).

1.8.6 Reproducibility of cardiopulmonary exercise testing

Only one study has addressed the question of reproducibility of cardiopulmonary exercise testing in patients with valvular heart disease(138). Six patients with AS, out of a total of 17, performed two treadmill exercise tests according to the Norton protocol, under standardised conditions with expired gas analysis. Total walking time, peak oxygen consumption, heart rate at anaerobic threshold, ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) all showed excellent correlations with r values between the two tests approaching one(138).

1.8.7 Exercise capacity after aortic valve replacement

Following aortic valve replacement an improvement in exercise capacity is seen whether patients attend a formal exercise rehabilitation programme or not(139,140). Improvements tend to occur slowly despite the immediate improvements in haemodynamics(141-165). Exercise capacity does not return to normal however. In one study of patients with left ventricular hypertrophy following aortic valve replacement, exercise capacity was only 63% of predicted despite subjects achieving their predicted maximum heart rate(36). This probably reflects incomplete regression of left ventricular hypertrophy and persistent diastolic dysfunction (see section 1.9.5). Another possibility is that patients have abnormalities of skeletal muscle similar to those seen in chronic heart failure (CHF), see section 1.10.4, which have not been investigated previously.

1.8.8 Exercise testing in the detection of coronary artery disease

As has been previously discussed, angina pectoris is a common symptom without evidence of coronary artery disease in patients with AS. Similarly, the development of ST segment depression during exercise tolerance testing does not indicate obstructive coronary artery disease. In 104 asymptomatic patients performing a total of 274 treadmill tests, 188 tests were complicated by significant horizontal or down sloping ST segment depression(75). Fifty-two patients subsequently had coronary angiography. Only 50% of these subjects had evidence of obstructive coronary artery disease and there was no correlation between the development of ST segment depression and angiographically proven disease(75). In patients with symptomatic moderate to severe AS, 10 of 14 subjects developed ST segment depression, but only 3 had reversible defects on thallium scanning(24). In 42 patients with a mean age of 37, with mild to moderate AS, 81% of the group developed > 1 mm of ST segment depression on exercise despite all of the subjects having normal coronary angiography(137). ST segment depression seems to occur equally frequently in those with as opposed to those without ECG determined left ventricular hypertrophy(24). Patients with coronary artery disease tend to be older and have more marked ST segment depression, with a greater reduction in maximum workload(92). However, no single equation can reliably predict the presence of coronary artery disease in any individual subject(92).

1.9 Valve replacement for AS

There is no medical therapy which is of proven benefit in the treatment of AS. Surgery, with aortic valve replacement, has led to vast improvements in prognosis(144), although there are no randomised control trials comparing surgical versus medical management. The peri-operative mortality for aortic valve replacement is dependent on the risk factor profile of the subject undergoing surgery.

1.9.1 Mortality

The peri-operative mortality for all patients is approximately 6.6%(145). In the United Kingdom the mortality for all aortic valve replacements without coronary artery bypass grafting(CABG) is 4% and with CABG 6%(146). In low risk patients, i.e. those without extra cardiac co-morbidity or coronary artery disease, the operative mortality is approximately 2-3%(130,147,148). For those patients who survive the peri-operative period, the age predicted survival is similar to that for the general population(147,149,150).

1.9.1.1 Age

In elderly patients peri-operative mortality is higher; for those over 80 years mortality varies between 5 and 18%(151,150,152,153). In 675 consecutive patients undergoing aortic valve replacement, the peri-operative mortality was 12.4%, but dropped to < 5% for those under 70 years of age(151). In 140 consecutive patients in France, aged over 80 years, 42% of whom had significant coronary artery disease, the inpatient mortality was 9.3%(152). Five year survival was 56% and 80% of survivors were able to live independently at home(152). In a similar study from the UK, in 103 patients, peri-operative mortality was 18% but there was a very good symptomatic outcome in survivors, with most patients in NYHA class I or II(150).

1.9.1.2 Left ventricular dysfunction and coronary artery disease

In two large series of patients with left ventricular systolic dysfunction, and severe AS, the peri-operative mortality was 9-11%(154,155). The five year survival after aortic valve replacement for patients without coronary artery disease, but left

ventricular systolic dysfunction pre-operatively is between 69 and 88%(154,155). For those with coronary artery disease and left ventricular systolic dysfunction survival is between 40-51%(154,155). In another series of 55 patients, all with severe left ventricular dysfunction the 30 day mortality was 18%(156). The only independent predictor of mortality was prior myocardial infarction, conferring a relative risk of 14.5 for peri-operative death(156).

1.9.1.3 Predictors of peri-operative mortality

The strongest predictors of peri-operative mortality are the presence of coronary artery disease(147,154,155) and increasing age(145,147,151). Other factors which are shown to independently predict mortality include a reduced cardiac output prior to valve replacement(155), the presence of severe left ventricular hypertrophy(147,157), an increase in left ventricular relative wall thickness(157) and impairment of systolic(145,151) and diastolic function(145). Gender is probably not an independent risk factor once other differences in haemodynamic and structural indices are taken into account(158).

1.9.1.4 Surgical waiting list- morbidity and mortality

With limited operating resources, there is inevitably a delay in the time to surgery from the decision being made to operate. For patients with severe AS, there were 12 deaths out of 99 patients listed for aortic valve replacement during a six month waiting list(159). The death rate whilst on the waiting was 13.5 per 100 patient years versus only 4.9 per 100 patient years for those undergoing aortic valve replacement(159). During the delay for operative intervention there was also a significant worsening of prognostic profile in eleven patients. Expected seven year survival in this group fell from 72% at the time of listing for surgery to 61% pre-operatively. Predictors of death whilst awaiting surgery were: increasing age, short duration of symptoms, severe left ventricular hypertrophy on ECG, female gender and diastolic dysfunction(159).

1.9.1.5 Late mortality

There is still an excess mortality for patients who survive the peri-operative period(149,160,161). This is primarily related to an increase in cardiac failure(149) and complications related to the valve prosthesis(149,161). Predictors of late

mortality are residual left ventricular hypertrophy, impairment of systolic left ventricular function and diastolic dysfunction indicated by a reduction in peak filling rate on radionuclide ventriculography(160).

1.9.2 Morbidity associated with aortic valve replacement

As well as the excess mortality previously discussed, there are several significant complications related to the valve prosthesis. Thromboembolism has a prevalence of 1.7/100 patient years, haemorrhage related to anticoagulants, 1.5% per patient year, sudden cardiac events, including arrhythmias and myocardial infarction, 1.8 per 100 patient years, and prosthetic endocarditis occurs 0.5/100 patient year(149).

1.9.3 Alterations in ventricular repolarisation abnormalities

Following valve replacement there is a reduction in QT dispersion early and late after surgery(32,33). Valve replacement has also been shown to increase heart rate variability in 12 patients who underwent surgery(162). These favourable alterations may in part be responsible for the reductions in sudden death after aortic valve replacement.

1.9.4 Symptomatic Status

The vast majority of patients who survive the peri-operative period will benefit from an improvement in symptomatic status(150,155,163). This applies to those with impairment of left ventricular function(155) and in elderly subjects with severe symptomatic AS(150).

1.9.5 Alterations in left ventricular structure and function

1.9.5.1 Left ventricular structure

Valve replacement leads to an immediate reduction in increased afterload, affecting left ventricular haemodynamics(164). Structural changes occur in the left ventricle within a few days and continued remodelling occurs for years after valve replacement(32,164-169). There is an early reduction in left ventricular hypertrophy and left ventricular mass index which does not usually return to

normal(32,33,165-169). This is mainly achieved by a reduction in myocardial fibre diameter and a reduction in interstitial fibrosis(168,169).

1.9.5.2 Left ventricular function

If left ventricular systolic function is impaired, the ejection fraction usually increases post surgery(155,163,165,166). In patients with normal systolic function, the ejection fraction remains preserved(167). Improvements in ejection fraction may be expected in patients with obstructive coronary artery disease(155). There are also immediate improvements in diastolic function which continue over several years, but do not return to normal values(169). Diastolic dysfunction appears to be related to the degree of persisting interstitial fibrosis late after surgery(168,169).

1.9.6 Balloon Aortic Valvuloplasty for AS

The outcome of aortic balloon valvuloplasty, unlike mitral valvuloplasty, is very poor(153,170). In 674 consecutive patients undergoing valvuloplasty in a multi-centre report from the United States, it was shown that 3 year survival was only 23%(170). There was a small improvement in symptomatic status, but frequent re-hospitalisation and haemodynamic restenosis was very common(170). In the severely symptomatic patient, valvuloplasty may be used as a temporary measure prior to definitive surgery(153). The survival post valvuloplasty is not significantly different for patients with moderate to severe symptomatic AS.

1.9.7 Timing of surgery

It is universally accepted that surgery is indicated for symptomatic patients with significant AS because of the very poor prognosis in this condition(16,18,73). The single most controversial area of management in AS is whether to recommend surgery in those with severe but asymptomatic disease and what is the optimal timing of aortic valve replacement? Clearly, even in centres of excellence with vast experience of the management of these patients, significant differences in clinical practice are seen(25,75,171).

Braunwald has changed his attitude somewhat, from not recommending aortic valve replacement in any asymptomatic individuals but to keep them under careful

surveillance(171). He now recommends aortic valve replacement for asymptomatic individuals with evidence of left ventricular systolic dysfunction and those with blunted or reduced systolic BP response to exercise(16).

Chambers in a recent editorial has suggested that asymptomatic patients undergo exercise tolerance testing and those developing angina pectoris should be referred for surgery(131). This suggestion does not, however, take into account those patients who may develop angina as a result of underlying obstructive coronary artery disease and, more importantly, classically patients with angina pectoris have a moderately good prognosis, compared to the symptom of dyspnoea and heart failure(80).

Otto has implied that patients with a peak aortic velocity of > 4 ms^{-1} undergo aortic valve replacement because of the low survival rate (21%) without surgery at 2 years(73). Once again these data are clouded by the fact that almost 50% of the patients undergoing surgery did so because of reduced exercise capacity or haemodynamic progression, neither of which have been shown prospectively to be associated with increased mortality. In a further recent editorial, Otto more emphatically does not recommend surgery for asymptomatic AS on the basis that sudden cardiac death in such patients is rare(<1%)(172). The data on which this conclusion is based are flawed. Almost 20% of the initial cohort were referred for surgery whilst still asymptomatic and they contained the highest risk patients; a more elderly cohort with higher pressure gradients than those managed medically(25).

Lund has suggested that patients should be operated on earlier, possibly whilst still asymptomatic(159). This is based on the worsening operative risk profile and mortality during the inevitable waiting time for surgery(159). Rahimtoola also recommends earlier AVR, possibly in asymptomatic patients, in those with evidence of left ventricular dysfunction, coronary artery disease or other serious co-morbidity(74). The majority opinion seems to favour waiting until subjects become symptomatic and then recommending aortic valve replacement as quickly as possible thereafter(16,18,172,173). This strategy is far from ideal as evidenced from the number of patients who develop symptoms and die before surgery can be performed(25,83,91,106)

1.10 Exercise limitation in (CHF)

In the normal subjects maximal aerobic exercise capacity is limited by cardiac output(174). During incremental exercise testing, oxygen consumption reaches a plateau despite an increase in workload and this phenomenon is termed maximal oxygen consumption (V_{O_2}max). V_{O_2}max is an objective measure of cardiopulmonary fitness and aerobic exercise capacity. CHF patients often do not reach a plateau in their oxygen consumption before cessation of maximum leg exercise(175). Furthermore, the addition of arm to maximum leg exercise in such patients produced a further increment in V_{O_2} which did not occur in control subjects(175). Since the CHF patients did not exhaust their cardiopulmonary reserve at the point of fatigue, it is apparent that their exercise capacity may have been limited by factors other than cardiac output. As patient groups often do not reach a plateau in oxygen consumption, the term peak V_{O_2} is applied to the maximal value obtained.

1.10.1 Haemodynamic predictors of exercise capacity

Resting indices of cardiac function such as ejection fraction, cardiac output and pulmonary artery capillary wedge pressure are poorly correlated with maximal exercise capacity in heart failure(176,177). Furthermore, interventions which lead to immediate improvements in cardiac haemodynamics do not translate into improved exercise capacity. On the other hand quadriceps muscle strength and endurance have been found to be good predictors of peak V_{O_2} in CHF(176-180).

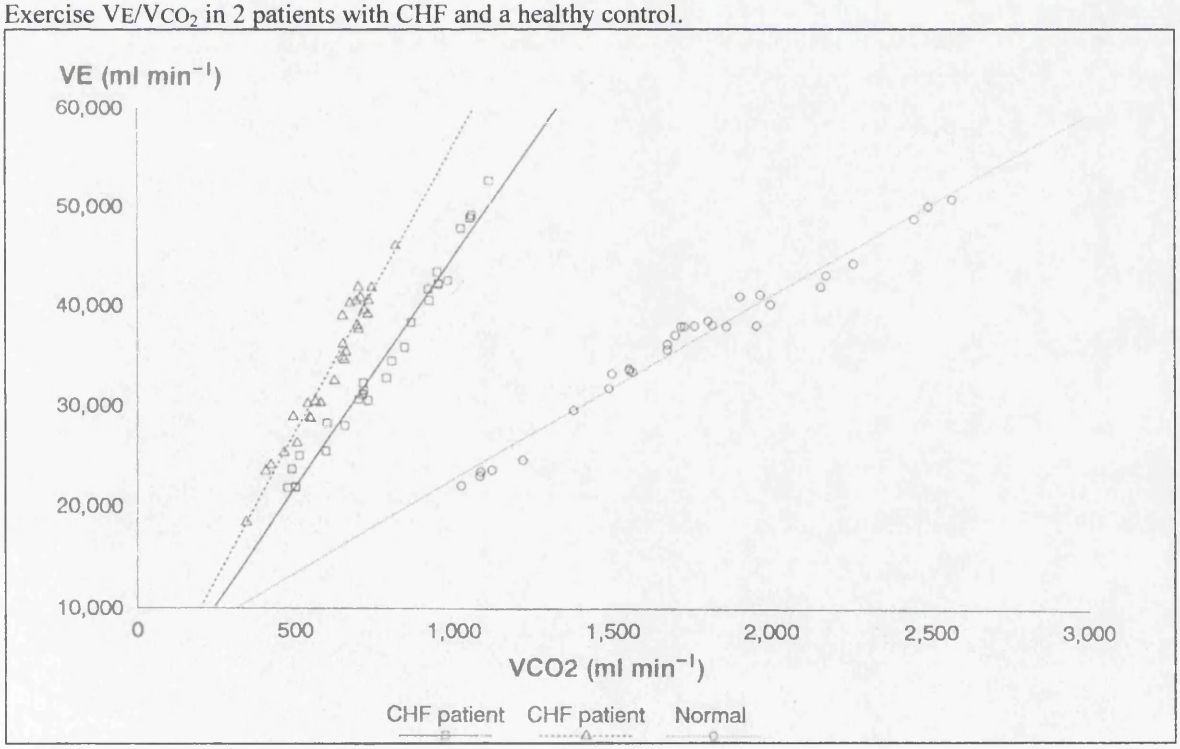
1.10.2 Symptoms limiting exercise in CHF

Patients with heart failure are most often limited by dyspnoea and fatigue. Patients terminating exercise because of fatigue do not show differences in central haemodynamic measures compared to those stopping because of breathlessness(181). In addition, any individual patient is frequently limited by different symptoms produced by different forms of exercise or by varying speeds in incremental tests(182). These data suggest that the different symptoms limiting exercise capacity in CHF may be generated by the same underlying mechanism(s).

1.10.3 Exercise ventilation in CHF

In CHF there is an exaggerated ventilatory response to exercise indicated by an increase in the V_E/V_{CO_2} slope(183,184,182) (figure 1-6). The V_E/V_{CO_2} slope correlates inversely with peak V_{O_2}(182). The mechanisms responsible remain controversial. Several authors have suggested that this exaggerated ventilatory response to exercise is a result of increased lung dead space in CHF patients(184,185,186) plus a combination of earlier lactic acidosis(186). Clark and Coats have argued that trying to explain the increased V_E/V_{CO_2} slope on the basis of the alveolar ventilation equation will always result in elevated dead space being increased(184). We have demonstrated that altering the exercise position from erect to supine, which should alter the ventilation perfusion ratio and, hence dead space, did not change the V_E/V_{CO_2} slope in either normal controls(187) or in patients with CHF(188). Also alteration of breathing pattern did not result in changes in the slope of V_E/V_{CO_2} in normal subjects(189).

Figure 1-6: Ventilatory response to exercise in CHF
Exercise V_E/V_{CO_2} in 2 patients with CHF and a healthy control.



It is also true that arterial blood gases rarely change in CHF patients during exercise despite the fact that ventilation continues to increase(182,183,187). It seems from these findings that neither arterial P_{CO_2} nor altered dead space is responsible for the increased ventilatory response to exercise seen in heart failure.

The slope of V_E/V_{CO_2} also confers prognostic information(190). In 303 patients with CHF, V_E/V_{CO_2} slope was an independent predictor of mortality in a multivariate model, including age, ejection fraction and NYHA functional classification, during a median follow up of seven months(190).

1.10.4 Skeletal muscle abnormalities in CHF

Skeletal muscle changes in CHF are well documented(184,191-193). A decrease in muscle bulk is seen, which may occur as a result of a catabolic state, characterised by high levels of tumour necrosis factor-α, insulin resistance, intestinal malabsorption and deranged intracellular thyroid hormone handling(184,191,194). A shift in the composition of the muscle fibres also occurs. There is an increase in the number of type IIB fibres (anaerobic fast twitch), and a reduction in type I fibres, which are slow twitch and oxidative(193,195). These changes are similar to those of a de-training effect and consequently result in reduced oxidative capacity and a lower lactate threshold. Although total number of skeletal muscle capillaries may be reduced, the number per unit of area is normal(192). Reduced physical activity levels may contributes to the development of skeletal muscle abnormalities in CHF although no study has specifically addressed this possibility.

1.10.4.1 Functional changes in skeletal muscle in CHF

The histological and biochemical abnormalities present in skeletal muscle result in abnormal metabolism during exercise. There is early lactate acidosis(185,196,197), increased inorganic phosphate/phosphocreatine concentrations(192,193,195,198), decreased oxygen utilisation by muscle(193), an early fall in intracellular pH(184,199) and delayed phosphocreatine recovery post exercise(184,199). These changes are consistent with a shift towards increased dependency on anaerobic metabolism.

1.10.4.2 Muscle strength in CHF

It has been demonstrated that both static (isometric) and dynamic strength of the quadriceps and hamstring muscle groups are significantly reduced in heart failure patients compared to matched controls(200). Contradictory results have also been published(178). The strength of small muscle groups such as foot

dorsiflexors, intrinsic hand muscles, arm extensors and flexors are usually well preserved in CHF(201-203). When strength of the large muscle groups is corrected for body size or muscle mass, strength per unit area of muscle is normalised(180,180). In patients with cardiac cachexia, it seems that muscle strength is reduced, even when corrected for muscle mass, implying an intrinsic abnormality in the force generation apparatus(179).

1.10.4.3 Muscle endurance in CHF

Muscular endurance is defined as the ability of the contracting muscles to perform repeated contractions against a load(172). Muscular endurance is assessed using an isokinetic dynamometer which continually records torque during muscle contractions at a selected angular velocity(204). Several studies have confirmed a reduction in quadriceps muscle endurance in patients with CHF(178-180,202).

1.10.5 Endothelial dysfunction and exercise limitation in CHF

It has long been recognised that vasodilation in CHF in response to various stimuli is abnormal(205). Both endothelium-dependent and endothelium-independent processes are affected(206-208). Skeletal muscle blood flow during exercise has been shown to be reduced in several reports(179,196,197,209). Blood flow has not usually been corrected for muscle mass, which may result in normalisation of flow per unit of muscle. Several other investigators have reported normal exercising blood flows, even in some patients with reduced exercise capacity and/or abnormal muscle metabolism(179,196,210,). During exercise with regional circulatory occlusion (RCO) fatigue remains more pronounced in CHF than controls(178,202). These data lend further support to the theory that there is an intrinsic abnormality in skeletal muscle rather than changes as a result of hypo-perfusion.

1.10.5.1 Endothelial function in valvular heart disease

Endothelium-dependent and endothelium-independent vasodilation are abnormal in patients with CHF secondary to valvular heart disease(211,212). The endothelium-dependent vasodilation is subsequently improved by valve replacement and this is associated with a corresponding increase in exercise capacity(212).

1.10.6 Ergoreflex activation

There is strong evidence from both human(213-219) and animal(220-224) models demonstrating a neural connection between skeletal muscle and the control of ventilation during exercise. This reflex, which has been termed the ergoreflex, contributes to the maintenance of ventilation(214,215,219), heart rate(216,221), BP(214,216) and peripheral vascular resistance(213,217). The reflex is most likely transmitted from skeletal muscle to the central nervous system via small nerve fibres(221,224). The ergoreflex is stimulated by both mechanical stretch(221,225) and the products of metabolism(222).

1.10.6.1 Ergoreflex activation in CHF

Ergoreflex activity has recently been demonstrated to be enhanced in patients with CHF(213). Twelve patients with heart failure were compared to ten control subjects during and following handgrip exercise at 50% of maximum voluntary contraction until exhaustion. Exercise was performed on two occasions and after one test RCO was obtained, by inflating a sphygmomanometer cuff to 30mmHg greater than BP, for three minutes(213). Ventilation (86.5 v 54.5%), systolic BP(89 v 59%), diastolic BP(97.8 v 53.5%) and leg vascular resistance(108.1 v 48.9%) were significantly increased in CHF patients compared to controls after RCO(213). We have subsequently shown that an exaggerated ergoreflex also exists in the lower leg musculature in CHF(226).

1.10.6.2 Ergoreflex and the muscle hypothesis

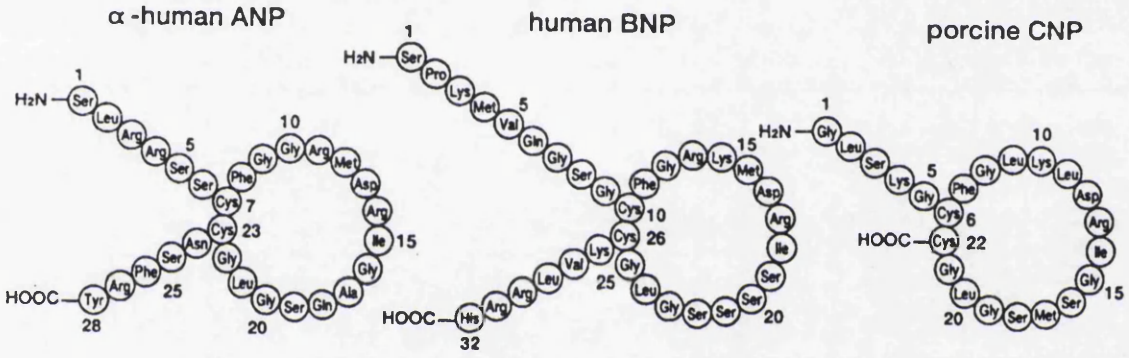
The demonstration of enhanced ergoreflexes in CHF has proven an attractive hypothesis in unifying the ventilatory and skeletal muscle abnormalities seen in CHF(191). According to this theory, when heart failure patients exercise early metabolic distress occurs in the abnormal skeletal muscles, which stimulates ventilation and the sympathetic nervous system. Ergoreflex activity results in the increased ventilation and may be perceived as dyspnoea and fatigue leading to exercise cessation before the cardiovascular system is maximally taxed. Left ventricular systolic dysfunction is the initiating insult in a cascading system of maladaptive responses, but in what order the other pathophysiological adaptations, e.g. endothelial dysfunction, skeletal muscle atrophy, catabolic state and neurohormonal activation, occur is uncertain(191).

1.11 Brain Natriuretic Peptide (BNP) and cardiac disease

1.11.1 BNP

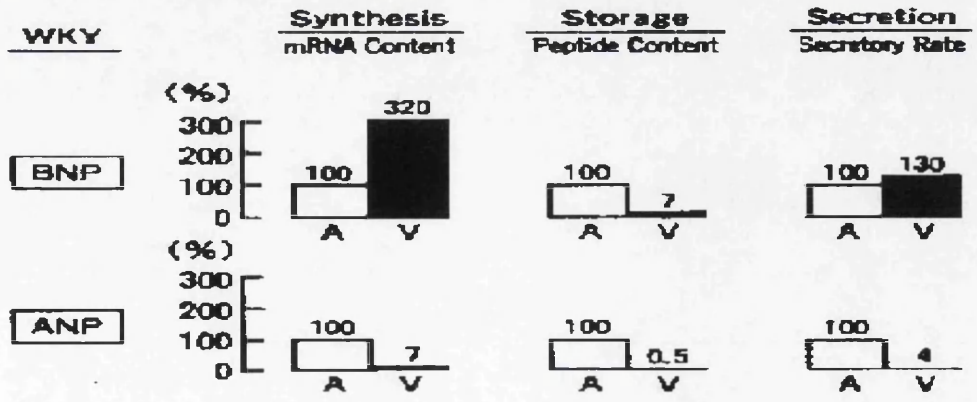
BNP is one of three members in the natriuretic peptide hormone family along with atrial natriuretic peptide (ANP) and C type natriuretic peptide (CNP). The molecular biology, synthesis, secretion and effects of BNP have been reviewed in detail elsewhere(227,228,229,230). Briefly, BNP is a peptide consisting of 32 amino acids which circulates in plasma. BNP is very similar in structure to ANP (figure 1-7) and both peptides are derived from larger pro-hormones; in BNP's case an 108 amino acid sequence called pro-BNP.

Figure 1-7: Structure of natriuretic peptides



Pro-BNP is cleaved into the amino (N)-terminal pro-BNP (NT-BNP) and the 32-amino acid BNP. BNP is contained in secretory granules in both the atria and the ventricles, but unlike ANP the primary source is from the left ventricle (figure1-8).

Figure 1-8: Synthesis and storage of ANP and BNP.



Adapted from ref(231). Values are expressed as a percentage of the atrial ANP value.

Although a small amount of BNP is secreted from storage granules, the majority of circulating BNP is produced from a constitutive pathway which is probably stimulated by myocyte stretch. It is unclear whether myocyte stretch acts directly or indirectly via endothelin, nitric oxide or angiotensin(230). Circulating BNP levels in cardiac disease, particularly heart failure, are correlated with left ventricular end diastolic pressure, pulmonary capillary wedge pressure, right atrial pressure and inversely correlated with ejection fraction.

1.11.1.1 Actions of BNP

BNP acts at 3-natriuretic peptide receptors. Receptor subtypes A and B, when stimulated activate transmembrane guanyl cyclases that mediate the biological effects. The C type receptor is thought to be a clearance receptor, but may also play a role in regulating vascular smooth muscle cell proliferation. The effects of both BNP and ANP are: natriuresis; diuresis; vasorelaxation with resultant reductions in peripheral vascular resistance, pulmonary artery and capillary wedge pressures; and an increase in cardiac index in heart failure patients. ANP and BNP also inhibit the renin-angiotensin aldosterone system, endothelin and vasopressin. In isolated heart preparations subjected to increased volume load, BNP synthesis and secretion respond more quickly than ANP secretion.

1.11.2 BNP responses to exercise

The pattern of change in BNP plasma levels on exercise is similar to that of ANP, but the magnitude of response is smaller(232-237). Studies examining responses of BNP to exercise in both normal subjects and in those with cardiac disease are summarised in the table 1-6. The results appear to be very consistent and most of the variation in results can be explained by differences in subject groups, mode of exercise employed, sampling time of BNP and the use of different assays for measurement.

1.11.2.1 Normal Subjects

In healthy subjects undergoing exercise, there is a small increase in plasma BNP in response to various forms of exercise, although this does not always reach statistical significance(234-236,238-240).

1.11.2.2 BNP Response to Exercise in Cardiac Disease

Virtually all the studies which have examined exercise-induced responses of BNP in patients with cardiac disease have reported significant increases (table 1-6). Resting and post-exercise values are highest in patients with CHF or left ventricular systolic function(233,237-239,241-243).

Author	Year	Exercise Mode		Subjects Status	No	Age	M/F	BNP (pg/ml) Rest	Ex
Normals									
Nicholson(232)	1993	TM	Inc	Healthy	5	48	4/1	5.5	6.8*
Wambach(240)	1995	B	Inc	Healthy	20	25	M	31[+]	45
Tanaka(245)	1995	B	Inc	Healthy	14	40	12/2	1.5	2.8*
Steele(238)	1997	B	Inc	Healthy	10	67	M	20	22*
Friedl(239)	1996	BS	Inc	Healthy	32	58	22/10	22.8	30.8
Moromoto(237)	1997	B	SS	Healthy	8	46	M	*5*	*7*
Nishikimi(246)	1997	BS	SS	Healthy	10	49	M	*7*	*7**
Geny(234)	1998	B	Inc	Healthy	8	42	M	7.4 pmol/L	8.5* pmol/L
Barletta(236)	1998	B	Inc	Healthy	8	30	M	1.6	2.48
	1998	HG	Iso	Healthy	8	30	M	1.85	2.40
Onuaha(235)	1998	TM	Inc	Healthy	10	71	F	9.1	11.7
Cardiac Disease									
Nicholson(232)	1993	TM	Inc	CAD	16	59	12/4	10.5 pmol/L	13.2 pmol/L
Friedl(242)	1998	BS	Inc	CAD	34	58	?	18	23
				CAD/LVSD	62	58	?	43	62
Yokoyama(241)	1996	TM	Inc	Post MI	60	62	55/5	66.5	82.3
Morimoto(237)	1997	B	SS	Post MI	9	59	8/1	*72*	*96*
Friedl(233)	1999	B	Inc	LVSD	16	61	15/1	86	104
Friedl(239)	1996	BS	Inc	ALVSD	37	58	30/8	42.3	61.2
				CHF	32	62	30/7	72.6	92.1
Steele(238)	1997	B	Inc	CHF	10	66	M	42	46
Clarkson(247)	1996	BS	Inc	Diastolic HF	6	62	4/2	9.1 pmol/L	12.3 pmol/L
Matsumoto(243)	1995	B	Inc	DCM	7	48	6/1	221	378
				MS	9	53	4/5	37	54
Geny(234)	1998	B	Inc	HTx	8	44.9	8/0	14.3 pmol/L	19.0 pmol/L
Hypertension									
Kohno(248)	1992	B	Inc	EH	9	56	4/4	6	13
Tanaka(245)	1995	B	Inc	EH	19	44	15/4	4.8	9.0
Tomiyama(249)	1995	HG	Iso	HTN	21	45	18/3	2.7	3.4*
Kohno(244)	1995	B	Inc	EH +LVH	21	57	8/13	7.3	22.3
				EH no LVH	24	56	9/15	4.6	10.9
Nishikimi(246)	1997	BS	SS	EH	15	56	12/3	*13*	*19*

Table 1-6: BNP responses to exercise.
All differences in BNP levels between rest and exercise are statistically significant unless marked*. Abbr: TM=treadmill; B=bicycle ergometry; BS: supine ergometry; HG=handgrip; Inc=incremental; Iso=isometric; SS=steady state; EH=essential hypertension; LVH=Left ventricular hypertrophy: LVSD=left ventricular systolic dysfunction; ALVSD =asymptomatic left ventricular systolic dysfunction; CHF=chronic heart failure; DCM=dilated cardiomyopathy; MS=mitral stenosis; HTx= heart transplant. Values in italics were estimated from graphical illustrations. [+]BNP levels after 5 days high salt diet.

In hypertensive subjects the resting and exercise BNP are higher in those with left ventricular hypertrophy than in those without(244). BNP plasma concentrations seem to rise with increasing age, even in healthy subjects.

BNP at rest and on exercise has been shown to correlate with various parameters of left ventricular function. In patients with heart failure or left ventricular systolic dysfunction, BNP correlates with left ventricular end diastolic pressure(237,243), left ventricular end diastolic volume(236,243) and there are inverse correlations with ejection fraction(233,238,239) and left ventricular peak filling rate(238). Several reports have shown that the increase in plasma BNP on exercise is correlated with left ventricular mass index in hypertensive subjects(244,246) and in heart transplant recipients(234). In CHF or post MI, increased BNP plasma levels are associated with reduced aerobic exercise capacity as measured by peak oxygen consumption(238,241,250) and anaerobic threshold(241). Importantly, the increases seen in BNP in response to exercise are closely correlated to resting BNP levels(232,244,246).

These studies collectively suggest that BNP is released in response to increases in left ventricular volume and pressure, which result in elevation of left ventricular wall tension. The fact that those who have high resting levels of BNP demonstrate the greatest response to exercise suggests that these patients have up-regulation of messenger RNA which allow them to synthesise BNP at a greater rate. None of the studies on exercise can definitely exclude reduced clearance of BNP as a possible mechanism for the increased plasma levels.

1.11.2.3 Comparison of BNP and ANP on Exercise

BNP is shown to correlate better with indices of left ventricular function than ANP(233,236,243). The BNP response to exercise is not related to angiotensin converting enzyme genotype (insertion/deletion alleles) although there was a weak association for ANP response to exercise(242). The maximum increase in BNP is seen at or within a few minutes of peak exercise(232,235,236,238,243).

1.11.3 BNP and AS

There have been only two published reports of alterations in natriuretic peptides in patients with AS(251,252).

Prasad et al studied 30 patients with a mean age of 70 and a peak aortic valve pressure gradient of 69.8 mmHg(251). They demonstrated increased levels of BNP compared to age matched controls (13.9 vs. 3.7 pmol/L respectively). The increase in BNP was not as high as that seen for ANP, as has been demonstrated in other cardiac diseases. Increased BNP levels were correlated with NYHA functional class, left ventricular mass index, mean aortic valve pressure gradient, left ventricular end diastolic pressure and peak-to-peak pressure gradient measured at cardiac catheterisation(251). On multiple regression analysis, however, only mean aortic valve pressure gradient was significantly correlated with BNP.

Ikeda et al have reported on a group of 13 patients with more severe disease undergoing aortic valve replacement(252). They demonstrated much higher mean levels of BNP in AS patients (367.2 pg/ml) compared to age matched patients undergoing coronary artery bypass grafting (53.8 pg/ml) and a group of slightly younger controls (16.9 pg/ml)(252). The BNP levels in AS patients were > four fold higher than ANP levels, which were also raised (77.9 pg/ml). There was an exceptionally strong correlation of both log transformed (to normalise the data) BNP and log ANP with end systolic wall stress calculated from echocardiographic and simultaneous blood pressure measurements ($r=0.96$ for BNP and $r=0.94$ for ANP)(252). Reductions in BNP following aortic valve replacement were also strongly associated ($r=0.8$) with reductions in end systolic wall stress. These data suggest that in patients with marked pressure overload, BNP synthesis and secretion is primarily regulated by end systolic wall stress. There were very similar correlations for ANP and end systolic wall stress, which may indicate that in severe AS, the ventricular production of ANP exceeds that of atrial production.

1.11.4 BNP as a Prognostic Indicator

Two recent publications have demonstrated that BNP is a very powerful predictor of outcome following myocardial infarction(253,254). In 131 patients suffering from an acute myocardial infarction, BNP has been shown to be a strong predictor of cardiovascular mortality and the development of heart failure, and confers additional information to that of left ventricular ejection fraction(253). In this study, BNP was not associated with a reduced left ventricular ejection fraction, although ANP and N-terminal ANP were. In a further large series of 121 patients following myocardial infarction NT-BNP and BNP were both shown to be strong predictors

of outcome at 2 years of follow up(254). NT-BNP and BNP (r = -0.63 and –0.62 respectively) both correlated relatively strongly with left ventricular ejection fraction, whereas ANP was not associated with left ventricular function. N-terminal BNP has also been shown to confer additional information in detecting high risk patients referred for echocardiography who were suspected of having left ventricular systolic dysfunction(255).

1.12 Endothelins and cardiac disease

The structure synthesis and biological actions of endothelins have been reviewed in detail elsewhere(256-258). Endothelin-1(ET-1), a 21-amino-acid peptide was first described in 1988. A pre-propeptide is secreted by the endothelium and may also be produced by the vascular smooth muscle cells. This pre-propeptide is cleaved to form big endothelin, which is subsequently cleaved by endothelin converting enzyme to the active 21-amino-acid peptide. There are three structurally distinct isoforms of this 21-amino-acid peptide, ET-1, endothelin-2 and endothelin-3. In humans, ET-1 appears to be the most biologically active of the three isoforms and is the most potent vasoconstrictor known. After exogenous administration, ET-1 increases peripheral resistance and BP in a dose-dependent manner. However, in the first few minutes after administration, there is initial vasodilation presumed secondary to the release of nitric oxide and other vasodilators from the endothelium. ET-1 is also positively inotropic when studied in papillary muscle and cardiac myocyte preparations and can induce myocyte division and hypertrophy. The coronary, renal and cerebral circulations appear to be particularly sensitive to the actions of endothelins. Vasoconstriction occurs in both arteries and veins, but seems to occur primarily in the resistance vessels. Vasoconstriction occurs by both a direct action and an indirect effect via augmentation of the pressor actions of angiotensin II, noradrenaline and serotonin.

1.12.1 Endothelin and CHF

Endothelins may play an important role in endothelial dysfunction, which has been clearly documented in CHF. Endothelin concentrations increase four-fold in moderate to severe heart failure and correlate with both haemodynamic severity and functional impairment(256,259). ET-1 predicts increased mortality from heart failure and the need for cardiac transplantation. Administration of endothelin

antagonists result in favourable haemodynamic changes, with reductions in mean arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and an increase in cardiac index in patients with heart failure. Endothelin concentrations are also reduced after prolonged administration of carvedilol in CHF, which has been shown to reduce morbidity and mortality(256).

1.12.2 Endothelin and exercise responses

1.12.2.1 Response to exercise in normal subjects

In normal subjects undergoing various forms of exercise, the reported plasma endothelin response has been contradictory. Study results are summarised in the table 1-7.

Author	Year	Exercise Mode		Subjects Status	No	Age	M/F	ET-1 (pg/ml) Rest	Ex
De Groote(267)	1995	B	Inc	Healthy	15	35	13/2	2.0 pmol/L	1.7* pmol/L
Ahlborg(262)	1995	B	SS	Healthy	7	26	M	4.0 pmol/L	6.5 pmol/L
Letizia(266)	1995	B	Inc	Healthy	7	53	M	10.8	11.3*
Predel(269)	1995	B	Inc	Healthy	10	?	M	5.5	5.5*
Rocker(261)	1996	B	Inc	Healthy	15	27	M	10.0	16.1
Cosenzi(270)	1996	B	Inc	Healthy	15	20-35	8/7	1.2	1.4*
Maeda(260)	1996	Ken	-	Athletes	5	19	M	1.3	2.0
Maeda(263)	1997	B	SS	Athletes	5	19	M	1.4	2.2
Mangieri(271)	1997	HG	Iso	Healthy	12	43	M	0.7	0.9*
Fontana(272)	1997	B	Inc	Healthy	8	45-60	6/2	4.4	3.0
Ishikawa(264)	1998	TM	Inc	Healthy	5	10	?	1.1	1.9
Mangieri(266)	1998	HG	Iso	Healthy	10	27	M	0.6	0.8

Table 1-7: ET-1 responses to exercise in normal subjects.
All differences in ET-1 levels are statistically significant unless marked*. Abbr: TM=treadmill; B=bicycle ergometry; HG=handgrip; Ken=kendo; Inc=incremental; Iso=isometric; SS=steady state

The majority of studies have shown that ET-1 increases immediately following exercise(260-266). During incremental exercise, the peak plasma endothelin response may not occur for up to 30 minutes following cessation of exercise(263). However, during steady state exercise at 70% V_{O_2}max ET-1 starts to increase by

10 minutes and peaks at approximately 20 minutes and then falls back towards baseline values(262).

The magnitude of ET-1 increase correlates with both reductions in left atrial diameter and body weight and with increases in plasma arginine vasopressin, suggesting that reductions in blood volume may stimulate endothelin secretion(260). Other factors that may contribute to the secretion of ET-1 during exercise are elevated levels of angiotensin II, skeletal muscle blood flow and catecholamine release(270).

Several studies have shown either non-significant increases in ET-1 following exercise(266,269,270) or an actual fall in concentration(272). Some of the variations in results may be accounted for by different exercise protocols, time of sampling and more conservative analysis, e.g. by analysis of variance rather than paired t-tests(266).

1.12.2.2 CHF

Several studies have examined the effect of various types of exercise on plasma endothelin concentrations(267,271,273,274), Results are displayed in table 1-8.

First Author	Year	Exercise Mode		Status	Subjects No	Age	M/F	ET-1 (pg/ml) Rest	Ex
McMurray(274)	1992	TM	Inc	CHF	8	67	6/2	11.0 pmol/L	10.8* pmol/L
De Groote(267)	1995	B	Inc	DCM	20	52	18/2	2.9 pmol/L	2.9* pmol/L
Mangieri(271)	1997	HG	Iso	CHF	10	37	M	8.4	11.9
Ishikawa(273)	1995	TM	Inc	Cong HD	7	13	6/1	1.2	1.0
Mangieri(266)	1998	HG	Iso	FHx HTN	11	25	M	1.1	1.9
Ishikawa(264)	1998	TM	Inc	Cong HD	6	10	?	1.2	1.2*
				Cong HD	8	12	?	1.2	1.1*

Table 1-8: ET-1 responses to exercise in cardiac disease.
All differences in ET-1 levels between rest and exercise are statistically significant unless marked *. Abbr: TM=treadmill; B=bicycle ergometry; HG=handgrip; Ken=kendo; Inc=incremental; Iso=isometric; SS=steady state; IHD=ischaemic heart disease, (-)/(+) negative/positive for reversible ischaemia; CHF=chronic heart failure; DCM=dilated cardiomyopathy; Cong HD=congenital heart disease; FHx HTN=sons of patients with hypertension.

Two studies, one using bicycle exercise(275) and one employing handgrip exercise(271) have shown increases in ET-1 at peak exercise. There have been conflicting results however in patients with dilated cardiomyopathy and CHF where no increase in endothelin was seen(267,274). It is difficult to explain these contradictory results since similar groups of patients and protocols were employed but both type I and II statistical errors are possible due to the small sample sizes.

Krum et al did demonstrate that peak plasma concentrations of ET-1 was inversely correlated($r = -0.65$) with peak V_{O_2} in heart failure patients and also ($r = -0.68$) in healthy controls(275). There was also a significant correlation between peak plasma levels of ET-1 and V_E/V_{CO_2} ($r = -0.72$) in 12 patients with NYHA class II and III heart failure(275). This study does suggest that endothelin may play an important role in the regulation of local muscular blood flow, possibly contributing to exercise intolerance in CHF.

In a large study looking at prognosis in CHF, endothelin was also shown to be a predictor of adverse outcome(276). In 23 patients with all classes of heart failure, who had undergone cardiopulmonary exercise testing, only ET-1, NYHA functional class, maximal workload achieved and plasma ANP were independent predictors of outcome, but not peak V_{O_2} itself(276).

1.12.3 Endothelin and coronary artery disease

In patients with coronary artery disease and normal left ventricular function resting plasma endothelin concentrations are similar to age matched controls(268,269,272). In response to incremental bicycle exercise, however, patients with coronary artery disease demonstrate a significant increase in ET-1 concentrations compared to controls(268,269,272)(see table 1-9).

These results suggest that ET-1 may play an important role in exercise induced myocardial ischaemia. Interestingly there are conflicting results as to whether those with reversible ischaemia are more likely to have increases of ET-1 on exercise(268,272).

Author	Year	Exercise Mode		Status	Subjects No	Age	M/F	ET-1 (pg/ml) Rest	Ex
Letizia(268)	1995	B	Inc	IHD (-)	13	53	?	7.8	13.6
				IHD (+)	7	53	?	8.7	9.6*
Fontana(272)	1997	B	Inc	IHD (-)	12	?	?	4.6	3.2
				IHD (+)	8	?	?	4.0	6.0
Predel(269)	1995	B	Inc	IHD	10	?	M	6.1	7.3

Table 1-9: ET-1 responses to exercise in coronary artery disease
All differences in ET-1 levels between rest and exercise are statistically significant unless marked *. Abbr: B=bicycle ergometry; Inc=incremental; IHD=ischaemic heart disease, (-)/(+) negative/positive for reversible ischaemia.

In patients with a clinical diagnosis of angina pectoris with cardiac syndrome X, resting ET-1 concentrations have been reported to be significantly higher than matched controls(277,278). Thus, ET-1 may be a marker of endothelial dysfunction in this group of patients.

1.13 Neurohormonal adaptations in AS

Unlike CHF there are only a few published reports of neurohormonal adaptations in AS.

1.13.1 ET-1 and AS

Resting ET-1 plasma concentrations have also been shown to be elevated in AS patients without overt heart failure(279,280). ET-1 levels correlated with pulmonary capillary wedge pressure, mean pulmonary artery pressure, left atrial diameter and inversely correlated with aortic valve area(279). In 15 patients with pulmonary hypertension secondary to rheumatic heart disease undergoing valve replacement, ET-1 was also elevated (281). ET-1 was significantly correlated with pulmonary artery and pulmonary capillary wedge pressure and returned towards normal two weeks after surgery(281). The ET-1 response to exercise in AS has not been studied to date.

1.13.2 Catecholamines/renin-angiotensin system

Plasma noradrenaline(279,282) and dopamine(279) are elevated in patients with haemodynamically significant AS without signs of CHF. Plasma renin and angiotensin were reported as being elevated in 14 aortic patients(280) but not in two other studies(279,282). However one of these latter studies did show aldosterone concentrations were raised(282) which would be consistent with activation of the renin-angiotensin system.

1.13.3 Tumour necrosis factor-α (TNF-α)

TNF-α has been shown to be elevated in 21 patients with significant AS but no coronary artery disease(283). Those in NYHA class II had greater levels than asymptomatic subjects and TNF-α levels correlated significantly with mean pressure gradient in 16 of the patients with normal left ventricular systolic function(283).

1.14 Similarities between valvular heart disease and CHF

1.14.1 Mitral stenosis

Mitral balloon valvuloplasty, an intervention which leads to immediate improvements in haemodynamic indices, does not result in early increases in exercise capacity(284,285). However, three-four months following mitral balloon valvuloplasty peak V_{O_2} had significantly improved and the exercise V_E/V_{CO_2} slope had reduced(284,285). These favourable alterations were associated with changes in skeletal muscle structure and function(284). Quadriceps muscle strength and area increased and there was a shift in fibre type from type II (anaerobic) to type I (aerobic). These data suggest that similar mechanisms limit exercise capacity in CHF and mitral stenosis, despite the fact that left ventricular function in mitral stenosis is generally preserved.

1.14.2 AS

It is unclear why some patients with AS are symptomatic and others asymptomatic despite similar degrees of haemodynamic severity. The symptoms of AS are

similar to those of CHF. Exercise cardiac output is limited and increases in pulmonary capillary wedge pressure, are similar in these two common cardiac conditions. Dyspnoea and fatigue are the commonest reasons for test termination during exercise tolerance testing. Resting haemodynamic indices are poor predictors of $V_{O_2}max$ and interventions which improve haemodynamics (aortic valve replacement in AS, vasodilators in CHF) result in slow improvements in exercise capacity.

Neuro-hormonal adaptations to AS and CHF may also be similar. Both are associated with elevated natriuretic peptides, endothelin, tumour necrosis factor-α, catecholamines and activation of the renin angiotensin system also occurs in both disease states. Abnormalities of arterial vasodilation are well documented in CHF and have been confirmed in patients with severe valvular disease requiring valve replacement. Undoubtedly there are only a few such reports in AS but CHF patients have been more extensively and intensively investigated, particularly with respect to exercise. These vascular and neuro-endocrine adaptations may play important aetiological roles in exercise limitation, perhaps by their effects on the development of skeletal muscle abnormalities which may contribute to exercise tolerance and symptom generation.

1.15 Summary

AS is a common disorder and the prevalence of this disease is increasing, particularly in elderly patients. Symptomatic AS is a malignant condition with a five year survival of <50%. Aortic valve replacement is virtually a curative procedure for those who survive the peri-operative period. Asymptomatic AS has a relatively good prognosis although the exact morbidity and mortality figures are uncertain due to the natural history of the disease in the modern era being interrupted by surgery. Aortic valve replacement is recommended for symptomatic patients but the timing of surgery is critical to optimise outcome. The mechanisms underlying symptom generation and exercise limitation in AS are poorly understood, but are likely to be closely related. An ability to reliably predict the development of symptoms would greatly help in determining the exact timing of aortic valve replacement in patients with significant AS.

The importance of peripheral, and in particular skeletal muscle, adaptations in the role of exercise limitation in CHF and mitral stenosis have been well documented. Piepoli and colleagues have recently demonstrated enhanced ergoreflex activity on exercise which allows a unified mechanism to explain both the skeletal muscle and ventilatory abnormalities seen in CHF(213). AS has many similarities to CHF in symptoms, pathophysiological adaptations and exercise haemodynamics.

1.16 Aims

This thesis investigates non-invasive predictors of exercise capacity in patients with haemodynamically significant AS, who will be compared to control subjects. The aims are to identify factors which may be associated with exercise intolerance and symptoms. Special attention will focus on predictors of exercise capacity and the relationship between skeletal muscle work-sensitive receptors and a neural connection for the control of ventilation (ergoreflex). BNP and ET-1 responses to maximal exercise will be examined. Patients will be classified by both disease severity and symptomatic status.

1.17 Hypotheses

The following hypotheses will be tested:

1.17.1 Cardiopulmonary exercise testing

1.17.1.1 Exercise capacity

H: Treadmill exercise duration and V_{O_2}max are reduced in AS patients compared to matched controls.

H_O: Treadmill exercise duration and V_{O_2}max are not significantly different in AS patients compared to matched controls.

1.17.1.2 Ventilatory response to exercise

H: The slope of exercise V_E/V_{CO_2} is increased in AS patients compared to matched controls.

H_O: The slope of exercise V_E/V_{CO_2} is not significantly different in AS patients compared to matched controls.

1.17.2 Skeletal muscle strength and endurance

H: Quadriceps strength and endurance are reduced in AS patients compared to matched controls.

H_O: Quadriceps strength and endurance are not significantly different in AS patients compared to matched controls.

1.17.3 Ergoreflex

1.17.3.1 Arm exercise

H: The magnitude of ergoreflex activity after handgrip exercise is increased in AS patients compared to matched controls.

H_O: The magnitude of ergoreflex activity after handgrip exercise is not significantly different in AS patients compared to matched controls.

1.17.3.2 Leg exercise

H: The magnitude of the ergoreflex activity after lower leg exercise is increased in AS patients compared to matched controls.

H_O: The magnitude of the ergoreflex activity after lower leg exercise will not be significantly different in AS patients compared to matched controls.

1.17.4 BNP

1.17.4.1 Resting and exercise BNP

H: Plasma BNP is greater at rest and after exercise in AS patients compared to matched controls.

H_O: Plasma BNP at rest and on exercise is not significantly different in AS patients compared to matched controls.

1.17.4.2 BNP and exercise capacity

H: Plasma BNP is associated with reduced exercise capacity in AS patients.

H_O: Plasma BNP is not associated with reduced exercise capacity in AS patients.

1.17.5 Endothelin

1.17.5.1 Rest and exercise ET-1

H: Plasma ET-1 is increased at rest and on exercise in AS patients compared to matched controls.

H_O: Plasma ET-1 at rest and on exercise is not significantly different in AS patients compared to matched controls.

1.17.5.2 ET-1 and exercise capacity

H: Plasma ET-1 is associated with reduced exercise capacity in AS patients.

H_O: Plasma ET-1 is not associated with reduced exercise capacity in AS patients.

1.17.6 Predictors of exercise capacity

1.17.6.1 Haemodynamic indices

H: Haemodynamic indicators of AS severity (pressure gradient, aortic valve area, ejection fraction) will not be significant predictors of aerobic exercise capacity.

H_o: Haemodynamic indicators of AS severity (pressure gradient, aortic valve area, ejection fraction) are significant predictors of aerobic exercise capacity.

1.17.6.2 Ventilatory indices

H: The slope of exercise V_E/VCO_2 and the magnitude of the ergoreflex are significant predictors of aerobic exercise capacity in AS.

H_o: The slope of exercise V_E/VCO_2 and the magnitude of the ergoreflex are not significant predictors of aerobic exercise capacity in AS.

2. METHODS

2.1 Subject selection

2.1.1 Patients

The case-notes of patients attending the General Cardiology and Adult Congenital Heart Disease clinics at the Western Infirmary, Glasgow were screened to determine eligibility for inclusion in the study. If deemed eligible, the patients were sent a letter giving brief details of the study, and requested to return a tear-off slip if they were interested in participating in the study. If patients indicated an interest they were contacted by telephone and an appointment was arranged to visit the hospital. Recruitment was also undertaken of those patients who met the criteria and were already on the Western Infirmary waiting list for aortic valve replacement. The cardiothoracic unit art the Western Infirmary is a tertiary referral centre covering Southwest Scotland and covering a population of approximately two million. Several patients were also recruited from the Cardiology clinics at the Royal Alexandra Hospital, Paisley.

2.1.2 Healthy volunteers

Twenty asymptomatic control healthy subjects were recruited from staff, friends and family members of the Department of Medicine and Therapeutics.

2.1.3 Inclusion Criteria for Patients

1. Aortic valve peak pressure gradient > 25 mmHg

2. Ability to perform treadmill exercise

2.1.4 Exclusion Criteria patients and controls

1. Obstructive coronary artery disease (previous MI, CABG or > 70% luminal stenosis on coronary angiography)

2. Atrial fibrillation

3. Exertional syncope

4. Uncontrolled heart failure or arrhythmias

5. Other significant valvular or structural heart disease

6. Uncontrolled hypertension > 180 mmHg systolic or 110 mmHg diastolic

7. Symptomatic hypotension or systolic BP < 90 mmHg

8. Diabetes mellitus

9. Peripheral neuropathy or myopathy

10. Chronic obstructive pulmonary disease

11. Pregnancy

12. Current warfarin therapy

Written, informed consent was obtained from all subjects prior to testing. The following Ethics Committees approved the study in full: the West Glasgow Hospital University NHS Trust, the Royal Alexandra Hospital and Ayr. Testing was split into two or three visits to the hospital, each lasting $2^1/_2$-3 hrs. A brief medical history was taken to ensure that subjects did not fulfil any of the exclusion criteria, for determination of NYHA class and documentation of medication.

2.1.5 Patient recruitment

A total of 226 patients with a diagnosis of AS were screened for eligibility by personal contact or case-note review. The commonest reasons for exclusion were other structural heart disease or previous valve surgery (56), peak pressure gradient <25mmHg (34) obstructive CAD (21), COPD (16), atrial fibrillation (8), other medical conditions (16) and already had aortic valve replacement (3). Seventy-two patients satisfied the study inclusion/exclusion criteria and were invited by letter to participate in the study. Fifty-one (71%) patients responded. Of these, 41 were and ten were not interested in taking part. Four of the 41 were unable to participate in the study: one was scheduled for aortic valve replacement the following week, one became pregnant, one was unable to get time off work and another lived too distant from the hospital.

2.2 Anthropometric measurements

Height was recorded using a metre stick and weight was measured on a SECA balance scale. Skinfold thickness was measured to the nearest 1 mm at four sites to determine percentage body fat according to the Durnin technique(286). Lean body mass (LBM) was calculated from the standard formula below:

Equation 8: Calculation of LBM

LBM = weight (in kg) – (weight x % body fat)

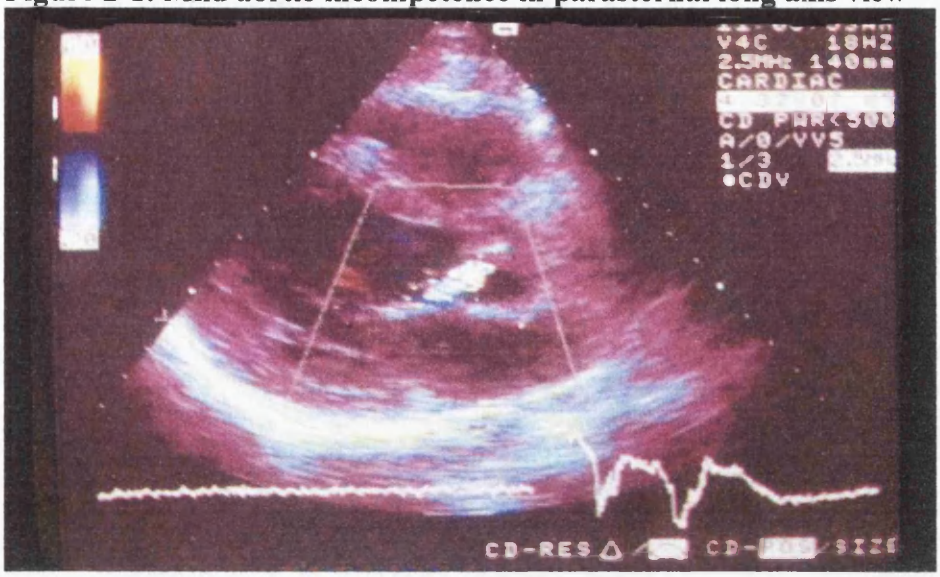
2.3 Echocardiography

All subjects underwent echocardiography carried out according to the ACC/AHA guidelines(44) and M-mode measurements were made as recommended by the American Society of Echocardiography(287). An Acuson 128XP/10c medical diagnostic ultrasound system was used to record all images on super VHS videotape for later analysis. This machine is equipped with a multi-hertz transducer capable of operating at 4, 3.5 and 2.5 MHz. Two dimensional and colour flow Doppler images were obtained from (1) parasternal long axis (2) parasternal short axis (3) apical four and five-chamber views and (4) apical two chamber view.

M mode recordings from the parasternal long axis were used for measurement of aortic root, left atrium and left ventricular dimensions, using leading edge for measurement as previously described. Penn convention was used to determine left ventricular mass(288). This was corrected for body surface area to give a left ventricular mass index.

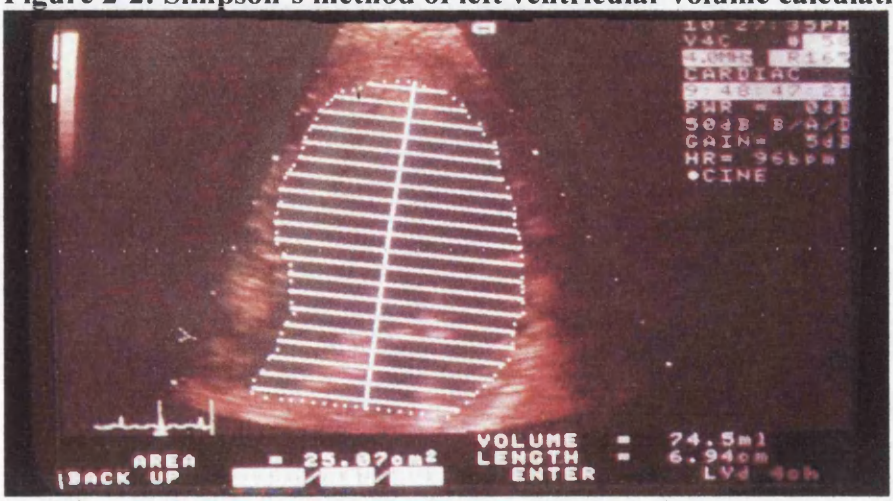
Valvular competency was assessed in parasternal long axis and apical and two chamber views with colour Doppler (see figure 2-1). Left ventricular outflow tract was measured on the long axis parasternal view in midsystole employing the cine function. Aortic valve area was calculated according to the continuity equation with use of the peak and mean aortic velocity and left ventricular outflow tract velocity, measured with pulse wave Doppler(50,59).

Figure 2-1: Mild aortic incompetence in parasternal long axis view



Trans-mitral left ventricular inflow patterns were measured using pulse wave Doppler located just below the tips of the mitral leaflets to record early (E) and atrial (A) diastolic filling and their ratio, E/A. Peak aortic velocity was assessed from multiple positions (apical, parasternal, suprasternal and subcostal views) using the non-imaging continuous wave transducer. The integral of the velocity obtained was determined to calculate mean velocity. Ejection fraction was calculated by Simpson's biplane method(289) (figure 2-2). All echocardiographic measurements were made in triplicate and the average was taken as the final value.

Figure 2-2: Simpson's method of left ventricular volume calculation



The left ventricular endocardial surface is traced in end-diastole and end-systole in both 4 chamber and 2 chamber views.

2.4 Muscle strength and endurance

2.4.1 Equipment

Isometric and isokinetic testing was performed on the Kin-Com II (500H, version 5.16) dynamometer (Chattex Corporation, Chattenooga, Tennessee, USA). The test took place in a laboratory within the Kelvin Building at Glasgow University which adjoins the Western Infirmary. All tests were performed on the right leg only, as previous investigations had found no significant difference between right and left legs(200). Right quadriceps muscles were assessed both isometrically and isokinetically, whereas the right hamstrings muscles were assessed isokinetically only.

2.4.2 Patient set up

The patient was seated in the Kin-Com chair with a seatbelt around the waist and a strap over the thigh for stabilisation. The lateral femoral condyle of the subject's right knee was visually aligned with the axis of rotation of the isokinetic dynamometer, by adjusting the position of the seat. The lower leg was attached to the distal end of the lever arm using a shin pad, positioned approximately 3 cm above the ankle and allowing full dorsiflexion of the ankle.

2.4.3 Computer set up

The subject's details and weight were entered on to the computer. Gravitational corrections were made for the effect of limb weight on both torque (isokinetic test) and force production (isometric test).

2.4.4 Isometric test

An isometric test was used to evaluate static quadriceps strength. The lever arm of the Kin-Com was positioned at 105^{o} (for the first isometric contraction) and then 110^{o} (for the second isometric contraction). The subjects performed two submaximal isometric contractions at the designated angles in order to familiarise themselves with the protocol. The protocol consisted of 1 maximal voluntary contraction with the knee at 105^{o} flexion and then another maximal contraction at

110°, each lasting for five seconds. There was a 30s recovery period between each contraction. During the test the subject was instructed to push against the immovable lever arm as hard as possible for five seconds and standardised verbal encouragement was given throughout. The dynamometer continuously recorded the force (N) produced by the quadriceps during the isometric contraction.

2.4.5 Isokinetic test

Firstly the subjects completed 4-5 submaximal contractions to familiarise themselves with isokinetic contractions. This test was utilised to assess dynamic strength and endurance of both the quadriceps and hamstring muscles. The start position for the test was with the knee in 90° flexion. The subject determined the stop angle: as the angle to which they could comfortably extend their knee. The isokinetic protocol consisted of 25 continuous flexion/extension concentric contractions at an angular velocity of 180°/sec. Subjects were instructed to kick and pull against the lever arm through the entire range of motion, as hard and as fast as possible. Since this was a maximal test, the subjects were informed not to pace themselves in order to complete the 25 repetitions. During the test standardised, strong verbal encouragement was given to maximise effort. The reliability of this isokinetic protocol in assessing various parameters of muscular endurance has previously been reported(290).

The dynamometer continuously recorded torque generated by the quadriceps and the hamstring muscles during the isokinetic test. Peak torque (Nm) produced by both muscle groups was used to measure dynamic strength. The decline in peak torque throughout the isokinetic test and total work assessed dynamic endurance. On cessation of the test, the straps were loosened allowing the subject to relax their leg.

2.4.6 Calculation of strength and endurance

2.4.6.1 Static quadriceps strength

1. Isometric peak force (N): the highest value of the peak force recorded during either of the two maximal contractions

2. Isometric average force (N): the highest value of the average force recorded during the two maximal contractions

2.4.6.2 Dynamic quadriceps and hamstring strength

1. Peak torque (Nm): the highest value of the peak torque generated during the 25 isokinetic contractions

2.4.6.3 Dynamic quadriceps and hamstrings endurance

Calculations used were as previously suggested (291)

1. Fatigue index (percentage): this was calculated as the mean peak torque of the last 5 contractions, expressed as a percentage of the mean peak torque of the best 3 of the first 5 contractions (the first five were not used as often peak torque is not achieved until the second or third contraction) (290).

2. Average work (W): the average work produced during the 25 contractions.

3. Total work (J): the total work generated during all 25 contractions.

Measures of static and dynamic strength, average power and total work were divided by lean body mass to correct for variations in muscle mass.

2.5 Ventilatory gas measurement

Ventilatory gas exchange variables were measured by a Medgraphics CPX/D breath by breath analyser utilising Breeze3 software (Medical Graphics Corp., St. Paul, Minnesota, USA). Subjects, wearing noseclips, breathed through a mouthpiece connected to a pneumotachograph which calculates expired gas volumes. Expired oxygen (O_2) and carbon dioxide (CO_2) were sampled continuously. The breath by breath analyser allows determination of minute ventilation (V_E) minute O_2 consumption (VO_2), minute CO_2 excretion (VCO_2), and calculates respiratory exchange ratio(RER), respiratory rate, tidal volume and O_2 pulse from these variables. Data can be displayed breath by breath or averaged over 10s or multiples thereof. Gas exchange was measured during treadmill testing and throughout arm and leg ergoreflex studies.

2.5.1 Calibration of ventilatory equipment

The temperature and humidity at the time of testing was recorded (Oregon Scientific Model BA-116) and entered into the analyser computer. Gas measurements are stated standardised for temperature and humidity. Prior to each test the CO_2 and O_2 analysers were calibrated against standard concentrations and the pneumotachograph was calibrated at five different flow rates with a three litre syringe.

2.6 Treadmill exercise tolerance testing

2.6.1 Protocol

A maximal symptom limited incremental exercise test was performed according to the Bruce protocol(292) in 36 AS subjects and all controls. Subjects were connected to a 12 lead ECG exercise recorder(Quinton 4000) with an integrated control panel for the treadmill(Quinton 65). Prior to formal testing each subject had a familiarisation walk on the treadmill at 1.7mph with 10^0 incline (stage 1). One patient could not walk at this pace and therefore the Modified Bruce protocol was used. They were then allowed to recover for 10 minutes. Subjects were allowed to rest their hands on the bar at the front of the treadmill to aid balance but were instructed not to lean on the bar or grip it tightly. During the test each subject was given standardised verbal encouragement by the investigator to continue for as long as possible. The test was terminated on a hand signal from the subject and the treadmill belt slowed over a period of 45s, allowing a warm down. Recovery data were taken for a further three minutes at which point the mouthpiece and noseclips were removed and subjects were asked what caused them to stop exercising. Tiredness and leg discomfort were classified as fatigue. Medication was not discontinued prior to testing.

Peak V_{O_2} was determined as the highest value averaged over 30s. The slope of V_E/V_{CO_2} was calculated using simple linear regression. The slope was calculated only for exercise data corresponding to a respiratory exchange ratio <1.0 since ventilation rises exponentially towards maximal exercise(174).

2.6.2 Medical indications for termination of the treadmill test:

1. A fall in SBP
2. Horizontal or downsloping ST depression >5mm
3. Any sustained arrhythmias

2.7 Ergoreflex

All tests were performed in the same quiet exercise laboratory without distraction. The order of leg and arm protocols was randomised.

2.7.1 Hand grip exercise

The protocol was based on that used by Piepoli(213).

2.7.1.1 Exercise position

The subject was seated with their right arm flexed to 90^0 and resting on a flat surface. Each subject performed 2 maximal handgrip dynamometer (Takei TKK 5001 Grip A) contractions with the right hand in order to assess peak force production. An inflatable cuff was placed above the right elbow and connected to a rapid cuff inflator (Hokanson E20, Hokanson AG-101 cuff inflator air source). A BP cuff was positioned above the left elbow to enable BP measurements to be taken (Accoson sphygmomanometer). The subject was then connected to the breath by breath analyser.

Three runs with data collection were completed in the following manner:

2.7.1.2 Control run

Baseline data were recorded for three minutes. The cuff on the right arm was then inflated to 30 mmHg above systolic BP for three minutes using the rapid cuff inflator to induce regional circulatory occlusion (RCO). The cuff was then deflated and three minutes of recovery data were obtained. This exercise free run served as a control run to determine any possible confounding effect of cuff inflation on ventilation and BP.

2.7.1.3 Cuff run

Resting data were obtained for three minutes. Right hand grip contractions were then commenced at 50% of the determined peak force at 60 repetitions/min (determined by digital metronome, Seiko DM-10) until volitional exhaustion. On termination of exercise, the cuff was inflated to 30 mmHg above systolic pressure, creating RCO for three minutes. After three minutes the cuff was deflated and a further 3 min recovery data were obtained.

2.7.1.4 Non-cuff run

The non-cuff run consisted of an identical protocol to the cuff run except the cuff was not inflated at the end of exercise, thus producing a protocol of: three minutes rest data, handgrip dynamometer at 50% peak force, 60 repetitions/min until exhaustion, 6 min recovery data (without RCO)

The control run was always performed first, however, the order of cuff and non-cuff was randomised with 15 minutes between each exercise run to minimise possible effects of fatigue.

2.7.2 Lower leg Exercise

2.7.2.1 Exercise position

The exercise undertaken was aimed at exercising the muscles below the knee only. The subject lay supine on a bed with the upper body inclined at 30^0 and was asked to remain as still as possible with the exception of the exercising lower limb. The subject isotonically dorsiflexed/plantarflexed the right foot to the beat of a metronome at 44 beats per minute with a weight (200g/10kg lean body mass) attached to the shoe by a rope. The weight was suspended over the end of the bed via a pulley system. Two pillows were placed under the calf, raising the leg and allowing movement of the foot without the heel striking the bed. The subject gave a hand signal to indicate when fatigued, at which point the weight was detached from the rope allowing the recovery period to commence.

2.7.2.2 Protocol

We have previously described the protocol used which is identical to that for handgrip exercise except lower leg exercise is performed instead(226). RCO was obtained by inflating an adult thigh sphygmomanometer cuff, attached to the right thigh, to 30mm above SBP. BP was measured in the right arm. The order of cuff and non-cuff runs was randomised.

2.7.3 Data analysis

2.7.3.1 Ventilatory data

For the purposes of analyses, data were averaged over 10s periods. Peak ventilatory data were taken averaged over the final 30s of exercise. As the recovery data (both cuff and non-cuff runs) are likely to be influenced by the peak exercise measurement, analysis was performed according to the method suggested by Altman and colleagues(293). The first three minutes of data after exercise were averaged to give cuff recovery and non-cuff recovery values. To compare the magnitude of the effect of RCO on recovery ventilation between the groups the following equation was used:

Equation 9: Ergoreflex (cuff) magnitude calculation

$$\text{Magnitude of ergoreflex} = \frac{\text{(3 min cuff value- resting value)}}{\text{(Peak exercise value - resting value)}} \times 100$$

The degree of ergoreflex activation during recovery without cuff inflation was also assessed representing a more physiological measure of 'normal' recovery:

Equation 10: Ergoreflex (non-cuff) magnitude calculation

$$\text{Magnitude of ergoreflex} = \frac{\text{(3 min non-cuff value – resting value)}}{\text{(Peak exercise value - resting value)}} \times 100$$

The magnitude of ergoreflex therefore equates to the percentage of the peak exercise increase persisting during the first 3 minutes recovery.

2.7.3.2 BP data

The final BP reading prior to exercise was deemed the resting BP. The last BP recording prior to exercise termination was taken as the peak BP and the three BP recordings during recovery were averaged and used for cuff and non-cuff recovery. Magnitude of ergoreflex was calculated as for ventilation.

2.8 Neurohormonal sampling and analysis

2.8.1 Blood sampling

Blood samples (20mL) were drawn by venepuncture with the subject in a seated position after resting for 30 minutes. Post-exercise venepuncture was performed immediately after the treadmill stopped. Ten mL was placed into a pre-chilled tube with EDTA containing 1000IU trasylol (for BNP) and 5mL into EDTA (for ET-1), both of which were immediately placed on ice. The samples were centrifuged, within 15 minutes, at 3000 rotation per minute for 10 minutes and the plasma was stored in aliquots at -20^0C until thawing for analysis.

2.8.2 BNP analysis

BNP was measured using a Shionoria immunoradiometric assay (CIS Bio International, France). This assay has a limit of detection of 1 pg/ml, a coefficient of variation of <7.5% and a normal range of 2 - 20 pg/ml.

2.8.3 ET-1

ET-1 was measured using an ELISA kit (Biomedica, Austria). This has a limit of detection of 0.05 fmol/ml, a coefficient of variation of <7.6% and a normal range of 0.2 - 0.7 fmol/ml.

2.9 Physical activity levels

All subjects were asked to complete the Scottish physical activity questionnaire (SPAQ) and return it in a pre-paid envelope. SPAQ is a seven day recall questionnaire in which subjects estimate their daily leisure time and work physical activity(294). SPAQ has been validated in a healthy Scottish population(294).

The order of testing is outlined in diagrammatic form in appendix A.

2.10 Data analysis

2.10.1 AS severity and symptomatic status

For analysis of the severity of AS, the patients were divided into 2 groups based on an arbitrary cut-off in mean pressure gradient: moderate to severe (**severe**) > 30 mmHg and mild to moderate (**mild**) < than 30 mmHg (see table 1-1 for classification). Subjects were also divided into **asymptomatic** and **symptomatic** groups by direct questioning. As previously, patients with only mild dyspnoea or fatigue (on at least moderate exertion) and no chest pain or syncope were classified as asymptomatic due to the non-specific nature of these symptoms(25,91).

2.10.2 Statistical tests

Analyses were performed utilising the computer software package Minitab, version 11.21. Normality of all data were assessed by examination of box plots. Paired student's t test was used to analyse the intra-group data and between group analysis was carried out by non-paired students t test. The chi-square test was employed in comparisons of proportions. Oneway analysis of variance with Tukey's family error rate at 5% was used when the patient subgroups were compared to controls. Non-parametric intra-group data were compared by the Wilcoxon signed rank test, and Kruskal-Wallis test for comparison of group medians with further analysis by Mann-Whitney test if results were significant.(295). Pearson's correlation coefficient was used to correlate individual variables with exercise capacity. Multiple regression was performed to assess independent predictors of exercise capacity incorporating variables that had a significant or near significant correlation. BNP results were log transformed to normalise the data. $P < 0.05$ was considered statistically significant. Twelve echocardiograms were analysed on two separate occasions by the investigator and intra-observer correlation coefficients were calculated. Data are expressed as mean±standard deviation or median and interquartile range.

3. ANTHROPOMETRIC, ECHOCARDIOGRAPHIC AND PHYSICAL ACTIVITY PROFILE

3.1 Anthropometric data

Thirty-seven patients attended at least one study visit. Twenty volunteers agreed to undergo testing to serve as a control group. The individual anthropometric details of the control group are displayed in table 3-1 and those of the patient group are detailed in table 3-2.

Subject No	Sex	Age (years)	Height (m)	Weight (kg)	LBM	BMI	NYHA
C01	M	21	1.77	68.4	61.6	21.8	1
C02	M	28	1.69	80.0	60.0	28.0	1
C03	F	25	1.77	77.1	56.7	24.6	1
C04	F	29	1.70	53.3	41.0	18.4	1
C05	F	81	1.52	78.6	48.2	34.0	1
C06	M	38	1.70	85.7	63.8	29.7	1
C07	M	39	1.67	63.6	49.6	22.8	1
C08	M	60	1.74	84.5	57.5	27.9	1
C09	M	48	1.70	81.5	58.3	28.2	1
C10	M	54	1.74	78.7	53.5	26.0	1
C11	M	54	1.76	74.5	54.4	24.1	1
C12	M	50	1.80	92.2	59.0	28.5	1
C13	F	54	1.53	50.4	34.0	21.5	1
C14	F	50	1.59	61.7	37.0	24.4	1
C15	M	49	1.74	94.6	66.1	31.2	1
C16	M	66	1.85	78.4	57.1	22.9	1
C17	M	77	1.77	90.6	63.6	28.9	1
C18	F	54	1.54	61.3	36.2	25.8	1
C19	F	74	1.51	61.4	38.7	26.9	1
C20	M	57	1.57	62.5	45.8	25.4	1

Table 3-1: Individual anthropometric data for control subjects
C= control

3.2 Medication

3.2.1 Controls medication

All of the control subjects were asymptomatic although 2 subjects (C05, C15) were being treated for essential hypertension. One subject(C08) was taking pravastatin for hypercholesterolaemia.

Subject No	Sex	Age (years)	Height (m)	Weight (kg)	LBM	BMI	NYHA	Sym
Asy AS								
as01	M	20	1.84	77.0	62.8	22.7	2	D
as02	M	40	1.78	81.8	60.1	25.8	1	-
as03	M	41	1.74	94.9	65.3	31.3	1	-
as05	M	81	1.68	78.2	54.0	27.7	1	-
as08	F	25	1.64	59.0	42.6	21.9	1	-
as11	F	39	1.66	81.1	50.7	29.6	2	D
as13	F	61	1.63	61.4	40.8	23.1	2	D,F
as16	M	70	1.67	71.9	51.4	25.8	1	-
as17	M	23	1.77	71.0	59.4	22.7	1	-
as18	M	57	1.80	83.9	61.7	25.9	1	-
as19	F	64	1.60	78.5	43.7	30.7	2	D
as20	M	73	1.69	76.8	55.8	26.9	2	D
as25	F	50	1.70	82.7	50.1	28.6	2	D,F
as26	F	32	1.58	55.3	37.2	22.2	1	-
as28	F	69	1.54	69.4	41.8	29.3	2	F
as30	F	55	1.54	63.2	37.4	26.6	2	D,F
as34	M	30	1.84	65.7	55.7	19.4	1	-
as35	M	27	1.73	120.9	*	40.4	2	D,F
Sym AS								
as04	F	82	1.46	58.6	39.3	27.5	2	D,F, CP, Pre-S
as06	F	58	1.67	88.5	52.2	31.7	2	CP,D
as07	F	69	1.60	75.2	46.6	29.4	2	CP
as09	M	69	1.67	75.4	51.6	27.0	2	CP,D,F
as10	M	62	1.58	68.7	51.1	27.7	2	CP,D,
as12	M	66	1.78	107.0	70.6	34.0	3	D,F
as14	M	60	1.64	64.2	47.2	23.9	2	CP,D,F
as15	M	57	1.66	92.9	55.3	33.9	3	D,F
as21	M	75	1.88	77.7	61.0	22.0	3	D
as22	M	83	1.52	57.3	39.5	25.0	3	F
as23	M	82	1.73	72.5	52.8	24.2	3	CP,D,F
as24	F	70	1.66	72.9	48.1	26.5	2	D,CP
as27	M	83	1.67	70.1	48.9	25.1	3	D,F
as29	M	59	1.81	98.3	62.3	30.0	3	D,F
as31	F	70	1.57	51.9	34.5	21.1	3	CP,D, Pre-S
as32	F	56	1.66	62.8	40.4	22.8	3	CP,D,F
as33	F	71	1.56	38.0	28.7	15.6	3	D,F
as36	F	40	1.54	59.2	38.4	25.0	3	CP,D,F
as37	M	78	1.63	56.5	47.5	21.3	3	D,F

Table 3-2: Individual anthropometric data for patient group.
Abbr: Sym= symptoms; D = dyspnoea; F= fatigue, CP= chest pain, Pre-S= pre-syncope. *Accurate skin fold thickness could not be obtained due to body habitus.

Of the patient group, nine were in NYHA functional class I, 16 in class II, 12 in class III and none in class IV. Dyspnoea was reported by 25, fatigue by 18, ischaemic sounding chest pain in 10 and pre-syncope in 2 patients. Of the 18 patients classed as being asymptomatic four had mild symptoms of dyspnoea, four had dyspnoea and fatigue and one had fatigue only.

3.2.2 Patient medication

Twenty-six of the 37 AS patients were regularly taking some form of medication. The cardiovascular drugs were: aspirin (13), diuretics (6), beta-blockers (5), calcium channel blockers (3), statins (3), ace-inhibitors (2), other anti-hypertensive (2), nitrate (1) and digoxin (1) although all were in sinus rhythm. Six patients were also taking a non-steroidal anti-inflammatories.

3.3 Comparison of patients and controls

As can be seen from the table 3-3 the AS patients are slightly older than the controls but this difference does not reach statistical significance. The two groups are well matched for height, weight, body mass index(BMI), lean body mass(LBM) and male to female ratio.

	Age (years)	Height (m)	Weight (kg)	BMI	LBM (kg)	M/F
AS n=37	58.0±18.6	1.67±0.10	73.5±16.1	26.3±4.6	49.6±9.7#	21/16
Controls n=20	50.4±16.8	1.68±0.10	74.0±12.9	26.0±3.7	52.1±10.2	13/7
95% CI	-2.2, 17.4	-0.07, 0.04	-8.3, 7.5	-2.0, 2.5	-8.1, 3.2	
P value	0.12	ns	ns	ns	ns	ns

Table 3-3 : Anthropometric data, patients v controls.
All values given as mean±SD. 95% CI= 95% confidence interval for the difference between means. # n=36.

3.4 Electrocardiography (ECG)

3.4.1 AS

All patients were in sinus rhythm. Ten subjects had a normal ECG. The following abnormalities were present: left ventricular hypertrophy (6), left ventricular hypertrophy plus strain (6), repolarisation abnormalities (12), pathological Q waves or poor R wave progression (6), left bundle branch block (2) and first degree block (2).

3.4.2 Controls

All subjects were in sinus rhythm. Two had repolarisation abnormalities and two had voltage criteria for left ventricular hypertrophy.

3.5 Echocardiography

All subjects underwent echocardiography. There were no significant abnormalities of valvular or left ventricular structure and function in the control group.

3.5.1 Intra-observer correlations

The intra-observer correlation coefficients are shown in table 3-4. They are good to excellent except those for ejection fraction by Simpson's biplane method and aortic valve area using the velocity time integral.

Variable	r
Ejection fraction (Simpson's)	0.63
Left ventricular mass	0.95
Left ventricular mass index	0.94
Maximal aortic velocity	0.90
Peak pressure gradient	0.83
Mean pressure gradient	0.91
Aortic valve area (V max)	0.83
Aortic valve area (VTI)	0.59
Peak E	0.89
Peak A	0.93
E / A	0.95

Table 3-4: Echocardiography: intra-observer correlation coefficients

3.5.2 Suitability of images for quantification

Seven of the patient group and three control subjects had M-mode recordings of inadequate quality to allow accurate determination of left ventricular dimensions. Three apical views in aortic patients and one in a control subject were unsuitable for determination of ejection fraction by Simpson's biplane method. Similarly, an inadequate Doppler signal across the mitral valve was obtained in one patient and the aortic velocity was not recorded in one control.

3.5.3 Echocardiographic characteristics of AS group

3.5.3.1 Aortic valve morphology

Calcification was present in the aortic valve leaflets of 26 of the 37 patients with AS, and in the others the valve was thickened (see table 3-5). Eight had a bicuspid valve morphologically, but calcification causing distortion of valve anatomy made it impossible to determine the number of leaflets in several others. The mitral valve annulus was calcified in four subjects but none had mitral stenosis.

3.5.3.2 Aortic incompetence

There was no aortic incompetence in twenty of the patients. Aortic incompetence, as assessed by colour flow Doppler imaging, was trivial in eight, mild in four, mild to moderate in three and moderate in two. Both subjects with moderate aortic incompetence had severe AS with aortic valve areas of $0.28cm^2$ (as20) and $0.59cm^2$ (as32) and mean pressure gradients of 56.6 and 44.4mmHg respectively.

Subject	Severity 1=mild, 2=severe	Calc	AI	EF %	LVMI g/m^2	AVA MAX (cm^2)	Mean PG (mmHg)	Peak PG (mmHg)
Asy AS								
AS01	1	-	+	49	112	0.89	12.2	35
AS02	2	+	-	54	-	0.60	65.4	123
AS03	1	+	-	41	212	1.01	27.1	46
AS05	1	+	-	-	-	0.68	18.9	39
AS08	1	-	-	58	54	1.56	13.7	32
AS11	1	-	-	41	64	0.63	14.5	28
AS13	1	+	+	83	93	1.24	24.1	46
AS16	1	-	-	54	170	0.81	13.4	26
AS17	1	+	+++	59	135	0.95	25.1	50
AS18	2	-	-	56	-	0.29	45.3	74
AS19	2	-	+++	63	116	0.35	31.0	54
AS20	2	-	++++	35	229	0.28	56.6	87
AS25	2	+	++	50	107	0.44	41.6	67
AS26	1	-	+	43	98	0.61	20.1	36
AS28	2	+	+	-	107	0.27	36.4	65
AS30	2	+	+	38	275	0.46	33.6	56
AS34	2	-	++	60	85	0.63	37.5	66
AS35	1	-	+++	41	150	1.04	28.5	55
Sym AS								
AS04	2	+	+	80	-	0.29	38.9	71
AS06	2	+	-	48	174	0.84	78.9	114
AS07	1	+	++	55	84	0.48	23.4	42
AS09	2	+	-	57	-	0.94	32.5	74
AS10	2	+	-	52	290	0.52	34.8	57
AS12	1	+	-	-	220	1.04	19.4	35
AS14	1	+	-	53	104	0.58	19.0	33
AS15	1	-	-	-	233	0.55	27.6	57
AS21	1	+	-	51	-	0.49	12.7	28
AS22	1	+	++	55	-	0.13	19.7	34
AS23	2	+	-	47	111	0.19	36.0	68
AS24	2	+	-	51	131	0.34	50.6	82
AS27	2	-	-	38	112	0.30	52.4	85
AS29	2	+	+	48	145	0.67	49.5	75
AS31	2	+	-	46	187	0.44	89.3	143
AS32	2	+	++++	54	154	0.59	44.4	68
AS33	2	+	+	37	222	0.32	59.4	96
AS36	2	+	-	67	159	0.33	101.7	157
AS37	2	+	+	40	182	0.35	55.2	88

Table 3-5: Individual echocardiographic characteristics for AS.
1= Mild-moderate AS; 2= moderate-severe AS; Calc= aortic valve calcification; AI= aortic incompetence: - none, + trivial, ++ mild, +++ mild-moderate, moderate ++++.

3.5.3.3 Left ventricular function

Two patients had obvious left ventricular wall motion abnormalities. Overall systolic function was mild-moderately impaired in one (as20), who had severe but

asymptomatic AS and mildly impaired in the other (as12), who had mild but symptomatic AS. In three further patients (as28, as30, as33) left ventricular contraction appeared sluggish but with overall preservation of systolic function.

3.5.4 Patients versus controls

3.5.4.1 Cardiac structure and function

The data for the size of the left atrium, left ventricle, ejection fraction and left ventricular mass/mass index are shown in table 3-6. There were no statistically significant differences in the size of the left atrium or the E/A Doppler ratio across the mitral valve. The AS patients have significantly greater left ventricular mass and mass index. The controls have significantly higher ejection fraction although the mean value for the AS group would be considered to be within the normal range.

	LA (mm)	E/A	LV mass	LVMI	EF (%)
Controls	35.5±0.4 (n=19)	1.15±0.34	196±82 (n=17)	104±36 (n=17)	61.8±8.8 (n=19)
AS	34.4±0.6 (n=36)	1.01±0.59 (n=36)	271±117 (n=30)	152±60 (n=30)	51.6±11.1 (n=33)
95% CI	-4.1, 1.7	-0.38, 0.11	**16, 133**	**1, 76**	**-15.8, -4.6**
p	ns	ns	**0.014**	**0.002**	**<0.001**

Table 3-6: LV structure and function, patients v controls.
LA= left atrium; LVMI= left ventricular mass index; EF= ejection fraction

3.5.4.2 Aortic valve area and pressure gradient

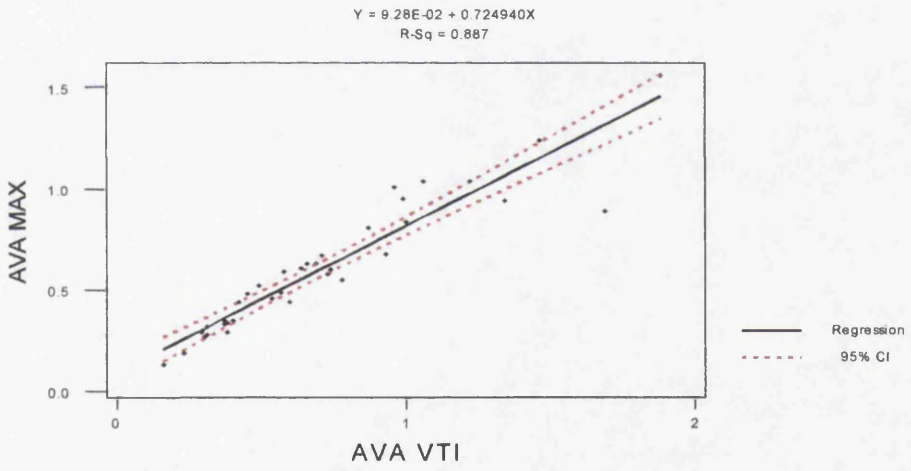
The patient group had significantly greater aortic valve velocity, peak and mean pressure gradients and reduced aortic valve area compared to the control group (table 3-7). The mean values of pressure gradients and aortic valve area would classify the group as having moderate-severe AS (see table 1-1), although the range was large (peak pressure gradient 26-157mmHg and aortic valve area 0.2-1.6cm^2). Ten control subjects had calculated aortic valve areas (<1.5cm^2) which would normally be indicative of aortic stenosis although anatomically the valves were normal. There were no differences in left ventricular outflow tract diameter, area or velocity between the two groups.

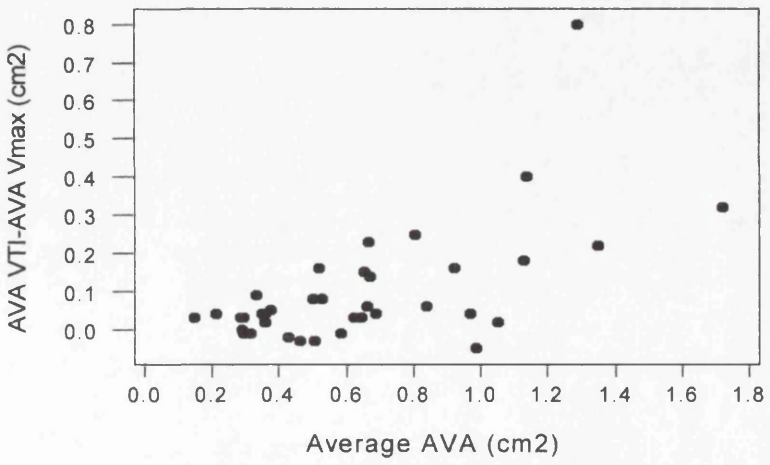
.	LVOT (mm)	Max V (ms^{-1})	Peak PG (mmHg)	Mean PG (mmHg)	AVA (max V) cm^2	AVA (VTI) cm^2
Controls	16.5±3.8	1.27±0.2	6.6±2.3	3.8±0.7	1.5±0.5	1.6±0.6
AS	17.1±3.9	3.92±0.9	64.7±32	37.6±21	0.6±0.3	0.7±0.4
95% CI	-1.6, 0.28	2.3, 3.0	47, 68	26, 69	-1.2, -0.6	-1.2, 0.6
P	ns	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

Table 3-7: Indices of AS severity.
LVOT= left ventricular outflow tract diameter; Max V= maximal aortic valve velocity; AVA= aortic valve area; VTI= velocity time integral

Figure 3-1 demonstrates the strong correlation between aortic valve area measurement by the two Doppler methods. Bland and Altman plot shows that VTI areas tend to be slightly higher than Vmax values, particularly at higher areas

Figure 3-1: Comparison of AVA by V(VTI) and V(max) in AS.
Top panel: correlation of AVA by the two methods. Bottom panel Bland and Altman plots indicating degree of agreement





3.6 Patient classification

3.6.1 AS severity: mild versus severe

Twenty-one patients were classified in the moderate-severe (**severe**) group and 16 in the mild-moderate (**mild**) group according to a mean pressure gradient >30mmHg or <30mmHg respectively, see tables 3-2 and 3-5.

If severity had been determined by aortic valve area (<0.75 cm^2) then a total of 27 patients would have been classified as having severe AS and only 10 having mild AS (see table 3-5). Eight patients (05,07,11,14,15,21,22,26) would have been re-classified from the mild to severe groups and two (06,09) would have moved from the severe to the mild group (see table 3-5).

3.6.1.1 ECG

Of the ten patients with normal ECG's seven had mild and three had severe AS. An abnormal ECG was significantly more likely to be associated with severe AS (18/21) than mild AS (9/16), $\chi^2 = 4.0$, $p<0.05$.

3.6.1.2 Anthropometric and left ventricular function

The three groups remain well matched for body size and the proportion of females in each group is not significantly different (table 3-8). The severe AS group were slightly but not significantly older than both other groups. E/A ratio was similar for all groups. Ejection fraction was higher in the controls compared to both aortic groups but there was no difference between those with mild and severe AS.

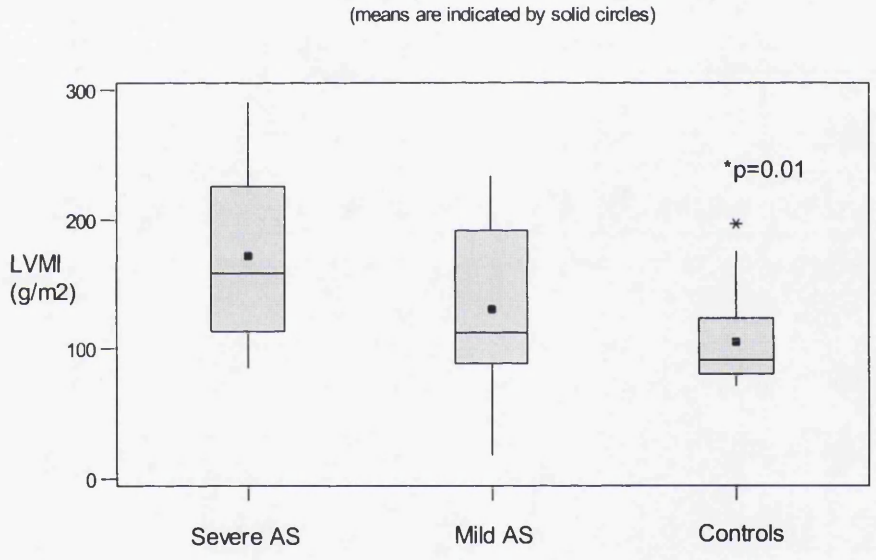
	M/F	Age	BMI	EF	E/A
Controls (n=20)	13/7	50.4±17	26±4	61.8±9 (n=19)	1.15±0.3 (n=20)
Mild AS (n=16)	11/5	51.8±22	27.2±6	52.5±11 (n=13)	1.12±0.7
Severe AS (n=21)	10/11	62.7±14	25.6±4	51.0±11 (n=20)	0.92±0.5 (n=20)
P	0.13	0.06	ns	**0.005***	ns

Table 3-8: Age, BMI, EF and E/A ratio in mild versus severe AS.
*Controls significantly different from severe and mild AS .

3.6.1.3 Left ventricular mass

Left ventricular mass indices for the subject groups are displayed in figure 3-2. Left ventricular mass index was significantly greater in the severe group (n=17) compared to the controls (n=17) but not the mild AS (n=13) group (163±61 v 104±36 v 130±64 g/m^2 respectively, p=0.01). Left ventricular mass was similarly distributed: severe 282±96 v mild 253±146 v controls 196±82g although these differences just fail to reach statistical significance (p=0.07). Left ventricular mass index did not significantly correlate with mean pressure gradient, aortic valve area or age in AS patients.

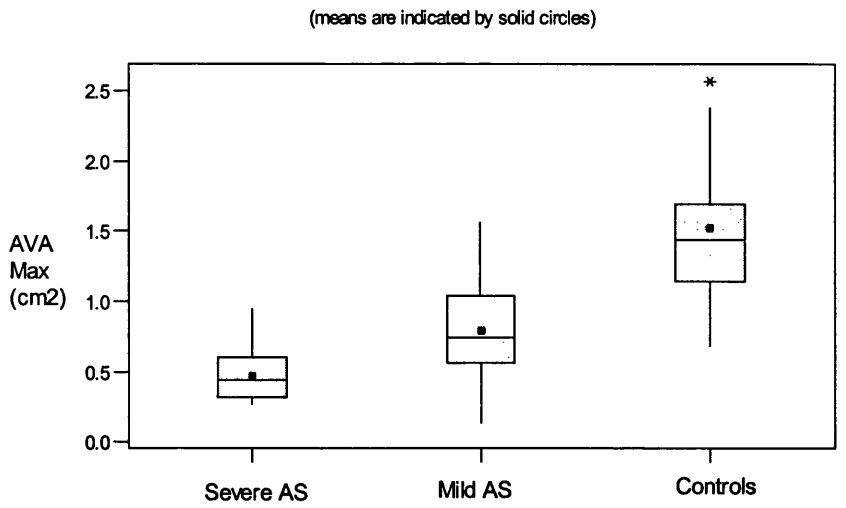
Figure 3-2: LVMI by subject group
*Severe AS significantly different from controls



3.6.1.4 AS severity

The distribution of aortic valve areas in the groups are shown in figure 3-3. The three groups are significantly different from each other: severe 0.45±0.2 v mild 0.79±0.4 v controls 1.52±0.5 cm^2, p<0.0001.

Figure 3-3: Aortic valve area by subject group.



Peak aortic valve velocity (4.5±0.7 v 3.1±0.4 ms^{-1}), peak pressure gradient (84.3±28 v 38.9±9.6 mmHg) and mean pressure gradient (51.0±19 v 20.0±5.6 mmHg) were all significantly ($p<0.0001$) higher in the severe AS group than mild group.

3.6.1.5 Left ventricular outflow tract diameter, area and velocity

There were no significant differences in left ventricular outflow tract diameter between groups: severe AS (1.73±0.4) v mild AS (1.69±0.4) v controls (1.65±0.4cm). The eight patients who would have been re-classified as having severe AS according to aortic valve area had significantly smaller left ventricular outflow tract diameter (1.48±0.30) than the other AS patients (1.78±0.39cm), $p=0.04$. The two patients who would have been re-classified as having mild AS according to aortic valve area had left ventricular outflow tract diameters of 2.71(AS06) and 2.11cm (AS09), considerably higher than average.

Left ventricular outflow tract area is significantly smaller in the eight patients who would have been re-classified as having severe AS (1.78±0.7cm^2), according to aortic valve area, compared to the other AS patients (2.60±1.1), $p=0.02$. There were no significant differences in left ventricular outflow tract velocities between groups, including the subjects who tended to have more severe AS calculated by aortic valve area than by mean pressure gradient.

3.6.1.6 NYHA status: mild v severe AS

	NYHA		
	I	II	III
Mild	6	7	3
Severe	3	9	9

Table 3-9: NYHA functional class and AS severity.

The number of subjects in each NYHA functional class according to severity of AS is displayed in table 3-9. There is a non-significant trend for patients in the severe group to be more symptomatic than the mild group (X^2 3.64, p=0.16).

3.6.1.7 Predictors of severe AS

None of body mass index, symptomatic status, sex, left ventricular mass/mass index, ejection fraction or E/A ratio were significantly associated with severity of AS as defined by a mean pressure gradient >30mmHg. NYHA functional classification (odds ratio 2.45, 95% CI 0.94, 0.63 p=0.054) and age (odds ratio 1.03, 95% CI 1.0, 1.07 p=0.07) were of borderline significance.

3.6.2 Symptomatic versus asymptomatic AS

Nineteen patients were in the symptomatic group and 18 in the asymptomatic group, see tables 3-2 and 3-5. Thirteen subjects had both severe and symptomatic AS. The nine patients in NYHA class I were significantly younger (44.3±21) than those in class II (60.1±18, n=16) and class III (66.6±13, n=12), p= 0.03. The nine patients in NYHA class 1 had similar characteristics to those with mild symptoms who were classed as asymptomatic: age 44.3±21 v 51±19 years; mean pressure gradient 29.6±17 v 30.1±14mmHg; peak pressure gradient 54.6±30 v 54.7±18mmHg and aortic valve area 0.79±0.4 v 0.62±0.4cm^2 respectively. There was a non-significant trend for the mildly symptomatic group to have more females (6 v 2) than those in NYHA I.

3.6.2.1 ECG

Of the ten patients with a normal ECG, three were asymptomatic and seven symptomatic. Only two of the nine patients in NYHA class I had a normal ECG.

The proportion of subjects with an abnormal ECG was not significantly different between asymptomatic (15/18) and symptomatic AS (12/19), $\chi^2 = 1.71$, p=017.

3.6.2.2 Anthropometrics and left ventricular function

Results are displayed in table 3-10. The symptomatic patients are significantly older than both the controls and asymptomatic AS, although the subjects remain well matched for body mass index and male to female ratio. There is no statistical difference in the E/A ratio between groups. The controls have significantly greater ejection fraction than both AS groups.

	M/F	Age	BMI	EF	E/A
Controls (n=20)	13/7	50.4±17	26±4	61.8±9 (n=17)	1.15±0.3 (n=20)
Asy AS (n=18)	10/8	47.6±19	27.0±5	51.6±12 (n=16)	1.13±0.7 (n=18)
Sym AS (n=19)	11/8	67.9±11	25.8±5	51.7±10 (n=19)	0.89±0.5 (n=18)
P	ns	**0.001***	ns	**0.006****	ns

Table 3-10: Anthropometric and left ventricular function by symptomatic groups. Symp= symptomatic AS, Asy= asymptomatic AS. * Sym group significantly different from both other groups. **Control group significantly different from both aortic groups

3.6.2.3 AS severity

Left ventricular mass index was greater in those with symptomatic AS compared to controls but not compared to the asymptomatic group (table 3-11). Left ventricular mass was also greater in the symptomatic group (296±110g) than the controls (196±82g) but not the asymptomatic group(243±126g), p=0.04.

	LVMI (g/m^2)	Peak V (m/s)	Peak PG (mmHg)	Mean PG (mmHg)	AVA V max (cm^2)	AVA VTI (cm^2)
Asy AS (n=18)	131±67 (n=15)	3.6±0.8	54.7±24	30.3±15	0.71±0.4	0.85±0.5
Sym AS (n=19)	167±57 (n=15)	4.2±1.0	74.1±36	44.5±25	0.49±0.2	0.56±0.3
95% CI	-82, 11	-1.16, 0.03	-39.6, 0.8	-27.8, -0.6	0.01, 0.42	0.02, 0.56
p	0.13	0.06	0.06	**0.04**	**0.04**	**0.03**

Table 3-11: AS severity, symptomatic v asymptomatic patients

The symptomatic patients have more severe disease. They have significantly lower aortic valve area and higher mean pressure gradient, although peak aortic velocity and peak pressure gradient are of borderline significance.

3.6.3 Predictors of symptomatic status

Age and aortic valve area were significantly correlated with the presence of symptomatic AS, see table 3-12. None of body mass index, sex, severity of AS (>30mmHg), ejection fraction, left ventricular mass/index or E/A ratio was significantly correlated.

	Odds Ratio	95% CI	p
Age	1.08	1.03, 1.15	**0.004**
>60 years	8.2	1.4, 49.4	**0.02**
LVMI	1.01	1.00, 102	0.13
E/A	0.45	0.11, 0.79	0.2
V max	2.1	0.93, 4.81	0.07
Peak PG	1.02	1.0, 1.05	0.08
Mean PG	1.04	1.0, 1.08	0.06
AVA (Vmax)	0.08	0.01, 1.03	**0.03**
AVA (VTI)	0.13	0.02, 0.97	**0.02**

Table 3-12: Echocardiographic predictors of AS symptomatic status.

Mean and peak pressure gradient were both of borderline significance in predicting symptomatic disease. In a multivariate model with age, aortic valve area, mean and peak pressure gradient, and maximum aortic velocity, only age (odds ratio 1.11, p=0.005) was an independent predictor of symptomatic disease.

3.7 Physical activity levels

Scottish Physical activity questionnaires were returned by 24 (65%) of the patient group and 15 controls (75%). There was no significant differences in either total or leisure time physical activity between the controls, mild and severe AS or symptomatic and asymptomatic AS (see table 3-13).

	Leisure PA	Total PA
Controls (n=15)	412±318	601±475
Mild AS (n=10)	403±303	780±811
Severe AS (n=14)	536±503	678±586
Asymptomatic AS (n=10)	303±171	674±478
Symptomatic AS (n=14)	613±514	758±822

Table 3-13: Mean physical activity (minutes/week) by subject group
PA= physical activity

There was no correlation between either leisure or total physical activity level and any anthropometric, symptomatic status or echocardiographic measure in AS or controls.

3.8 Summary of chapter results

Patients and controls were well matched for age, sex and body size.

AS patients had increased LV mass, reduced ejection fraction and aortic valve area compared to controls.

An abnormal ECG was common in mild and asymptomatic AS. Patients with severe AS were more likely to have an abnormal ECG compared to those in the mild group.

The severe AS group had reduced aortic valve area and increased pressure gradient compared to the mild and control groups.

The symptomatic AS group were older and had more severe AS than the asymptomatic group.

Age, but not aortic valve area or pressure gradient, was independently associated with symptomatic status in AS.

Physical activity levels, as measured by the Scottish Physical Activity Questionnaire, were not significantly different between groups.

4. CARDIOPULMONARY EXERCISE TOLERANCE TESTING

All subjects underwent treadmill exercise testing (see section 2.6 for methods). One patient (AS19) could not tolerate the mouthpiece and noseclips and therefore gas exchange was not measured in this subject.

No adverse events were encountered on treadmill exercise testing. Two controls (C12 and C14) developed asymptomatic horizontal or downsloping ST segment depression > 1mm on exercise. These subjects were not excluded from analysis.

4.1 Resting haemodynamics

There was no difference in resting heart rate between controls (69±14bpm) and patients (mild AS 74±14, severe AS 72±13bpm). Mean systolic and diastolic BP were also similar across the groups: controls 135±15/86±8 v mild AS 142±23/85±12 v severe AS 138±22/84±11mmHg.

4.2 Symptoms limiting exercise capacity

The 37 AS patients reported the following symptoms as the main reason for exercise termination: fatigue (n=18), dyspnoea (n=14) dyspnoea and fatigue (n=2), dyspnoea and chest pain (n=2) and leg pain (n=1). Two controls stated they were limited by breathlessness and the others were limited by fatigue.

4.2.1 Mild v severe AS

There was a non-significant trend for patients in the severe group to be limited more by dyspnoea/chest pain (14/20) than by fatigue (6/20) compared to the mild AS group (6/16 dyspnoea/chest pain, 10/16 fatigue), χ^2=3.1, p=0.08.

4.2.1.1 Symptomatic v asymptomatic AS

Symptomatic AS patients were not more likely to be limited by dyspnoea/chest pain (11/18) than asymptomatic AS (8/18), χ^2=1.3, p=0.25. Similarly, there was no difference when patients were examined by NYHA class: I (6/9 fatigue, 3/9 dyspnoea), II (7/15 fatigue, 8/15 chest pain/dyspnoea) and III (4/12 fatigue, 8/12 dyspnoea/chest pain) χ^2=2.3, p=0.31.

4.3 Blood pressure response

All controls increased their systolic blood pressure on exercise by at least 40mmHg. Twenty-six patients had a normal increase in SBP (>30mmHg), nine had a blunted response (<30mmHg) and two had a fall in systolic blood pressure during exercise. Both subjects (AS31 and AS37) with a decrease in blood pressure on exercise had severe, symptomatic AS. Patients with a blunted blood pressure response were fairly evenly divided between groups (5 symptomatic, 4 asymptomatic, 6 severe AS and 3 mild AS).

4.4 Exercise ECG

Twenty-two of the AS patients developed new or worsening horizontal or downsloping ST segment depression > 1mm on exercise. There was no sustained arrhythmia in any patient.

4.4.1 Mild v severe AS

The exercise ECG responses for the mild and severe AS groups are displayed in the table below. The severe group were significantly more likely to have an abnormal ECG with worsening ST depression during exercise, χ^2 = 10.48, p=0.005.

Rest - exercise ECG	Mild AS	Severe AS
Normal - normal	9	4
Normal -ST depression	6	4
Abnormal -worsening ST depression	1	11
LBBB	0	2

Table 4-1: Exercise ECG responses: mild v severe AS.
Normal = no ST-T abnormalities; ST-depression = horizontal or downsloping >1.0 mm

4.4.2 Symptomatic v asymptomatic AS

The exercise ECG responses for the asymptomatic and symptomatic AS groups are displayed in table 4-2. The proportion of patients with new or worsening ST

depression was not significantly different between the symptomatic and asymptomatic AS groups, $\chi^2 = 0.78$, p=ns.

Rest - exercise ECG	Asy AS	Sym AS
Normal - normal	7	6
Normal rest-ST depression	6	4
Abnormal -worsening ST depression	5	7
LBBB	0	2

Table 4-2: Exercise ECG responses: asymptomatic v symptomatic AS.
Normal = no ST-T abnormalities; ST-depression = horizontal or downsloping >1.0 mm

4.5 Exercise capacity and ventilatory response

4.5.1 Mild v severe AS

Results are displayed in table 4-3.

4.5.1.1 Haemodynamic responses

Maximum and predicted maximum heart rate were reduced in both patient groups compared to controls. Maximum systolic blood pressure on exercise was lower in the severe AS group compared to both controls and mild AS. The increase in systolic blood pressure was significantly attenuated in the severe AS group compared to mild AS and in both AS groups compared to controls.

4.5.1.2 Exercise capacity and cardiopulmonary responses to exercise

Exercise capacity, as reflected in exercise duration, predicted exercise time and VO_2max was significantly reduced in AS patients compared to controls. Maximal exercise ventilation and peak respiratory exchange ratio (RER) were also reduced in both AS groups compared to controls. The slope of exercise VE/VCO_2 was higher and oxygen pulse lower in severe AS compared to controls but not mild AS.

	Controls (n=20)	Mild AS (n=16)	Severe AS (n=21)	P
Max HR (Predicted.)	170±16 (100±8%)	149±28 (89±13%)	132±26 (84±14%)	**<0.0001^{++}** **<0.0001^{++}**
Peak Ex. SBP(mmHg)	198±20	180±26	158±25	**<0.0001****
Peak-rest SBP (mmHg)	64±19	38±25	20±22	**<0.0001^{+}**
Ex time(min) (Predicted)	12.1±3.0 (126±17%)	7.3±3.9 (78±36%)	4.9±3.3 (61±27%)	**<0.0001^{++}** **<0.0001^{++}**
VO_2max (ml/kg/min)	31.3±12.0	23.0±9.3	18.6±8.0 (n=20)	**0.001^{++}**
VE (L/min)	94.1±34	65.3±26	48.8±19 (n=20)	**<0.0001^{++}**
RER	1.20±0.13	1.08±0.10	1.06±0.11 (n=20)	**0.001^{++}**
O_2 pulse	14.1±6	11.9±4	10.0±4 (n=20)	**0.025***
VE/VCO_2	28.6±4	30.2±5	34.5±8	**0.01***

Table 4-3: Maximal exercise variables by severity of AS
*Severe AS significantly different from controls but not mild AS. **Severe AS significantly different from mild AS and controls. $^{+}$Each group significantly different from each other. $^{++}$Controls significantly different from mild and severe AS.

4.5.2 Symptomatic v asymptomatic AS

Results are displayed in table 4-4.

4.5.2.1 Haemodynamic response to exercise

Maximum heart rate was significantly reduced in symptomatic AS compared to asymptomatic AS and controls. Predicted maximum heart rate was lower in both AS patient groups compared to controls. Maximal exercise SBP was reduced in both AS groups compared to controls. Increase in exercise SBP was attenuated in the aortic patients and this was significantly more pronounced in the symptomatic AS group.

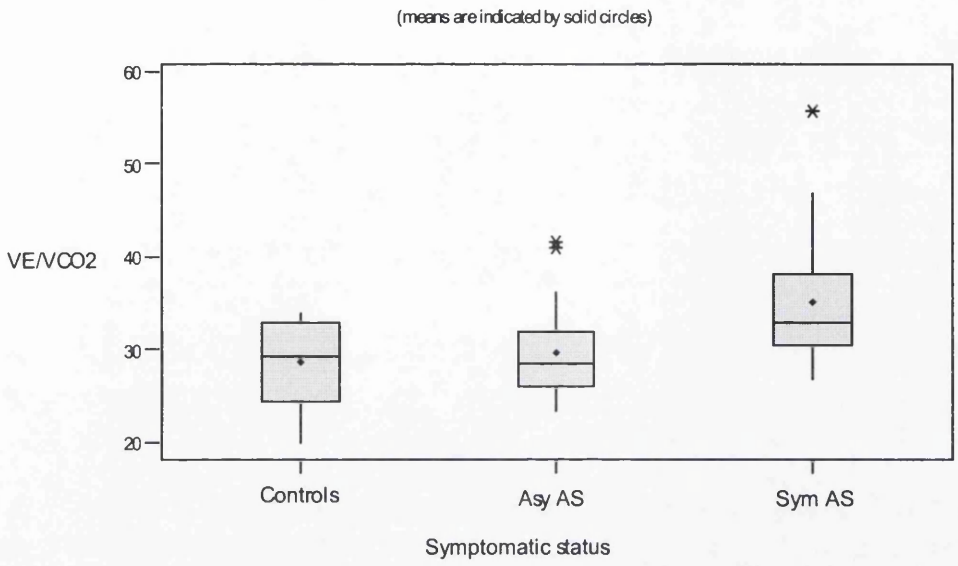
	Controls (n=20)	Asy AS (n=18)	Sym AS (n=19)	P
Max HR (Predicted)	170±16 (100±8%)	155±29 (90±15%)	124±17 (83±12%)	**<0.0001**** **<0.0001^{++}**
Peak Ex. SBP (mmHg)	198±20	173±30	162±25	**<0.0001^{++}**
Peak-rest SBP (mmHg)	64±19	37±25	19±21	**<0.0001^{+}**
Ex time(min) (Pred)	12.1±3.0 (126±17%)	8.3±3.6 (86±28%)	3.7±2.1 (52±27%)	**<0.0001^{+}** **<0.0001^{+}**
VO_2max (ml/kg/min)	31.3±12.0	25.3±10.4	16.4±3.5 (n=18)	**<0.0001****
VE (L/min)	94.1±34	70.5±24	43.3±14 (n=18)	**<0.0001^{+}**
RER	1.20±0.13	1.12±0.07	1.02±0.10 (n=18)	**<0.0001****
O_2 pulse	14.1±6	12.2±4	9.6±4	**0.015***
VE/VCO_2	28.6±4	29.8±5	35.1±7 (n=18)	**0.003****

Table 4-4: Maximal exercise variables by symptomatic group.
Sym= Symptomatic; Asy= asymptomatic; *Sym AS significantly different from controls but not asymptomatic AS. **Sym AS significantly different from Asy AS and controls. $^{+}$Each group significantly different from each other. $^{++}$Controls significantly different from mild and severe AS.

4.5.2.2 Exercise capacity and cardiopulmonary responses

Exercise duration and predicted exercise time were significantly reduced in symptomatic AS compared to asymptomatic AS and in both compared to controls (table 4-4). Maximal aerobic capacity and peak RER were reduced and VE/VCO_2 (figure 4-1) was increased in symptomatic AS compared to controls and asymptomatic AS. Maximal ventilation was reduced in symptomatic AS compared to asymptomatic AS and in both compared to controls. Oxygen pulse at peak exercise was lower in symptomatic AS compared to controls but not asymptomatic AS.

Figure 4-1: Slope of V_E/VCO_2 by symptomatic group
Asy=asymptomatic AS, Sym AS=symptomatic AS



4.5.2.3 Mildly symptomatic v asymptomatic AS.

The nine patients with only mild symptoms responded differently to the nine completely asymptomatic patients despite similar baseline characteristics. Selected results are shown in table 4-5.

	Controls (n=20)	AS NYHA I (n=9)	AS Mild Sym (n=9)	Sym AS (n=19)	P
Max HR (%)	100±8	98±10	82±14	83±12	**<0.001****
% Pred Ex time	126±17	103±24	68±20	52±27	**<0.001****
Ex-rest SBP	64±19	49±23	26±22	19±21	**<0.001***
VO_2max (ml/kg/min)	31.1±12	29.5±9	20.5±10	16.4±4	**<0.001***
RER	1.20±0.13	1.16±0.06	1.09±0.07	1.02±0.10	**<0.001***
O_2 pulse	14.1±6	12.9±4	11.4±3.8	9.6±3.5	**0.03*****
V_E/VCO_2	28.6±4	28.0±3	31.7±7	35.1±7.4	**0.004***

Table 4-5: Exercise performance, asymptomatic v mildly symptomatic AS
AS Mild Sym =Dyspnoea or fatigue only on moderate exertion. *Con and Asy AS v Sym AS** Con and Asy AS v mild and Sym AS. ***Con v Sym AS

There were no significant differences in exercise performance between controls and patients in NYHA class I. There were no significant differences between patients with mild symptoms and those with more severe symptoms. The mildly symptomatic AS group had significantly reduced exercise capacity and lower

exercise heart rate than asymptomatic AS. In general the patients with mild symptoms had exercise performance closer to the group with more severe symptoms rather than those in NYHA class I.

4.5.3 Predictors of aerobic exercise capacity

4.5.3.1 Vo_2max

Significant echocardiographic, anthropometric and haemodynamic predictors of Vo_2max are shown in table 4-6. Age, NYHA, symptomatic status (asymptomatic/symptomatic see 2.10.1), VE/VCO_2, increase in exercise SBP, aortic valve area/index, peak A and E/A were all significant univariate predictors of Vo_2max in patients. For controls age, peak E and E/A were significantly associated with Vo_2max.

4.5.3.2 Multivariate predictors of Vo_2max

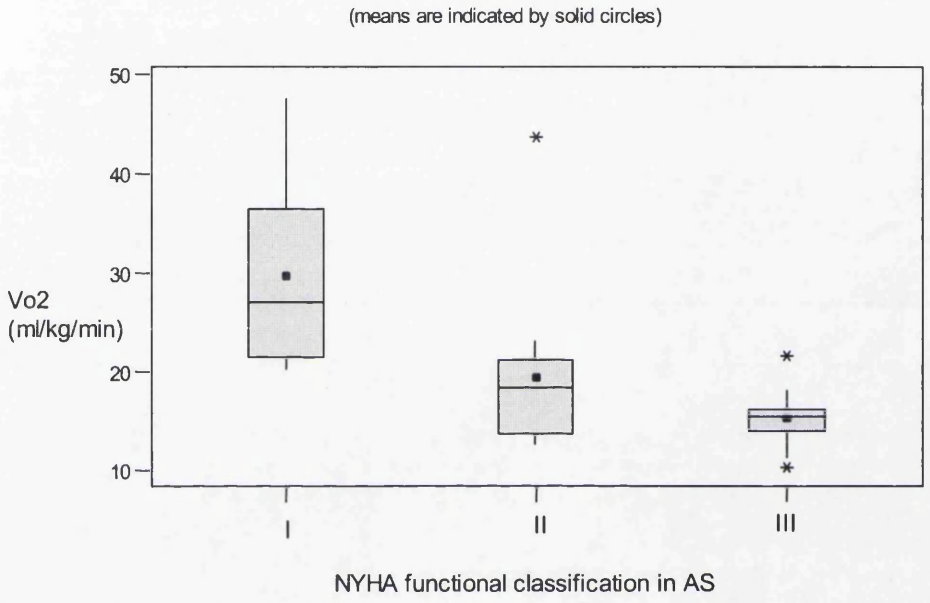
In a multivariate regression analysis with all of the significant univariate predictors in AS patients, age (p=0.001) and NYHA (p=0.02) were independent predictors of Vo_2max.

	R^2 (p)	
	AS	**Controls**
Age (years)	55.5% (<0.0001)	74.4% (0.0001)
NYHA	38.0% (<0.0001)	-
Symptomatic status (asy/sym)	27% (0.001)	-
VE/VCO_2	32.5% (<0.0001)	46.0% (0.001)
SBP response	28.7% (0.001)	ns
AVA (V max)	23.6% (0.003)	ns
AVAI	28.8% (0.001)	ns
Peak E	ns	27.7% (0.02)
Peak A	23.8% (0.003)	ns
E/A	10.7% (0.06)	50.9% (0.001)

Table 4-4: Predictors of maximal aerobic capacity(Vo_2max) in AS and controls.
Asy= asymptomatic, sym= symptomatic AS.

There was little overlap of VO_2max in patients in NYHA class II and III compared to those in class I (see figure 4-2). There is one exception, the outlier in the figure below in class II. This is (AS01) a young patient with mild AS whose only symptom was dyspnoea on heavy exercise and he continued to work in a manually demanding job. In controls only age is of independent significance (p=0.004).

Figure 4-2: NYHA class v VO_2max in AS.



4.5.3.3 Predicted exercise time

Significant predictors of exercise time (% predicted) are shown in table 4-7. No echocardiographic or anthropometric measure was associated significantly with % predicted exercise time in control subjects.

In patients age, symptomatic status, left ventricular mass/mass index, AS severity (by gradient or area) and exercise VE/VCO_2 and SBP response were all univariate predictors of exercise time.

4.5.3.4 Multivariate predictors of exercise time

In patients NYHA (p=0.04) (see figure 4-3), left ventricular mass (p=0.02) (figure 4-4), and left ventricular mass index (p=0.04) were independent predictors of exercise duration. SBP response was of borderline significance (p=0.07).

	R2 (p)	
	AS	**Controls**
Age	12.5% (0.03)	ns
NYHA	47.0% (<0.001)	-
Symptomatic status (asym/symp)	29.0% (0.001)	-
V_E/VCO_2	18.8% (0.008)	29.2% (0.017)
SBP response	32.8% (<0.001)	ns
Mean pressure gradient	11.6% (0.04)	ns
LV Mass	17.2% (0.02)	ns
LVMI	12.4% (0.06)	ns
Peak pressure gradient	9.0% (0.07)	ns
AVAI	17.3% (0.01)	ns
AVA (Vmax)	11.3% (0.04)	ns

Table 4-5: Univariate predictors of exercise duration in AS and controls.

Figure 4-3: Predicted exercise time by NYHA in AS

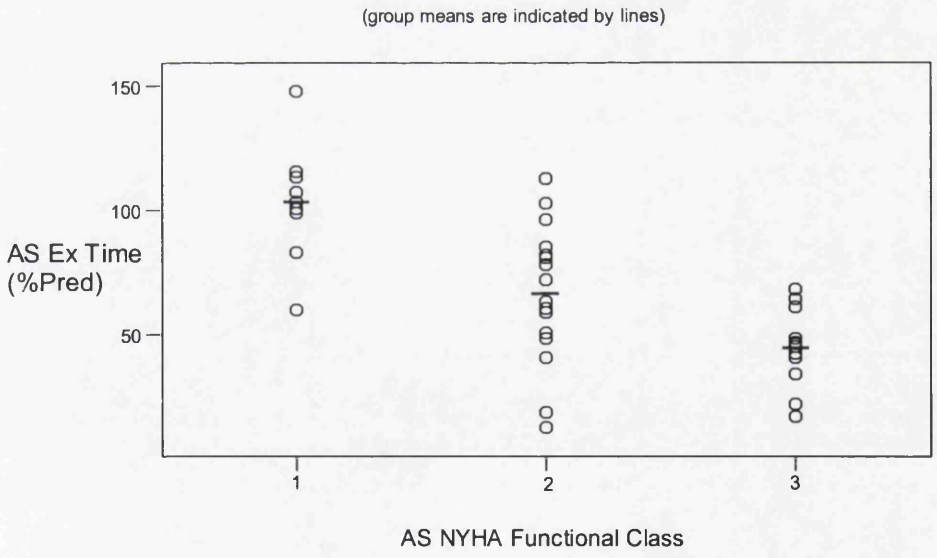
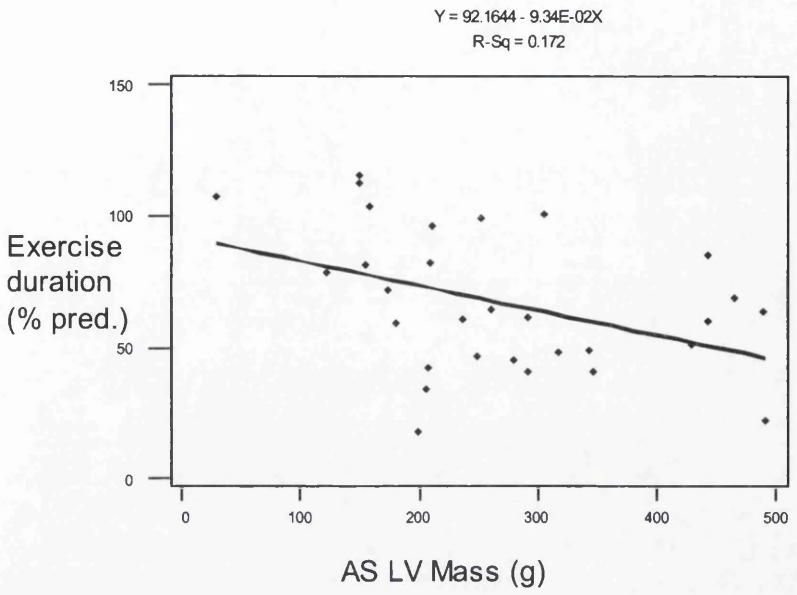


Figure 4-4:Predicted exercise time by left ventricular mass in AS.



4.6 Summary of chapter results

No complications were encountered on maximal exercise testing in AS.

Fatigue and dyspnoea are the commonest symptoms on exercise testing in AS.

There was no significant difference in the proportion of symptomatic patients limited by dyspnoea/chest pain than by fatigue compared to asymptomatic AS.

Significant ST depression on exercise occurs with a similar frequency in mild and asymptomatic AS compared to severe and symptomatic AS.

Maximum heart rate, SBP response, exercise capacity, maximum V_E and RER were reduced in severe AS v mild AS and controls.

Maximum heart rate, SBP response, exercise capacity were reduced in symptomatic AS v asymptomatic AS and controls.

Maximum V_E, VO_2max and RER were reduced and V_E/VCO_2 increased in symptomatic AS v asymptomatic AS and controls.

Mildly symptomatic patients generally had poorer exercise performance than completely asymptomatic patients.

Age and NYHA classification were independent predictors of V_{O_2}max in AS.

NYHA functional classification and left ventricular mass/ mass index were independent predictors of exercise duration in AS.

5. MUSCLE STRENGTH AND ENDURANCE

Thirty patients and 18 controls underwent skeletal muscle strength and endurance testing (see section 2.4 for methods).

5.1 Isometric strength

There were 13 subjects in the mild,17 in the severe, 16 in the asymptomatic and 14 in the symptomatic groups. There was no significant difference in age (controls 48.7±17 v mild AS 53.5±20 v severe AS 59.6±14 years) or lean body mass (controls 53.6±10 v mild AS 52.7±10 v severe AS 48.2±9kg) between the groups classified according to severity. The symptomatic patients (64.4±11) remained older than the controls (48.7±17) but not the asymptomatic group (50.4±19), p=0.02. There was no difference in lean body mass between symptomatic groups.

5.1.1 Mild v severe AS

Results are displayed in table 5-1. There was no significant difference in any of the isometric strength measures between the three groups.

	Peak Force (N)	Normalised Peak Force (N/Kg)	Average Force (N)	Normalised Average Force (N/Kg)
Controls (n=18)	567±199	10.5±2.9	496±185	9.2±2.8
Mild AS (n=13)	527±224	9.8±3.2	451±195	8.4±2.9
Severe AS (n=17)	515±220	10.4±3.2	430±203	8.7±3.1
p	ns	ns	ns	ns

Table 5-1: Isometric strength by severity of AS

5.1.2 Asymptomatic v symptomatic AS

Isometric strength results are displayed in table 5-2.

	Peak Force (N)	Normalised Peak Force (N/Kg)	Average Force (N)	Normalised Average Force (N/Kg)
Controls (n=18)	567±199	10.5±2.9	496±185	9.2±2.8
Asy AS (n=16)	564±251	10.9±3.6	479±221	9.2±3.2
Sym AS (n=14)	470±169	9.4±2.5	394±161	7.8±2.5
p	ns	ns	ns	ns

Table 5-2: Isometric strength by symptomatic status
Asym=asymptomatic; symp= symptomatic.

There were no significant differences in any of the measures of isometric strength between the groups as classified by symptomatic status.

5.2 Isokinetic muscle strength

Of the 30 patients, three females (AS05, AS12, AS36) were unable to complete the isokinetic test. One control subject (C10) was excluded from analysis because gravity correction was not performed at the time of testing. Symptomatic patients (66.3±9 years) were older than controls (48.4±17 years) and asymptomatic AS (48.4±17 years) p=0.006. There was no difference in lean body mass between any of the groups and age was not significantly different between groups classified by severity of AS.

5.2.1 Mild v severe AS

Results are displayed in table 5-3. There were no significant differences in isokinetic muscle strength in either quadriceps or hamstrings in the groups classified by severity of AS.

	Q Peak Torque (Nm)	Q Normalised Peak Torque (Nm/Kg)	H Peak Torque (N)	H Normalised Peak Torque (Nm/Kg)
Controls (n=17)	138±45	2.6±0.6	75±28	1.4±0.4
Mild AS (n=12)	132±51	2.4±0.7	82±40	1.5±0.6
Severe AS (n=15)	116±46	2.3±0.5	64±30.7	1.3±0.4
p	ns	ns	ns	ns

Table 5-3: Isokinetic muscle strength by severity of AS.
Q= quadriceps; H= hamstrings; Asym= asymptomatic; symp= symptomatic.

5.2.2 Symptomatic v asymptomatic AS

Results are displayed in table 5-4. There was no difference in quadriceps peak torque, hamstrings peak torque or normalised hamstrings peak torque between the groups. Quadriceps normalised peak torque was significantly lower in the symptomatic group compared to both controls and the asymptomatic AS.

	Q Peak Torque (Nm)	Q Normalised Peak Torque (Nm/Kg)	H Peak Torque (N)	H Normalised Peak Torque (Nm/Kg)
Controls (n=17)	138±45	2.6±0.6	75±28	1.4±0.4
Asy AS (n=15)	136±48	2.6±0.6	80±42	1.5±0.6
Sym AS (n=12)	107±45	2.0±0.5	63±24	1.2±0.3
p	ns	**0.03***	ns	ns

Table 5-4: Isokinetic muscle strength by symptomatic groups.
Q= quadriceps; H= hamstrings; Asym= asymptomatic; symp= symptomatic. *Symptomatic significantly different from asymptomatic (95% CI 0.1, 1.0) and controls (95% CI 0.1, 1.0).

5.3 Isokinetic muscular endurance

5.3.1 Mild v severe AS

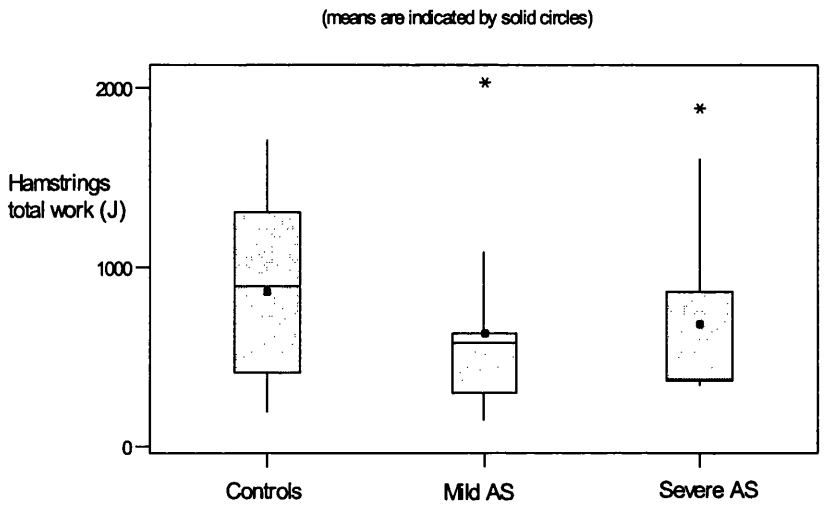
Results are displayed in table 5-5. Normalised total quadriceps work was significantly reduced in the severe group compared to controls. There were no other significant differences in endurance measures between the three groups.

	Controls (n=17)	Mild AS (n=12)	Severe AS (n=15)	p
Q fatigue index (%)	76.1±7	82.8±17	72.4±14	ns
H fatigue index (%)	76.2±16	76.8±18	82.3±11	ns
Q Total work (J)	1977 (1355, 2697)	1348 (978, 2222)	1108 (818, 2389)	0.11
Q normalised total work (J/Kg)	35.4 (30,45)	28.9 (18,38)	22.0 (20,40)	**0.049***
H Total work (J)	896 (411, 1307)	581 (304, 631)	377 (366, 863)	ns
H normalised total work (J/Kg)	16.4, (8,23)	9.6 (6,12)	10.4 (8,16)	ns

Table 5-5: Isokinetic muscular endurance by severity of AS.
Measures of total work expressed as median (IQ range). *Severe AS significantly different from controls (95% CI 1.1, 17.1) but not mild AS (95% CI –7.9, 9.5)

The distribution of total work and normalised total work measures were non-parametric in the AS groups (see figure 5-1).

Figure 5-1: Isokinetic total hamstrings work by severity of AS.



5.3.2 Symptomatic v asymptomatic

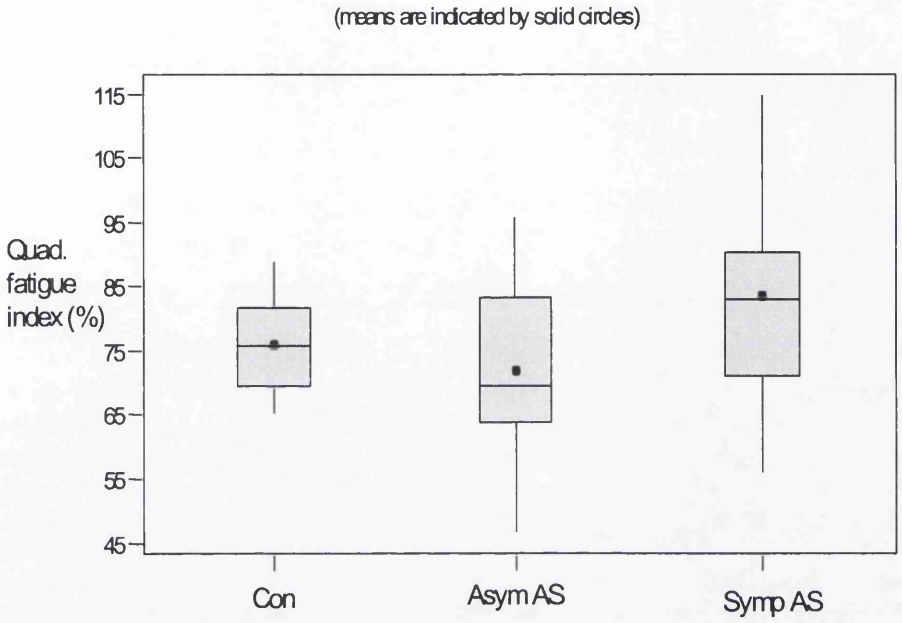
Results are displayed in table 5-6. Total quadriceps and total normalised quadriceps work were significantly reduced in symptomatic AS compared to controls but not the asymptomatic AS. Quadriceps fatigue index tended to be

	Controls (n=17)	Asy AS (n=15)	Sym AS (n=12)	p
Q fatigue index (%)	76.1±7	71.9±14	83.4±16	0.07
H fatigue index (%)	76.2±7	82.1±12	77.1±	ns
Q Total work (J)	1977 (1355,2697)	1228 (1015,2416)	969, (732,1912)	**0.05***
Q normalised total work (J/Kg)	35.4 (30,45)	29.9 (20,41)	16.4 (16,32)	**0.01****
H Total work (J)	896 (411,1307)	578 (366,1088)	510 (370,728)	ns
H normalised total work (J/Kg)	16.4, (8,23)	10.4 (8,26)	9.4 (8,12)	ns

Table 5-6: Measures of isokinetic endurance by symptomatic group.
Measures of total work expressed as median (IQ range). *Symptomatic AS significantly less than controls (95% CI 138, 1247); **Symptomatic AS significantly less than controls (95% CI 4.6, 20.9);

higher (i.e. demonstrating less fatigue) in symptomatic AS but this fails to reach statistical significance. As can be seen from figure 5-2, some subjects, particularly in the symptomatic group, had no discernible reduction in quadriceps muscle strength (close to 100 in the fatigue index) during the isokinetic test.

Figure 5-2: Quadriceps fatigue index by symptomatic group
Asym= asymptomatic; symp= symptomatic AS.



5.4 Skeletal muscle predictors of aerobic exercise capacity

5.4.1 Vo_2max

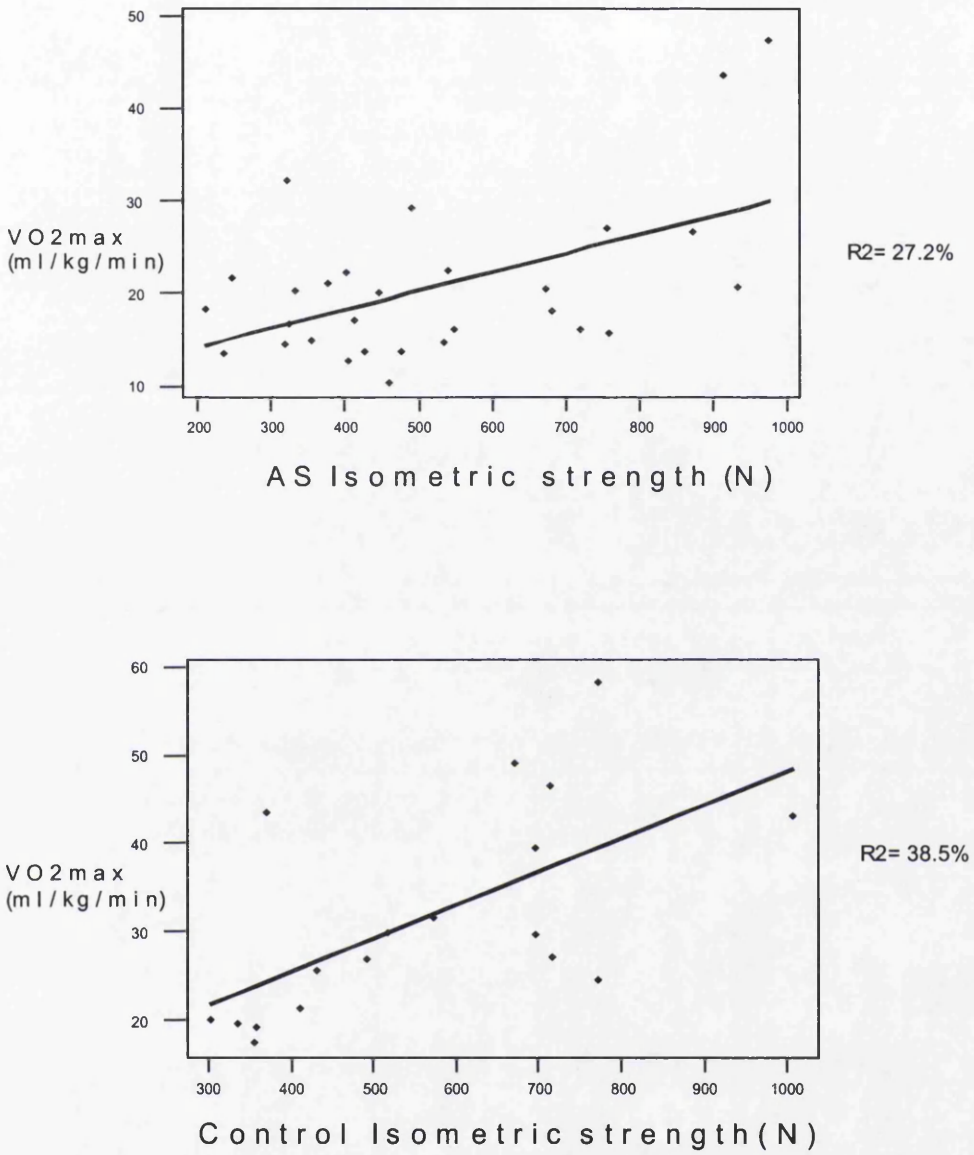
All of the isometric and isokinetic strength variables were significant predictors of maximal aerobic capacity in patients and controls. See table 5-7.

Variable	R^2 (p)	
	Controls	AS
Isometric strength	(n=18)	(n=29)
Peak force	38.5% (0.006)	27.2% (0.004)
Average force	40.8% (0.004)	25.8% (0.004)
Normalised peak force	29.3% (0.02)	30.2% (0.002)
Normalised average force	32.9% (0.01)	27.1% (0.004)
Isokinetic strength	(n=17)	(n=26)
Q peak torque	42.8% (0.004)	18.8% (0.03)
Q normalised peak torque	44.3% (0.004)	30.2% (0.004)
H peak torque	30.6% (0.02)	19.9% (0.02)
H normalised peak torque	28.7 (0.03)	26.8% (0.007)
Isokinetic endurance	(n=17)	(n=26)
Q Total work (J)	54.5% (0.001)	24.6% (0.01)
Q normalised total work (J/Kg)	44.9% (0.003)	35.0% (0.001)
H Total work (J)	28.1% (0.03)	28.1% (0.005)
H normalised total work (J/Kg)	23.7% (0.05)	31.8% (0.003)
Anthropometric	(n=18)	(n=29)
Age	72.8% (<0.0001)	54.5% (<0.0001)
LBM	2.7% (ns)	10.1% (ns)

Table 5-7: Skeletal muscle predictors of VO_2max.

Neither quadriceps nor hamstrings fatigue index was a significant predictor of Vo_2max in patients or controls, although all other endurance measures were. The correlations of isometric muscle strength with Vo_2max for patients and controls are shown in figure 5-3.

Figure 5-3: Isometric strength as a predictor of V_{O_2}max
AS top panel, Controls lower panel.



5.4.1.1 Multivariate analysis

In a multivariate model with peak strength, normalised peak strength, average and normalised average strength and age as predictors, only age was an independent predictor of V_{O_2}max in patients and controls ($p<0.0001$). Similarly when isokinetic variables were considered only age remained an independent predictor ($p<0.003$ for AS and $p<0.0001$ for controls).

5.4.2 Predicted exercise time

None of the anthropometric, isometric or isokinetic strength measures were significant predictors of predicted exercise time in either controls or patients.

5.4.3 V_E/VCO_2

All of the isometric strength measures were inversely correlated with V_E/VCO_2 in patients and controls. All of the isokinetic variables were also predictors of V_E/VCO_2 in controls but only normalised total work was significant in AS patients The strongest predictors are shown in table 5-8.

	R^2 (p)	
	AS	**Controls**
Isometric		
Q Peak force	16.8% (0.03)	53.8% (0.001)
Q Normalised peak Force	27.8% (0.003)	43.8% (0.004)
Isokinetic		
Q normalised peak torque	3.7% (ns)	46.9% (0.003)
Q normalised total work	25.5% (0.009)	36.6% (0.013)

Table 5-8: Skeletal muscle predictors of V_E/VCO_2

5.4.3.1 Multivariate predictors of V_E/VCO_2

When age, peak and normalised peak isometric force and quadriceps total work were considered in a multivariate model only normalised peak quadriceps strength (p=0.02) was an independent predictor of V_E/VCO_2 in AS. Peak strength is of borderline significance (p=0.07). In a multivariate regression analysis in control subjects none of the univariate predictors were of independent significance.

5.5 Summary of chapter results

Isometric quadriceps strength was not significantly different in AS groups and controls.

Isokinetic strength was similar in AS and control groups. Normalised quadriceps isokinetic strength was reduced in severe and symptomatic AS v controls.

Total quadriceps work was reduced in symptomatic AS v controls.

Skeletal muscle strength and endurance measures were univariate predictors of $V_{O_2}max$ in AS and controls but were not of independent significance when considered in a multivariate model with age.

Normalised isometric quadriceps strength was an independent predictor of V_E/V_{CO_2} in AS but not controls.

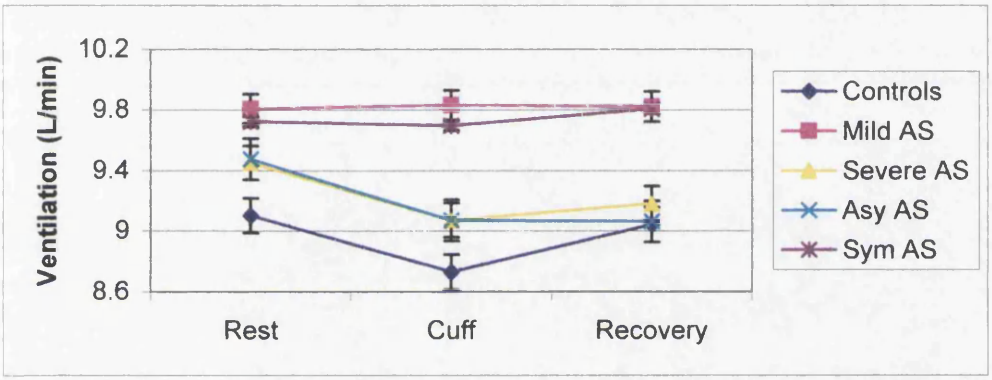
6. ARM ERGOREFLEX

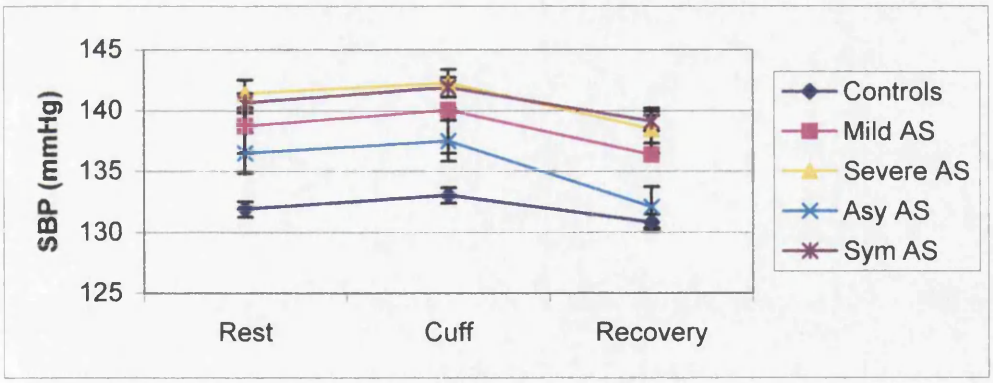
Thirty-one AS patients and 17 controls completed the arm exercise studies (for methods see section 2.7). All subjects reported discomfort during cuff inflation but none required the cuff to be deflated during testing.

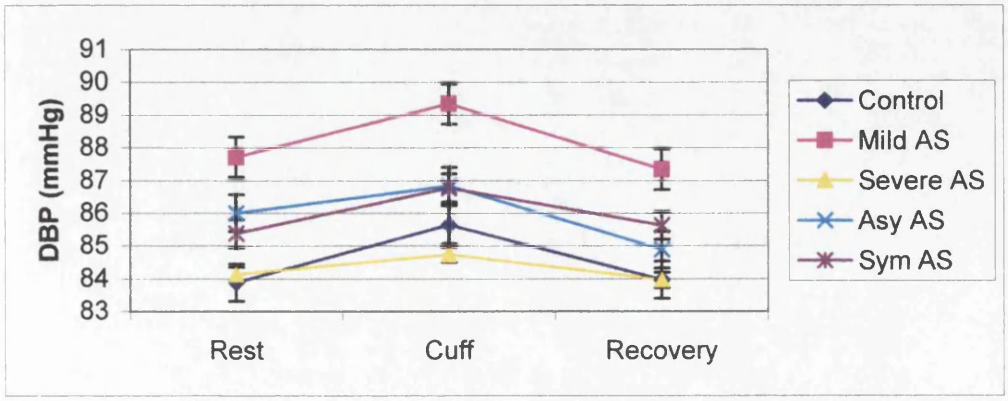
6.1 Control cuff inflation

There was no significant effect of cuff inflation on resting ventilation or SBP (figure 6-1) in controls or patients. There was a small increase in DBP with cuff inflation which was significant for the mild (95% CI 0.2, 3.0 p=0.03) and the symptomatic AS groups (95% CI 0.2, 2.5 p=0.02).

Figure 6-1:Control cuff inflation: effect on resting ventilation and blood pressure
Top panel ventilation, middle panel SBP, bottom panel DBP. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.







6.2 Cuff v non-cuff run

6.2.1 Exercise duration and metabolic demand

Results are displayed in table 6-1. There were no significant differences in resting or peak exercise measures between cuff and non-cuff runs in any group. Exercise duration was similar for both runs in each subject group. There was a trend for respiratory rate at rest to be higher in symptomatic AS compared to controls but this difference fails to achieve significance, p=0.06. A similar metabolic load was placed on each group as there were no significant differences in measured variables at peak exercise.

	Ex. time (min)		**V_{O_2} (ml/min)**		**V_{CO_2} (ml/min)**		**RR (bpm)**	
	Cuff	Non-cu	Rest	Ex	Rest	Ex	Rest	Ex
Controls	3.1±0.9	3.0±1.0	240±58	361±82	188±52	334±99	16.0±6	20.7±5
Mild AS	3.2±1.0	2.9±1.1	256±74	409±110	203±69	363±128	18.0±3	21.8±5
Sev AS	2.6±0.4	2.7±0.5	226±56	365±80	182±48	340±92	17.7±3	23.9±6
Asy AS	2.8±0.9	2.7±1.1	246±76	397±101	195±65	371±119	16.8±3	21.9±5
Sym AS	2.9±0.6	2.9±0.5	233±56	376±94	189±54	334±99	18.7±3	23.8±6

Table 6-1: Cuff v non-cuff runs; exercise duration, V_{O_2}, V_{CO_2}, and respiratory rate.
Ex= peak exercise, RR= respiratory rate, Sev= severe AS, Asy= asymptomatic AS, sym= symptomatic AS. V_{O_2} and V_{CO_2} and RR presented as average of cuff and non-cuff runs.

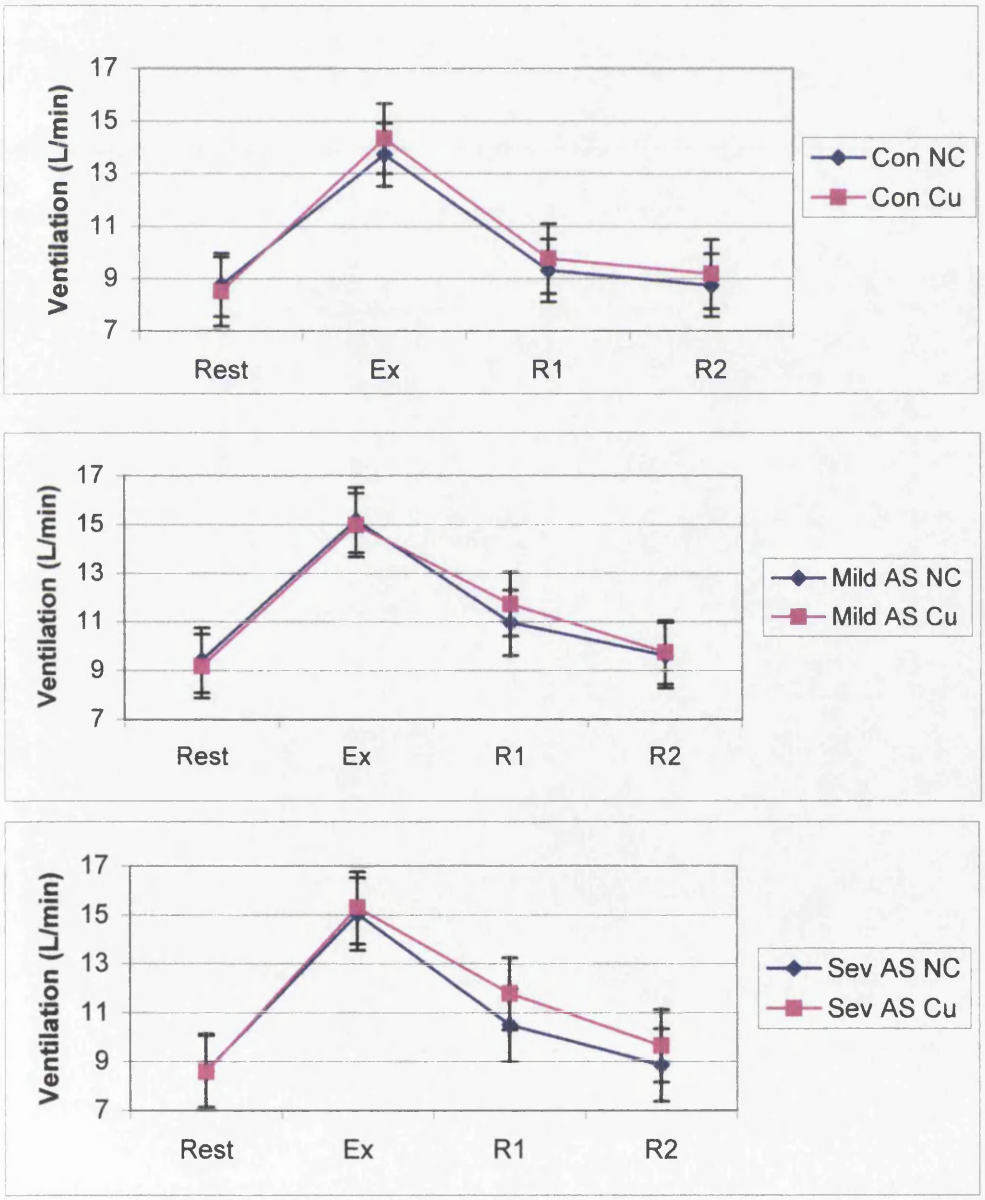
6.2.2 Mild v severe AS

The 17 AS patients in the severe group were significantly older (66.3±12) than the controls (48.7±17yrs) but not the 14 subjects with mild AS (52.6±23) p=0.02.

6.2.2.1 Ventilation

Results are displayed in figure 6-2. There was no significant differences in ventilation between groups at rest, peak exercise or during recovery.

Figure 6-2: Ventilation, non-cuff v cuff run: mild v severe AS
Data represent mean±sem (error bars). NC= non-cuff, Cu= cuff run, Con= controls, Sev= severe AS. R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



Recovery ventilation in the cuff run was significantly increased in the severe AS group compared to the non-cuff run. However the magnitude of ergoreflex was

not significantly different between the three groups, see table 6-2 (and equations 9 and 10 for ergoreflex calculation, section 2.7.3.1).

	Ventilation				Ergoreflex magnitude	
	Cuff recovery	**Non-cuff recovery**	**95% CI Cu-NC**	**p**	**Cuff (% peak)**	**Non-cuff (% peak)**
Controls	9.8±1.7	9.3±1.8	-0.4, 1.3	ns	18±29	12±36
Mild AS	11.7±4.4	11.0±2.0	-1.0, 2.5	ns	45±60	33±25
Severe AS	11.8±3.7	10.5±2.2	**0.0, 2.6**	**0.05**	44±49	29±22
p	ns	ns	-	-	0.19	0.10

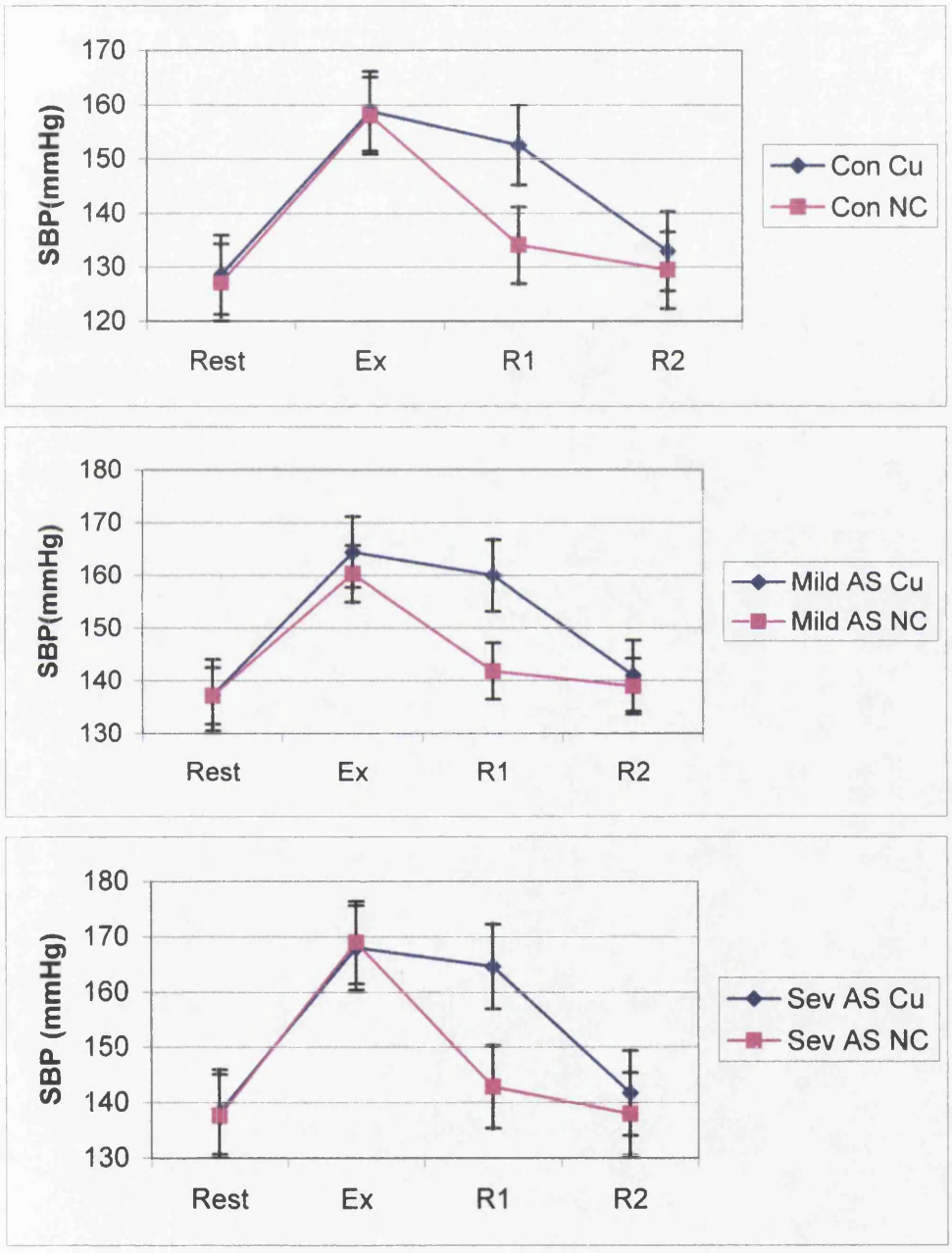
Table 6-2: Cuff v non-cuff ventilation and magnitude of ergoreflex by severity of AS.
Cu= cuff recovery; NC= non-cuff recovery.

There were no significant differences in ergoreflex magnitude between non-cuff and cuff runs in any group.

6.2.3 Blood pressure

There was no significant difference in blood pressure between groups at rest, peak exercise or during recovery. SBP responses are shown in figure 6-3.

Figure 6-3: SBP non-cuff v cuff run, by severity of AS.
Top panel controls, middle panel mild AS and bottom panel severe AS. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



SBP was higher in each group during recovery with regional circulatory occlusion than without (see table 6-3). Diastolic blood pressure followed a similar pattern to SBP.

The magnitude of ergoreflex activation for blood pressure was not significantly different between groups for either cuff or non-cuff recovery (see table 6-3).

	Average Blood pressure (mmHg)				Ergoreflex magnitude	
	Cuff Recovery	Non-Cu Recovery	95% CI of Cu-NC	p	Cuff (% peak)	Non-cuff (% peak)
Controls						
SBP	152±21	134±15	14.9, 28.7	**<0.0001**	79±42	25±19
DBP	98±11	86±10	7.6, 16.1	**<0.0001**	81±67	8±30
Mild AS						
SBP	160±29	141±26	10.6, 25.8	**0.0002**	92±40	20±30
DBP	98±14	88±13	6.0, 12.0	**<0.0001**	58±40	2±34
Severe AS						
SBP	165±33	143±27	13.7, 25.4	**<0.0001**	100±56	-1±65
DBP	95±14	86±13	5.6, 11.8	**<0.0001**	72±85	6±3
Asy AS						
SBP	158±33	137±25	10.4, 25.9	**0.0002**	88±33	14±27
DBP	96±15	85±14	7.6, 13.8	**<0.0001**	55±42	0±24
Sym AS						
SBP	166±28	147±27	11.9, 25.5	**<0.0001**	103±58	4±68
DBP	95±13	87±12	5.9, 11.3	**<0.0001**	74±84	7±37

Table 6-3: Blood pressure response by group; cuff v non-cuff and magnitude of ergoreflex.
Cu= cuff run, NC= non-cuff run. Asym= asymptomatic AS, Sym= symptomatic AS.

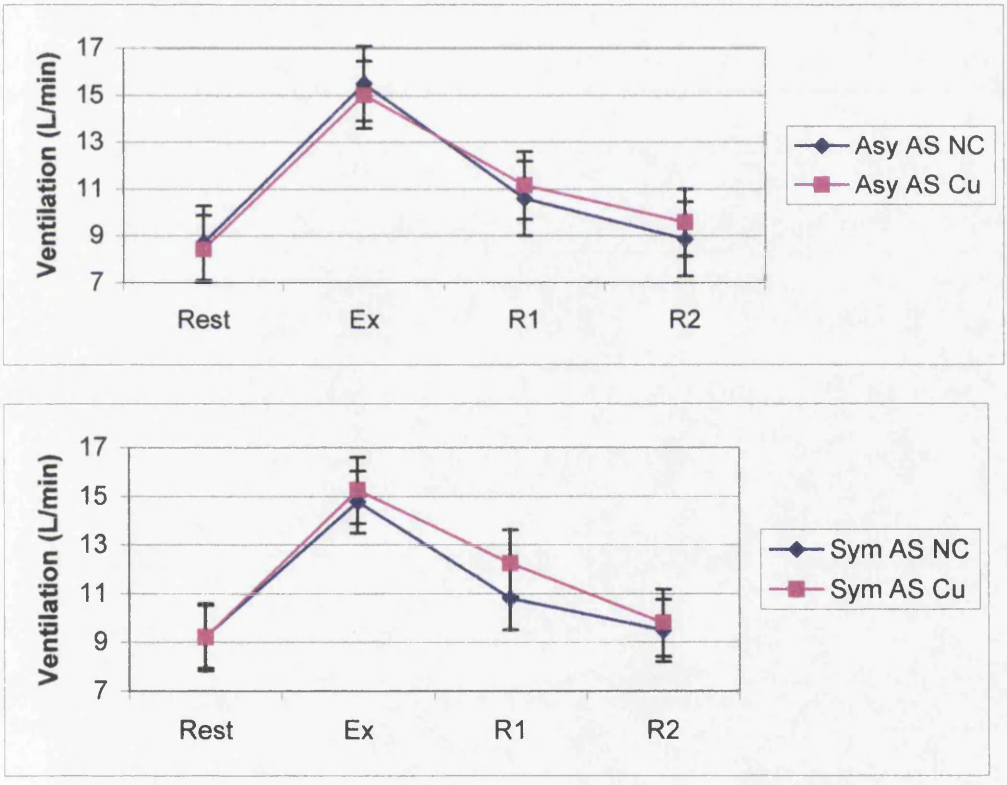
6.2.4 Symptomatic v asymptomatic AS

The 17 patients in the symptomatic AS group were significantly older (70.0±10) than both the asymptomatic AS group (n=14, 48.1±20) and the controls (48.7±17 years), p<0.0001.

6.2.4.1 Ventilation

Results are displayed in figure 6-4. There were no significant differences in ventilation between groups at rest, peak exercise or in recovery.

Figure 6-4: Ventilation, non-cuff v cuff run; asymptomatic v symptomatic AS.
Top panel asymptomatic AS, bottom panel symptomatic AS. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



There was an increase of borderline significance in ventilation in the symptomatic group in the cuff run compared to the non-cuff run (see table 6-4). There was a non significant trend for the magnitude of the ergoreflex to be higher in AS patients, see table 6-4. Intra-group analysis did not demonstrate any significant differences in the magnitude of cuff and non-cuff ergoreflex magnitude.

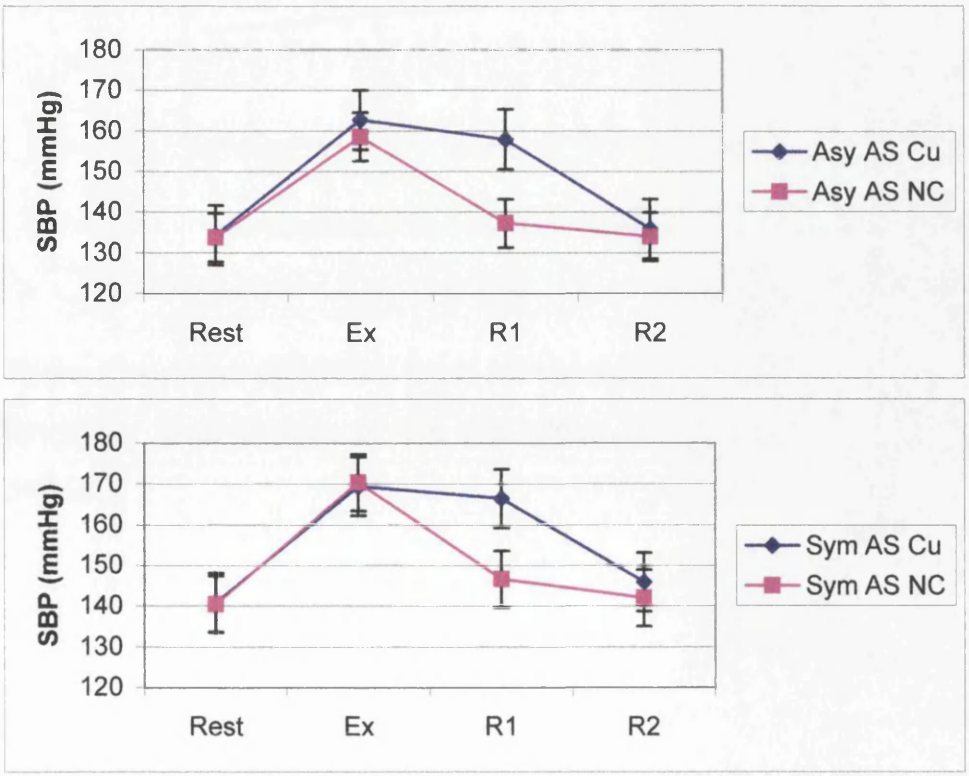
	Ventilation				Ergoreflex magnitude	
	Cuff recovery	Non-cuff recovery	95% CI Cu-NC	p	Cuff (% peak)	Non-cuff (% peak)
Controls	9.8±1.7	9.3±1.8	-0.4, 1.3	ns	18±29	12±36
Asy AS	11.2±3.5	10.6±2.0	-0.8, 2.0	ns	36±30	32±28
Sym AS	12.2±4.3	10.8±2.2	-0.1, 3.0	0.06	51±67	29±19
p	0.11	0.08			0.12	0.10

Table 6-4: Cuff v non-cuff ventilation and magnitude of ergoreflex by symptomatic status.
Cu= cuff run, NC= non-cuff run

6.2.4.2 Blood pressure

There was no significant differences in blood pressure between the AS symptomatic groups and controls at any time point. SBP blood pressure responses are displayed in figure 6-5.

Figure 6-5: Cuff v non cuff, effect on SBP; asymptomatic v symptomatic AS.
Top panel asymptomatic AS, bottom panel symptomatic AS. R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.

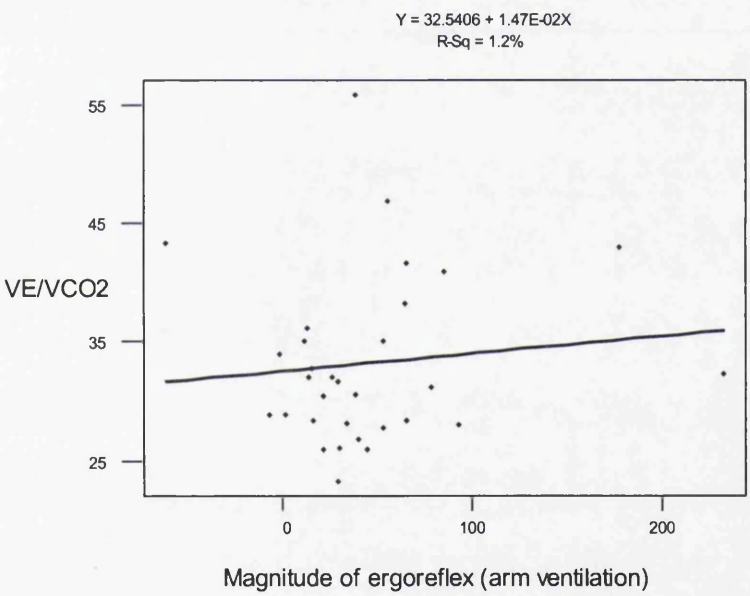


The pattern of change of diastolic blood pressure was similar to that of SBP. Systolic and diastolic blood pressure was significantly elevated during recovery with regional circulatory occlusion compared to without in symptomatic and asymptomatic patients. There were no significant differences in the magnitude of ergoreflex between groups (see table 6-3).

6.3 Ergoreflex magnitude associations

No anthropometric or echocardiographic variables were significantly associated with the magnitude of ergoreflex activity. The slope of exercise V_E/VCO_2 was not significantly correlated to the magnitude of arm ergoreflex (figure 6-6).

Figure 6-6: Association of exercise V_E/VCO_2 and magnitude of ergoreflex in AS.



There was a non-significant trend for ergoreflex magnitude to increase with NYHA functional classification in the AS group (I 22±24, II 38±25 and III 65±81%, p=0.25).

6.4 Summary of chapter results

Arm ergoreflex contributes to the maintenance of post-exercise BP in AS and controls.

Arm ergoreflex activation does not contribute to the maintenance of post-exercise ventilation in AS or controls.

Arm ergoreflex activation was not enhanced in AS v controls.

The magnitude of arm ergoreflex activation was not associated with exercise capacity in AS or controls.

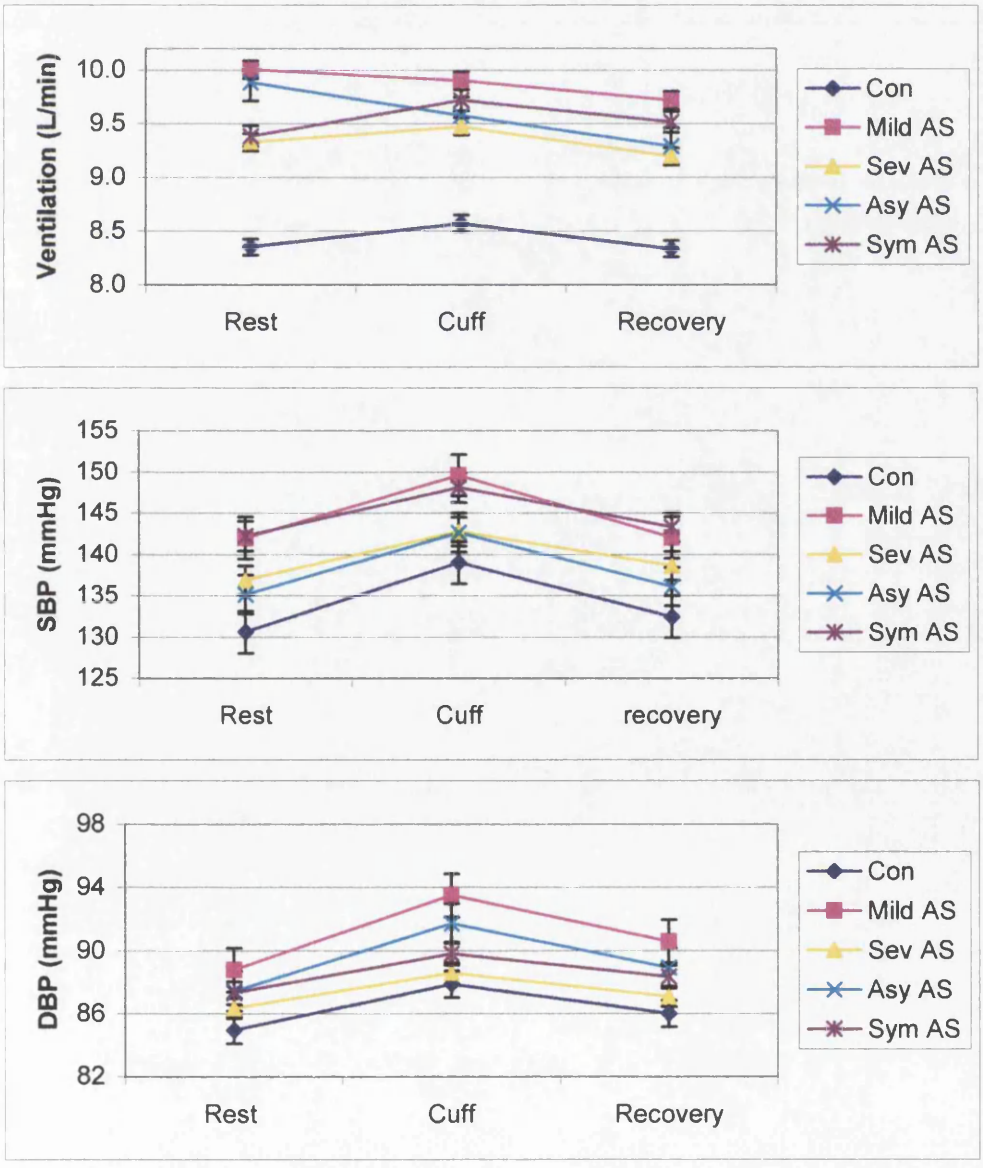
7. LEG ERGOREFLEX

Two subjects (AS21, AS22) could not tolerate control cuff inflation, all other subjects reported discomfort during recovery with RCO but none required the cuff to be deflated prematurely. Thirty-one AS patients and 17 controls completed the leg exercise studies (methods section 2.7.2).

7.1 Control cuff inflation

There was no significant effect of cuff inflation on resting ventilation (figure 7-1). SBP increased by a small but significant amount (6.2-8.4mmHg $p<0.01$) in all groups. There was also a significant increase in DBP with cuff inflation in all groups (2.9-4.7mmHg), $p \leq 0.03$.

Figure 7-1: Leg ergoreflex: Control cuff inflation
Top panel ventilation, middle panel SBP, bottom panel DBP. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



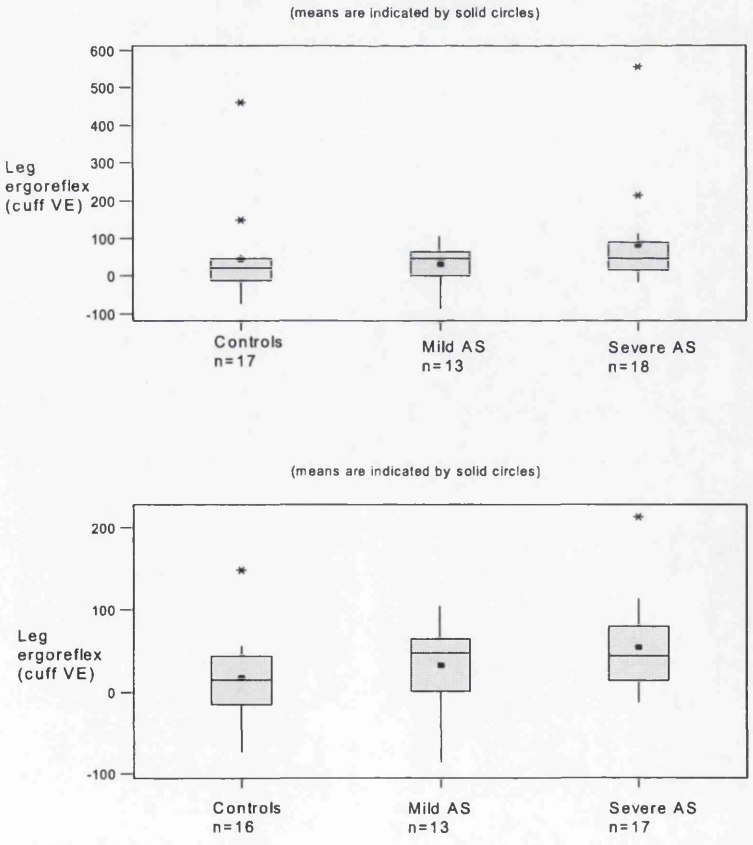
7.2 Cuff v non-cuff run

Two subjects were excluded from ergoreflex calculations because of their abnormal ventilatory responses to exercise. These data are shown in table 7-1. Both subjects had a very limited increase in ventilation on exercise but a relatively large further increase with cuff inflation, resulting in exceptionally high ergoreflex magnitudes. These results had undue influence on statistical testing (see figure 7-2 for effect on means) and were excluded from analysis.

Subject	Ventilation (L/min)			Ergoreflex Magnitude (% peak)
	Rest	Peak Ex	Cuff	
AS36	6.1	6.6	9.0	558
C08	8.1	8.4	9.8	459

Table 7-1: Outliers excluded from leg ergoreflex analysis.

Figure 7-2: Leg ergoreflex by severity of AS.
Top panel: all subjects. Bottom panel: one outlier excluded from control and severe AS groups.



7.2.1 Exercise duration and metabolic demand.

Results are displayed in table 7-2. There were no significant differences in resting or peak exercise measures between cuff and non-cuff runs in any group. Exercise duration was similar for both runs in each subject group. The controls exercised slightly longer than AS subjects but this difference was not significant. Respiratory rate was increased in symptomatic AS compared to controls at rest but not at peak exercise. A similar metabolic load was placed on each group as there were no significant differences in measured variables at peak exercise.

	Ex. time (min)		V_{O_2} (ml/min)		V_{CO_2} (ml/min)		RR (bpm)	
	Cuff	Non-cu	Rest	Ex	Rest	Ex	Rest	Ex
Controls	4.5±2.0	4.1±1.5	235±76	329±92	189±71	305±124	16.6±4	21.6±5
Mild AS	3.6±1.3	3.6±1.4	265±73	388±99	214±69	339±92	19.2±4	23.2±5
Sev AS	3.5±1.0	3.4±1.3	235±49	369±83	194±43	325±72	19.2±3	22.1±5
Asy AS	3.7±1.2	3.5±1.1	253±69	380±96	205±61	339±82	18.4±4	22.3±5
Sym AS	3.4±1.1	3.4±1.6	243±54	374±85	200±53	325±81	19.8±3*	22.8±5

Table 7-2: Cuff v non-cuff runs; exercise duration, V_{O_2}, V_{CO_2}, and respiratory rate.
Ex= peak exercise, RR= respiratory rate. V_{O_2} and V_{CO_2} and RR presented as average of cuff and non-cuff runs. *Sym AS > controls, p=0.02.

7.2.2 Mild v severe AS

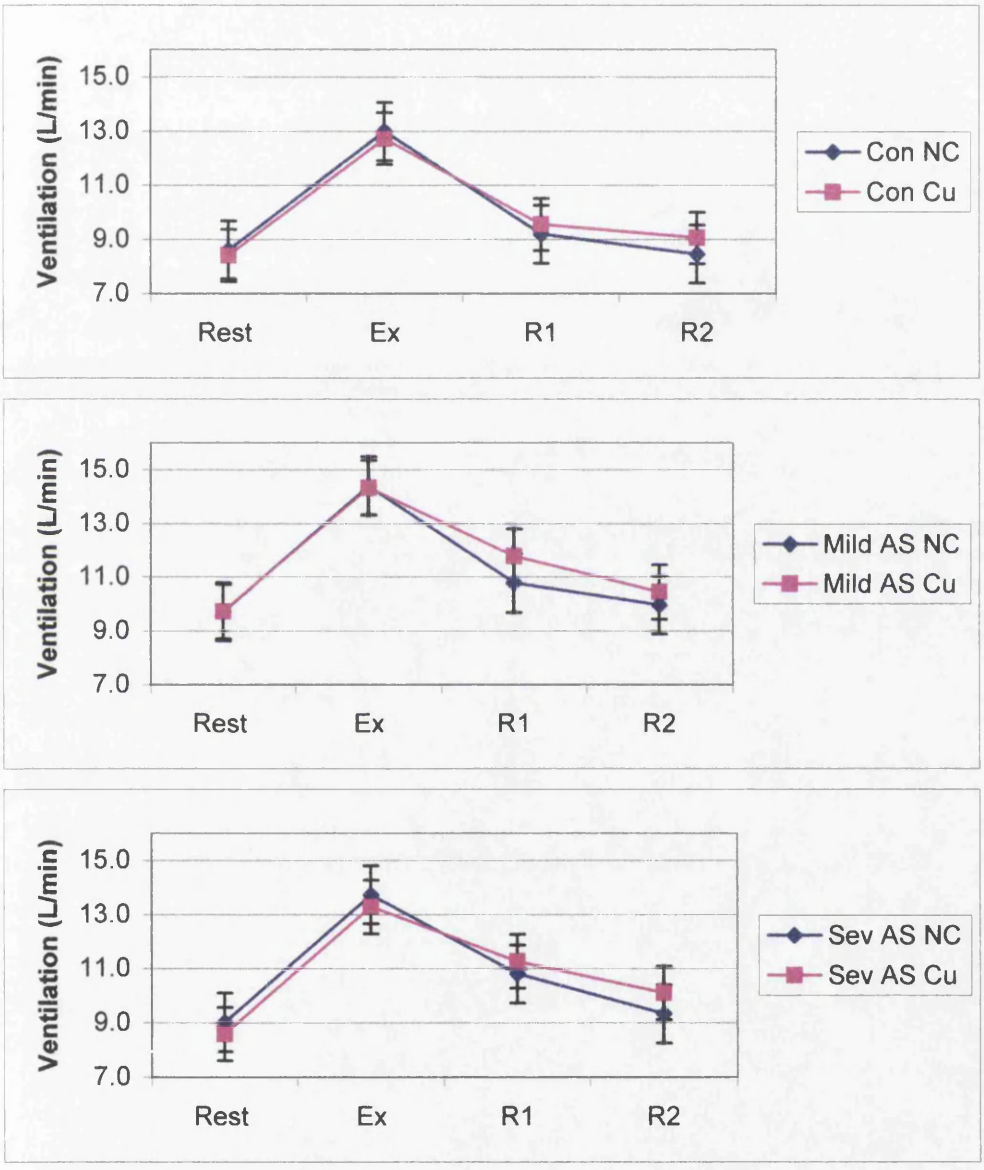
There were 17 AS patients in the severe group who were significantly older (64.0±15) than the 16 controls (48.0±18 years) but not the 13 patients with mild AS (50.3±22), p=0.03.

7.2.2.1 Ventilation

Results are displayed in figure 7-3. Ventilation increased in all groups on exercise by a similar magnitude (48-59%) in both cuff and non-cuff runs.

Figure 7-3: Ventilation, non-cuff v cuff run by severity of AS

Top panel controls, middle panel mild AS and bottom panel severe AS. Data represent mean±sem (error bars). NC= non-cuff run, Cu= cuff run, Con= controls, Sev= severe AS. R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



Recovery ventilation with RCO tended to be higher in the AS groups than controls although this difference fails to reach statistical significance (see table 7-3).

Recovery ventilation in the cuff run was significantly increased compared to the non-cuff run in the mild AS group. There was a non-significant trend for the magnitude of the ergoreflex to be increased in the severe group. Intra-group analysis did not demonstrate any significant differences in the magnitude of ergoreflex activation between cuff and non-cuff runs.

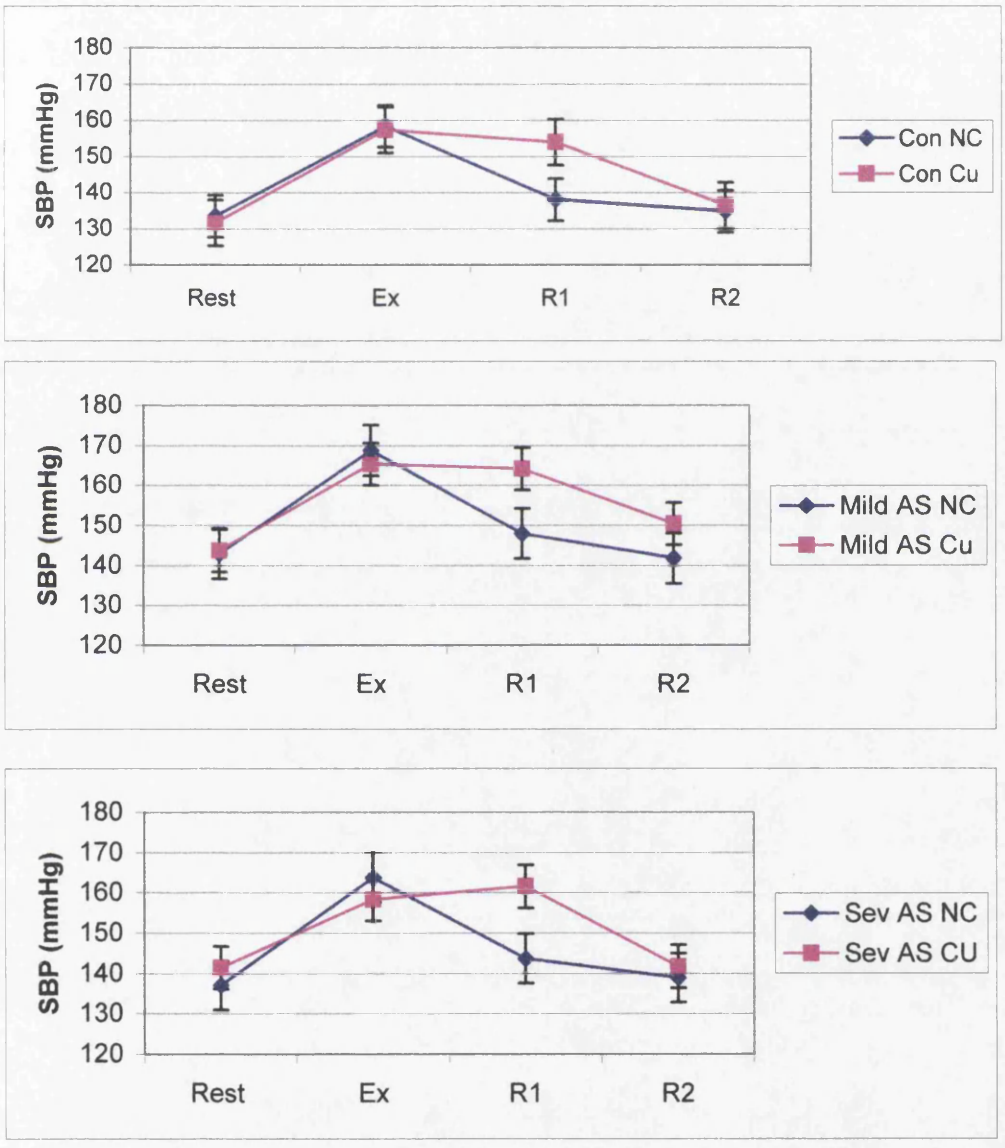
	Ventilation				Ergoreflex magnitude	
	Cuff recovery	**Non-cuff recovery**	**95% CI Cu-NC**	**p**	**Cuff (% peak)**	**Non-cuff (% peak)**
Controls	9.5±2.2	9.2±1.9	-0.5, 1.2	ns	17±48	8±77
Mild AS	11.8±2.9	10.8±2.2	0.2, 1.8	**0.02**	32±51	21±32
Severe AS	11.3±2.8	10.7±3.2	-0.5, 1.7	ns	54±54	38±58
p	0.06	ns	-	-	0.13	ns

Table 7-3: Cuff v non-cuff ventilation and magnitude of leg ergoreflex by severity of AS.
Cu= cuff recovery; NC= non-cuff recovery

7.2.2.2 Blood pressure

There were no significant differences in either systolic or diastolic blood pressure between groups at rest, peak exercise or during recovery. SBP responses are shown in figure 7-4.

Figure 7-4: SBP non-cuff v cuff run, by severity of AS.
Top panel controls, middle panel mild AS and bottom panel severe AS. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



Systolic blood pressure was higher in each group during recovery with regional circulatory occlusion than without. Diastolic blood pressure followed a similar pattern to systolic blood pressure (see table 7-4).

The magnitude of ergoreflex activation for BP was not significantly different between groups, classed by severity of AS. The magnitude of ergoreflex was significantly increased for SBP and DBP in the cuff v non-cuff run in all groups.

	Average Blood Pressure (mmHg)				Ergoreflex magnitude	
	Cuff Recovery	Non-Cu Recovery	95% CI of Cu-NC	p	Cuff (% peak)	Non-cuff (% peak)
Controls						
SBP	154±16	138±12	10.1, 19.6	**<0.0001**	87±37	14±52
DBP	99±8	89±9	6.6,13.4	**<0.0001**	87±44	14±45
Mild AS						
SBP	164±28	148±24	9.2, 23.2	**0.0003**	82±51	22±25
DBP	101±14	93±13	4.0, 12.0	**0.001**	108±170	18±46
Severe AS						
SBP	161±28	144±24	12.2, 23.6	**<0.0001**	125±79	27±53
DBP	96±12	88±10	4.9, 11.1	**0.0001**	129±109	27±42
Asy AS						
SBP	152±24	139±19	7.7, 18.0	**0.0001**	77±75	21±33
DBP	9914±	92±12	2.5, 10.3	**0.004**	112±74	37±34
Sym AS						
SBP	172±28	151±26	15.9, 27.3	**<0.0001**	**132±58***	28±50
DBP	97±13	88±11	6.4±12.3	**<0.0001**	124±110	12±47

Table 7-4: Blood pressure response by group; cuff v non-cuff and magnitude of ergoreflex.
Cu= cuff run, NC= non-cuff run.

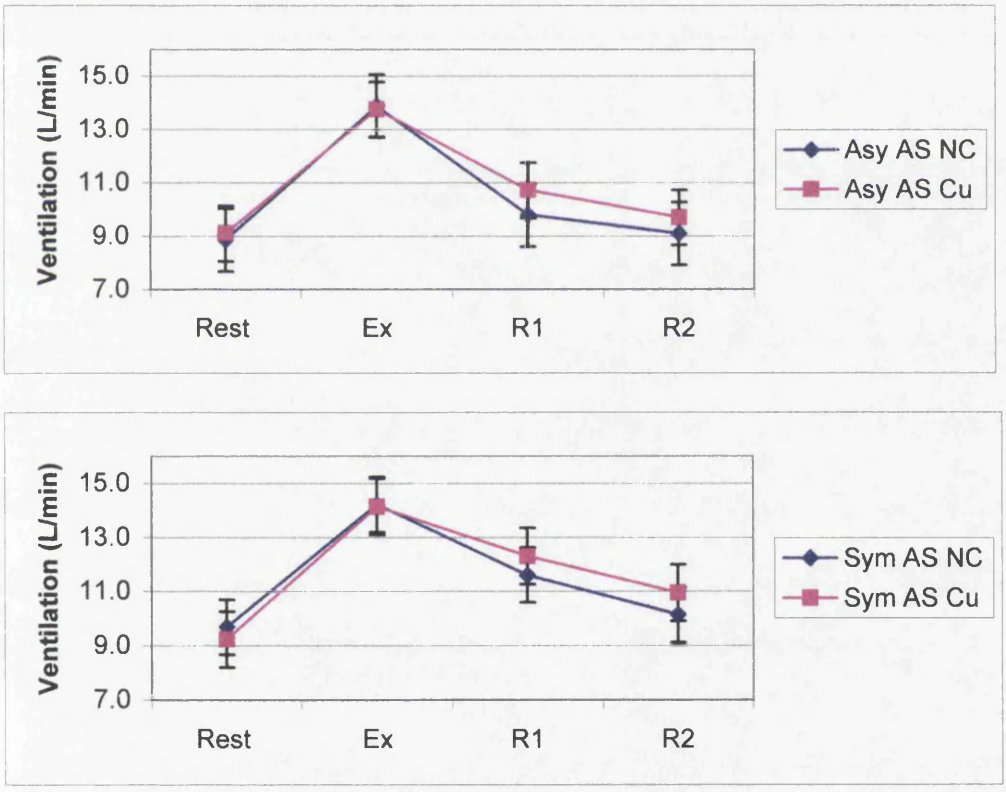
7.2.3 Symptomatic v asymptomatic AS

Subjects AS36 and C08 were again excluded from ergoreflex analysis. The 16 patients in the symptomatic AS group were significantly older (69.2±11) than both the asymptomatic AS group (n=14, 45.4±20) and the controls (n=16, 48.0±18 years), $p<0.001$.

7.2.3.1 Ventilation

Results are displayed in figure 7-5. There were no significant differences in ventilation between groups at rest or at peak exercise in either cuff or non-cuff run.

Figure 7-5: Ventilation, non-cuff v cuff run by symptomatic group.
Top panel controls, middle panel asymptomatic AS, bottom panel symptomatic AS. Data represent mean±sem (error bars). R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



Ventilation during recovery with RCO was significantly increased in the symptomatic group compared to controls (see table 7-5). Ergoreflex magnitude (cuff run) was also increased with RCO in the symptomatic AS group compared to both other groups.

Absolute ventilation was significantly higher in symptomatic patients during non-cuff recovery compared to asymptomatic AS and controls although the magnitude of non-cuff ergoreflex differences did not reach statistical significance (see table 7-5).

	Ventilation (L/min)				Ergoreflex Magnitude	
	Cuff recovery	Non-cuff recovery	95% CI Cu-NC	p	Cuff (% peak)	Non-cuff (% peak)
Controls	9.5±2.2	9.2±1.9	-0.5, 1.2	ns	17±48	8±77
Asy AS	10.7±2.9	9.8±1.8	-0.01, 1.9	0.052	20±47	17±29
Sym AS	12.3±2.7	11.6±3.2	-0.4, 1.9	ns	67±50	44±59
p	**0.015***	**0.02****	-	-	**0.01****	ns

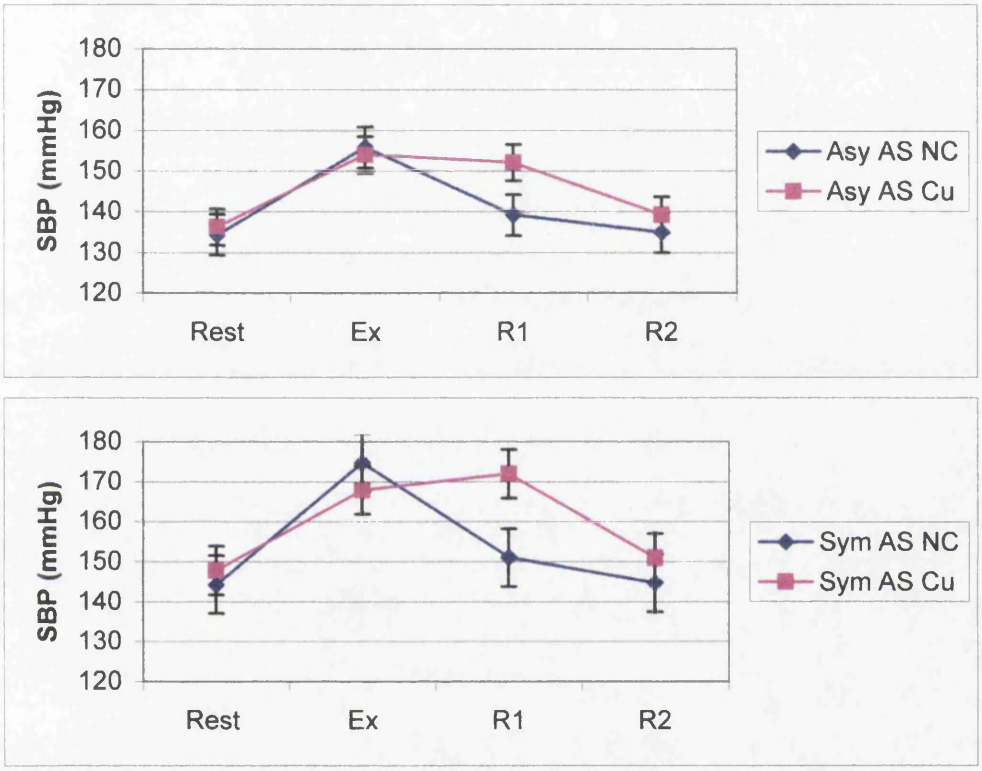
Table 7-5: Cuff v non-cuff ventilation and magnitude of ergoreflex by symptomatic status.
* Sym AS v controls but not Asy AS. **Sym AS v Asy AS and controls.

Intra-group comparisons of the magnitude of ergoreflex between cuff and non-cuff runs were not significant for the controls or asymptomatic AS, in the symptomatic group this difference is of borderline significance (95% CI -3.8, 49.5, p=0.09).

7.2.3.2 Blood pressure

There was no significant difference in systolic or diastolic blood pressure between the AS symptomatic groups and controls at any time point. Systolic blood pressure blood pressure responses are displayed in figure 7-6.

Figure 7-6: Cuff v non cuff, effect on SBP; asymptomatic v symptomatic AS.
Top panel asymptomatic AS, bottom panel symptomatic AS. R1= first 3 min recovery with/without RCO, R2= recovery 4-6min.



The pattern of change of diastolic blood pressure was similar to that of systolic blood pressure (see table 7-4). Systolic and diastolic blood pressure was significantly elevated during recovery with regional circulatory occlusion compared to without in symptomatic and asymptomatic patients. Intra-group analysis showed increased ergoreflex activation in cuff v non-cuff runs for both SBP and DBP in both groups.

The magnitude of cuff ergoreflex activation for SBP was significantly increased in symptomatic AS compared to controls (95% CI 85, 5) and asymptomatic AS (95% CI 96, 14), p=0.02. There were no significant differences between groups in the magnitude of cuff ergoreflex for DBP or in non-cuff ergoreflex activation in either SBP or DBP.

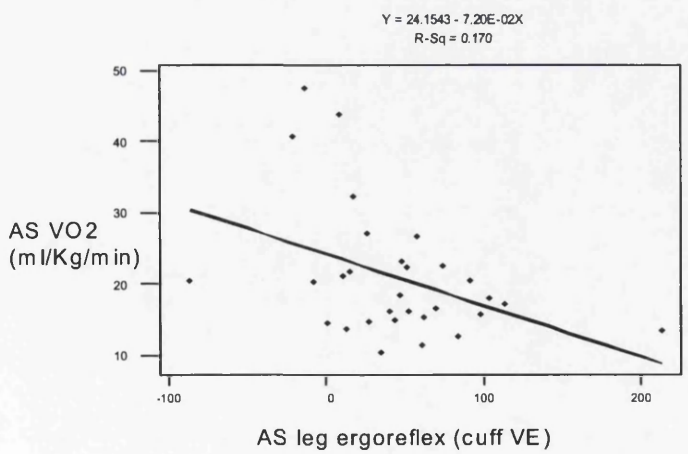
7.3 Ergoreflex magnitude associations

Leg ergoreflex (cuff ventilation) was significantly associated with several variables in AS (see 7-6). The magnitude of leg ergoreflex was significantly associated with age, E/A ratio, aortic valve area and V_{O_2}max (figure 7-7) but not with predicted exercise time. There was a weak but non-significant association with the slope of exercise V_E/V_{CO_2}. There was no relationship between ergoreflex magnitude and any measure of skeletal muscle strength in patients or controls. There was no significant correlation of ergoreflex with any anthropometric, echocardiographic or exercise variable in controls.

Variable	R^2 (p)	
	AS	Controls
Age	26.4% (0.02)	0% (ns)
AVA (VTI)	13.1% (0.05)	17.7%(ns)
E/A	24.8% (0.006)	2.8% (ns)
V_{O_2}max	17.0% (0.02)	0.2% (ns)
V_E/V_{CO_2}	8.1% (0.13)	0.1% (ns)

Table 7-6: Association of leg ergoreflex (cuff ventilation) with anthropometric, echocardiographic and exercise variables.

Figure 7-7: Leg ergoreflex (cuff V_E) v V_{O_2}max in AS.



Ergoreflex magnitude was not an independent predictor of V_{O_2}max when considered in a multivariate regression with age.

7.4 Summary of chapter results

Leg ergoreflex contributes to the maintenance of post-exercise BP in AS and controls.

Leg ergoreflex activation contributes to the maintenance of post-exercise ventilation in symptomatic AS but not asymptomatic AS or controls.

Leg ergoreflex activation was enhanced in symptomatic AS v asymptomatic AS and controls.

The magnitude of leg ergoreflex (cuff V_E) activation was a univariate, but not an independent predictor of exercise capacity in AS.

The magnitude of leg ergoreflex (cuff V_E) activation was not significantly correlated with exercise V_E/VCO_2.

8. BNP

Sixteen controls and 34 patients had blood sampled pre and post exercise. One AS sample post-exercise was insufficient for analysis. BNP data were not normally distributed and were log transformed to allow application of parametric statistical analyses. (see section 2.8 and 2.10).

8.1 Mild v severe AS

All sixteen patients with mild AS and 17 with severe AS had samples suitable for analysis. Results are displayed in table 8-1. Patients with severe AS tended to be older than those with mild AS and controls but this difference does not reach statistical significance.

	Age	BNP Rest (pg/ml) (Log BNP)	BNP Ex (pg/ml) (Log BNP)	BNP Ex-rest (pg/ml)	95% CI Ex-rest (pg/ml)	p
Controls	48.4±1	6, (4-15)	12, (9-36)	9.0	5, 16	**0.001**
(n=16)	8	(0.81±0.4)	(1.1±0.4)			
Mild AS	51.8±2	21.5, (10-49)	32.5, (15-65)	9.8	3, 15.5	**0.003**
(n=16)	2	(1.31±0.6)	(1.44±0.6)			
Severe AS	62.3±1	78.0, (23-256)	90, (24-280)	22	9.5, 39	**0.001**
(n=17)	5	(1.88±0.6)	(1.94±0.5)			
p	0.08	**<0.0001**$^{+}$	**<0.0001****	ns	-	-

Table 8-1: BNP pre and post exercise by severity of AS
BNP data are presented as median, interquartile range. (BNPlog±SD). **Severe AS significantly different from mild AS and controls. $^{+}$Each group significantly different from each other.

Resting BNP was greater in AS compared to controls and in severe AS compared to mild AS. BNP increased following maximal exercise in all subject groups and the absolute magnitude of increase was similar in each group.

8.2 Symptomatic v asymptomatic AS

There were 16 patients in the symptomatic and 17 in the asymptomatic AS groups. Results are displayed in table 8-2. The symptomatic AS group were significantly older than both the asymptomatic and control groups.

	Age (years)	BNP Rest (pg/ml) (Log BNP)	BNP Ex (pg/ml) (Log BNP)	BNP Ex-rest (pg/ml)	95% CI Ex-rest (pg/ml)	p
Controls (n=16)	48.4±18	6, (4-15) (0.81±0.4)	12, (9-36) (1.1±0.4)	9.0	5, 16	**0.001**
Asy AS (n=17)	47.6±19	22, (10-86) (1.38±0.7)	33, (17-114) (1.52±.6)	13.5	5, 23	**0.002**
Sym AS (n=16)	67.8±12	57, (22-228) (1.84±0.6)	68, (26-198) (1.88±0.5)	13.8	5.5, 37.5	**0.001**
p	**0.002****	**<0.0001****	**0.001***	ns	-	-

Table 8-2: BNP pre and post exercise by symptomatic status.
BNP data are presented as median, interquartile range, (logBNP±SD). *Symptomatic AS significantly different from controls but not asymptomatic AS. **Symptomatic AS significantly different from asymptomatic AS and controls.

Resting BNP was greater in symptomatic AS compared to asymptomatic AS and control groups. BNP increased in all groups following maximal exercise and the magnitude of increase was similar between groups. Following exercise the difference in BNP between symptomatic and asymptomatic AS was no longer significant.

8.3 Predictors of BNP

8.3.1 Resting BNP

Significant predictors of BNP are displayed in table 8-3. BNP was related to age, left ventricular mass/mass index and severity of AS in patients but only ejection fraction in controls. No other anthropometric, haemodynamic or echocardiographic measures were related to BNP in AS or controls.

Variable	R^2 (p)	
	AS	**Controls**
Age (n=34 for AS)	26.1% (0.002)	7.3% (ns)
Ejection fraction (n=15 for controls)	1.3% (ns)	32.2% (0.028)
Left ventricular mass (n=28 for AS)	13.9 (0.05)	0.2% (ns)
LVMI (n=28 for AS)	25.0% (0.007)	0.9% (ns)
Aortic velocity (max) (n=34 for AS)	29.7% (0.001)	8.1% (ns)
Peak pressure gradient (n=34 for AS)	27.0% (0.002)	6.9% (ns)
Mean pressure gradient (n=34)	29.0% (0.001)	3.9% (ns)
AVA (Vmax) (n=34 for AS)	26.4% (0.002)	15.0% (ns)
AVA (VTI) (n=34 for AS)	25.4% (0.002)	12.8% (ns)

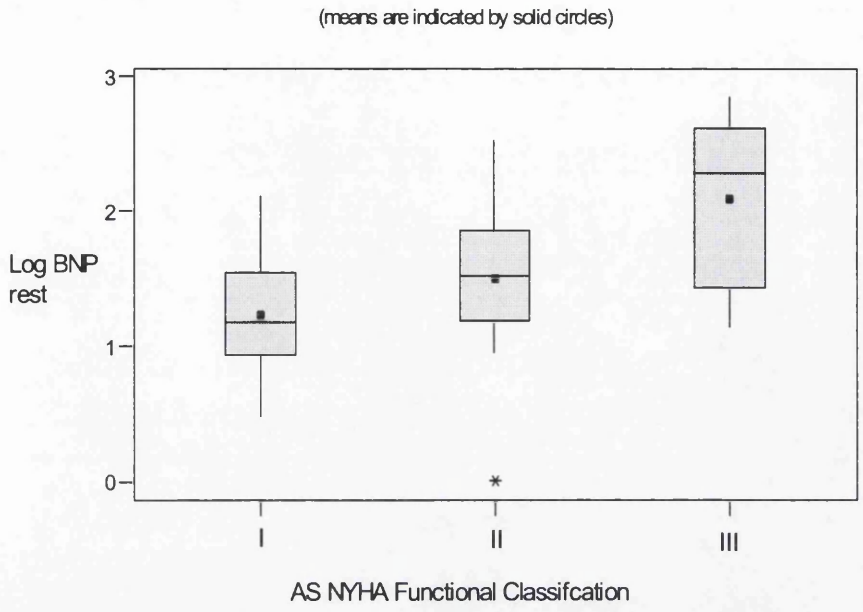
Table 8-3: Univariate predictors of resting plasma BNP.

Resting BNP was also significantly greater in NYHA class III (192.5, 27-407) than in class II (33.5, 16-74) and class I (16, 9-36 pg/mL), p=0.009. (See figure 8-1).

8.3.2 Multivariate predictors of resting BNP

Age (p=0.01), maximal aortic velocity (p=0.01) and mean pressure gradient (p=0.05) remained significant predictors of resting BNP on multivariate analysis.

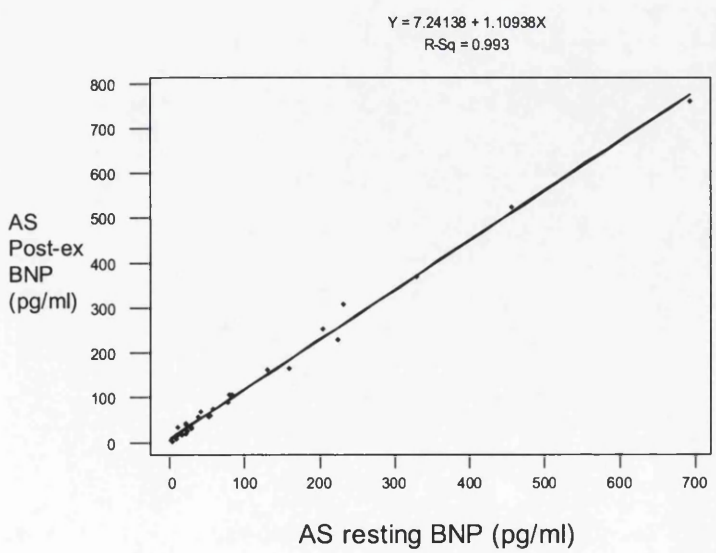
Figure 8-1: Resting plasma BNP by NYHA classification in AS



8.4 Exercise BNP

Post exercise BNP was very closely related to resting BNP in both AS (R^2=99.3%, p<0.0001) and in controls (R^2=89.0%, p<0.0001), see figure 8-2. In both AS patients and controls only resting BNP was an independent predictor of exercise BNP.

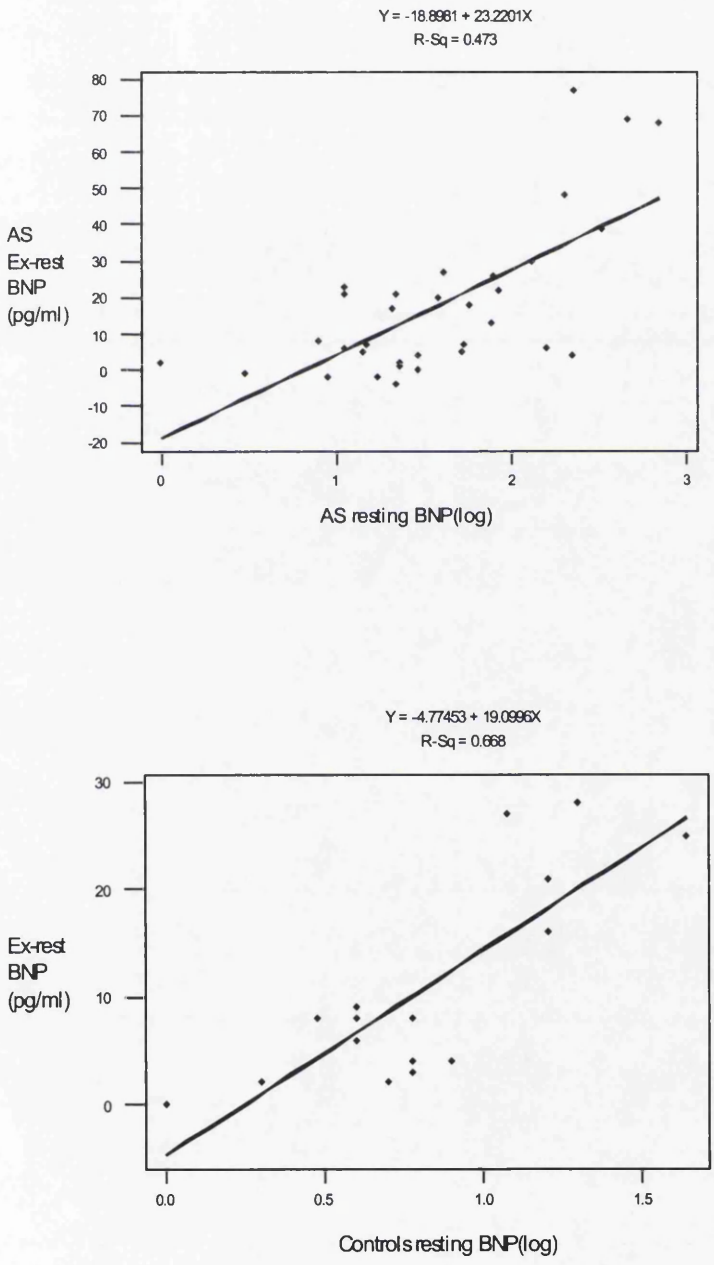
Figure 8-2: Resting v post-exercise plasma BNP in AS.



8.4.1 Magnitude of increase in exercise BNP

Only resting $BNP_{(log)}$ was an independent predictor of exercise induced BNP in AS (R^2=47.3%, p<0.0001) and controls (R^2 66.8%, p<0.0001). See figures 8-3 and 8-4.

Figure 8-3: Exercise-induced increase in BNP v resting $BNP_{(log)}$.
Top panel AS, bottom panel controls.



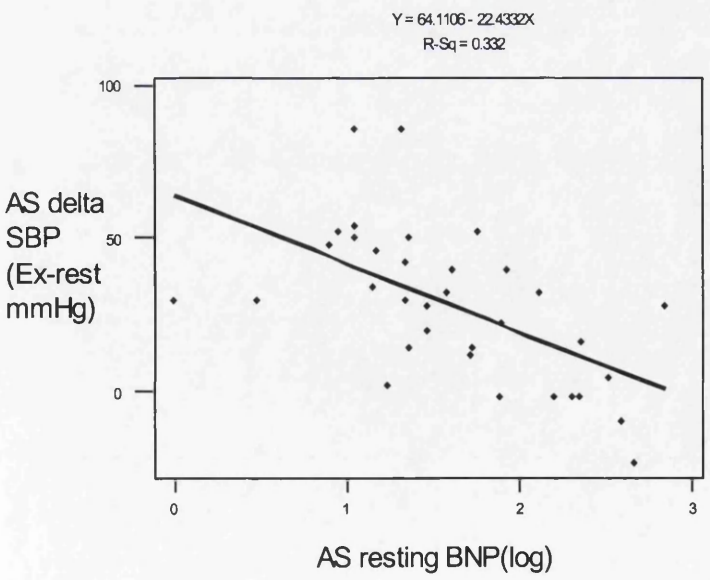
8.5 BNP as a predictor of exercise variables

Associations of resting plasma $BNP_{(log)}$ with various parameters of exercise performance are displayed in table 8-4. BNP did not significantly correlate with any exercise variables in controls. In AS resting $BNP_{(log)}$ correlated with V_E/VCO_2 (r=0.52) and inversely with maximal aerobic capacity (VO_2max r=-0.46, and % predicted exercise time r=-0.41). There was a significant inverse relationship between resting BNP and magnitude of SBP response on exercise (r=-0.58, figure 8-4). BNP did not significantly correlate with the magnitude of leg ergoreflex (cuff ventilation).

Variable	R^2 (p)	
	AS	Controls
VO_2max (n=33)	20.8% (0.008)	3.7% (ns)
Pred Ex time (%) (n=34)	17.2% (0.015)	1.8% (ns)
V_E/VCO_2 (n=33)	27.0% (0.002)	5.9% (ns)
Leg ergoreflex (V_E)	ns	ns
SBP increase (n=34)	33.2% (<0.0001)	0% (ns)

Table 8-4: Resting $BNP_{(log)}$ as a predictor of exercise performance in AS.

Figure 8-4: Log BNP rest v exercise-induced SBP increase in AS.



BNP was not an independent predictor of VO_2max when considered in a multivariate analysis with age. When BNP is considered with left ventricular mass it remains an independent predictor of predicted exercise time (p=0.04).

8.6 Summary of chapter results

Plasma BNP is increased in severe and symptomatic AS compared to controls and mild/asymptomatic AS.

BNP increases following maximal aerobic exercise and the magnitude of increase is similar in AS and controls.

Age and AS severity are independently associated with resting BNP in AS.

The magnitude of the exercise-induced increase in BNP is strongly related to resting BNP in AS and controls.

Resting BNP is correlated with exercise VE/VCO_2 and inversely and independently correlated with exercise duration and the magnitude of SBP response to exercise in AS but not in controls.

9. ET-1

Seventeen controls and 34 patients had ET-1 analysed pre and post exercise. ET-1 data were not normally distributed and remained non-parametric after logarithmic transformation.

9.1 Mild v severe AS

Of the 34 AS patients 19 were in the severe and 15 in the mild group. Results are displayed in table 9-1. There were no significant differences in age between the subject groups. Resting and post-exercise ET-1 were similar in the three groups. There was no appreciable change in ET-1 on exercise in the AS patients but a small significant increase in the control subjects.

	Age (years)	ET-1 Rest (fmol/ml)	ET-1 Ex (fmol/ml)	ET-1 Ex-rest (fmol/ml)	95% CI Ex-rest	p
Controls	49.9±18	0.52,	0.69	0.15	0.01,	**0.04**
(n=17)		0.21, 1.58	0.48, 1.90,		0.38	
Mild AS	51.8±22	1.00,	0.40,	-0.01	-0.34,	ns
(n=15)		0.28, 1.40	0.19, 1.50		0.12	
Severe AS	62.0±14	0.90,	0.60,	-0.02	-0.30,	ns
(n=19)		0.22, 1.30	0.18, 1.30		0.22	
p	0.11	ns	ns	ns	-	-

Table 9-1: ET-1 pre and post exercise by severity of AS
ET-1 data are presented as median, interquartile range.

9.2 Symptomatic v asymptomatic AS

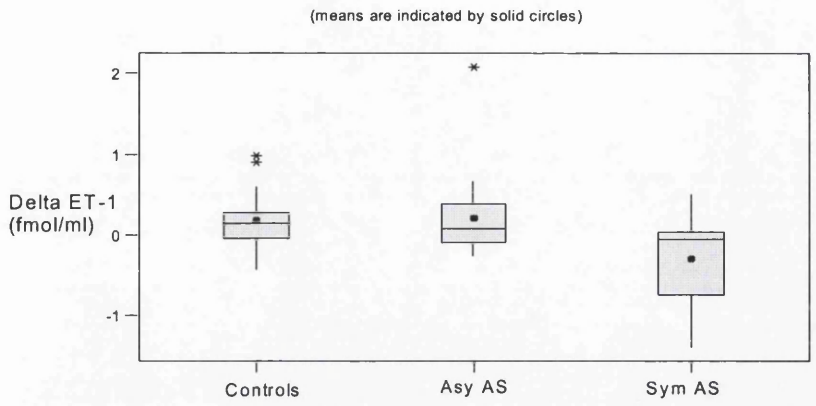
There were 17 patients in the symptomatic and asymptomatic AS groups. Results are displayed in table 9-2. The symptomatic AS group were significantly older than both the asymptomatic and control groups. Resting ET-1 concentrations were similar in the three groups.

	Age (years)	ET-1 Rest (fmol/ml)	ET-1 Ex (fmol/ml)	ET-1 Ex-rest (fmol/ml)	95% CI Ex-rest	p
Controls	49.9±18	0.52,	0.69,	0.15	0.01,	**0.04**
(n=17)		0.21, 1.58	0.48, 1.90,		0.38	
Asy AS	47.1±20	1.00,	1.13,	0.09	-0.02,	ns
(n=17)		0.21, 1.35	0.24, 1.60		0.30	
Sym AS	67.1±11	0.40,	0.30,	-0.22	-0.55,	0.06
(n=17)		0.24, 1.55	0.01, 0.80		0.005	
p	**0.002****	ns	0.06*	**0.02****		

Table 9-2: ET-1 pre and post exercise by symptomatic status.
ET-1 data are presented as median, interquartile range. *Symptomatic AS significantly different from controls but not asymptomatic AS (see text below). **Symptomatic AS significantly different from asymptomatic AS and controls.

On exercise there was a small but significant increase in controls, a trend to decrease the symptomatic group but no significant change in the asymptomatic group (table 9-2). Post-exercise ET-1 appears to be lower in the symptomatic group compared to controls and asymptomatic AS. Kruskal-Wallis testing of medians (see section 2.10.) gave a p value of borderline significance. *Post-hoc testing by Mann-Whitney analysis demonstrated that following maximal exercise ET-1 was significantly lower in symptomatic AS compared to controls (95% CI 0.05, 1.09, p=0.02). but not asymptomatic AS (95% CI -0.03, 1.15, p=0.08). The magnitude of change in ET-1 was significantly different in symptomatic AS compared to the other groups; ET-1 tended to decrease in the symptomatic group, increased in the controls and was little altered in asymptomatic AS (see figure 9-1).

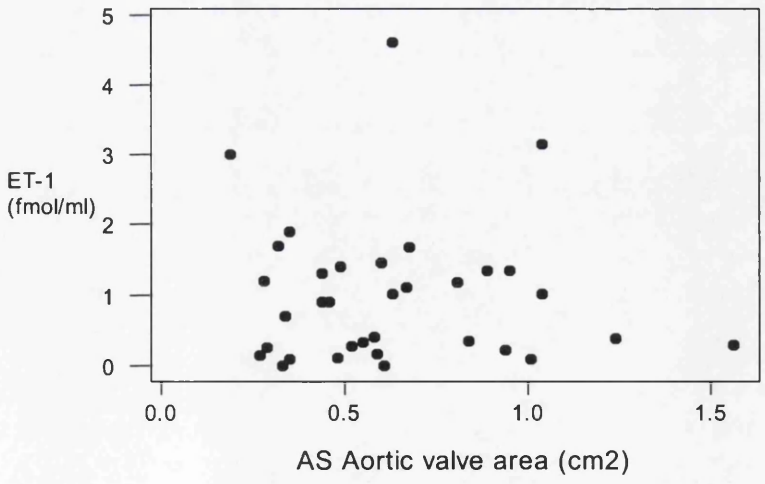
Figure 9-1: Change in ET-1 on exercise by symptomatic group.



9.3 ET-1 associations

ET-1 was not significantly associated with age, anthropometric measures, echocardiographic variables or exercise performance in AS or controls. The lack of a relationship between resting ET-1 and AS severity is shown in figure 9-2. There was also no significant relationship between resting ET-1 and BNP in either controls or AS.

Figure 9-2: ET-1 in AS by aortic valve area.



9.4 Summary of chapter results

Resting and post- exercise ET-1 are similar in AS and controls.

ET-1 increases following exercise in controls, is unchanged in asymptomatic AS and tends to decrease in symptomatic AS.

The magnitude of change in ET-1 on exercise is reduced in symptomatic AS compared to controls and asymptomatic AS.

10. DISCUSSION

10.1 Subject recruitment and characteristics

Of the patients screened, only 26% of patients were eligible to participate in the study. This relatively low figure reflects the rather stringent exclusion criteria, which were drawn up to limit the potential contribution to exercise intolerance from pathological processes other than AS. The commonest reasons for exclusion were other valvular disease (36%), obstructive coronary artery disease (14%), chronic obstructive pulmonary disease (10%) and atrial fibrillation (5%). Also many patients did not meet the inclusion criteria, i.e. they did not have AS of significant haemodynamic severity (22%) or were excluded because of an inability to perform treadmill exercise, due either to severe peripheral vascular disease or arthritis. The patient cohort is therefore not representative of the general AS population but was chosen to elucidate the factors contributing to exercise intolerance in isolated aortic valve disease. Subjects who had aortic regurgitation (AR) were not excluded from this study since Doppler echocardiography identifies many AS patients with co-existent regurgitation. Patients with severe or predominant AR, judged clinically and by echocardiography and/or angiography, were excluded. Those with moderate AR had to display evidence of AS with thickened or calcified leaflets associated with reduced opening.

The actual response rate for an unsolicited approach was good with 52% of patients written to participating in the study. The control group was very well matched for height, weight, body mass index, lean body mass and male-to-female ratio. The patient group was slightly, but not significantly, older. All controls were asymptomatic, although subjects with hypertension were not excluded since several of the AS patients were also being treated for high blood pressure.

10.1.1 Patient Characteristics

As in previous studies, there was a very wide range of age in the patient cohort (25,75), reflecting the inclusion of patients with both congenitally bicuspid aortic valves and the more common degenerative AS. Similarly, there was a wide range in AS severity, with calculated aortic valve areas varying from 0.28 cm^2 to 1.56 cm^2 and peak pressure gradients ranging from 26-157 mmHg. The average severity of AS for the whole patient group would be at least moderate to severe,

with peak and mean pressure gradients of 65 and 37 mmHg respectively and an effective aortic valve area of 0.6 cm^2.

10.1.2 Symptomatic Status

Nine of the patients were completely asymptomatic, 16 were in NYHA class II and 12 in NYHA III. Those in NYHA I were significantly younger than the other patients. Of the 28 patients with symptoms, a very high proportion (25/37) reported exertional dyspnoea, which is just slightly higher than previous reports(4,90). Only 10 patients had angina pectoris, which was lower than in most other studies (4,81,83), but this is undoubtedly a reflection of the fact that patients with proven obstructive coronary artery disease were excluded. Similarly, syncope was an exclusion criteria because of the potential risk on exercise testing. Eighteen of the 28 symptomatic patients also complained of fatigue, but this symptom is seldom reported in previous studies.

10.1.3 Echocardiography

10.1.3.1 Reproducibility of Measurements

The intra-observer correlation coefficients for most of the echocardiographic measurements were good to excellent (r=0.83-0.95). Those for aortic valve area by VTI and ejection fraction using Simpson's rule were only moderately good (r=0.59 and 0.63 respectively). The fact that aortic valve area by VTI gave a poorer correlation coefficient than that by determined by maximal velocity (Vmax), is probably a reflection of the fact that the value is determined by two components: the maximal jet velocity and the systolic ejection period, compared to the maximum velocity for Vmax only. The two values, however, were very closely correlated, the Vmax value tending to be lower than that by VTI, particularly in those with less severe disease (see figure 3-1). This finding is unexpected since VTI generally is regarded as the effective aortic valve area and Vmax corresponds to the point of maximal pressure gradient, which if the valve is elastic, should equate to the maximal area during systole(50). As the vast majority of patients had valve leaflet calcification, the valves may be less elastic and result in little change in the valve area with increased flow.

The low intra-observer correlation coefficient for ejection fraction probably reflects inadequate visualisation of the endocardial surface of the left ventricle. Ejection fraction calculation by Simpson's biplane method requires 80% of the endocardial surface to be visualised(289) and this could not be achieved in several patients and one control subject.

10.1.3.2 Left ventricular structure and function

As in previous studies, left ventricular systolic function was normal in the majority of patients (22-25). Two patients did have wall motion abnormalities, however the mean ejection fraction of 51.6% for the AS group is very close to the expected mean for this population(915), although slightly less than controls. Not surprisingly, the patients had significant increases in both left ventricular mass and mass index compared to controls(17,18). Using a crude measure of diastolic function (E/A ratio), there was no significant difference between aortic patients and controls.

10.2 Patient subclassification

10.2.1 AS severity

10.2.1.1 Classification of AS severity

There is not uniform agreement in selecting which values or even measures to use when grading the severity of AS(18,71-73). Historically aortic valve area has been used and is the preferred measurement of the ACC/AHA task force on management of valvular heart disease(18). The original Gorlin equation suggested that large increases in pressure gradient only occurred with valve areas $<0.75cm^2$(38). The AHA/ACC acknowledge that the severity of AS in any individual may vary depending on body size, have classified an aortic valve area of $<1.0cm^2$ as severe AS(18). In the presence of normal left ventricular function they expect this degree of stenosis to be associated with a mean transvalvular pressure gradient >50mmHg.

Clinicians in the modern era seem more at ease with classification according to pressure gradients rather than aortic valve area(74). Indeed the ACC/AHA task force on sports participation quantify a *mean* pressure gradient >40mmHg as

severe and <20mmHg as mild AS in acquired disease(71). To add to the confusion they recommend the use of *peak* pressure gradient in congenital AS(71). Regardless of the measure used, selecting cut-off values to classify the severity of a continuous variable will always be an inexact science and the limitation of each quantification technique should be borne in mind. It is generally recommended that aortic valve area and pressure gradients are examined together in determining the severity of AS in a given individual(55,74).

In the current study a mean pressure gradient > 30 mmHg was chosen to select patients with moderate to severe disease. Aortic valve area was not used for this purpose, as the values obtained in controls were lower than expected from anatomic specimens(3,4). This can be accounted for by the low mean left ventricular outflow tract diameters measured by echocardiography in both controls (1.65cm) and patients (1.71cm). These values are markedly lower than two previous American reports, 2.3cm(75), 2.29cm(62) but less so than the single British study 1.94cm(55). Small left ventricular outflow tract diameters result in low calculated left ventricular outflow tract area and, according to the continuity equation(50) a low calculated aortic valve area (see equation 7, section 1.4.3). Accurate measurement of left ventricular outflow tract diameter is recognised as an important limitation in calculating aortic valve area by the continuity equation(50,59,60). The average aortic valve area of the control group was 1.5cm^2 and half of the subjects had areas lower than this, normally indicative of the AS range, despite having anatomically normal valves and transvalvular pressure gradients. For these reasons, an absolute value of aortic valve area could not be used reliably to classify the groups according to severity.

10.2.1.2 Discrepancy between valve area and pressure gradient

Twenty-one patients were classified as having moderate-severe AS with a mean pressure gradient >30mmHg. The eight patients who would have been re-classified in the severe group using aortic valve area had significantly lower left ventricular outflow tract diameters (1.48cm) and areas (1.78cm^2) than the other patients (1.78cm and 2.60cm^2). Conversely the two subjects with high mean pressure gradients but only mild AS by area had large left ventricular outflow tract diameters compared to the other patients(see section 3.6.1.5).

Other theoretical possibilities for the discrepancy between pressure gradients and aortic valve areas are less likely to be significant. Aortic regurgitation can result in an increase in measured trans-valvular pressure gradient without a significant reduction in aortic valve area(58). However the five patients with more than mild aortic regurgitation (+++ or ++++ see table 3-5) all had high pressure gradient-low area or low gradient-high area. The modified Bernouilli equation was used to calculate to calculate pressure gradients (equation 5) since in AS this makes little difference to the calculated values(47). Although the left ventricular outflow tract velocities are not used in this equation they were measured as they are required for calculation of aortic valve area by the continuity equation (equation 7). The average reduction in pressure gradients if the proximal velocity had also been used are very small in the AS patients; 3.7mmhHg for peak pressure gradient and only 0.25mmHg for mean pressure gradient.

Aortic pressure recovery is a mechanism by which Doppler measurement of transvalvular pressure gradient may overestimate the true gradient(54-57). This phenomenon is particularly apparent in patients with small aortic roots(54,55). The two patients (AS06 and AS08, see table 3-5) with high pressure gradients and large aortic valve areas did not have small aortic roots making this mechanism unlikely as a cause of overestimation of pressure gradient. They did have large left ventricular outflow tract diameters, again leading to large calculated aortic valve areas.

Severe AS can be present with low pressure gradient in the presence of left ventricular dysfunction. Similarly the aortic valve area may be lower than expected as the reduced contractile force fails to open the calcified aortic leaflets fully(74). In the current study only two patients had had evidence of left ventricular regional wall motion abnormalities (AS 12 and AS20 see table 3-5). AS 20 had both high mean pressure gradient and low aortic valve area in keeping with severe AS. AS 12 had only mild impairment of systolic function and did not have severe stenosis either by pressure gradient or valve area.

The absolute value of the aortic valve area is probably of less importance in this type of investigation than the separation of groups by aortic valve measurements. Clearly the aortic valve area of control subjects is distinct from the aortic patients, with little overlap between groups (see figure 3-3). Similarly, the severe aortic group were significantly lower than those with mild AS.

10.2.1.3 Symptoms and Disease Severity

There was considerable overlap in symptomatic status between patients in the mild-moderate and the moderate-severe aortic groups (table 3-9) which has been demonstrated previously(106). There was a tendency for the more severe group to have increased symptomatology. Considering that other co-morbidities were largely excluded in this study, it is somewhat surprising that ten of the mild group still reported symptoms. As in previous reports, several patients with severe disease were entirely asymptomatic (3,82-4,90,91,). The severity of AS was not significantly associated with anthropometric measurements, left ventricular mass, ejection fraction or E/A ratio. There was a trend for increased NYHA functional classification and increased age to be associated with severe AS (see 3.1.5.5).

10.2.2 Symptomatic versus asymptomatic AS

10.2.2.1 Classification by symptomatic status

Nine of the patients were completely asymptomatic, with a further nine, who had only mild dyspnoea or fatigue, also classed as asymptomatic for subgroup analysis. Such a strategy which could be criticised, has been used in previous large studies(25,75) in assessing the predictors of outcome in asymptomatic AS. Dyspnoea, in combination with signs of heart failure, is regarded as a cardinal symptom in AS(80). However dyspnoea is frequently reported as an early symptom and is present in the majority of symptomatic patients(4,90). Clinicians may be reluctant to recommend aortic valve replacement in patients who have only mild limitation due to dyspnoea and fatigue since these symptoms are non-specific. Also in elderly subjects operative mortality increases dramatically(150-153) and may be deemed prohibitive, in subjects with only mild limitation due to fatigue and dyspnoea , for at best, a modest improvement in symptoms. None the less, the fact that patients with mild and non-specific symptoms were included in the asymptomatic group is likely to reduce the differences in exercise responses between the two groups and is a limitation of the current study.

10.2.2.2 Predictors of symptomatic status

When aortic patients were divided into symptomatic and asymptomatic groups, there was a similar male to female ratio in all three groups. There were no

differences in anthropometric measures or left ventricular structure and function between the two aortic groups. Symptomatic patients, however, were significantly older with more severe disease measured by either pressure gradient or aortic valve area. Other authors have demonstrated that symptomatic patients are significantly older than asymptomatic subjects(106). Age and aortic valve area were associated with symptomatic status and peak and mean pressure gradients were of borderline significance(see table 3-12). However, in a multivariate model predicting symptomatic status, only age was of independent significance. If age > 60 years was considered the odds ratio for being symptomatic was 8.2 (95% CI 1.4, 49.4, p=0.02). This tells us that in patients with haemodynamically significant AS, advancing age is more important in the development of symptoms than stenosis severity. Although somewhat surprising these results are consistent with previous studies which have shown a good prognosis in young patients, particularly those who are asymptomatic(72,111). Age is also a univariate predictor of clinical events in initially asymptomatic patients with severe AS but is not of independent significance when considered with valve calcification(25).

Advancing age may therefore be the most important determinant in explaining why some patients with similar haemodynamic severity of AS develop symptoms and others remain asymptomatic. The importance of age as a predictor of outcome may be related to the co-existence of asymptomatic coronary artery disease(108).

10.2.3 Physical Activity Levels

There was no difference in physical activity levels between the groups as measured by the Scottish Physical Activity Questionnaire. This finding is rather surprising, especially in not detecting differences between symptomatic patients and controls. The SPAQ has been validated as a measure of physical activity in a healthy Scottish population(294). The questionnaire however has not been validated in patient populations and is probably not sensitive enough to detect differences in a cardiac population. A particular problem is that the type of activity is not weighted qualitatively. This means that highly intense exercise such as running or squash is considered equally as a gentle walk or gardening.

10.3 Cardiopulmonary Exercise Tolerance Testing

The current study is one of the largest on exercise testing in AS to include symptomatic patients. There were no complications on maximal exercise testing in this group of patients, some of whom had very severe and symptomatic disease. There is now a considerable body of evidence demonstrating the safety of exercise testing in AS (see section 1.8 and table 1.4). A strong argument could therefore be made for removing AS as a contraindication to exercise testing from the many guidelines which are in circulation (18,124-126).

10.3.1 Rest and exercise ECG

10.3.1.1 Resting ECG

Only ten of the 37 patients had a normal ECG. Twelve patients had voltage criteria for left ventricular hypertrophy and 12 had repolarisation abnormalities. Patients with severe AS were more likely to have an abnormal ECG although 9/16 in the mild group also had ECG abnormalities. There was no difference in the proportion of symptomatic and asymptomatic subjects with an abnormal ECG and interestingly only two of the nine patients in NYHA class I had a normal ECG.

10.3.1.2 Exercise ECG

ST segment changes on exercise testing is not a reliable method for diagnosing obstructive coronary artery disease in AS(137). In the current study all 12 patients with resting repolarisation abnormalities developed further ST depression during exercise and two subjects with left bundle branch block were excluded from further analysis.

Of the 23 patients with no resting repolarisation abnormalities 10 developed ST depression, despite those with a history of, or angiographically proven, obstructive coronary artery disease being excluded. This proportion is slightly lower than reported in a similar group of patients with mild-moderate AS but patients with coronary artery disease were included in that study(137). Somewhat surprisingly, ST changes were seen as frequently in patients with mild or asymptomatic AS compared to those with severe or symptomatic AS (see tables 4-1 and 4-2). From

these data it is concluded that the exercise ECG is not a helpful investigation in discriminating between asymptomatic and symptomatic AS patients.

10.3.2 Symptoms limiting exercise capacity

As in previous reports, the vast majority of the patients in the current study were limited by fatigue, breathlessness or a combination of the two(34,194). Three of the nine patients in NYHA class I were limited by dyspnoea but two of the controls also stated breathlessness as the reason for termination. Patients with severe AS tended to be limited more frequently by dyspnoea or chest pain rather than fatigue compared to mild AS as has been shown previously(34). Similar differences were not seen when the symptomatic and asymptomatic groups were compared. This may be partly explained by the fact that mildly symptomatic patients were included in the asymptomatic group for analysis. However when examined by NYHA class there were no differences in the proportions limited by dyspnoea/chest pain although this analysis may be limited by the small numbers in each group (see section 4.2.1.1)

The fact that the symptomatic patients had significantly reduced exercise capacity with reduced RER, peak ventilation and reduced maximum heart rate is consistent with symptomatic development causing early termination of the test.

Two patients had a drop in SBP during exercise and both were symptomatic at the time of test termination.

10.3.3 Exercise capacity

Exercise capacity was significantly reduced in all groups of AS patients confirming the hypothesis (1.17.1.1).

10.3.3.1 Asymptomatic AS

Exercise duration was 86% of predicted in asymptomatic patients, which is consistent with that reported previously by Otto in a similar group of subjects(75). V_{O_2}max was 20% lower in asymptomatic patients compared to the control group who were very well matched for age and sex, but this reduction just fails to reach statistical significance (table 4-4). The mean V_{O_2}max of 25.3 ml/kg/min is also

similar (26.7 ml/kg/min) to that reported in slightly younger asymptomatic AS patients(24). The asymptomatic group achieved close to maximum predicted heart rate (90±15%), which was not significantly different from the control group. They did demonstrate a reduced SBP response to exercise compared to controls(see table (see table 4-4), as has previously been reported(24).

10.3.3.2 Mild AS

When one considers all patients with mild, albeit haemodynamically significant AS, the reductions in exercise capacity are more pronounced. There were significant reductions in exercise duration, VO_2max, maximum heart rate, ventilation and RER compared to controls, even though these groups were very well matched for age, sex and body size (tables 3-8 and 4-3).

10.3.3.3 Severe AS

Patients with severe AS, regardless of symptomatic status, tended to have reduced exercise capacity and a blunted haemodynamic response compared to control subjects. There were few statistically significant differences between the severe and the mild AS groups however (table 4-3). They did have a lower increase in SBP but maximum cardiopulmonary measures were not significantly different between the mild and severe AS groups.

10.3.3.4 Symptomatic AS

Of more interest is the significant differences in exercise variables in the symptomatic compared to the asymptomatic group. Maximum heart rate, increase in exercise SBP (19 vs. 37 mmHg) and predicted exercise duration were all significantly reduced in the symptomatic group (table 4-4). Similarly, VO_2max was reduced by 35% although this difference may be partially explained by the fact the symptomatic patients were significantly older. Exercise capacity remained impaired however, even when corrected for age and sex (% predicted exercise time estimated from the Bruce nomogram(292), table 4-2). In this study exercise duration as a percentage of predicted is probably a more meaningful measure of aerobic capacity given the large age range in subjects. VO_2max is known to decrease with advancing age whereas predicted exercise time is based on the age and sex of the subject.

The ventilatory response to exercise was also significantly altered in the symptomatic group (confirming hypothesis 1.17.1.2). V_E/VCO_2 measured at submaximal exercise intensity was significantly increased, as has been demonstrated previously in patients with CHF(182,183). V_E/VCO_2, across a wide range of values (30-55), was a strong predictor of mortality at two years in 293 patients with CHF(190). Although the symptomatic AS group were slightly older (68 v 59 years) than the CHF patients, V_E/VCO_2 (AS 35 v CHF 37) and VO_2max (AS 16.4 v CHF 17.8 ml/kg/min) were comparable. It remains to be seen whether V_E/VCO_2 and VO_2max may be strong independent predictors of mortality or the need for aortic valve replacement in AS.

These differences in exercise performance were seen despite patients with mild symptoms being included in the asymptomatic group for analysis. As can be seen from table 4-5 the nine patients in each group responded differently to exercise despite having similar ages and degree of stenosis severity. The patients in NYHA class I were not significantly different from the control group and the mildly symptomatic patients were not significantly different from the more symptomatic group. These findings would seem to support the advocates of exercise testing in asymptomatic patients with AS as a guide to aortic valve replacement. The fact that the two groups responded differently to exercise also questions the validity of whether mildly symptomatic patients should be included in outcome studies of asymptomatic AS. This is especially true as functional status, measured by a standardised questionnaire, was an independent predictor of outcome in Otto's prospective study of asymptomatic AS(75) but was not considered in Rosenhek's similar study(25).

10.3.4 Predictors of aerobic exercise capacity in AS

This is the first study to report that resting haemodynamic measures of AS severity are significantly associated with maximal aerobic capacity (thereby confirming the null hypothesis 1.17.6.1). Age, symptomatic status, aortic valve area, peak A and E/A ratio of left ventricular filling were all univariate predictors of aerobic exercise capacity (see table 4-6). The only independently significant predictors of VO_2max were patient age and NYHA functional classification. It is not surprising that age is such a strong predictor of VO_2max in this study. It is well recognised that maximum aerobic capacity decreases with age and there was a very large age range (20-84 years) of the subjects tested(174). It was also expected that

symptomatic status would be a significant predictor of exercise capacity since these patients will tend to develop symptoms on exercise resulting in early termination of the test.

10.3.4.1 Functional status and exercise capacity

Previous studies in AS have reported that functional classification of symptomatic status is poorly associated with exercise capacity(93,135). The discrepancy between the current study and these previous reports may be due to the fact that subjects with significant co-morbidity, e.g. obstructive coronary artery disease, which may limit exercise capacity, were excluded. However, similar to previous results, some patients with only mild symptoms have severe limitation on exercise testing and there is a large overlap between patients in each functional class, see figure 4-3(93). NYHA classification, left ventricular mass and mass index were independent predictors of exercise duration (% predicted). As predicted exercise time is based on the sex and age of the subject, it is not surprising that age is not a independently associated with exercise duration.

10.3.4.2 Left ventricular mass and diastolic function

The fact that left ventricular mass and mass index were independent predictors of exercise duration probably reflects the importance of diastolic function in exercise limitation in AS. Left ventricular diastolic filling and stroke volume on exercise are inversely related to left ventricular mass in AS(24). Oxygen pulse, which is the amount of oxygen consumed per heartbeat, and is the product of stroke volume and arterial venous oxygen extraction, was significantly reduced in AS patients (tables 4-3 and 4-4). This finding is consistent with impaired left ventricular function. Also, the E/A ratio of ventricular diastolic filling (a crude measure of diastolic function) was a univariate predictor of V_{O_2}max in AS patients. This ratio is known to decrease with advancing age and was no longer significant when considered in a multivariate analysis with age.

10.3.5 Cardiopulmonary exercise variables as predictors of outcome

Clearly these results demonstrate that there are significant differences in the haemodynamic and cardiopulmonary responses to exercise in patients with

symptomatic disease compared to asymptomatic individuals. Symptom-limited exercise testing is commonly performed in most hospitals, but is rarely undertaken in patients with AS. It has been demonstrated that exercise testing such patients is safe and provides both an objective measure of aerobic capacity and allows determination of the haemodynamic response to exercise. The variables which seem to give most differentiation between symptomatic (i.e. those at most risk of future events) and asymptomatic AS are: the increase in SBP, exercise duration as compared to predicted and the slope of V_E/V_{CO_2} which has been shown to provide independent prognostic information in patients with CHF(190). Other than measuring V_E/V_{CO_2}, every hospital in the country has the facility to undertake exercise testing which might provide important prognostic information in AS.

10.4 Muscle strength and endurance

No previous studies have examined skeletal muscle strength or endurance in aortic valve disease.

10.4.1 Isometric strength

No significant differences in any measure of isometric quadriceps muscle strength were found between the AS patients, either classified by severity or symptomatic status, and the controls (tables 5-1 & 5-2). Similar results have been reported in patients with heart failure, certainly when skeletal muscle mass is normalised for body size(180,202). The absolute value of quadriceps strength (>500N) in AS patients in this study is higher than that reported for CHF patients of a similar age (≤400N) with comparable maximal aerobic capacities(176,179,202). This also applies to the control subjects compared to those in a previous study(202). These different results are not directly comparable, however. The previous reports tested subjects isometrically at 90^0 or 45^0 whereas the current study employed 105^0 and 110^0. It is not surprising that these higher angles produce greater force since they equate to the approximate ideal length-tension relationship for force production of the quadriceps muscles.

Clark et al did report that isometric muscle strength was reduced in patients with mild CHF (mean V_{O_2}max 21.3ml/kg/min) compared to age-matched controls(200). However the male to female ratio of subjects was not given and the aerobic

exercise capacity of the control group was very high (mean Vo_2max 44.7 compared to 31.3 ml/kg/min for the controls in the present study). This raises the possibility that the controls in Clark's paper were either poorly sex-matched or fitter and more physically active than expected for 'normals'.

Muscle strength has been shown to be reduced in CHF patients with cardiac cachexia(179). The AS patients in the current study had almost identical lean body masses to the control subjects and it is therefore it may not be surprising that no differences were detected between groups.

10.4.2 Isokinetic Muscle Testing

10.4.2.1 Isokinetic strength

There were no differences in peak isokinetic strength between any of the AS groups and controls (tables 5-3 & 5-4). There was a small reduction in quadriceps peak torque when normalised for lean body mass in symptomatic AS compared to controls, who were significantly younger. Most studies in CHF have also found no reduction in dynamic strength compared to controls(178,180). Clark et al did find decreased isokinetic strength in patients with mild CHF, but as previously discussed, the controls were probably not adequately matched(200). The absolute values of peak torque in the current study cannot be directly compared to those in CHF patients. Different protocols, both with lower number of repetitions or different angular velocities(180,200), have been used and one study reported torque in imperial measures(178). Standardisation of protocols in similar future studies is required to allow meaningful comparison of results.

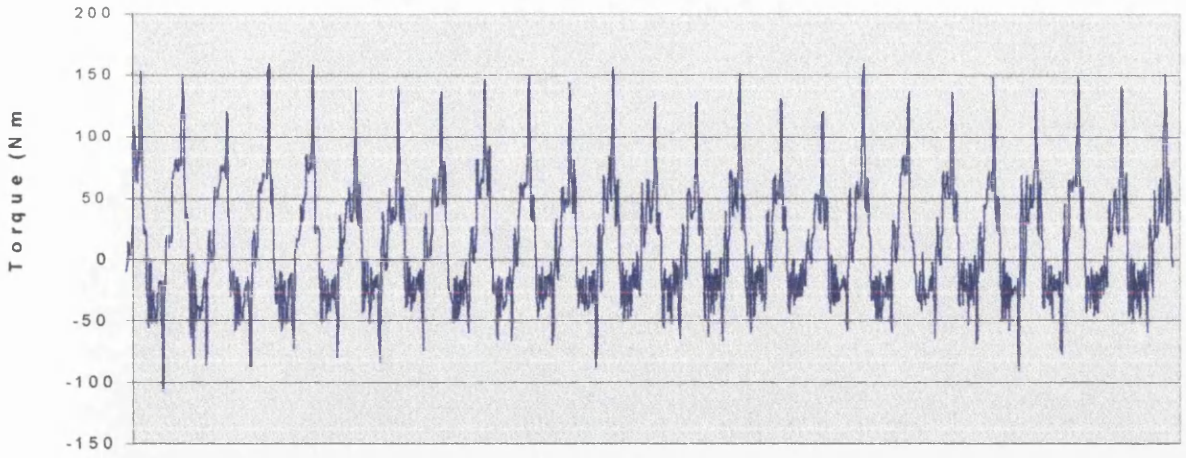
10.4.2.2 Isokinetic muscular endurance

Various parameters of muscular endurance were measured in this study. Total quadriceps (and normalised) work was significantly reduced in symptomatic AS patients compared to controls (table 5-6). Normalised quadriceps total work was also reduced in the severe AS patients compared to controls (table 5-5). Muscular endurance in CHF patients has also shown to be reduced(178,180,202).

These results would tend to indicate a reduced ability to perform repetitive muscular work in patients with severe and symptomatic AS. They must be

interpreted with caution, however. Firstly, three of the patients were unable to complete the required 25 contractions. Secondly, there was wide variation in the endurance measures in each group (see table 5-5 and figure 5-1). Thirdly, the fatigue index in many of the subjects was surprisingly small. This suggests that at least some subjects paced themselves throughout the 25 contractions despite instructions to the contrary and strong verbal encouragement throughout the test. An example of such a patient is given below.

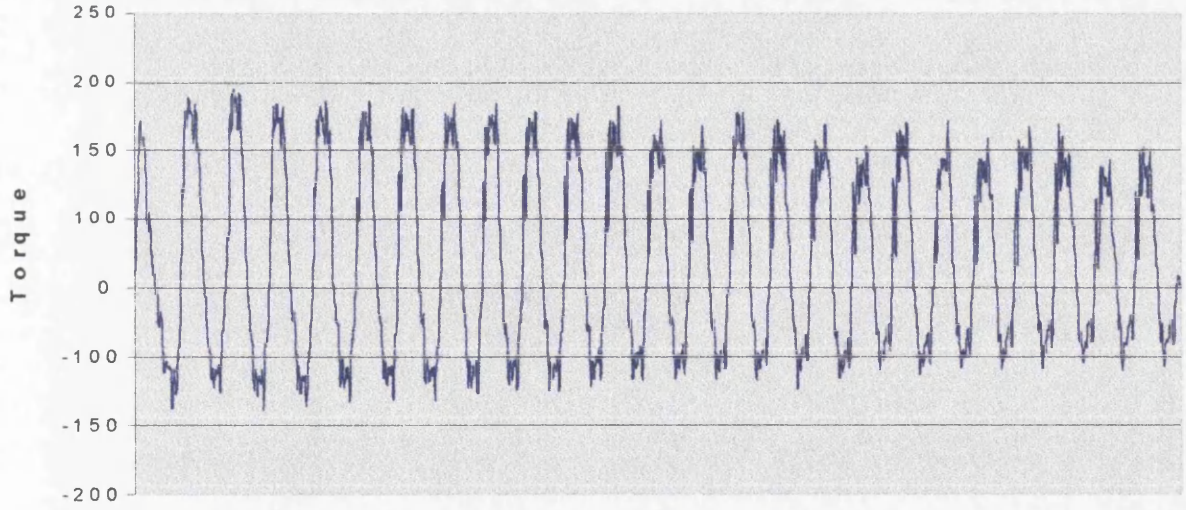
Figure 10-1: Isokinetic test, bad example.



This figure shows that peak torque generated is virtually constant throughout the 25 contractions. Some symptomatic subjects actually had fatigue indices greater than 100 indicating no fatigue (figure 5-2).

A good example of an isokinetic test is shown in figure 10-2.

Figure 10-2: Isokinetic test, good example



This figure demonstrates that peak isokinetic torque is achieved with the third contraction and then there is a gradual decline in the initial high level of torque throughout the test. Skeletal muscle strength and endurance testing is dependent upon the central drive or effort from the subject(291). Clearly, at least some of, the subjects in this study gave a submaximal effort which may partly explain the reduced endurance results.

Fatigue indices are not regarded as the best or most reliable measure of isokinetic endurance. Total work is felt to be a more reliable marker of isokinetic endurance

than fatigue index(290). Quadriceps total and normalised work were reduced in symptomatic patients (table 5-6). Normalised work was also reduced in severe AS (table 5-5). Also, as the three patients unable to complete the isokinetic test were all female, their omission probably results in falsely high values for the isokinetic test rather than lowering endurance measures. Therefore, despite the limitations discussed earlier, It is likely that the reductions in quadriceps work in AS patients are significant although at least part of the differences may be explained by the older age of the symptomatic group.

10.4.3 Skeletal muscle predictors of exercise capacity

All of the strength and endurance measures other than fatigue indices were significantly correlated with V_{O_2}max (see table 5-7), as is the case for CHF(176,179,200) The authors of these previous papers have proposed that the association between exercise capacity and strength measures is evidence in favour of the muscle hypothesis in CHF(191). These previous reports could be criticised for not including control subjects(176), not including age as a predictor of exercise capacity(176,200) and not examining independent predictors by multivariate analysis(179).

The strength and endurance univariate predictors of V_{O_2}max in AS patients would seem to lend support to the muscle hypothesis. However correlations were generally higher in the controls than in the patients. Also once age was considered, none of the skeletal muscle variables were independent predictors of exercise capacity in either controls or patients. When predicted exercise time, which corrects for age and sex, was considered none of the skeletal muscle variables were significant predictors of aerobic exercise capacity. These data suggest that skeletal muscle strength and endurance are strongly related to age, which is the strongest predictor of maximal aerobic capacity.

These results therefore necessitate rejection of hypothesis 1.17.2. The differences between the severe/symptomatic AS groups and controls are likely to be as a result of the differences in age between the patient and control groups, or an inability of the patient group to give maximal effort on isokinetic testing.

10.4.4 Skeletal muscle predictors of V_E/V_{CO_2}

Although strength and endurance measures were not independent predictors of exercise capacity this was not the case for exercise V_E/V_{CO_2}. All of the isometric strength measures were significantly associated with V_E/V_{CO_2} in patients and controls (see table 5-8). Only normalised peak isometric strength (in AS and not in controls) was of independent significance when considered in a multivariate analysis. This finding does suggest that there may be a link between skeletal muscle abnormalities and the increased ventilatory response to exercise seen in AS (see tables 4-1 and 4-2), and which has previously been demonstrated in CHF and mitral stenosis(182,290).

10.5 Ergoreflex activation

The leg and arm experiments in the current study provide further support of a work sensitive reflex (ergoreflex), with afferents arising in skeletal muscle, involved in cardiorespiratory control.

10.5.1 Blood Pressure

All of the subject groups demonstrated a sustained increase in absolute and percentage increase in DBP and SBP on recovery from both arm and leg exercise with RCO than without (see tables 6-3 and 7-4). Control cuff inflation in the leg did produce a small but significant increase in SBP and DBP, but this was much less than that seen during RCO following exercise. Control cuff inflation of the upper limb produced minimal changes in BP, although the exercise responses were very similar in magnitude to that seen with lower leg exercise. Similar results have been reported in CHF, CAD and healthy controls (see table 10-1). The magnitude of ergoreflex for BP was only significantly increased in symptomatic patients after leg exercise compared to both controls and asymptomatic AS. In CHF, ergoreflex activity is enhanced for both DBP and SBP after leg(226) and handgrip(213) exercise compared to controls. Although not significant the actual magnitude of leg ergoreflex DBP differences are very similar e.g. 37% higher in symptomatic AS compared to healthy controls versus 44% and 38% in the two CHF papers (see table 10-1).

10.5.2 Ventilation

The ventilatory responses to localised exercise differed in the patient and the control groups.

10.5.2.1 Controls

There were no differences between cuff and non-cuff recovery after either handgrip exercise or leg exercise. The magnitude of ergoreflex activity was not enhanced during recovery with RCO (tables 6-2 and 7-3). These results are consistent with those in healthy controls previously tested in our laboratory with leg exercise(226) (table 10-1). It should be noted that although the controls in Piepoli's paper demonstrated enhanced ergoreflex activity following RCO after handgrip exercise(213), these subjects all had CAD and therefore cannot be considered to be 'normal'.

10.5.2.2 Mild v severe AS

Absolute ventilation during recovery with cuff inflation was significantly greater than non-cuff recovery in patients with severe AS after arm exercise (table 6-2), and in patients with mild AS after leg exercise (table 7-3). The magnitude of ergoreflex activity tended to be higher in both AS groups than controls but these differences did not reach statistical significance.

10.5.2.3 Symptomatic v asymptomatic AS

Following handgrip exercise, there was a non-significant increase in recovery ventilation during RCO in the symptomatic group compared to the non-cuff run (table 6-4). The magnitude of (cuff) ergoreflex activity was not significantly elevated however; symptomatic AS 51% v asymptomatic AS 36% v controls 18%, p=0.12. Recovery ventilation after leg exercise was significantly increased in symptomatic AS compared to controls and asymptomatic AS both with and without RCO (table 7-5).

The magnitude of cuff ergoreflex activity was significantly increased in symptomatic patients despite there being no difference in absolute ventilation during cuff and non-cuff recovery in this group (table 7-5). It may seem

paradoxical that the ergoreflex should be increased in the symptomatic AS group when there was no difference in the absolute ventilation between recovery with and without RCO. This may be explained by the fact that non-cuff ventilation tended to be slower to return to baseline in symptomatic AS than the other groups (non-cuff ergoreflex, see table 7-5 and figure 7-5). Also the magnitude of ergoreflex calculation (equations 9 and 10) does not take into consideration the actual differences in ventilation between cuff and non-cuff runs, but the percentage increase over resting ventilation persisting during the three minutes recovery period.

10.5.3 Ergoreflex comparative studies.

Table 10-1 outlines the main results of ergoreflex studies in various cardiac populations incorporating the present results in AS. All of the studies have used very similar methodology based on the protocol described by Piepoli et al(213).

Study	Ex	Subjects				VO_2	Ventilation (L/min)		Ergoreflex (%)		
		Dx	No	Age	M/F		Rest	Ex	VE	SBP	DBP
Piepoli(213)	HG	CHF	12	60	9/3	14.6	7.5	20.2	86*	89*	98*
		CAD	10	59	9/1	28.3	7.6	14.3	54	54	54
Grieve(226)	Leg	CHF	10	66	?	?	8.0	12.7	39*	91*	86*
		Con	9	62	?	?	7.6	12.8	-1	48	49
McCann	HG	Con	17	49	11/6	32.1	8.6	14.0	18	79	81
		Asy AS	13	48	8/6	22.8	8.6	15.3	35	88	55
		Sym AS	18	70	10/7	16.2	9.2	15.0	51	103	74
	Leg	Con	16	48	10/6	31.9	8.4	13.0	17	87	87
		Asy AS	14	45	9/5	25.3	9.1	13.8	20	77	112
		Sym AS	16	64	9/7	16.4	9.2	14.1	66*	132*	124

Table 10-1: Ergoreflex studies in cardiac populations.
Ex=exercise, HG= handgrip exercise; leg= ankle dorsiflexion, Dx=diagnosis; Con=controls; VO_2= VO_2max (ml/kg/min).Asy AS= asymptomatic AS, Sym AS = symptomatic AS. *Ergoreflex activation significantly greater in patient than control group.

In Piepoli's study the exercise duration tended to be longer in both control (6.4min) and CHF (4.9min) subjects than in the current study (controls 3.1min, symptomatic AS 2.9 min). This difference is probably due to slight variation in the protocol. Although both studies used rhythmic handgrip exercise at 50% maximum

voluntary contraction, Piepoli used a frequency of 40 contractions per minute whereas in the current study 60/min was used. The higher frequency resulted in earlier fatigue although the metabolic load placed on the subject groups was similar as measured by peak exercise V_{O_2} and V_{CO_2}(226).

The peak exercise ventilation seen in CHF patients following handgrip exercise (20L/min) was markedly increased compared to the AS patients in this study (15L/min) and CHF patients following leg exercise (12.7L/min). This difference may in part be explained by the peak exercise values in the current study being averaged over the last 30s of exercise whereas Piepoli may have used single breath measurements which would tend to give higher values(213). Another possibility is that the ventilatory response to exercise (V_E/V_{CO_2}) is higher in CHF than in AS patients. Against this assumption is the fact that CHF patients achieved a comparable peak ventilation to AS patients after leg exercise and the mean value of V_E/V_{CO_2} for the symptomatic AS group is very similar to that previously reported for a large cohort of CHF patients(190).

10.5.3.1 Leg v arm ergoreflex.

Ergoreflex activation was significantly increased after leg but not handgrip exercise in symptomatic AS. In CHF, both leg and arm exercise results in enhanced ergoreflex activation(213,226). It is not surprising that the leg and arm ergoreflex results are significantly different. One can imagine that when a patient develops significant cardiac compromise, activities which require large muscles and high energy expenditure would be the first to be avoided. If skeletal muscle abnormalities are primarily the result of physical deconditioning then one would expect the leg musculature to be affected before the upper limbs. It is possible that peripheral muscle abnormalities in CHF result from the systemic action of neurohormonal increases, such as catecholamines and TNF-α(181).

10.5.4 Ergoreflex Associations

Previous studies have not examined the relationship between ergoreflex activity and ventilatory response to exercise, exercise capacity, symptomatic status or measures of disease severity.

In AS patients, leg ventilation ergoreflex was inversely related to V_{O_2}max (r=-0.41, see figure 7-7). Ergoreflex activity was not however an independent predictor of V_{O_2}max when considered with age and was not significantly associated with exercise duration (% predicted). There was only a weak (r=0.28) non-significant correlation with V_E/V_{CO_2} and no relationship to skeletal muscle strength or endurance. There were significant correlations in AS with both E/A ratio and aortic valve area but both these variables are also related to age. There were no significant correlations in controls.

10.5.5 Mechanism of ergoreflex activation

Localised handgrip exercise has been shown to reduce skeletal muscle pH(296) and leads to an increase in systemic blood lactate concentration in CHF but not in normal subjects(297). Animal studies support the role of metabolic receptors in skeletal muscle as the afferents to ergoreflex activation(221,222). In the current study all groups demonstrated sustained increases in BP with RCO following both leg and handgrip exercise consistent with metaboreceptor activation. RCO is however an unnatural physiological stimulus. All subjects reported discomfort with RCO after exercise and two AS patients could not tolerate control cuff inflation in the leg. A further two subjects were excluded from leg ergoreflex analysis because of a limited increase in exercise ventilation but striking increases in ventilation following cuff inflation after exercise. Pain cannot therefore be discounted as the main aetiological factor in ergoreflex activation in the current study.

If pain causes ergoreflex activation however, it should not explain the differences seen between the symptomatic AS patients and other groups with regards to increases in ventilation The symptomatic aortic patients may have experienced more discomfort if the local skeletal muscle changes were more pronounced with earlier metabolic distress as in CHF, perhaps increasing lactate and hydrogen ion concentration and decreasing phosphocreatine(196,199). Moreover, the neural afferents involved in the ergoreflex are mediated by pain fibres, or very similar group III and IV nerve fibres(298,299). It is possible that pain or discomfort may be an integral component in ergoreflex activation.

Non-cuff ergoreflex activation is a more physiological measure of the rate of recovery from localised exercise. There were non-significant increases in non-cuff

ergoreflex activation in AS but these cannot be regarded as evidence for enhanced ergoreflex activity, as the products of metabolism are not trapped in the exercising muscles and may stimulate ventilation by other mechanisms(296).

10.5.6 Significance of ergoreflex activation in AS

Ventilation ergoreflex activity was enhanced in symptomatic AS following leg exercise compared to both asymptomatic patients and controls. If ergoreflex activation was an important contributor to the enhanced ventilatory response and exercise intolerance seen in AS, one would expect it to be strongly related to both exercise capacity and V_E/VCO_2. Ergoreflex magnitude was not independently predictive of VO_2max and was not significantly related to V_E/VCO_2. Importantly, it was also not correlated with measures of leg skeletal muscle strength or endurance.

It seems unlikely that significant skeletal muscle abnormalities exist in AS that cause enhanced ergoreflex activation, enhanced ventilatory response to exercise and result in exercise intolerance. The ergoreflex was related to age and as the symptomatic patients were older than the other groups, age cannot be excluded as the cause for enhanced activity in this study. Hypotheses 1.17.3.1 and 1.17.3.2, that ergoreflex activity is enhanced in AS, must be therefore be rejected.

10.6 BNP

In various cardiac conditions BNP levels are correlated with left ventricular mass, particularly in hypertension(246,300). In CHF BNP is correlated with left ventricular end diastolic pressure, pulmonary capillary wedge pressure, right atrial pressure and inversely with ejection fraction(229). In AS patients, Prasad et al have demonstrated that the severity of AS, measured by mean pressure gradient, is an independent predictor of plasma BNP levels(251). Most BNP in humans appears to be synthesised and secreted from the left ventricle(231). In AS patients it seems that the most likely stimulus to secretion of BNP is wall stress, particularly end systolic stress(252)

10.6.1 Resting BNP

BNP was significantly increased in AS patients compared to controls, as has been previously demonstrated(251), confirming hypothesis 1.17.4.1. Furthermore, BNP was significantly greater in severe and symptomatic AS compared to mild and asymptomatic AS (tables 8-1 and 8-2).

10.6.1.1 Predictors of BNP

Factors which were significantly associated with plasma BNP levels in AS on univariate analysis included age, left ventricular mass / mass index and AS severity (table 8-3). BNP was significantly greater in NYHA class III compared to class II and I. Maximal aortic velocity and mean pressure gradient were all independently associated with resting BNP. It is not surprising that aortic velocity and mean pressure gradient were predictors of BNP since both of these variables are directly related to left ventricular peak systolic pressure which is a major determinant of left ventricular end systolic wall stress. Wall stress in the current study could not be measured as simultaneous blood pressure recordings were not obtained with echocardiography.

It is surprising that age remains a multivariate predictor of BNP in AS patients. Age was not a significant predictor in control subjects and although diastolic function is known to deteriorate with ageing, one would expect that the haemodynamic effects of pressure overload from AS would counteract the effects of ageing. It is difficult to explain why ejection fraction was weakly associated with resting BNP in control subjects. No other echocardiographic or haemodynamic variables, including left ventricular mass were similarly associated.

10.6.2 BNP Response to Maximal Exercise

BNP increased in all subject groups following maximal exercise and the magnitude of increase was very similar between groups. There have been many similar reports in patients with cardiac disease (table 1-6) but also in healthy controls(234-236,239). The magnitude of increase is generally small, with median increases on exercise of 9 pg/ml in controls, 10 pg/ml in mild AS and 22 pg/ml in severe AS (table 8-1). It is difficult to directly compare the magnitude of increase in BNP in the current study with previous reports. All of the published data on exercise

responses in BNP have reported the results as mean ± SD, when the results from the current investigation are clearly non-parametric in distribution.

Several groups have demonstrated that the rise in BNP on exercise is related to left ventricular mass index(234,244,246), but the strongest predictor of the increase in BNP is resting BNP(246) and has been confirmed in the current study in both controls and AS subjects (figure 8-3 and 8-4). Given what is known about the synthesis and secretion of BNP, it is not surprising that those with the highest resting levels demonstrate the greatest increase on exercise. Unlike ANP, only a small amount of BNP is stored in secretory granules and the majority is secreted via a constitutive pathway(229,301). It is hypothesised that those subjects with elevated resting levels of BNP will have higher messenger RNA concentrations and activity and are able to synthesise and secrete more BNP in response to an increase in left ventricular wall stress on exercise. As in previous studies, reduced clearance of BNP on exercise or haemo-concentration cannot be excluded as contributors to the increased plasma levels following exercise.

10.6.3 BNP as a Predictor of Exercise Capacity

Elevated levels of BNP have been demonstrated to be significantly associated with reduced aerobic exercise capacity in patients following myocardial infarction and in those with heart failure(241,250,238). In the AS patients in the current study, resting BNP was significantly correlated with V_E/V_{CO_2} (r=0.52) and inversely with V_{O_2}max (r=-0.46), confirming hypothesis 1.17.4.2. BNP was also significantly and independently inversely correlated with exercise time as a percentage of predicted and with the magnitude of increase in SBP on exercise (table 8-4).

10.6.4 BNP as a Potential Prognostic Marker in AS

BNP has previously been shown to confer prognostic information in patients following myocardial infarction, even independent of left ventricular function(253). Such useful prognostic indicators are sorely needed in AS, particularly to help define the ideal time for recommending aortic valve replacement in patients with severe disease. Waiting until the development of symptoms is not an ideal situation. Firstly, a small number of completely asymptomatic patients (approximately 1-2% per year) will die suddenly(25,91). Secondly, there is

significant morbidity and mortality whilst on the surgical waiting list with worsening of the prognostic profile for surgical outcome(159).

Other than the development of symptoms due to significant AS, there are few markers which reliably predict outcome. Surrogate markers looking at the rate of disease progression or predictors of aortic valve replacement have generally been used. Evidence of left ventricular systolic dysfunction and increased pressure gradients, particularly in elderly subjects tend to indicate a worse outcome(90). Exercise testing has recently been proposed as a possible investigation on which to recommend aortic valve replacement(16,131). In the current study, resting BNP was significantly associated with predicted exercise time and a blunted SBP response to exercise, both of which have been suggested as indications for aortic valve replacement(16). Whether BNP has the necessary sensitivity and specificity to predict outcome requires to be tested in a prospective study of AS.

10.7 ET-1

10.7.1 Resting ET-1

Resting ET-1 concentrations were not significantly different in the aortic groups compared to controls, thus rejecting hypothesis 1.17.5.1. These results also contradict those previously reported in aortic valve disease, although two of these reports have not been specifically in patients with AS, but combining either patients with aortic regurgitation(280) or also patients with mitral stenosis(281).

10.7.2 ET-1 response to exercise

There were no significant differences in ET-1 following maximal exercise between any of the groups, thus confirming the null hypothesis 1.17.5.1.

The magnitude of response to exercise was different however, particularly in symptomatic AS compared to controls. The controls demonstrated a very small, statistically significant, increase on exercise which would be consistent with previous studies in healthy volunteers(260,264,266,270). ET-1 tended to decrease on exercise in symptomatic subjects, but not in asymptomatic AS. This is a different response compared to patients with CHF where endothelin tends to increase(271,275,302). Other authors have reported non-significant decreases in

patients with heart failure, due to various aetiologies, on treadmill exercise(273,274). It is difficult to hypothesise mechanisms for the differences in endothelin response to exercise in the groups because of the lack of any significant associations of ET-1 with echocardiographic, haemodynamic or exercise variables. As ET-1 was not a predictor of exercise capacity, hypothesis 1.17.5.2 is rejected.

Since ET-1 was sampled almost immediately (<1 min) following exercise, it is possible that the maximum response was not obtained although this should not result in different responses between groups(262,263).

10.7.2.1 ET-1 reduction on exercise in symptomatic AS

The reduction in endothelin on exercise in symptomatic subjects may be related to the abnormal peripheral vasodilatation on exercise which occurs in patients with AS and syncope(103). Patients with syncope were excluded in the present study because of the potential risks of exercise testing. The seventeen symptomatic subjects currently studied would be expected to have similar haemodynamic responses on exercise as those with syncope.

If inappropriate left ventricular baroreceptor activation occurs on exercise with an initiated vagal response(101), then ET-1 production should fall since it is stimulated by catecholamines(256). Another possible mechanism to explain the fall in ET-1 in symptomatic AS is the role of BNP. BNP may cause vasodilation by inhibiting the production and/or release of ET-1(256). The symptomatic AS group had significantly increased resting and post-exercise levels of BNP compared to control subjects. It is possible that symptomatic patients had the greatest inhibitory effect on ET-1 synthesis and release, although there were no direct correlations between BNP and ET-1 to lend support to this theory.

10.7.3 ET-1 and exercise capacity

The fact that ET-1 was not significantly associated with either $V_{O_2}max$ or V_E/V_{CO_2} in patients or controls also contradicts a previous report in CHF patients and controls(275). The significant correlations in this previous study were probably spurious, as a result of small subject numbers and largely influenced by outlying subjects in each group, obviously strengthening the relationship.

A major limitation of the current results is that ET-1 is primarily a paracrine / autocrine hormone and therefore plasma levels may not be an accurate reflection of tissue levels in the endothelium(256).

10.8 Conclusions

10.8.1 Cardiopulmonary exercise testing

Aerobic exercise capacity, maximum heart rate, SBP response, RER and oxygen pulse are reduced in severe and symptomatic AS.

The ventilatory response to exercise (V_E/VCO_2 slope) is increased in severe and symptomatic AS.

Age and NYHA functional class and are independent predictors of VO_2max in AS. Left ventricular mass/mass index and NYHA are independent predictors of exercise duration.

10.8.2 Skeletal muscle strength and endurance

Isometric strength is not reduced in AS.

Isokinetic endurance is not reduced in AS.

Quadriceps strength (normalised for lean body mass) is an independent predictor of exercise V_E/VCO_2.

10.8.3 Arm ergoreflex

Ergoreflex activation contributes to the maintenance of BP, but not ventilation, following handgrip exercise in AS and controls.

Arm ergoreflex activation is not enhanced in AS.

The magnitude of arm ergoreflex activation is not a predictor of V_E/VCO_2 or aerobic exercise capacity.

10.8.4 Leg ergoreflex

Leg ergoreflex contributes to the maintenance of BP in controls and AS.

Leg ergoreflex activation contributes to the maintenance of ventilation in symptomatic AS but not in controls or asymptomatic AS.

The magnitude of leg ergoreflex activation is neither a predictor of exercise V_E/VCO_2 nor an independent predictor of VO_2max.

10.8.5 BNP

Plasma BNP is increased in severe and symptomatic AS compared to controls and mild/asymptomatic AS.

Age and AS severity are independently associated with resting BNP in AS.

BNP increases following maximal aerobic exercise and the magnitude of increase is similar in AS and controls.

The magnitude of the exercise-induced increase in BNP is strongly related to resting BNP in controls and AS.

Resting BNP is correlated with exercise V_E/VCO_2 and inversely and independently correlated with exercise duration and the magnitude of SBP response to exercise in AS but not controls.

10.8.6 ET-1

Resting and post- exercise ET-1 are similar in AS and controls.

ET-1 increases following exercise in controls and tends to decrease in symptomatic AS.

The magnitude of change in ET-1 on exercise is reduced in symptomatic AS compared to controls and asymptomatic AS.

10.9 Future research

Many exercise variables have been identified in this study which not only differentiate AS patients from controls and severe AS from mild AS, but potentially more importantly, symptomatic from asymptomatic patients.

The variables which seem to give most differentiation between symptomatic (i.e. those at most risk of future events) and asymptomatic subjects are the increase in systolic blood pressure, exercise duration as compared to predicted and the slope of V_E/V_{CO_2} which has been shown to provide independent prognostic information in patients with CHF(190). In this study plasma BNP is independently associated with exercise duration, exercise SBP and V_E/V_{CO_2} and may provide prognostic information in AS, similar to that following MI(254). These differences are apparent despite mildly symptomatic patients being included in the asymptomatic group for analysis. Given the different responses to exercise of the asymptomatic and mildly symptomatic patients these results are likely to underestimate the differences between truly asymptomatic and symptomatic patients.

It is apparent that nearly all the pre-eminent clinicians publishing in the field of AS agree that exercise tolerance testing gives additional objective evidence in the assessment of these patients which may be taken into account when recommending the optimal timing of surgery in asymptomatic patients. What is abundantly clear is that there is currently no evidence from blinded prospective trials indicating that exercise variables are independent predictors of outcome. This thesis gives indirect evidence to support the role of exercise testing in AS by demonstrating different responses in symptomatic and asymptomatic AS.

It is therefore recommended that a large prospective study assessing the usefulness of exercise variables (exercise capacity, SBP response, V_{O_2}max and V_E/V_{CO_2}) and resting BNP in predicting outcome should be performed. Symptomatic patients should be included so that one may compare responses in this group of high risk subjects with the relatively good prognostic group of asymptomatic patients. It would be imperative that the results of the exercise data remain blinded, to ensure that decisions regarding surgery are not influenced by clinician's possible bias in the value of exercise testing.

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APPENDIX A

Order of Testing

Testing was undertaken over two half days unless patients were travelling from outwith the Glasgow area in which case the tests were split into morning and afternoon sessions with a one hour break.

Day one:

History taking for Inclusion/exclusion criteria, NYHA classification and medication.

Anthropometric measurements (2.2) and resting BP. Echocardiography (2.3)

Venepuncture for BNP and ET-1 (2.8.1)

Familiarisation to treadmill. (2.6.1)
3 min resting ventilatory data
Symptom limited Bruce protocol
Venepuncture for exercise BNP and ET-1. (2.8.1)

Quadriceps Isometric strength (2.4.4)
Isokinetic muscular endurance (2.4.5)

Day two:

Order of leg / arm exercise randomised.

Arm Ergoreflex (2.7.1)
Control cuff inflation
Non-cuff or cuff run in randomised order, 15 min between runs

Leg ergoreflex (2.7.2)
Control cuff inflation
Non-cuff or cuff run in randomised order, 15 min between runs

Scottish Physical Activity Questionnaire completed (2.9)