An Investigation into the Factors Influencing Aerobic Power among Patients with Ankylosing Spondylitis with Special Reference to Respiratory Muscle Performance and Perceived Exertional Dyspnoea

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" This Trunk had been found in

some Church-yard or Charnel-House,

as appeared by its dark red Colour and dryness. "

" The Figure of this Trunk was crooked, making part of a circle, the Spine making the Convex and the inside of the Vertebrae the Concave part of the Segment. "

" The great difficulty seeming to be in the Respiration,

how that could be performed when the

Ribs were thus Immoveable "

Bernard Connor, 1695 [1]

An extract of his letter to Sir Charles Walgrave,

giving an account of

" An Extraordinary Human Skeleton "

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DECLARATION

I declare that the work comprising this thesis was carried out due to my own efforts. I am the sole author, however, it would be remiss not to thank my supervisors who have kindly offered constructive criticism of this manuscript. I have consulted all the references listed.

Whilst several ideas were instilled by various colleagues in the formative stages of this research, the planning and co-ordination for all the projects was my own work and I was wholly responsible for the way in which the studies evolved.

While the apparatus and methods employed in this project are standard, to the best of my knowledge, the applications of many of these in the context of ankylosing spondylitis are, to date, original. This is particularly the case in respiratory muscle endurance assessment, using inspiratory resistive protocol; the evaluation of gas exchange during exercise, using a combined O_2 and CO_2 transcutaneous electrode; and the measurement of isometric contraction of the quadriceps.

All the studies were approved by the hospital ethics committee and written informed consent was obtained from the subjects prior to the investigations.

Date .....

Signed .....

P Riantawan MB MRCP(UK)

DEDICATION

To my dear wife, Naowarat,

for the years of great forbearance, and

to my parents, whom I have so missed over

these years of post-graduate training in the UK

ACKNOWLEDGEMENTS

I wish to express my eternal gratitude to Dr Stephen W Banham, Consultant Physician in Respiratory Medicine, Glasgow Royal Infirmary, for first introducing me to the subject encompassed in this thesis, and for his longsuffering encouragement throughout this research.

I would like especially to thank Professor Roger D Sturrock, Professor of Rheumatology, University Department of Medicine, University of Glasgow, for allowing me access to study his patients, and for his never-tiring advice spanning the entire project.

I am also indebted to Mr Roger Carter, Principal Scientist, Department of Respiratory Medicine, Glasgow Royal Infirmary, for providing numerous hours of good humoured and stimulating discussions on pulmonary function measurement and exercise physiology.

Thanks are also due to all the respiratory technicians, Pulmonary Function Laboratory, Glasgow Royal Infirmary, for assisting in various pulmonary function measurements.

Finally, I should like to thank all the patients and the healthy volunteer subjects, without whose willing help this project would not have been possible.

SUMMARY OF CONTENTS

This thesis embraces a series of related studies spanning fourteen months. An initial questionnaire-based survey identified the presence of undue breathlessness perceived in a significant proportion of patients with ankylosing spondylitis (AS). The finding was substantiated by an oxygen-cost diagram study comprising matched healthy controls. Measurements of respiratory muscle strength and endurance were made in a subsequent study. Although maximal strength of the respiratory muscles was preserved in the AS patients, their respiratory muscle endurance during work requiring high inspiratory pressures was clearly impaired. Upright symptom-limited exercise confirmed that exercise tolerance and aerobic power were commonly curtailed among the AS patients. Relative to matched controls, ventilatory response and heart rate response to exercise in the AS patients were raised. However, the elevated ventilatory and heart rate responses were not accompanied by abnormalities in pulmonary gas exchange, breathing reserve, or other cardiocirculatory indices. Although the AS subjects perceived a higher degree of breathing effort for an equivalent level of work rate or ventilation, they were not ventilatory limited. By contrast, the finding of a greater magnitude of leg fatigue perceived among the AS subjects despite achieving a lower work rate strongly suggested a significant element of peripheral musculoskeletal deconditioning. The elevated heart rate response was compatible with an element of cardiac deconditioning secondary to a relative lack of physical activity.

Finally, the relative contribution of pulmonary factors, chest restriction, and muscular function to the reduction in aerobic power among the AS patients was quantitively examined. Peripheral muscle strength was found to exert the strongest influence on aerobic power in the AS patients. The addition of lean body mass further improved the variability explained by the regression model derived. No significant influence of impaired respiratory muscle endurance on aerobic power was observed. Vital capacity and limited chest expansion exerted only weak influences on aerobic power in the AS subjects.

The results from the studies comprising this thesis thus emphasise the importance of physical activity in this condition. Suggestions for further interventions/strategies of clinical value were made.

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Chapter 1

Introduction and Review of the Literature

1.1 Ankylosing spondylitis : An Overview

Ankylosing spondylitis (AS) is the main representative of the clinical entities collectively coined seronegative spondarthritides. It is characterised pathologically by lesions described as enthesopathies,[2] the inflammation of ligamentous insertions. The discovery in 1973 of its strong relation to human leukocyte antigen (HLA) B27[3] has greatly stimulated academic interest in the study of genetic[4] and environmental factors[5,6] in causing the disease; however, the aetiology remains obscure.

The diagnosis of AS is based on clinical and roentgenographic features.[7-9] Regardless of the criteria used, the presence of sacroiliitis is the *sine qua non* for a diagnosis of AS, but radiographically detected sacroiliitis may not be an early or obligate manisfestation of the disease.[10]

Prevalence

Epidemiological studies attempting to define the prevalence of AS have suffered from a lack of easily applied diagnostic criteria. Nonetheless, clinical and radiographic studies from Britain[11] and the Netherlands[12] gave an AS prevalence of 0.19 % and 0.08 % respectively, among individuals older than age 15. Men are four to six times more commonly affected.

Clinical manifestations

AS typically starts in adolescent men, with insidious onset of low back pain and stiffness. Although the axial skeleton is predominantly affected, any joint may be involved. Peripheral arthritis occurs in at least one third of all cases and may start many years after spinal disease.[13] Progressive ascending involvement of lumbar, thoracic and cervical vertebrae leading to complete ankylosis and kyphosis is the extreme form of AS and occurs only in a minority of cases.[14] Figure 1.1shows the typical posture of a patient with advanced AS.

Acute anterior uveitis is the most common extraskeletal involvement in AS and occurs in 20 to 40 % of cases[15] at some time in the course of their disease. Several forms of cardiac involvement are recognized. Aortic incompetence is the most characteristic lesion and, although occasionally severe, it is often asymptomatic. Conduction defects, arrhythmias and pericarditis are also well documented. Moreover, the development of noninvasive cardiac imaging techniques has raised the sensitivity in the detection of valvular[16] as well as myocardial disease[17] in AS.

Involvement of the thoracic spine (including costo-vertebral joints) and enthesitis at costosternal areas and manubriosternal joints may cause chest pain. Rigidity of the chest wall is a hallmark of the disease. Pulmonary function impairment, one of the main issues of interest in this thesis, merits special review in section 1.5.

Pulmonary parenchymal involvement in AS is uncommon. A review of 2,080 AS patients by Rosenow *et al*[18] disclosed 28 cases with pleuropulmonary diseases,the most common one being upper lobe fibrobullous lesions (an incidence of 1.25 %).

Rare complications which have been reported include amyloidosis of the AA type,[14] IgA nephritis,[19] and cauda equina syndrome.[20]

Course and prognosis

AS generally runs a chronic and benign course but with a risk, in a minority of cases, of handicap and life-threatening complications, e.g. atlantoaxial joint subluxation,[21] acute fulminant aortic disease[22] etc. Progressive impairment of spinal mobility occurs in half the cases or more, however, functional outcome is often satisfactory.[23] The early presence of peripheral joint disease, iritis, pulmonary fibrosis, and persistently high sedimentation rate is indicative of a poor prognosis.[14]

Excess mortality in AS in early reports is primarily ascribed to complications of radiotherapy and amyloidosis.[24,25] Although a shorter life span has also been observed among nonirradiated men with AS,[26,27] this is most likely a result of the impact of referral bias producing patients cohorts with more severe disease. It is likely that survival of patients with mild disease who form the majority of cases is comparable to that of general population.[28]

Management

The importance of physical therapy in AS cannot be overemphasized. While treatment with nonsteroidal anti-inflammatory drug (NSAID) is effective in relieving pain and possibly minimizing stiffness, disease modifying agents are, to date, not available in AS. Sulphasalazine is used for patients with peripheral arthritis but no lung function studies have been done on patients treated with this drug. In a study[29] on lung function in 33 AS patients receiving NSAID for 12 weeks, there was no change

in vital capacity (VC) during a follow-up period of 48 weeks. The result from this study suggests that NSAID therapy does not influence lung function or, alternatively, VC is not an appropriate outcome measure of short term therapy in AS.

The goals of physical therapy are to relieve pain and maintain functional capacity by a daily exercise programme. Knowledge of the mechanism(s) underlying exercise limitation in AS patients is thus needed in order that rational physical training can be formulated tailored to individual abilities.

However, little is known about the factors influencing exercise capacity in AS and the mechanism(s) responsible for effort intolerance among AS patients remains poorly defined.

Hence, the focus of the present series of studies is the factors influencing exercise power among patients with AS. The following are an overview of exercise physiology and reviews on the areas pertinent to the the focus of this thesis, namely, exercise limitation, pulmonary function abnormalities, exertional dyspnoea, and respiratory muscle performance among AS patients.

1.2 Physiology of exercise

The conversion of stored energy into physical work is the function of the skeletal muscles. Energy for muscular contraction is obtained predominantly by the oxidation of fuel in the mitochondrion. This energy is used to form high-energy compounds, mainly creatine phosphate and adenosine triphosphate, from which energy can be made available for cellular reactions involved in systhesis, active transport and muscle contraction.[30] Thus, exercise entails an increased utilization

of O_2, to be matched by increased delivery of O_2 from the atmosphere to the mitochondrion and the simultaneous removal of CO_2, the major end product of exercise.

These needs of cellular (internal) respiration of muscles can only be met by complex interactive systems providing gas exchange between the muscle cells and the atmosphere (external respiration)(Fig.1.2). These systems comprise[31] 1) efficiently operating lungs and chest bellows, 2) an effective pulmonary circulation through which the regional blood flow is matched to the appropriate ventilation, 3) a heart capable of pumping the quantity of oxygenated blood necessary to sustain tissue energy exchange processes, 4) an effective circulatory system that can distribute blood flow to match tissue requirements, 5) blood with an adequate haemoglobin concentration, and 6) respiratory control mechanisms capable of regulating arterial blood gas tensions and pH.

This metabolic-cardiocirculatory-ventilatory coupling system has large functional reserves so that there may be a wide variation in loss of function before symptoms are experienced.[32] A subject may perform daily activities quite normally with resting physiological variables in the normal range, and yet present with an effort tolerance more limited that most of his fellows. The relative subtle loss of function in this scenario may only be detected by measuring various physiological variables during exertion. Exercise testing thus provides a sensitive means both for assessing symptoms and for quantifying functional impairment.

1.3 Measurements during exercise testing

The development of rapidly responding O_2 and CO_2 analysers and computer-

assisted data processing have led to a broader application of cardiopulmonary exercise testing (CPX).[33] CPX allows simultaneous measurement during known exercise stress of the following :

1. Aerobic uptake (VO_2), expressed in terms of capacity (total energy output), or power (energy output per unit of time). Maximal O_2 uptake attained for a given form of exercise (VO_2max) is highly reproducible such that it has been regarded as an international reference standard of cardiorespiratory fitness by the World Health Organization.[34]

2. Respiratory variables, namely, a) breathing frequency (f), b) tidal volume (V_T) and minute ventilation (V_E), and c) arterial blood gases measured directly with an indwelling arterial cannula or noninvasively with a combined O_2 and CO_2 trans-cutaneous electrode.[35]

3. Cardiocirculatory variables comprising : a) heart rate, b) blood pressure, and c) cardiac rhythm and pattern by an electrocardiogram. In addition, O_2 pulse, which is the volume of O_2 extracted by the peripheral tissue per heart beat, can be derived from $\Delta VO_2/\Delta HR$. It can also be considered an index of stroke volume.

4. Anaerobic threshold (AT), which is the level of VO_2 above which aerobic energy production is supplemented by anaerobic mechanisms. As exercise increases above a certain work rate, the oxygen required by the exercising muscles cannot be totally supported by O_2 delivery, anaerobic processes meet this demand by converting pyruvate to lactate.[36] This is accompanied by an almost equal reduction in bicarbonate concentration in the blood, causing CO_2 production to accelerate.[37]AT has been used as an effective gauge of physical fitness and a low

AT implies impairment of O_2 delivery to the exercising muscles. It can be detected by measuring blood lactate level. More recently, Beaver *et al* [38] has developed a noninvasive means for detecting AT referred to as ' V-slope ' method. This uses computerized regression analysis of the slope of VCO_2 *vs* VO_2 plot, which detects the beginning of the excess CO_2 output generated from the buffering of $[H^+]$. Figure 1.3 shows an example of AT of a patient with AS detected by this method during CPX testing.

5. Other variables obtained include CO_2 production (VCO_2), and respiratory exchange ratio (R)(derived from VCO_2/VO_2). Furthermore, cardiac response ($\Delta HR/\Delta VO_2$) and ventilatory response ($\Delta VCO_2/\Delta V_E$) to exercise may also be derived.

These variables follow a predictable pattern in response to exercise so much so that measured deviations in the various relationships can pinpoint with remarkable accuracy which component of the system is at fault.

1.4 Exercise limitation among AS patients

Scanty data exist on exercise performance among sufferers from ankylosing spondylitis (AS). Renzetti *et al*[39] is credited for first studying gas exchange at rest and after ' a standard exercise test ' in 12 AS subjects. Mild arterial oxygen desaturation at rest (mean 94.9 %) and after exercise (94.7 %) was noted in half the group. However, it is unknown whether the gas exchange abnormality reported contributed to exercise intolerance in this group of subjects. Furthermore, the method of exercise test employed was not cited.

It was not until 1985 when attention was paid to a formal assessment of cardiorespiratory response to exercise in AS patients. Elliott *et al,*[40] in a study comprising 6 AS subjects and 6 age-matched controls, observed a significant reduction in exercise capacity in the AS group. This exercise limitation was ascribed to deconditioning or cardiovascular impairment. Owing to the small sample size, the authors highlighted the need for more observations to further elucidate the mechanism underlying effort intolerance in this condition.

The latest work in the English literature in this field came from Fisher *et al.*[41] This study reconfirmed the exercise intolerance in 33 AS subjects studied and noted a correlation between vital capacity and VO_2max. However, this study did not seek to explore the factor(s) causing exercise limitation in AS.

Thus, while general physical therapy and rehabilitation programme has been well established for sufferers from AS, an understanding of the factors underlying exercise intolerance in this condition is far from complete.

1.5 Pulmonary function in AS

Rigidity of the thorax in ankylosing spondylitis (AS) was first recognized as long ago as 1695, when Bernard Connor[1] described a skeleton showing the characteristic rigidity of the thoracic cage and lumbar spine and remarked that respiration must have been greatly restricted during life of the unfortunate sufferer. This astute observation remained unique until 1877, when Hilton Fagge[42] reported on the ankylosis of the ribs with vertebrae.

Lung volume and subdivisions

The recognition of abnormalities in lung volumes in AS originated from the reports in the 1940s. Hart *et al*[43] observed a reduction in vital capacity (VC) in 18 of 21 AS patients, the mean VC being 79 per cent predicted. Subsequent reports[44-51] corroborated this finding, although the degree of reduction in VC and total lung capacity (TLC) varies from mild to moderate. Opinion is divided, however, over the effect of AS on residual volume (RV) and functional residual capacity (FRC). Some investigators[45-48] reported an increase in RV and/or FRC, while others[49-51] found these to be normal. Conflicting data are also noted on the ratio RV/TLC. These discrepancies results from difference in stage of the disease and, to a greater extent, difference in reference values used. Furthermore, when relating measured values to predicted values, some observers used predisease height[47,48,51] whilst others used actual height,[45] not taking into account the flexion deformity caused by the disease. A review of lung volumes in AS from some of the previous reports is presented in Table 1.1.

The size of RV is important in understanding the disorder of the mechanics of respiration in AS. The finding of increased RV[45-48] suggests that ankylosis of the thoracic cage occurs with the ribs in a position of partial inspiration, the increase in RV and FRC being a consequence of a rise in the resting expiratory level.

Thoracic and lung compliances

Previous studies consistently found lung compliance to be normal[47,52] and total thoracic compliance to be reduced[47,51,52] in AS. These findings, in conjunction with the finding of normal diffusing capacity[49,50] have led to the

premise that the restrictive ventilatory defect in AS is consequent to limitation of chest expansion rather than intrinsic pulmonary parenchymal disease.[44,49,50]

Pulmonary gas exchange

Previous reports on pulmonary gas exchange in AS gave divergent results. In a study of 12 patients, Miller&Sproule[53]observed normal alveolar-arterial oxygen pressure difference, and normal physiological deadspace-tidal volume ratio. These findings are in contrast with those of Renzetti *et al*[39], who reported increased physiological dead space and significant arterial oxyhaemoglobin desaturation at rest and on exercise in most of the 12 subjects studied. The authors postulated that the spondylitic process led to a relative decrease in ventilation in the upper part of the lung whereas increased diaphragmatic excursions caused a relative increase in ventilation in the lower lung regions. Studies on regional ventilation in AS have shown conflicting results,however. Using krypton 81^{m} washout, Parkin *et al*[54] found no significant difference in regional lung ventilation between 27 AS and 18 controls. By contrast, Stewart *et al*[55] observed a reduction in inhaled xenon reaching the lung apices but normal xenon perfusion in 9 AS subjects and invoked a relative impairment of apical ventilation in AS. Whether the possible reduction in ventilation to the lung apices of these isotope gases is of clinical importance remains speculative.

1.6 Exertional dyspnoea among AS patients

Dyspnoea is a cardinal manifestation of diseases involving cardiorespiratory systems. There is no universally accepted definition of dyspnoea, but it can be regarded as "difficult and uncomfortable breathing"[83] or "the necessity for increased

respiratory effort".[84]

A unitary explanation for the sensation of dyspnoea does not exist. The source and mechanism of exertional dyspnoea are most likely multifactorial. Increased respiratory muscle tension[85] and altered resting lung volumes[86] are among the factors which have been proposed as contributing to the sensation of increased breathing effort in different patients. It follows that patients with ankylosing spondylitis (AS) may perceive relatively higher intensity of breathing effort on the basis of impaired thoracic mechanics and altered lung volumes. The prevalence of dyspnoea on exertion among AS patients has, however, received little attention.

Although numerous studies have examined lung function indices in AS,[43-55] the effect of impaired lung volumes on the sensation of breathing in AS patients is little known. Furthermore, the impact of exertional breathlessness (if any) among patients with AS on effort tolerance remains unclear.

It is widely believed that AS patients rarely experience respiratory symptoms,[41,45,46] although in one report[74] 4 of the 8 AS patients studies perceived dyspnoea on exertion. The symptoms may be masked by the more striking spinal pains which so predominate the clinical picture and render exertion difficult and exertional dyspnoea impossible in most cases.

Nonetheless, complaints such as " I cannot fill my lungs properly " ; " My chest feels stiff " ; or " I cannot exert myself " are not uncommon among AS sufferers.[56]

1.7 Respiratory muscle performance

As outlined in section 1.2, the performance of respiratory muscles, pivotal to the efficiency of chest bellows, is an important part of the complex systems providing adequate gas exchange during exercise and, indeed, at rest. Assessment of of respiratory muscle function thus forms an essential part of any comprehensive evaluation of exercise tolerance. The following are a review of the structure and function of respiratory muscles, methods of assessment, and the current knowledge on respiratory muscle performance in patients with AS.

Structure and function

The respiratory muscles consist primarily of the diaphragm, the intercostal, abdominal and accessory muscles. The diaphragm is the principal muscle of inspiration. It consists of two parts, the costal diaphragm, originating over the inner surface of the six lowest ribs, and the crural portion, which arises from the second to fourth lumbar vertebrae.[57] Contraction of the diaphragm has several effects resulting in inspiration. The central dome descends causing a decrease in pleural pressure and an increase in lung volume. This produces the rise in abdominal pressure, causing the anterior abdominal wall to move outwards. The costal fibres, using the abdominal contents as a fulcrum, act to lift the lower rib cage. The intercostal muscles play an important role in stabilizing the rib cage, preventing paradoxical inward motion of the rib cage during inspiration.[58] The accessory muscles, comprising mainly the scalenes and sternomastoids, also help stabilize the upper rib cage.

The mechanics of the thoracic cage, including the vertebrae, is therefore an important determinant of the chest bellows function. Each thoracic vertebra has eight articular surfaces : the right and left costo-vertebral and costo-transverse, the right and left intervertebral articular facets superior and inferior. Considering the involvement of these joints throughout the thorax with gradual bony fusion, soft tissue shrinkage and calcification, it is not surprising that thoracic expansion is greatly diminished in advanced AS. Such a complete picture, however, does not always occur and does not necessarily parallel changes elsewhere in the body.[56] Nonetheless, these changes render the vast majority of AS patients heavily dependent on their diaphragm.

Assessment of respiratory muscle strength

The simplest approach is to measure inspiratory and expiratory pressures at the mouth with the subject performing maximal efforts against a closed airway (MIP and MEP, respectively). The most widely used technique is that described by Black & Hyatt.[59] The only equipment needed is a tube connected to aneroid pressure gauges. In order to minimize the pressure generated by the facial muscles, a small air leak is created at some point in the tubing circuit so that the additional pressure generated in the mouth can dissipate.[60] More recently Hamnegard *et al* [61] has shown that a microcomputer-based mouth pressure meter (to be described in details in chapter 3.2) provides reliable and accurate MIP and MEP measurements in normals as well as in patients with respiratory disorder. This equipment is robust and portable and should play an important role in providing respiratory muscle evaluation as a research and clinical technique.

The lengths of the respiratory muscles and therefore their contractile forces, vary with lung volumes.[62] The expiratory muscles are longer and nearer to their optimal resting length (L_0) at high lung volume. Conversely, the inspiratory muscles are longer and nearer to their L_0 at low lung volume. Accordingly, MIP is measured at FRC or RV and MEP at TLC.

Respiratory muscle pressures may also be recorded within the pleural and abdominal cavities by means of oesophageal and gastric balloons. The nature of the test and the procedure involved are, at best, unpleasant to the subject, thereby rendering their clinical applications limited.

Normal values for maximal respiratory pressures

The usefulness of maximal respiratory pressures (MRP) has been obscured by the remarkably large between-studies variability in the literature.[59,63-66] Reference values for MRP from some of the prominent studies are summarized in Table 1.2. For instance, Black and Hyatt[59] reported a mean MIP of 124 (SD 22) cmH_2O in men of 20-54 yrs of age whereas a mean of 106 (SD 31) cmH_2O was quoted for men of 19-65 yrs of age by Wilson *et al*[63] despite employing similar apparatus. An even more remarkable difference is found in the MEP values quoted in the two studies. Such discrepancies might be linked to several factors including the differences in the population sizes, in the techniques used, in the number of efforts produced,[67,68] and in the types of mouthpiece used.[69]

Respiratory muscle endurance and its measurement

Unlike other groups of skeletal muscles, the respiratory muscles operate continuously throughout life. Respiration is thus an endurance effort. In conjunction with

isolated peak pressures, assessment of respiratory muscle performance in terms of endurance could therefore provide further insight into its efficiency.

The direct tests of respiratory muscle endurance (RME) are based on the capacity of the respiratory muscles to generate and sustain high levels of pressure. The high pressures can be achieved by means of either inspiratory resistive load[70,71] or inspiratory threshold load.[72] In the former method, subjects breathe through inspiratory resistance of varying magnitude. The latter involves inspiring through a device that contains a weighted plunger, for example. A sufficient inspiratory pressure must be generated to lift the plunger out of its socket.

Regardless of the type of load employed in RME testing, the breathing pattern must be standardized so that airflow does not vary. Bellemere & Grassino,[73] in a study on 4 male volunteers, found that intense diaphragmatic contractions of brief duration could be sustained for as many breaths as could less intense contractions that occupied a larger fraction of total breath time. Based on the data from that study, they proposed tension-time index of the diaphragm (TTIdi). TTIdi is the product of contractile force and duration, where force is expressed as the ratio of transdiaphragmatic pressure (Pdi) to maximum Pdi, and duration is expressed as duty cycle. Duty cycle is the ratio of inspiratory duration (Ti) and total breath duration (Ttot). Endurance time (Tlim) could be related to TTIdi by the expression: $Tlim = 0.1(TTIdi)^{-3.6}$ which is valid when TTIdi is in excess of 0.15. It predicts that TTIdi of 0.15 would cause diaphragmatic fatigue in approximately 1.5 hours whereas TTIdi of 0.3 would produce fatigue in less than 10 minutes.

Respiratory muscle performance patients with AS

It is well established that diaphragmatic contribution to tidal breathing is increased in AS patients,[74-75] implying functional insufficiency of the rib-cage muscles in this condition. However, quantitative data on respiratory muscle strength (RMS) and endurance (RME) in AS is scarce.

In a study of 30 patients with AS, Vanderschueren *et al*[76] found that16 of the patients had MIP of two standard deviations or more below the mean of the normal values of Arora.[66] Furthermore, 27 of these patients were reported to have MEP of two standard deviations or more below the mean of the normal values. These led to the conclusion that RMS in patients with AS was clearly reduced.

This notion has remained, to date, unchallenged. On the one hand, it seems plausible considering that the impaired thoracic cage mechanics may render the rib-cage muscles anatomically disadvantageous. On the other hand, it is contradictory to the observation that the diaphragm, the principal muscle of respiration, compensates well in AS.[74-75] The crux of the matter may lie in the reference values for MRP used in the above-mentioned study. Given the inconsistency among the reference values in the literature (Table 1.2), a different conclusion may have been drawn from this study if the MRP values had been related to reference values from other sources.

Furthermore, the effects of altered lung volumes and chest restriction on RMS and RME in AS are unknown as is the influence of impaired RMS and RME (if any) on exercise tolerance in this condition.

Thus, further studies in this field are needed and studies comprising matched controls would be preferable.

1.8 Peripheral muscle strength

Also crucial to exercise performance is the strength of exercising muscles. Indeed, exercise tolerance is normally dictated by skeletal muscle fatigue related to lactic acid accumulation which results from anaerobic metabolism.[77] In a study of 200 patients with chronic airflow limitation, Allard *et al*[78] observed a significant reduction in peripheral muscle strength (quadriceps and handgrip), which contributed significantly to work capacity independent of the lung function indices.

Although convincing evidence of involvement of skeletal muscles in AS is lacking,[79]it is conceivable that peripheral muscle deconditioning, by virtue of disuse, may limit exercise performance in this condition. Research into this area is hence needed. Should deconditioning prove to be an important factor limiting exercise among AS patients, strategies for improving peripheral muscle strength and/or endurance might be directly beneficial as has been shown in, for example, patients with chronic airflow limitation.[80]

1.9 Aims of the present studies

Based on the foregoing, the aims of the present studies are as follows :

1) To evaluate respiratory muscle strength (RMS) and endurance (RME) in AS patients.
2) To assess the possible effect(s) of altered lung volume and subdivisions and chest restriction on RME and RMS in AS patients.
3) To systematically evaluate the degree of perceived exertional dyspnoea and its possible relation with chest restriction and altered resting lung volumes in AS patients.

4) To comprehensively examine the cardiorespiratory response to exercise in AS patients.

5) To comprehensively examine the mechanism(s) responsible for exercise limitation in AS patients.

6) To identify and determine the individual and additive influence of the magnitude of chest expansion, lung volume, respiratory muscle strength and endurance, peripheral muscle strength, and body composition on exercise power among AS patients.

1.10 Plan and study design

The studies comprising this thesis attempted to address well defined, pre-specified questions. It was considered desirable to commence the project with a questionnaire survey on a group of patients with AS attending a tertiary rheumatology clinic (chapter 2). This strategy served to provide a broad picture of respiratory symptoms among the patients and to identify willing subjects. The studies then proceeded with assessment of respiratory muscle performance, evaluation of exertional dyspnoea and cardiorespiratory response to exercise and, finally, an analysis of factors influencing exercise power in the subsequent chapters.

In view of the large variability among reference values for some of the variables measured, a group of age-and gender-matched controls were also recruited for comparative studies. This was the case for the assessment of respiratory muscle performance and the evaluation of perceived exertional dyspnoea.

Sample size determination

In order to achieve significant quanta of analytical power, the required sample

size was predefined, where possible. For example, the required sample size for the study on respiratory muscle performance (chapter 3) was estimated prior to the study, utilizing the nomogram proposed by Altman[81](fig 1.4).

Statistical methods

The appropriate statistics employed were planned in the formative stages. Values are presented as mean (SD) or (SEM), or mean (95% CI) as appropriate. As Normal distribution was not assumed for many variables studied, nonparametric statistics were used to assess differences between controls and AS subjects with respect to various physiological variables. The magnitude of linear association between pairs of continuous variables was measured with product moment correlation coefficients. The mean values of various measurements were considered significantly different when the probability of the difference of that magnitude, assuming the null hypotheses to be correct, fell below 5 % (i.e. $p < 0.05$). As in other explanatory studies, it is sometimes unavoidable to perform multiple comparisons or significance testings, the bonferroni correction was applied to avoid type I error.[82] Forward stepwise regression analysis was used to determine the additive influence of various parameters on exercise power (chapter 5). A standard statistical software (MINITAB, release 9.2, Minitab Inc., PA, USA) was used for all statistical analyses. Fisher's exact test, employed in chapter 2.2.1, was performed by a special macrofile of MINITAB, by courtesy of the Robertson Centre for Biostatistics, University of Glasgow. The statistics used were further specified in the respective chapters.

Summary

An overview of ankylosing spondylitis (AS) and physiology of exercise have been presented. While a great deal of data on lung function abnormalities in AS are available, little is known about the impact of these abnormalities on the sensation of breathing and on exercise power in this condition. Limited information on respiratory muscle performance in AS exists and the contribution of the possible impairment in respiratory muscle strength and endurance on exercise limitation in this condition remains unknown. Although previous studies have consistently shown that exercise intolerance is common in AS, understanding of the influence of cardiocirculatory, respiratory as well as peripheral muscular factors on exercise performance in this condition is incomplete. Finally, aims of the present studies have been proposed and plan and study design described.

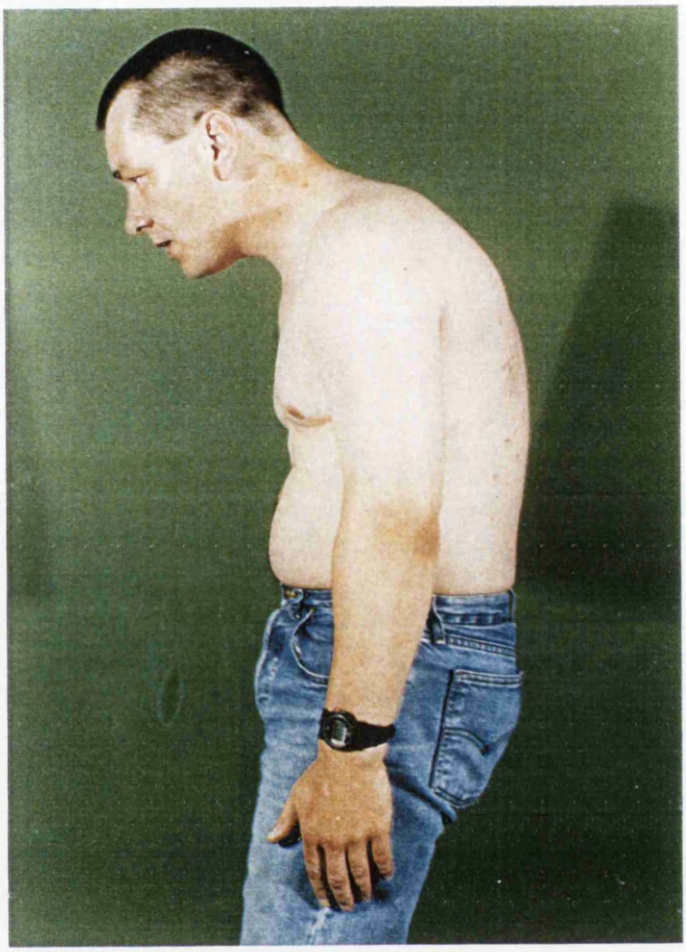


Figure 1.1 *Typical posture of a patient with advanced ankylosing spondylitis, illustrating forward flexion, thoracic kyphosis, and loss of lumbar lordosis.*

(With kind permission from the patient)

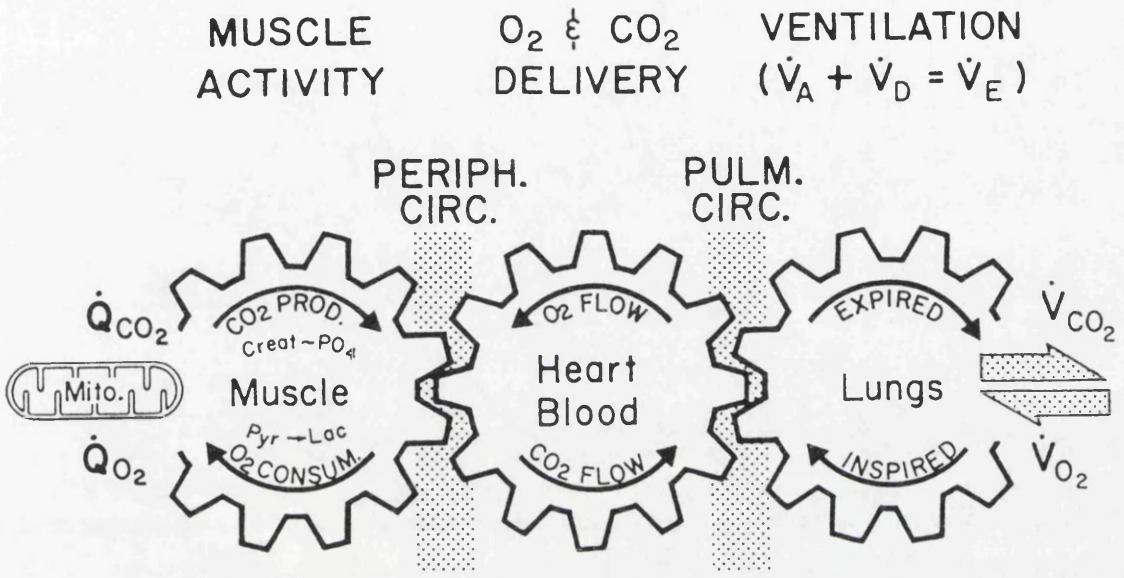


Figure 1.2 *A scheme illustrating the gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration. The gears represent the functional interdependence of the physiological components of the system. The increase in O_2 utilization by the muscles (Q_{O_2}) is achieved by increased extraction of O_2 from the blood perfusing the muscles, an increase in cardiac output, an increase in pulmonary blood flow, and finally, an increase in ventilation.*

(Reproduced with written permission from the authors [31])

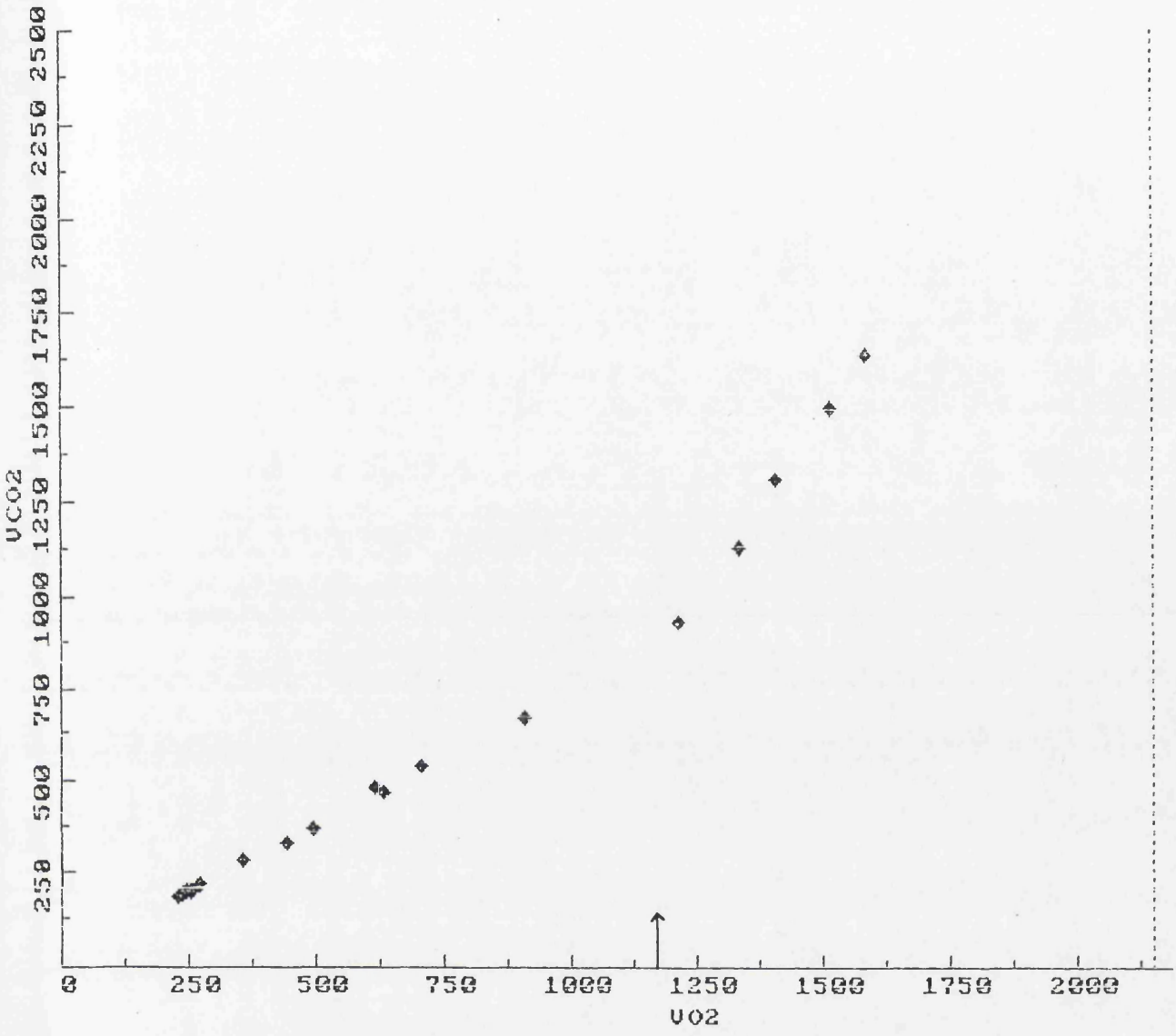


Figure 1.3 *Anaerobic threshold (AT) of a patient with ankylosing spondylitis, determined by the ' V-slope ' method during a cardiopulmonary exercise testing. AT is identified as the breakpoint (arrow) in the CO_2 output vs O_2 uptake plot.*

This subject's predicted VO_2max was 2.15 $L \cdot min^{-1}$.

The AT = 1.17 $L \cdot min^{-1}$ (55 % pred. VO_2max).

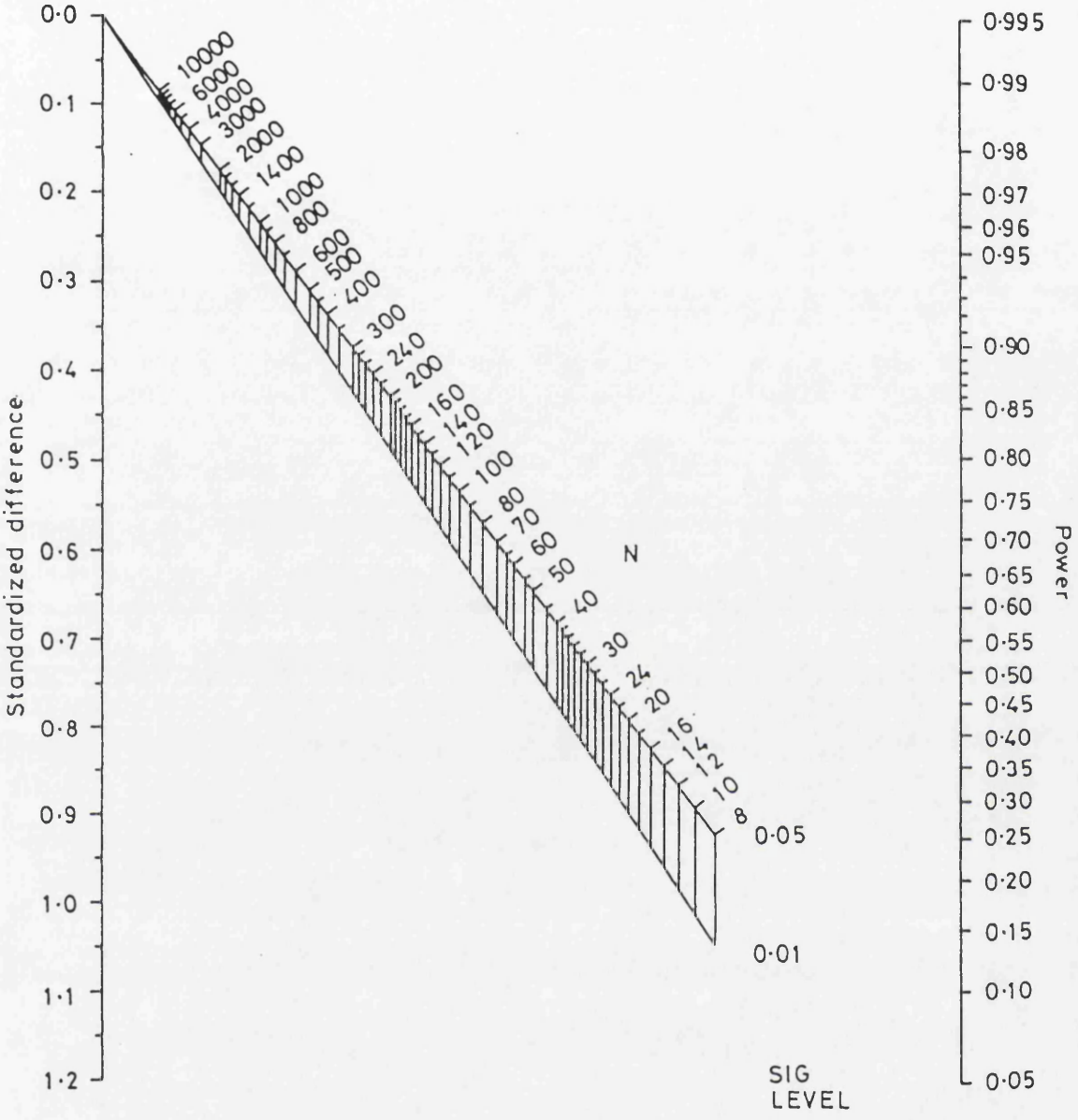


Figure 1.4 *Nomogram for a two-sample comparison of a continuous variable, relating power, total study size, the standardized difference, and significant level.*

(Reproduced with written permission from the author [81] *)*

Table 1.1

Review of the literature on lung volume and subdivisions in patients with ankylosing spondylitis.

Reference number	Number of subjects	VC	FRC	RV	TLC	RV/TLC
44	35	↓	N	N	↓	↑
45	16	↓	↑↑	↑↑	N	↑
46	53	↓	↑	↑	N	NM
47	22	↓↓	↑	↑	↓	NM
48	17	↓	↑	↑	↓	NM
49	38	↓	NM	N	↓	↑
50	32	↓	N	N	N	N
51	16	↓	N	N	↓	↑

Abbreviations and symbols :

N = Normal

NM = Not mentioned

↓ = Lower than predicted values

↓↓ = Markedly lower than predicted values

↑ = Higher than predicted values

↑↑ = Markedly higher than predicted values

Table 1.2

Review of the literature on the reference values for maximal static respiratory pressures in normal population.

Reference number	Gender	Age (range)	Sample size	MIP (cmH_2O)	MEP (cmH_2O)
59	Male	20-54	60	124 (22)	233 (42)
63	Male	19-65	48	106 (31)	148 (34)
64	Male	18-83	100	130 (32)	237 (46)
65	Male	18-70	326	119 (36)	139 (30)
66	Male	19-49	80	127 (28)	216 (45)
59	Female	20-54	60	87 (16)	152 (27)
63	Female	18-65	87	73 (22)	93 (17)
64	Female	18-83	100	98 (25)	165 (30)
65	Female	18-70	423	83 (30)	95 (20)
66	Female	19-49	121	91 (25)	138 (39)

Abbreviations : MIP = Maximal static inspiratory pressure ;

MEP = Maximal static expiratory pressure.

N.B. MIP and MEP values are expressed as mean (SD).

Although MIP is in fact a negative value with respect to ambient pressure, it is reported here as a positive value for clarity of presentation.

Chapter 2

Exertional Dyspnoea among AS Patients : Prevalence

2.1 Introduction

As dyspnoea is one of the principal symptoms limiting effort tolerance among patients with various conditions, an investigation into the prevalence of dyspnoea on exertion is an appropriate first step for studies on exercise limitation. For a clinical entity in which the prevalence of the symptom concerned is little known, a questionnaire represents a useful tool which enables clinical information to be obtained from a large number of patients.

Accordingly, the studies comprising this thesis commenced with a medium scale questionnaire-based survey with an emphasis on exertional dyspnoea in a group of patients with ankylosing spondylitis (AS) attending a rheumatology clinic with a large pool of patients with this condition.

This strategy served a number of purposes, namely :

1 to obtain a broad picture of respiratory symptoms as well as other clinical information of interest among AS patients.

2 to estimate the prevalence of undue exertional dyspnoea in AS patients.

3 to compare the frequency of undue breathlessness between patients classed as exercisers/non-exercisers and smokers/non-smokers.

4 the clinical information obtained would be used in the subsequent studies.

5 the patients willing to participate in the subsequent physiological studies would be identified.

2.2 Questionnaire survey

The problems in obtaining and utilising data from medical questionnaires have been discussed in a series of articles by Wright & Haybittle,[87] and a number of factors were considered in the design of the questionnaire.

a) General design

The questions were kept as simple as possible with the answers mainly " Yes " or " No ", and the replies consisted of ticks to appropriate boxes to minimise error in completion. The form was designed to be completed in about 10 minutes. The draft questionniare was tested on an initial 10 patients and their comments sought before finalising the format.

b) Form-filling

Some difficulties are commonly encountered with a self-completed questionnaire. The questions are sometimes misunderstood and contradictory answers given. Unsatisfactory replies are often obtained for questions requiring numerical details, e.g. amount of cigarettes smoked per day, number of hours spent for sports or exercises per week etc. In order to minimise these problems, the questionnaires used in this study were completed in a direct interview.

c) Content

The full questionnaire is detailed on Appendix A. It was orientated to respiratory symptoms and was simplified from the standard questionnaire designed by the

Medical Research Council committee.[88] The information concerned the following topics :

question 1	Duration of the disease, since the symptoms started
questions 2-3	Level of physical activity
question 4	Undue breathlessness
questions 5-8	Chronic cough or sputum production
questions 9-12	Smoking habit
questions 13-14	Background medical history
questions 15-16	Tiredness and physical fitness

2.2.1 Study population and methods

This questionniare survey was conducted during May-July 1993 by the investigator (P Riantawan) in a tertiary referral seronegative arthropathy clinic(Glasgow Royal Infirmary). Consecutive patients with definite AS (modified New York criteria[9]) were interviewed. Since no previous quantitative data regarding breathlessness in AS existed, the required sample size could not be prespecified with confidence. Nonetheless, it was considered necessary to obtain data from at least 60 subjects. For question 4 (undue breathlessness), the interviewees were asked specifically to focus on the difficult and uncomfortable breathing and not vague chest discomfort or rib pains.

Statistical methods

The frequency of various symptoms are presented as per cent. Analyses of the differences in the frequency of various symptoms between exercisers/non-exercisers and smokers/non-smokers were performed, using Chi squared test or

Fisher's exact test, as appropriate. For the purposes of this study, exercisers were defined as the subjects who regularly took exercise or played sport on a weekly basis. Smokers were defined as current smokers or ex-smokers of ≥ 5 pack yrs. Non-smoker category comprised never-smokers and ex-smokers of < 5 pack yrs. Statistical significance was assessed at 5 % level.

2.2.2 Results

A total of 62 AS patients were interviewed (47 male, 15 female; mean age 46.8, SD 10.3 yrs). The frequency of symptoms and information of interest is presented in Table 2.1. Undue breathlessness was reported in 26 % of the subjects. Chronic cough and sputum production were noted less commonly, 16 % and 13 % respectively. 47 % of the patients were classed as exercisers and 61 % as smokers. 25 patients (40 %) were ex-smoker of ≥ 5 pack yrs. whereas 13 patients (21 %) were current smokers. Not unexpectedly, tiredness and worsened fitness were reported in 72 % and 64 %.

Tables 2.2 a) and b) compare the proportions of the patients reported undue breathlessness with respect to exercise and smoking habits. The frequency of this symptom was significantly lower among exercisers ($\chi^2 = 4.107$, $p = 0.04$). The proportion was however not significantly different between smokers / non-smokers ($\chi^2 = 1.708$, $p = 0.18$).

Tables 2.3 a) and b) compare the proportions of chronic cough and sputum production between smokers and non-smokers. At 5 % significant level, the two

groups did not differ in the frequency of these symptoms ($p = 0.12$ and 0.64, respectively).

2.2.3 Discussion

Clinical studies within the confines of academic centres may suffer from biases inherent in the study of referral patients. The best patient population would be a group of individuals randomly selected from the range of referral centres, general hospitals and general practitioners. In addition, those who are not followed by the medical profession would be of interest. Clearly, this ideal population does not exist. Furthermore, definitive survey on a large scale community-based study would be an almost, if not, impossible task.

The questionnaire employed in this survey, like other clinical questionnaires, is not infallible. The chronic respiratory questionnaire (CRQ)[89], which comprises four clinical dimensions, has recently been reevaluated and the dyspnoea dimension found to be unreliable.[90] The well established questionniares orientated towards arthritic problems, for example the arthritis impact measurement scale,[91] do not directly address dyspnoea. Although formal piloting was not carried out, the draft questionnaire was tested on the initial 10 subjects before finalising the format. Most importantly, undue breathlessness, the main focus of the survey was carefully defined to all the interviewees.

The finding of undue breathlessness in 26 % of the AS subjects interviewed contrasts with the prevailing concept that respiratory symptoms are rare in this condition.[41,45,46] This symptom was not directly linked to tobacco smoking,

suggesting that other factors, rather than airways disease are at play. This served to indicate the need for subsequent physiological studies (chapters 3-5).

The overall prevalence of smokers among the AS patients interviewed (61 %) was rather high, as compared to that of general population in the U.K. (30 - 35 %).[92] Nevertheless, the majority were ex-smoker, and only 21 percent were current smokers. The anticipated association between smoking habit and chronic cough and sputum was not confirmed at 5 % significant level. The most likely explanation seems to be the relatively small sample size; nonetheless, the raw data suggested that smokers were more commonly affected by these symptoms. The interview replies therefore did not seem to have been subject to inconsistency or major distortion.

The relatively high prevalence of feelings of tiredness and worsened fitness observed in this survey is not unusual in AS. This finding underpins the demand for strategies to help maintain physical fitness among sufferers from this condition.

2.3 Oxygen-cost diagram study

The initial survey suggested that undue breathlessness was not uncommon among sufferers from ankylosing spondylitis (AS). However, assessment of dyspnoea based on questionnaires suffers from two major limitations. The intensity of dyspnoea cannot be defined in quantitative terms by using a questionnaire.Moreover, comparative studies are not feasible. The latter is of clinical importance considering the subjective nature of dyspnoea; therefore, studies comprising control subjects would yield a better precision as to the presence of heightened perception of breathing effort among the patient population concerned.

Dyspnoea, like other sensations, can be quantified by the use of visual analogue scales (VAS).[93] VAS is a straight line representing the continuum from no effort to maximum effort perceived; the subject indicates the point on the line which he judges to represent his sensation.

Hence, a further appraisal of dyspnoea among AS patients was made in a study comprising matched controls using an Oxygen-cost diagram *(vide infra)*.

2.3.1 Study population and methods

Subsequent to the initial survey, a group of patients with definite AS were invited to participate in the further studies. The recruitment was carried out with no reference to the presence of respiratory symptoms, or exercise/smoking habits. The invitation was met with enthusiastic supports, although many could not participate on account of travel difficulty, or being too physically limited. Furthermore,in order to minimise confounding factors, exclusion criteria were necessarily applied as follows: 1) patients with a history of cardiac disease or taking β-blocking agents, 2) patients with previous exposure to radiation, asbestos or drugs associated with pneumonitis, 3) patients with chest pain on deep inspiration affecting performance of various breathing manoeuvres in the subsequent studies, and 4) patients with significant pain in the hip, knee or ankle joints or with hip replacement precluding optimal performance on cycle ergometry (chapter 4 & 5).

A total of 20 patients participated in the present study. 20 age-and gender-matched healthy volunteers served as a control group. Clinical characteristics of the two groups are summarised in table 2.4.

Oxygen-cost diagram

The subjects were shown an Oxygen-cost diagram[94](Figure 2.1). The diagram consisted of a list of everyday activities positioned alongside a 100-mm vertical scale proportionally to their oxygen cost. The subjects were allowed sufficient amount of time to study the activity list. They were then instructed to mark the line at a point above which they would become breathless at their best. The result was expressed as the distance of the mark in millimetres above zero. Breathlessness was defined to the subjects as a feeling of an uncomfortable need to breathe rather than any other sensations, such as fatigue or vague chest discomfort.

Statistical methods

Comparisons of clinical characteristics between the AS and control groups were made, using Chi squared test with Yates' correction. The difference in the values from the Oxygen-cost diagram between the two groups was assessed, using Wilcoxon signed-rank matched-pairs test.

2.3.2 Results

Both groups were well-matched in terms of age and gender distributions (Table 2.4). Unintentionally, the two groups did not differ with respect to exercise and smoking habits. The values from the Oxygen-cost diagram in the AS group was significantly lower than that in the control group [mean (SEM); 80.3 (3.4) mm in AS *vs* 89.4 (2.1) mm in controls, $p = 0.042$] (Figure 2.2).

2.3.3 Discussion

The significantly lower values from the Oxygen-cost diagram in the AS group

indicate a greater magnitude of dyspnoea perceived during everyday activities among these patients. Thus, the result substantiates the finding from the initial survey as regards the presence of undue breathlessness among sufferers from AS.

Explanation must be given for the choice of VAS used in this study. Different forms of VAS for assessment of dyspnoea have been validated.[94-96] Although fundamentally similar to the others, an Oxygen-cost diagram has the particular strength that it comprises a list of everyday activities positioned alongside the scale. This ensures considerable precision of the scale in representing the breathing effort for various physical tasks perceived among different subjects.

Summary of Findings

1 The prevalence of undue breathlessness (26 %) reported among patients with ankylosing spondylitis (AS) in the questionnaire survey is in contrast with the prevailing concept that respiratory symptoms in AS are rare.

2 The AS patients who took regular exercise or sports suffered from undue breathlessness less commonly than non-exercisers.

3 The symptom of undue breathlessness among the AS patients interviewed was not significantly influenced by smoking habit.

4 Relative to age-and gender-matched controls, the magnitude of dyspnoea, assessed by an oxygen-cost diagram, was greater among the AS patients, thus corroborating the main finding in the initial survey.

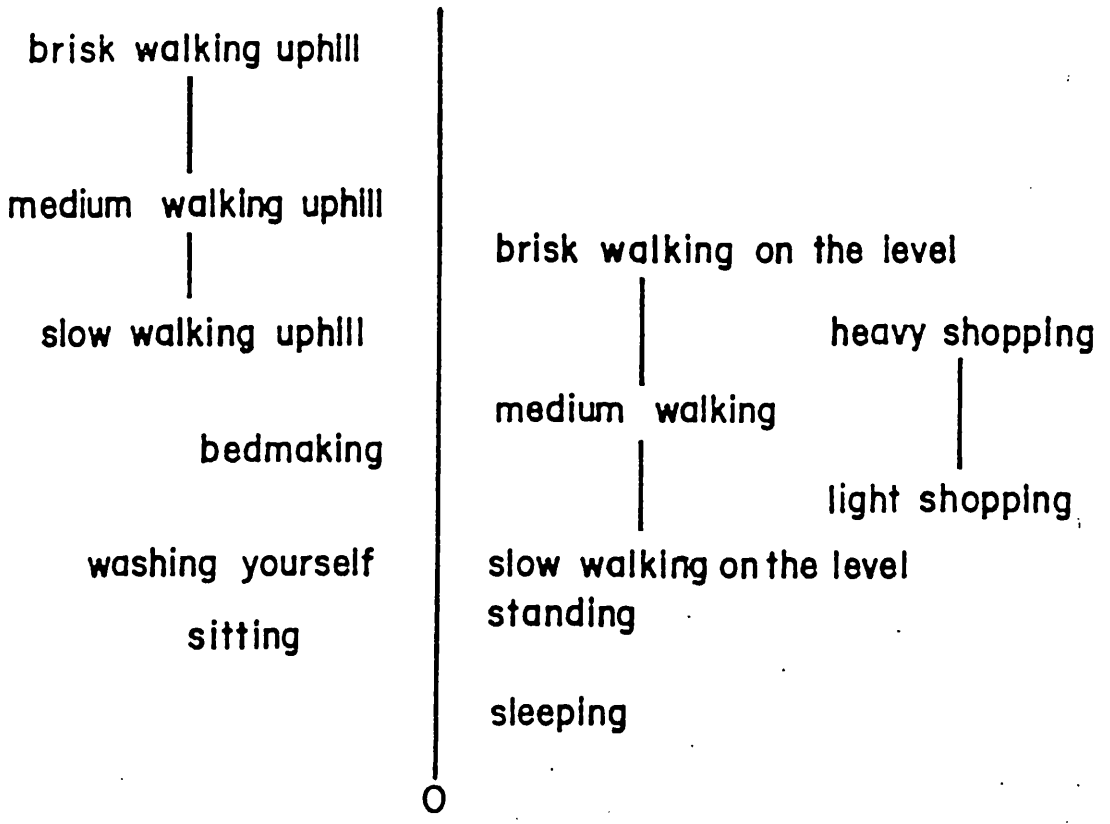


Figure 2.1 *Oxygen-cost diagram. Vertical line is 100 mm long, and everyday activities listed are placed proportionately to their oxygen cost. Subjects were asked to indicate the point above which they thought they would become breathless.*

(From reference 94)

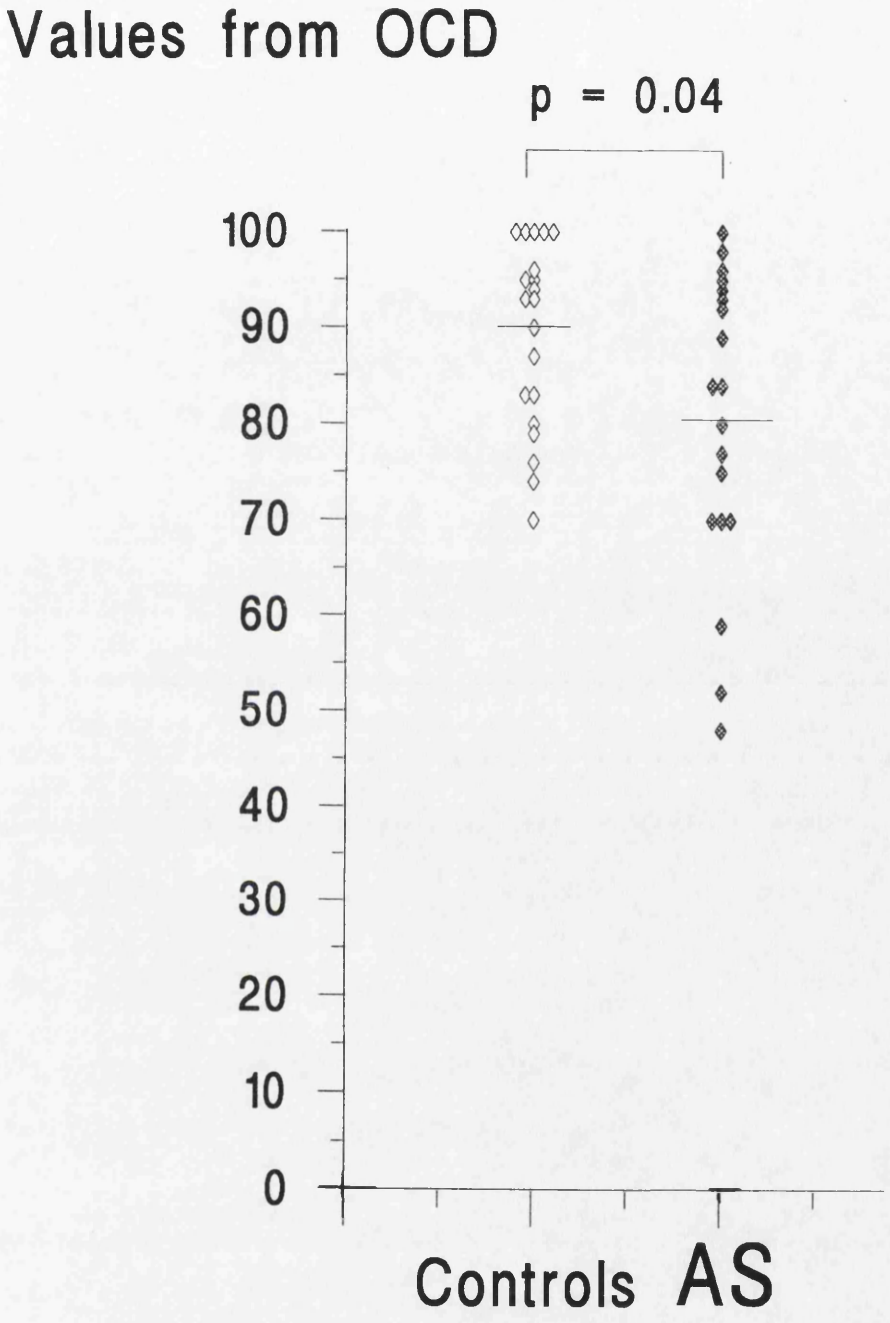


Figure 2.2 *Comparison of the values from Oxygen-cost diagram (OCD) between 20 patients with ankylosing spondylitis (AS) and 20 matched controls. The AS group reported significantly lower values, indicating a greater magnitude of dyspnoea perceived. Bars represent group means.*

Table 2.1

Frequency of symptoms and some information of interest in 62 patients with ankylosing spondylitis

	Number	%
Undue breathlessness	16	26
Chronic cough	10	16
Chr.sputum production	8	13
Tiredness	45	72
Worsened fitness	40	64
Exercisers	29	47
Smokers	38	61

Tables 2.2

2×2 frequency tables comparing undue breathlessness between AS patients classed as a) exercisers/non-exercisers and b) smokers/non-smokers *

a)	**Exercisers**	**Non-exercisers**	Total
Undue breathlessness	4 (7.4)	12 (8.5)	16
No undue breathlessness	25 (21.5)	21 (24.4)	46
Total	29	33	62

a) df = 1, χ^2 = 4.107, p = 0.04

b)	**Smokers**	**Non-smokers**	Total
Undue breathlessness	12 (9.8)	4 (6.1)	16
No undue breathlessness	26 (28.1)	20 (17.8)	46
Total	38	24	62

b) df = 1, χ^2 = 1.708, p > 0.05

* Values in parentheses are expected frequencies

Tables 2.3

2×2 frequency tables comparing AS patients classed as smokers / non-smokers with respect to a) chronic cough and b) sputum production

a)	**Smokers**	**Non-smokers**	Total
Chronic cough	8	1	9
No chronic cough	30	23	53
Total	38	24	62

a) Two-tailed p value = 0.12 (Fisher's exact test)

b)	**Smokers**	**Non-smokers**	Total
Chr. sputum production	6	2	8
No chr.sputum production	32	22	54
Total	38	24	62

b) Two-tailed p value = 0.64 (Fisher's exact test)

Table 2.4

Clinical characteristics of 20 AS and 20 control subjects in the Oxygen-cost diagram study *

	Controls	**AS subjects**
Total number	20	20
Age , yrs	46.4 (12.2)	46.5 (12.3)
Gender , male : female	13 : 7	13 : 7
Exercisers : Non-exercisers	9 : 11	13 : 7
Smokers : Non-smokers	7 : 13	9 : 11

* Values are in mean (SD)

Chapter 3

Respiratory Muscle Performance among Patients with Ankylosing Spondylitis

3.1 Introduction

Rigidity of the chest wall, consequent to ankylosis of the costo-transverse and costo-vertebral joints, is a characteristic feature in ankylosing spondylitis (AS) and occurs early in the course of the disease.[47] Thus, reduced thoracic compliance has been consistently shown.[47,51,52]

The impaired mechanics of the thoracic cage in AS is likely to render the rib-cage muscles anatomically disadvantaged and their performance diminished. However, quantitative data on respiratory muscle strength (RMS) and endurance (RME) in patients with AS is scarce. Furthermore, the effects of altered lung volumes and restricted chest expansion on RME and RMS in AS are unknown.

As described in chapter 1.7, the reference values for maximal respiratory pressures (MRP) vary considerably among various sources in the literature (Table 1.2). Further studies comprising matched controls would be of clinical value in delineating the efficiency of respiratory muscle performance in this condition.

Therefore, the aims of the present case-controlled study were as follows :

1. To comprehensively evaluate RMS and RME in AS patients
2. To assess the possible influence of diminished thoracic expansion and

altered lung volume and subdivisions on RMS and RME in AS patients.

3.2 Methods

Sample size determination

The required sample size in the present study was predefined based on the nomogram proposed by Altman[81](Table 1.4). This makes use of the standardised difference, which is the smallest clinically relevant difference divided by the estimated standard deviation (SD) of the outcome variable concerned. The nomogram is appropriate for calculating power for a two-sample comparison of a continuous variable with the same number of subjects in each group.

One of the main outcome measures in this study was maximal inspiratory pressure (MIP). Previous studies have shown an SD of MIP among middle-aged population to be in the region of 22-31 cmH_2o(Table 1.2). The smallest clinically relevant difference of MIP values is a matter of clinical judgement. The coefficient of variation of MIP among various reports averages 25 per cent; therefore, it seems logical to assume that a difference in MIP of at least 25 cmH_2o between two populations would be of clinical importance. Accordingly, the standardised difference for MIP is approximately 1.0.

From the nomogram, for a study to achieve statistical power of 85 % at 5 % significance level with a standardised difference of 1.0, the total sample size of approximately 36 would be required.

Subjects

18 patients with definite AS were recruited in this study subsequent to the

initial questionnaire survey. Exclusion criteria were similar to those in chapter 2.3.1. 18 individually age-and gender-matched healthy volunteers served as controls. The subjects were classed as smokers/non-smokers in a similar manner as in chapter 2.2.1

Chest Expansion (CE)

CE was measured circumferentially around the chest wall at the level of the fourth intercostal space with the subject standing with hands on head and arms flexed in a frontal plane.[97]

Pulmonary Function Measurements

a) Lung volumes and Airway resistance

Lung volumes and airway resistance (Raw) were measured using a constant-volume body plethysmograph[98,99](PK Morgan Ltd, Kent, UK). It consists of a large chamber, a pneumotachograph, and three tranducers, which measure changes in box pressure (ΔPbox), mouth pressure (ΔPm), and flow at the mouth (V). The subject, seated in the closed chamber, breathes through a special mouthpiece-shutter assembly. At end-expiration, the shutter is closed to occlude the mouth-piece, and the subject is asked to rhythmically compress and decompress his thorax by panting lightly against the closed shutter. While the shutter is closed, no airflow occurs within the airways, so ΔPm equals the alveolar pressure changes (ΔPalv). During this manoeuvre, the ΔPbox reflects the changes in thoracic volume, and is proportional to the ΔPalv. The linearity of the inverse relationship of Pm and Pbox is preserved, because conditions in the respiratory system are isothermal. Thus, Boyle's law ($P_1V_1 = P_2V_2$), can be applied to these pressure-volume changes to calculate the volume being compressed, the subject's thoracic gas volume (TGV).

TGV was considered to represent functional residual capacity(FRC). Expiratory reserve volume(ERV), relaxed vital capacity(VC) were determined from pneumotachograph. Residual volume (RV) was derived by subtracting ERV from FRC, i.e. RV = FRC - ERV. Total lung capacity can be calculated by adding VC to RV, i.e. TLC = VC + RV. All volumes were corrected to body temperature and pressure saturated with water vapour (B.T.P.S.).

For the measurement of airway resistance, the same shallow panting method is employed, in order to keep the subject's glottis open and prevent respiratory temperature artifacts in the box. While the subject pants through the open mouthpiece, flow at the mouth and the corresponding cyclical changes in Pbox are recorded. The shutter is then closed briefly for TGV measurement. The ratio of $\Delta Pm/\Delta Pbox$ (shutter closed) is divided by the ratio $V/\Delta Pbox$ (shutter open). The quotient represents the airway resistance.

b) Diffusing capacity of the lung for carbon monoxide (DLco)

DLco was measured by the single-breath technique as described by Ogilvie *et al*[100](Transfer test, PK Morgan Ltd, UK). The subject is connected to a spirometer with a "balloon-in-box" system, inhales a maximum breath from RV (VC) of a gas containing 0.3 % Carbon monoxide, and Helium and air mixture, and is instructed to hold his breath for 10 seconds. During exhalation, an alveolar sample is collected in a small bag and analyzed for CO concentration. The CO uptake during the breath-holding time can be calculated from the inspired and expired CO concentrations.

All procedures were performed in accordance with the guidelines as

recommended by the British Thoracic Society and the Association of Respiratory Technicians and Physiologists.[101] Standard reference values for lung volumes[102] and DLco[103]were used. In the AS subjects, the calculation of per cent predicted values was based on the height prior to onset of the disease where this was reliably known.

Determination of Respiratory Muscle Strength (RMS)

Maximal respiratory pressures (MRP) were used as indices of global respiratory muscle strength. Maximal inspiratory pressure (MIP) and expiratory pressure (MEP) were measured using a digital mouth pressure meter (Precision Medical, Yorks, UK)(Figure 3.1). This equipment samples the signal at 16 Hz and an integral microprocessor identifies the one second period containing the maximum average pressure during inspiratory and expiratory manoeuvres provided a minimum duration of 1.5 seconds is made for each effort. A 2 mm hole (leak) exists at the centre of inspiratory and expiratory valves, preventing the subject from generating additional pressure with facial muscles. It has been shown to provide reliable and accurate measure of MRP in normals and in patients with respiratory disorders.[61] An oval flanged rubber mouthpiece(internal diameter 26 mm, external diameter 34 mm) was firmly attached to the mouthpiece adaptor of the meter. Subjects were seated and noseclips applied. MIP was measured from FRC and MEP from TLC. A minimum of 5 efforts were made for each manoeuvre until the two highest readings matched within 10 % in an attempt to minimize learning effect.[68] An interval of at least 1 minute was adopted between each effort. MIP was measured before MEP and instructions and demonstrations of the correct manoeuvre were always given. Although MIP

is in fact a negative value with respect to ambient pressure, it is reported here as a positive value for clarity of discussion.

Assessment of Respiratory Muscle Endurance (RME)

RME was assessed using an inspiratory resistive breathing protocol adapted from the techniques previously described[70,71](Figure 3.2). The subject with a nose-clip in place sat and breathed through a resistive training device (RTD)(PFLEX, Healthscan, USA) incorporating six adjustable alinear inspiratory orifices and a one-way expiratory valve. Mouth pressure (Pm) was continuously displayed on an oscilloscope for a visual feedback via a differential pressure transducer (Gould Statham P50) connected with the mouthpiece of the RTD. A pressure range of -130 to +130 cmH_2O was calibrated before each trial. The subject was instructed to inspire and expire according to the sound signal generated from an electrical metronome. Inspiratory duration (Ti) was set at 1.7 s and total breath duration (Ttot) at 2.6 s, thus giving rise to a duty cycle (Ti/Ttot) of 0.4 and a breathing frequency of 14/min. A square wave and a target line were drawn on the oscilloscope screen and the subject was encouraged to maintain the required breathing pattern and target pressure throughout the run. Oxygen saturation (SaO_2) was continuously monitored using a pulse oximeter (Biox 3740). For the purposes of this study, only orifice 4 of the RTD was used throughout since, in a preliminary study on 5 AS patients, orifice 4 was found to be the most suitable for producing sufficient airflow resistance yet allowing adequate ventilation. This is in contrast with a previous study on patients with chronic airflow limitation[71] in which larger orifices (1,2 and 3) were found suitable. The explanation clearly lies in the fact that the latter group of patients were inherently limited by

airflow obstruction. As the orifice size was fixed, the mean flow rate required to achieve each target pressure was unique. Consequently, no attempts were made in this study to measure inspiratory flow rate as this was constrained via control of the other components of the breathing strategy.

In order to familiarize the subjects with the breathing apparatus and the audio-visual feedback, a practice session was held the day prior to the actual testing in which the subject breathed through the RTD and the target Pm was set at approximately 20 % of the baseline MIP for 10 minutes. This target Pm and the required breathing pattern were easily accomplished by all subjects. In the actual test session, another practice run of 5 minutes was given. Thereafter, the target Pm was raised to 70 % of MIP. The subject was constantly encouraged to maintain the target pressure and the breathing pattern. Endurance time (Tlim) was defined as the moment at which the target Pm could not be maintained for three consecutive breaths or oxygen desaturation (a fall of $SaO_2 \geq 4$ % from the baseline value) developed.

Statistical methods

Values are presented as mean (SD) or mean (95 % CI) as appropriate. Comparisons of categorical variables between the AS and control groups were made by Chi squared test with Yates' correction. Lung function data, MIP, MEP and Tlim between the two groups were compared using Wilcoxon signed-rank matched-pairs test. Relationships between lung subdivisions and MIP, MEP and Tlim in each group were assessed using product-moment correlation coefficients (r). Statistical significance was assessed at 5 % level. In view of the multiple significance testings involved in the correlations between lung subdivisions and MIP, MEP and Tlim, the

Bonferroni correction[82] was applied.

3.3 Results

The two groups were well-matched with respect to age, gender, body mass index and smoking habit (Table 3.1).

Pulmonary Function Results (Table 3.2)

The AS group had significantly smaller VC (p=0.001) and TLC (p=0.002) as compared with the control group, corresponding to mean percentage predicted values of 76 % and 85 % respectively. Although the mean FRC in the AS group was comparable with that of control group, the FRC/TLC was significantly higher (p=0.041) because of the smaller TLC. FEV_1 was smaller in the AS group; however, the FEV_1/VC remained normal. Raw and DLco were also normal.

Maximal Respiratory Pressures (Figures 3.3 and 3.4)

In the AS group, mean MIP was 83 (95% CI 69,97) cmH_2O and mean MEP was 111 (95% CI 96,126) cmH_2O. Both indices did not differ from those of controls (p=0.45 and 0.80 respectively).

Respiratory Muscle Endurance (Figure 3.5)

In contrast with MRP, Tlim was significantly shorter in AS group with a mean of 128 (95% CI 79,176) seconds as compared with control group, mean 258 (95% CI 205,310) seconds (p=0.009). In no occasion was the test terminated on account of O_2 desaturation.

Correlations between MRP, Tlim and Lung Subdivisions

In the control subjects, there were no significant correlations between lung

subdivisions and MRP or Tlim (Table 3.3).

In the AS subjects, MIP did not correlate with any lung subdivisions or CE (Table 3.4). MEP correlated with VC (r=0.67, p=0.042) and TLC (r=0.68, p=0.042). In contrast, Tlim correlated inversely with FRC/TLC (r=-0.68, p=0.042) but not with other lung subdivisions or CE. Figure 3.6 shows the inverse correlation between Tlim and FRC/TLC in the AS group.

3.4 Discussion

The present study provides no strong evidence that respiratory muscle strength, assessed by maximal respiratory pressures, in patients with ankylosing spondylitis is reduced. However, the efficiency of respiratory muscles in this condition becomes evidently impaired during sustained breathing at high inspiratory pressures. It would be of clinical value to furthur study whether the impaired respiratory muscle endurance plays an important role in exercise intolerance among these patients.

Sample size determination

A study with an overlarge sample may be deemed unethical through the unnecessary involvement of extra subjects and the correspondingly increased costs. On the other hand, a study with a sample that is too small will be unable to detect clinically important effects. One of the common features among clinical studies is the involvement of multiple outcome measures which renders sample size determination difficult.

The same applies to the present study, of which there were three main outcome variables, namely MIP, MEP and Tlim. Nonetheless, this study has attempted to predefine the required sample size based on the currently available data on MIP in normals.

Pulmonary Function Impairment in AS

The findings of a slight reduction in TLC and, to a greater extent, VC in patients with AS are broadly in agreement with previous studies.[44,47-49,51] The normal mean FRC and RV agrees with some reports[44,50,51] but differs from others.[45-48] These discrepancies may be due to differences in stage of the disease and, to a larger extent, differences in reference values used. The normal DLco is in line with previous reports.[40,49]

Of more clinical significance is the finding, in the AS group, of a higher ratio FRC/TLC which has previously received little attention. In contrast with interpreting the absolute FRC, using the ratio FRC/TLC takes into consideration the relatively smaller total lung size present in the majority of AS patients. The higher FRC/TLC in the AS subjects implies that their resting lung position is elevated. This finding lends further support to the notion that the level of fixation of the thorax in AS occurs closer to full inspiration than in normal persons.[46-48]

It is noteworthy that, whilst the FRC/ TLC ratio is increased in the AS group, RV is not similarly increased. Residual volume, the volume of gas in the lung at the end of a full expiratory effort, is determined by a balance of force, including the strength of the accessory muscles of expiration, the inherent incompressibility of the thoracic cage, and the traction exerted on airways by fibrous stroma of the lungs.[103] While resting lung position may be altered, a forced manoeuvre may involve use of reserve capacity, notably the accessory muscles of expiration which was found to be preserved in the present study. Thus, the FRC/ TLC ratio could be an early evidence of a process which will later show in an abnormality of residual volume.

Also worthy of note is the finding of a slight reduction in mean FEV_1 in the AS subjects. FEV_1 is dependent upon airway resistance and the force and speed of contraction of the thoracic and abdominal respiratory muscles. However, neither the airways resistance nor the indices of respiratory muscle strength was impaired in this group of AS patients. This reduction may therefore be explained by the relatively small lung volume since the ratio FEV_1/VC remained normal in the AS group.

Respiratory Muscle Strength (RMS)

Maximal respiratory pressures (MRP) measured at the mouth are simple, non-invasive indicators of global RMS.[104] There was no evidence that global RMS in patients with AS was reduced in the present study.

Furthermore, this study has shown that MEP correlates with VC and TLC in AS patients. These findings corroborate the concept that the expiratory muscles are longer and nearer to their optimal resting length at high lung volume.[62] The normal lung volumes in the control group, however, did not allow the lung volumes to exert their influences on MEP.

Vanderschueren *et al*,[76] in a study of 30 patients with AS, reported a significant reduction in MRP among these patients when compared to the reference values of Arora.[66] A different conclusion may have been drawn if these values had been related to reference values from other sources. As a matter of fact, the MIP at FRC in AS patients in the present study, mean 83 (SD 30.3) cmH_2O, was in close agreement with their study, mean 75.1 (SD 29.4) cmH_2O, as were the MEP at TLC from both studies, means 111 and 110.5 (SD 32.5 and 36.8) cmH_2O respectively.

Respiratory Muscle Endurance

Endurance time (Tlim) determined by the method used is subject to several sources of error. The high target pressure undoubtedly requires a high level of motivation and the necessity to control the breathing strategy means that adequate familiarization needs to be attained prior to the actual testing. From the practical standpoint, it is sometimes difficult to ascertain the moment at which the target mouth pressure (Pm) is not maintained for three consecutive breaths. In the present study, all the subjects who participated were well motivated and sufficient practice runs were given to both groups. Furthermore, the endpoint criterion of Tlim was carefully and strictly applied in all trials.

In a study of 5 healthy volunteers on the relationship between Tlim and Pm, Roussos *et al*[105] found that Pm $\leq$ 60 % of MIP could be generated indefinitely (Pm_{crit}). Consequently, the target Pm in the present study was set at 70 % of MIP. Bellemare & Grassino[73] proposed tension-time index of the diaphragm (TTIdi). TTIdi is the product of contractile force and duration, where force is expressed as the ratio of transdiaphragmatic pressure (Pdi) to maximum Pdi, and duration is expressed as duty cycle. Tlim could be related to TTIdi by the expression:$Tlim = 0.1(TTIdi)^{-3.6}$, which is valid when TTIdi is in excess of 0.15. Since MIP has been shown to correlate closely with Pdi,[106] tension-time index can be applied to the global inspiratory muscles based on the relationship of Pm / MIP instead of Pdi/Pdimax. The tension-time index in the present study was 0.28 and Tlim would be predicted to be between 7-10 mins. Although not in excellent agreement, the mean Tlim in the control group was 4.18 mins.

The striking finding is the markedly shorter Tlim in the AS group with a mean of 2.08 mins. In a study on 25 patients with AS and matched controls, Josenhans *et al*[75] calculated a mean diaphragmatic contribution to a tidal volume of 84.8 % in AS subjects compared with 68.4 % in controls. Moreover, Grimby *et al*[74] observed that the relative contribution of the rib cage to ventilation decreased further during hyperventilation. When taking the findings from the two studies and the present study together, it is evident that the diaphragm in patients with AS, although it can compensate sufficiently during tidal breathing, tires more quickly than in normal individuals during breathing at high inspiratory pressures indicating relative inefffi-ciency of the diaphragm in this condition.

While a correlation does not necessarily indicate a causal relationship, the inverse correlation between Tlim and FRC/TLC in the AS group suggests that an elevated resting lung position, as reflected by the higher FRC/TLC, plays a significant role in the shorter endurance time. This adds further evidence to the observation that at lung volumes above normal FRC, the diaphragm and other inspiratory muscles are foreshortened and their contractile force curtailed.[106] It is noteworthy that this effect, in the presence of normal FRC/TLC, was not evident in the control group.

Although RME testing evaluates the performance of the respiratory muscles, their work can by no means be assessed *in vivo* in isolation from other groups of skeletal muscles. Hence the relative lack of physical fitness consequent to the chronic nature of the disease may also contribute to the shorter Tlim in AS patients.

Respiratory muscle endurance can be interpreted in terms of the balance between energy stores, utilization and renewal.[66] Thus nutritional status has been

shown to influence diaphragmatic mass[107] and respiratory muscle strength.[108] Impeded diaphragmatic blood flow during cardiogenic shock has also been shown to impair respiratory muscle force in experimental dogs[109] although this has not been fully established in the presence of normal arterial blood pressure and cardiac output in man. Data from the present study did not permit an analysis of the role of these factors since all the subjects were well-nourished, as judged by body mass index, and no subject was in a compromised cardiocirculatory status.

Summary of Findings

1 There was no evidence that respiratory muscle strength, assessed by maximal respiratory pressures, in the 18 AS subjects was reduced.

2 Relative to age-and gender-matched controls, respiratory muscle endurance in the AS group was significantly shorter. This finding indicates that, although the diaphragm compensates well in AS during tidal breathing, the respiratory muscle performance becomes evidently impaired during sustained breathing at high inspiratory pressures.

3 The reduced respiratory muscle endurance in AS may in part be attributed to the elevated resting lung position, hence the inverse relationship between the endurance time and the ratio FRC/TLC.

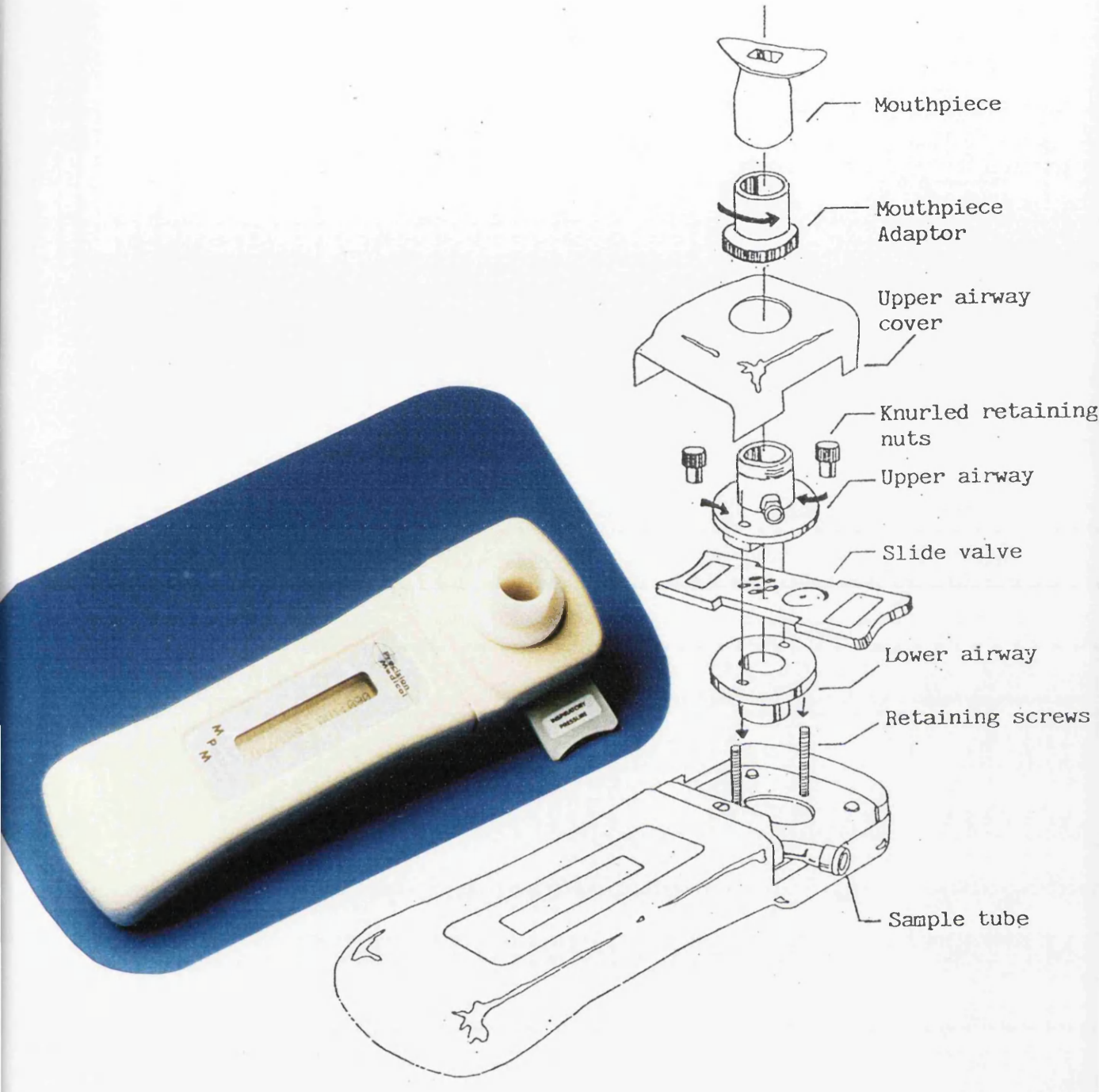


Figure 3.1 *Mouth pressure meter and its schematic illustration.*

(The schematic illustration is by courtesy of

Precision Medical, N Yorks, UK)

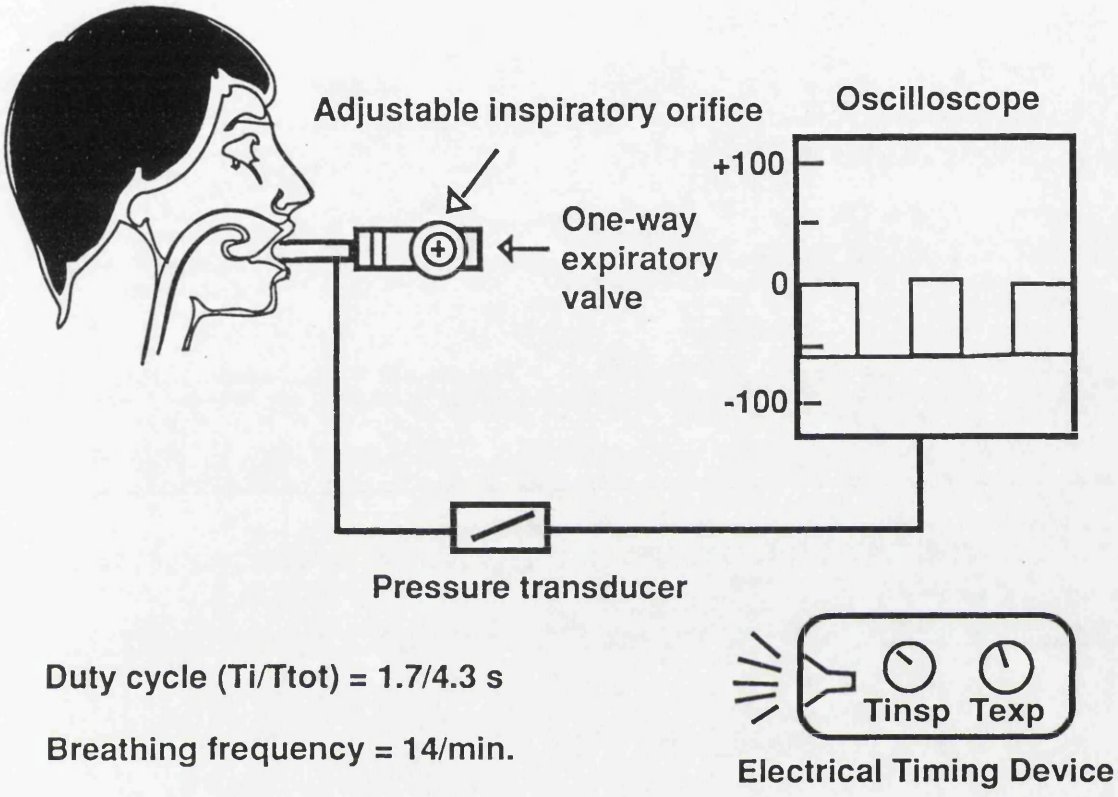


Figure 3.2 *Schematic illustration of the experimental set-up for the assessment of respiratory muscle endurance. The subject was encouraged to maintain a target mouth pressure of 70 % MIP. Duty cycle (Ti/Ttot) and breathing frequency were kept constant by means of an electrical timing device.*

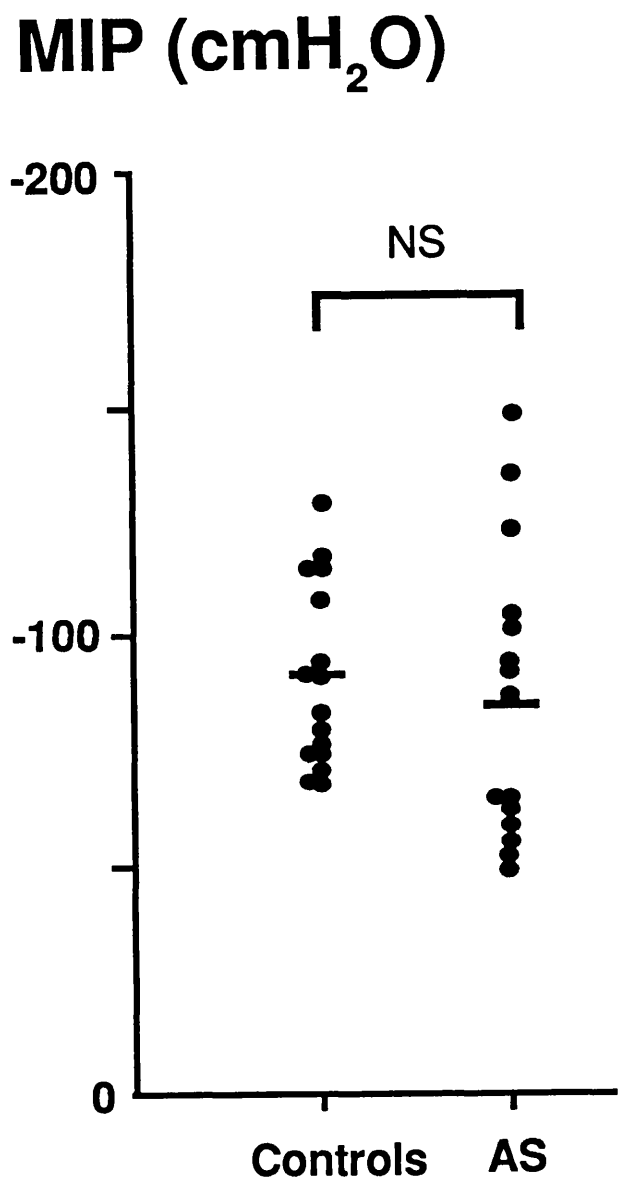


Figure 3.3 *Comparison of maximal inspiratory pressure (MIP) between 18 subjects with ankylosing spondylitis (AS) and 18 matched controls. Horizontal bars represent group means. NS = not statistically significant ($p > 0.05$)*

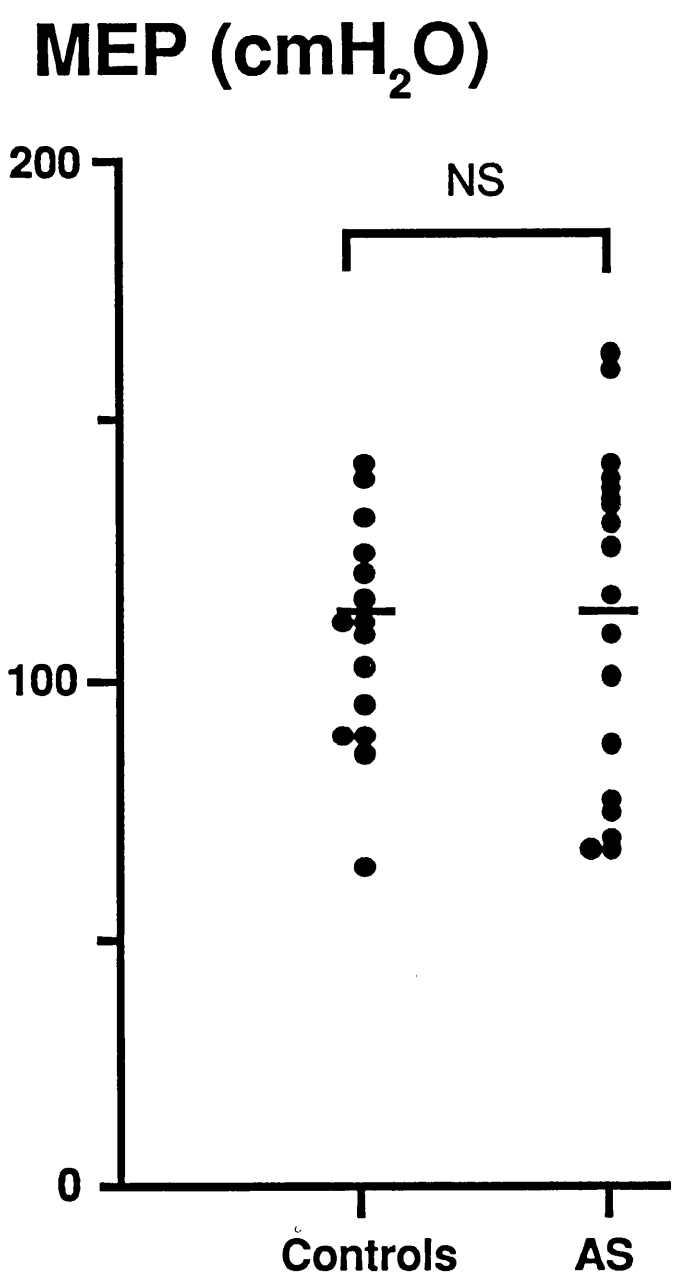


Figure 3.4 *Comparison of maximal expiratory pressure (MEP) between 18 subjects with ankylosing spondylitis (AS) and 18 matched controls. Horizontal bars represent group means.*

NS = not statistically significant ($p > 0.05$)

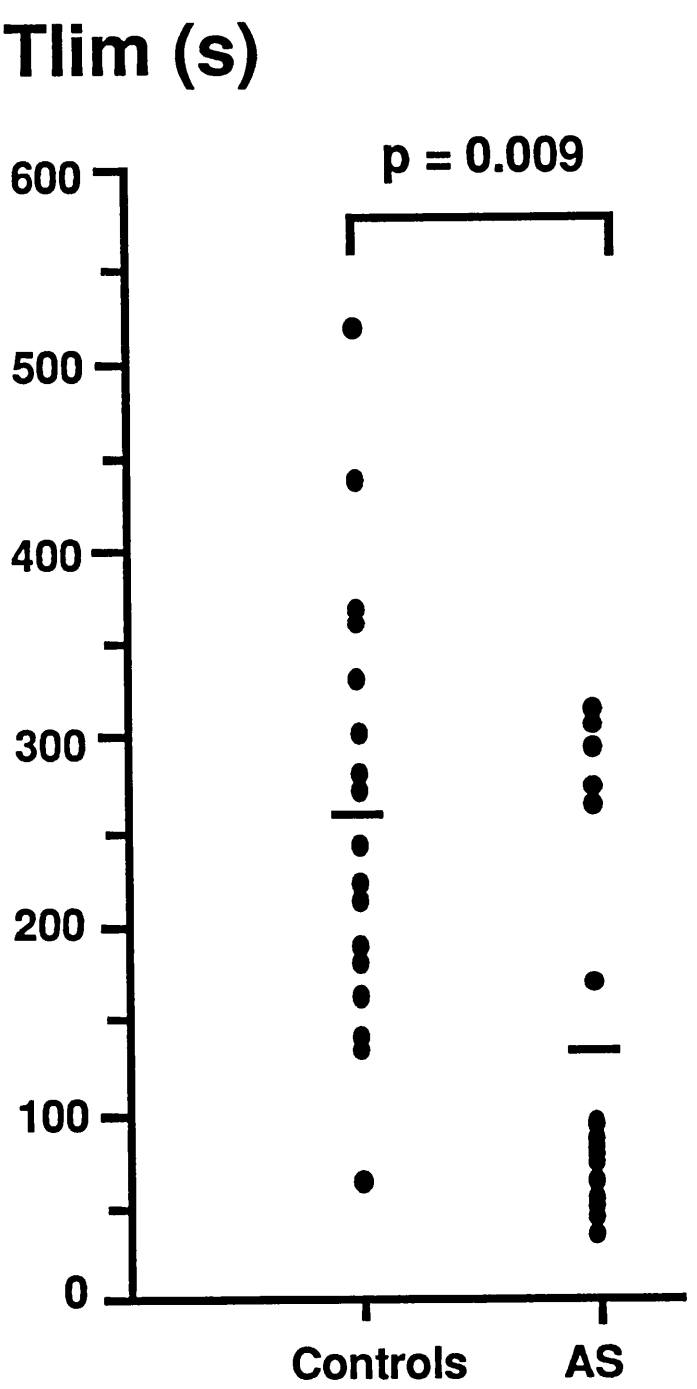


Figure 3.5 *Comparison of respiratory muscle endurance time (Tlim) between 18 subjects with ankylosing spondylitis (AS) and 18 matched controls.*

Horizontal bars represent group means.

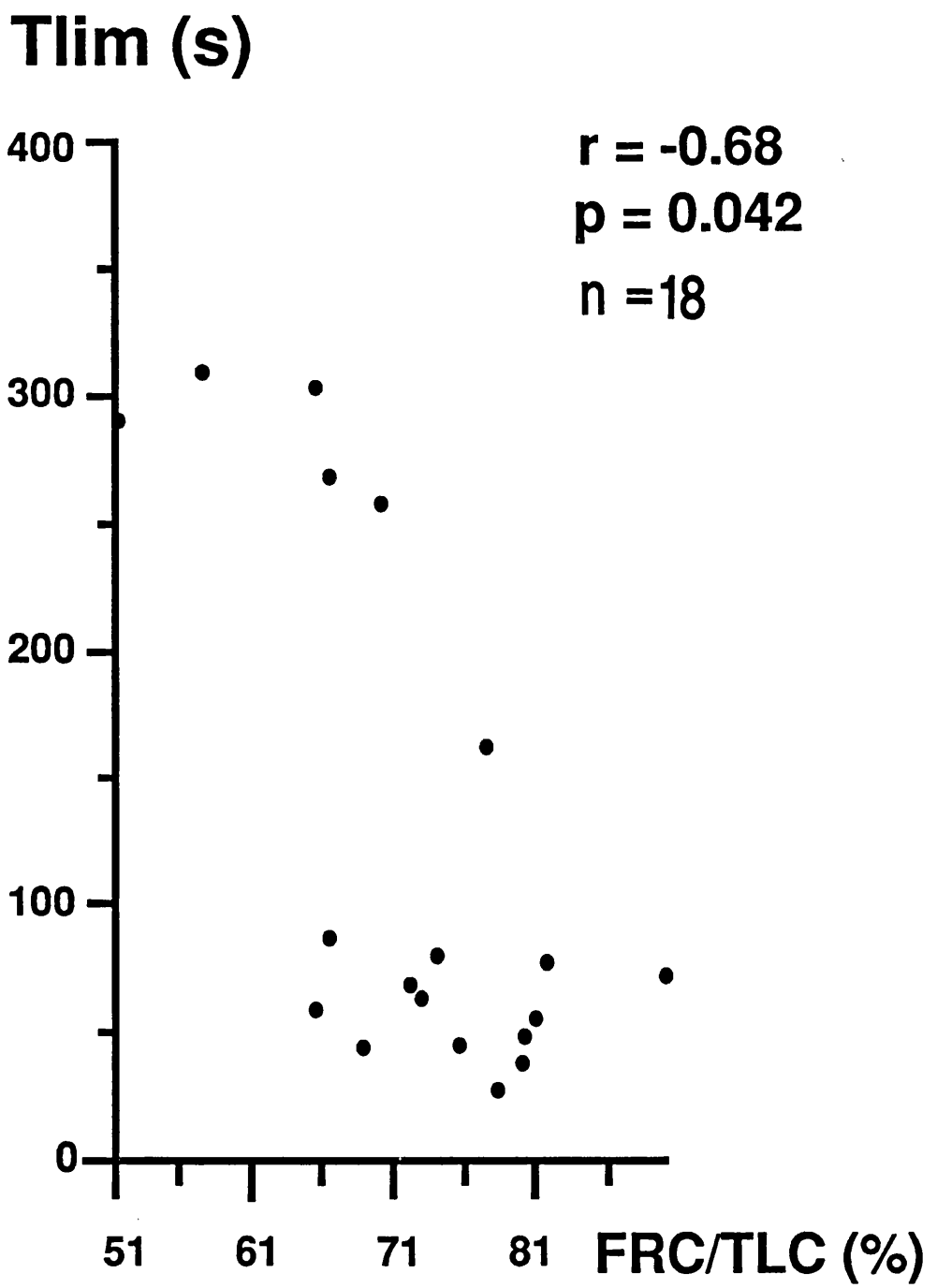


Figure 3.6 *Inverse relationship between endurance time (Tlim) and FRC / TLC ratio in 18 subjects with ankylosing spondylitis*

Table 3.1

Clinical characteristics of the AS and Control subjects in the respiratory muscle performance study *

	Controls	**AS subjects**
Total number	18	18
Age , yrs	44 (11.1)	44 (11.1)
Gender , male : female	12 : 6	12 : 6
Smokers : Non-smokers	6 : 12	8 : 10
BMI , $kg \cdot m^{-2}$	25.1 (2.7)	26.7 (4.5)
Chest expansion , cms	not measured	2.0 (0.7)

* Values are mean (SD).

Table 3.2

Pulmonary function data in 18 AS and 18 controls *

	Controls	AS subjects
FEV_1 , L	3.53 (0.80)	2.78 (0.70) +
% predicted	102 (12.9)	80 (13.0) +
VC , L	4.65 (1.04)	3.55 (0.88) +
% predicted	107 (19.8)	76 (12.1) +
FEV_1 / VC , %	76 (6.5)	78 (7.2)
FRC , L	4.01 (0.92)	3.83 (1.08)
% predicted	118 (20.4)	121 (40.4)
RV , L	1.69 (0.46)	1.78 (0.63)
% predicted	101 (23.9)	111 (31.8)
TLC , L	6.34 (1.41)	5.33 (1.23) +
% predicted	103 (15.5)	85 (12.7) +
FRC / TLC , %	63.7 (8.6)	71.6 (9.5) #
RV / TLC , %	26.6 (4.3)	33.2 (7.4) +
Raw , $kPa^{-1} \cdot sec^{-1} \cdot L^{-1}$	0.15 (0.05)	0.15 (0.04)

* Values are mean (SD)

+ $p < 0.005$

# $p < 0.05$

Table 3.3

Correlation coefficients between MIP, MEP, Tlim and lung volumes in 18 control subjects *

	MIP	MEP	Tlim
VC	0.07	0.18	0.30
FRC	0.05	0.38	0.45
RV	0.07	0.42	0.35
TLC	0.08	0.28	0.34
FRC / TLC	-0.03	0.21	0.20
RV / TLC	-0.01	0.38	0.13

* None of these correlations reached statistical significance at 5% level.

Table 3.4

Correlation coefficients between MIP, MEP, Tlim and lung volumes, chest expansion in 18 AS subjects

	MIP	MEP	Tlim
VC	0.50	0.67 +	0.08
FRC	0.33	0.37	-0.48
RV	0.36	0.39	-0.49
TLC	0.54	0.68 +	-0.19
FRC / TLC	-0.18	-0.38	-0.68 +
RV / TLC	-0.04	-0.13	-0.58
Chest expansion	0.01	0.11	0.12

+ $p = 0.042$ (adjusted p value according to Bonferroni method).

" A respiratory physiologist offering a unitary explanation for breathlessness should arouse the same suspicion as a tattooed archbishop offering a free ticket to heaven "

The warning of Campbell and Howell [122]

Chapter 4

Exercise Limitation, Exertional Dyspnoea, and Cardiorespiratory Response to Exercise among Patients with Ankylosing Spondylitis

4.1 Introduction

As set out in the introductory chapter, the mechanism(s) underlying exercise intolerance in patients with ankylosing spondylitis (AS) remains unclear despite research spanning many decades. Although deconditioning or cardiac impairment is believed to play an important role, the supporting data have been scanty.[40]

The recent development of noninvasive cardiac imaging techniques has led to increased recognition of valvular[16] as well as myocardial disease in AS.[17] In a study of 30 AS patients with no history of cardiorespiratory disease,[17] early diastolic abnormalities of the left ventricle were documented by echocardiography in 16 patients; this finding was reconfirmed a year later in 15 of them. Whether the apparently high prevalence of cardiac diseases in AS has a major impact on exercise tolerance is little known, however.

Previous studies in chapter 2 have confirmed that AS patients perceive greater magnitude of breathing effort than normal individuals during everyday activities. It would be of clinical value to assess whether the higher intensity of breathing effort

among AS patients limits their exercise tolerance and also to explore the possible relation between exertional dyspnoea and diminished chest expansion and impaired lung volumes.

Therefore, the present study was aimed to :

1) Systematically evaluate the degree of perceived exertional dyspnoea and its possible relation with chest restriction and altered resting lung volumes in AS patients.
2) Comprehensively examine the cardiorespiratory response to exercise in AS patients.
3) Comprehensively examine the mechanism(s) responsible for exercise limitation in AS patients.

4.2 Methods

Subjects

The appropriate sample size for the present study could not be predefined with confidence in view of the involvement of multiple outcome variables. Nonetheless, a total sample size of 40 was considered adequate for the purposes of the study. 20 AS patients and 20 age-and gender-matched healthy volunteers were recruited in a similar manner as in the previous study (chapter 3.2). Exclusion criteria were as described in chapter 2.3.1. Clinical characteristics of the two groups are summarised in Table 4.1.

Chest Expansion and Pulmonary Function Measurements

Chest expansion (CE), static lung volumes, airway resistance (Raw) and diffusing capacity of the lungs for carbon monoxide (DLco) were measured using the

techniques and reference values as described in chapter 3.2.

In addition, maximum voluntary ventilation (15-s MVV) was measured, using a pneumotachograph. Each subject produced 3 efforts seperated by a minimum of 3-minute rest. The highest value was chosen for the subsequent calculation of breathing reserve (BR), as following : $BR = [\ 1-V_Emax/MVV\ ]\times 100\ \%$.

All pulmonary function tests were carried out within one week prior to exercise testing. Pulmonary function data are presented in Table 1.

Cardiopulmonary Exercise Testing (CPX)

a) Apparatus (Figure 4.1)

Subjects were familiarised with the apparatus prior to the actual testing. CPX was performed on an electrically braked cycle ergometer (Cardiokinetics Ltd, UK) with the subject breathing through a low dead space (35 ml), low resistance valve box. The valve box incorporated a turbine ventilometer in the inspired limb for measuring ventilation. Expired gas was collected in an 8-L mixing chamber and analysed for O_2 and CO_2 contents by an infra-red spectrometer and a paramagnetic analyser, respectively (PK Morgan Ltd, UK). The output of the ventilometer and gas analysers were processed by an online microcomputer (PK Morgan Exercise Test System) giving continuous recording of O_2 uptake (VO_2), CO_2 production (VCO_2), inspired minute ventilation (V_E) and breathing frequency (f). Electrocardiogram (ECG) was monitored throughout the test.

b) Monitoring of blood gases during exercise

Transcutaneous O_2 and CO_2 tensions ($tcPO_2$ and $tcPCO_2$) were monitored using a combined O_2/CO_2 transcutaneous electrode(TINA electrode, Radiometer Ltd,

Copenhagen) and its monitoring system (TCM3)(Figures 4.2 a and b). The electrode consists of a Clark polarographic electrode that measures O_2 and modified Severinghaus glass pH electrode integrated into a single unit that can be applied directly to the skin.[110] The unit also incorporates a thermostatically controlled heater which promotes local hyperaemia, enabling O_2 and CO_2 levels in cutaneous capillaries to approach arterial levels. The electrode was sited on the volar aspect of the forearm and allowed to settle, heating to 45°C. When stable reading was apparent (approximately 5 minutes), the baseline $tcPO_2$ and $tcPCO_2$ were recorded. In a recent study,[35] a combined transcutaneous O_2 and CO_2 electrode has been shown to provide a reliable noninvasive estimate of gas exchange during exercise provided a maximal permissible temperature is attained (45°C), together with gradual stepups in workload at 2 minute intervals.

c) Protocol for exercise testing

The subjects were seated on the ergometer, and monitored at rest for two mins. to establish a steady state. They then began pedalling at a work rate of 25 watts(W) at a speed of 40-50 rpm. Thereafter the load was increased by 15-25 W every two mins. to symptom limitation (breathlessness, leg fatigue, chest pain). Work capacity (Wcap) was defined as the highest work rate sustained for at least 30 seconds. Exercise variables were measured and averaged over the last 30 seconds of each work load and at peak exercise. VO_2 and VCO_2 were corrected to standard temperature and pressure, dry (STPD). Exercise parameters were compared with reference values of of Jones.[111] Anaerobic threshold (AT) was derived by the V-slope method.[38] Since the typical 90 % response time is 30 seconds for the O_2 electrode and 60 seconds for

the CO_2 electrode,[112] the $tcPO_2$ and $tcPCO_2$ readings were taken at the end of each work rate. These values allowed the calculation of alveolar-arterial O_2 pressure difference [$P(A\text{-}a)O_2$] and physiological dead space-tidal volume ratio (V_D/V_T), using standard formulae[113] as follows :

$$P_AO_2 \text{ (mmHg)} = FIO_2 \times (P_B\text{-}47) - PaCO_2/R \text{ , and}$$

$$P(A\text{-}a)O_2 = P_AO_2 - PaO_2$$

where P_AO_2 is the ideal alveolar O_2 pressure; FIO_2 is the fraction of inspired O_2, dry; P_B is barometric pressure in mmHg; R is the gas exchange ratio; PaO_2 and $PaCO_2$ refer to arterial O_2 and CO_2 pressures, determined transcutaneously as described above.

$$V_D/V_T = (PaCO_2\text{-}PECO_2)/PaCO_2 - V_{DM}/V_T$$

where $PECO_2$ is mixed expired PCO_2; V_{DM} is mechanical dead space in litres; V_T is tidal volume in litres.

Evaluation of Breathlessness Leg Fatigue

The modified Borg category scale[114](Figure 4.3)was used to rate the intensity of breathlessness and leg fatigue perceived during exercise. Simple verbal expressions were linked to numbers from 0 to 10, zero being no appreciable breathlessness or leg fatigue and 10 being maximum. Full explanations were given prior to the test and the scale was hung in front of the subject printed on a large sheet of paper. During the CPX, the subject was instructed to estimate the breathing effort (breathlessness score, BS) at the end of each work load by pointing to the corresponding number on the chart. In order to avoid any bias on the part of the investigator, no further clarification was given unless requested. However, care was taken to instruct the subject only to rate

the breathing effort and not other sensation during exercising. At peak exercise, the subject was asked to give BS as well as leg fatigue score (LS). BS values so obtained allowed the changes in magnitude of breathlessness in relation to work rate($\Delta BS/\Delta WR$), ventilation ($\Delta BS/\Delta V_E$), and oxygen uptake expressed as per cent predicted maximum [$\Delta BS/\Delta VO_2$(%pred.max)] to be examined.

Statistical Methods

Values are presented as mean (SD) or mean (SEM) as appropriate. Comparisons of categorical variables between the AS and control groups were made using Chi squared test with Yates' correction. Wilcoxon signed-rank matched-pairs test was used to evaluate the differences between the two groups with respect to baseline lung function, and various physiological variables. Relationships between $\Delta BS/\Delta V_E$ and chest expansion, lung volumes, breathing frequency (f), and tidal volume at peak exercise as a per cent of VC ($V_T max/VC$) were assessed, using Pearson's correlation coefficients. The slopes of $\Delta BS/\Delta WR$, $\Delta BS/\Delta V_E$, and $\Delta BS/\Delta VO_2$(%pred.max) were expressed as means of slope from linear regression analysis of each subject's data according to the " standard two stage " method.[115] Statistical significance was assessed at 5 % level.

4.3 Results

Pulmonary Function Results (Table 4.1)

VC and TLC were significantly smaller in the AS group averaging 78 % and 86 % predicted values, respectively. The AS subjects achieved significantly lower

MVV with a mean of 106 $L \cdot min^{-1}$ but Raw and DLco were within normal ranges.

Work Capacity and Symptoms Associated with Exercise (Table 4.2)

The AS subjects achieved lower work capacity averaging 123 W compared with 148 W in controls (p=0.01)(Figure 4.4 a). Total exercise time was significantly shorter in the AS group (p=0.008)(Figure 4.4 b). VO_2max was significantly lower in the AS group with a mean of 25.2 $ml \cdot kg^{-1} \cdot min^{-1}$(75 % predicted). The majority of the subjects in both groups ceased exercising on account of leg fatigue. Leg fatigue scores (LS) reported by the AS subjects were higher than those reported by the control subjects (p=0.003)(Figure 4.5 a). Mean breathlessness scores (BS) at peak exercise were comparable between the two groups(Figure 4.5 b). However, mean slopes of $\Delta BS/\Delta WR$, $\Delta BS/\Delta V_E$, and $\Delta BS/\Delta VO_2$(% pred.max) were steeper in the AS group (p=0.03, 0.01 and 0.01, respectively), indicating higher intensity of breathing effort perceived among the AS subjects for equivalent levels of work rate, ventilation, and O_2 uptake achieved (Figures 4.6 and 4.7). No subjects experienced or ceased exercising due to chest pain.

Relation between Exertional Dyspnoea and Physiological Variables

As the slopes of $\Delta BS/\Delta V_E$ were steeper than the slopes of $\Delta BS/\Delta WR$, the former were used to explore the possible relation between exertional dyspnoea and CE, resting lung volumes, f, and $V_T max/VC$) in the AS subjects. However, there were no significant linear correlations between $\Delta BS/\Delta V_E$ and any of these variables. Correlation coefficients (r) between $\Delta BS/\Delta V_E$ and CE = 0.05, VC(%) = 0.08, RV (%) = 0.13, FRC (%) = 0.15, TLC (%) = 0.06, f = 0.28 and VTmax/VC = 0.25 (all p values > 0.05).

Ventilatory Response to Exercise

Baseline respiratory variables were comparable between the two groups (Table 4.3). Table 4.4 shows respiratory variables at peak exercise in the two groups. When compared with the controls, the mean $\Delta V_E/\Delta VCO_2$ in the AS subjects was significantly higher (p=0.01)(Figure 4.8 a). Importantly, both the AS group and the controls developed a fall in V_D/V_T and there was no major change in $P(A\text{-}a)O_2$ in either group. Also, their breathing reserve remained adequate(40 %). Peak-exercise V_E was higher in the control group but this did not reach statistical significance (p=0.55). At peak exercise, mean tidal volume in the AS group was significantly smaller (p=0.003) and was accompanied by a higher mean breathing frequency (p=0.03) when compared with the control group, indicating a tendency of the AS subjects to reach a high level of ventilation by increasing breathing frequency.

Cardiocirculatory Response to Exercise

At rest, mean heart rate was higher in the AS group than controls, albeit not statistically significant (p=0.12)(Table 4.3).

At peak exercise, the AS subjects achieved a mean heart rate of 85 % predicted and their blood pressure response was normal. Heart rate response to aerobic uptake ($\Delta HR/\Delta VO_2$) was significantly higher in the AS group (p=0.008) (Figure 4.8 b). Although when compared with the control group the AT and O_2 pulse at peak exercise in the AS subjects measured significantly lower (p=0.001)(Figure 4.9), their mean values were still within physiological ranges (AT = 44 % predicted VO_2max[111] and O_2 pulse = 95 % predicted normal[140]).

Oxygen pulse values at submaximal exercise in the AS group were constantly lower than those in the control group (Figure 4.10).

4.4 Discussion

The present study has shown that effort tolerance in AS patients without cardio-respiratory disease is considerably curtailed, the main limiting factor being musculo-skeletal deconditioning. Although the ventilatory response to exercise in the AS group was raised, their breathing reserve remained adequate and gas exchange indices normal. The heart rate response to aerobic uptake was higher in the AS group; however, other cardiocirculatory variables were within physiological ranges. Thus, the elevated heart rate response appears to reflect a relative lack of physical fitness among the AS patients rather than an intrinsic cardiac pathology. Several points merit discussion.

Pulmonary Gas Exchange in Ankylosing Spondylitis

Criticisms may be made on the calculation of gas exchange indices based on the $tcPO_2$ and $tcCO_2$ values in this study. The ease of use and reliability of a combined O_2 and CO_2 transcutaneous electrode have led to increasing clinical applications in the critical care setting,[116] in exercise testing,[117] and in sleep studies.[118] By adopting a protocol with two minute workload increments and allowing the electrode to heat to 45°C, it has been shown to provide a valid estimate of gas exchange during exercise testing across the range of apparently normal persons to those with advanced cardio-respiratory diseases.[35] The accuracy of the transcutaneous electrode monitoring system is further enhanced by initial *in vivo* calibration.[35] However, in the present study it was apparent that the $tcPO_2$ and $tcPCO_2$ values in both groups of subjects were

within the normal physiological ranges and direct arterial sampling would be difficult to justify in the control group; consequently, initial *in vivo* calibration of the trans-cutaneous electrode was deemed unnecessary.

The findings of a physiological fall in V_D/V_T, together with a lack of pathological widening in $P(A\text{-}a)O_2$, in the present study indicate that there is not a major gas exchange problem among the AS subjects. This finding agrees with the finding of Miller & Sproule,[53] who observed normal $P(A\text{-}a)O_2$ and V_D/V_T in 12 AS patients. However, the finding differs from that of Renzetti *et al*,[39] who reported increased V_D/V_T and significant arterial oxyhaemoglobin desaturation at rest and on exercise in most of the 12 AS subjects. The discrepancy may result from the differences in the methods used, and in the study populations. The subjects in the present study had no evidence of pulmonary parenchymal disease, as judged by recent chest radiograph.

Caution must be exercised when interpreting the finding of a higher V_Emax/VCO_2 in the AS group, as compared with the controls. V_E/VCO_2 is a good overall determinant of the efficiency of the lung as a gas exchange unit. Normally at maximal exercise the value ranges from 25 to 35.[31,141] Patients with gas exchange abnormality typically produce a V_Emax/VCO_2 of greater than 40.[141] Although comparatively higher in the AS group, their V_Emax/VCO_2 values still fall within normal range. This exemplifies the fact that statistical significance does not equate clinical relevance.

Factors Limiting Exercise Tolerance in Ankylosing Spondylitis

The majority of the AS subjects achieved a maximum heart rate of 85 % pre-

dicted and a respiratory exchange ratio of 1.10, suggesting that they performed up to their physiological limits. Furthermore, in this study MVV was measured rather than derived from a predictive equation, thus yielding accurate information on the breathing reserve of the individual subject.

Martinez *et al*[119] recently highlighted the limitation of a cardiopulmonary exercise test in seperating cardiac limitation due to disease from deconditioning. Further, in the deconditioned patients, it is a cardiac limitation to exercise performance which determines endpoint. Nonetheless, in the current study, the anaerobic threshold and oxygen pulse among the AS patients by falling within the lower end of normal ranges indicate that the exercise intolerance was not due to cardiac disease.

The mean resting heart rate was higher in the AS group than controls, although not reaching statistical significance. This could be evidence of deconditioning. More importantly, the configuration of oxygen pulse at submaximal exercise among the AS patients (Figure 4.10) strongly indicates an element of deconditioning rather than cardiac disease, as the latter would have produced a flat response.

The raised heart rate response to aerobic uptake should reflect the relative lack of physical fitness in this group of subjects. This is further supported by the higher degree of leg effort perceived at peak exercise among the AS subjects despite achieving lower work capacity. On the basis of these findings together with the normal breathing reserve and gas exchange, it is evident that deconditioning was the major factor limiting exercise tolerance in the AS subjects.

It is noteworthy that the anaerobic threshold, determined noninvasively, in the AS subjects measured significantly lower than in the control group although the abso-

values still averaged > 40 % predicted VO_2max. Nonetheless, this finding indicates that the aerobic metabolism among the AS subjects was supplemented by anaerobic processes earlier than in the controls, implying a lack of aerobic fitness. Moreover, the resultant lactic acid accumulation is likely to contribute to the greater degree of leg fatigue perceived among these patients.

Exertional Dyspnoea in Patients with Ankylosing Spondylitis

While a visual analogue scale (VAS) was used in the assessment of dyspnoea in chapter 2.3, the Borg scale for ratings of perceived exertion was employed in the present study. The rationale behind this is based largely on the findings by Wilson *et al*[120] that, during exercise testing, the Borg scale is more reproducible, and also correlated with the level of ventilation more closely than the VAS. The greater degree of dyspnoea on exertion in th AS group, as reflected by steeper slopes of $\Delta BS/\Delta WR$, $\Delta BS/\Delta V_E$, and $\Delta BS/\Delta VO_2$, corroborated the previous findings in chapter 2. Since the majority of the AS subjects ceased exercising owing to muscular deconditioning and did not reach a similar level of work rate or ventilation of the control subjects, peak-exercise breathlessness scores were comparable between both groups.

The extent of shortening of the inspiratory muscles as indirectly indicated by the tidal volume at peak exercise as a per cent of vital capacity, and the frequency of contraction, as indicated by breathing frequency, have been found to contribute independently to the sensation of exertional dyspnoea in patients with a variety of cardiorespiratory diseases.[85,121] Data from the present study, however, did not reveal any strong association between the magnitude of exertional dyspnoea and CE, V_Tmax/VC, f, and resting lung volumes among the AS patients.

The present study suffers from some limitations. The use of expired gas mixing chamber did not allow assessment of the possible influence of duty cycle (inspiratory duration as a proportion of total breath time) on the sensation of exertional dyspnoea.[28] Furthermore, the lack of simultaneous measurements of mouth pressure and peak inspiratory flow during exercise precluded a direct assessment of the relation between respiratory muscle tension and ratings of exertional dyspnoea.[121]

Nevertheless, the findings from the present study suggest that the severity of chest restriction, the impairment in resting lung volumes, and the magnitude of exertional dyspnoea are seperate quantities which independently characterise the condition of patients with ankylosing spondylitis and that the warning of Campbell & Howell[122] should still be heeded.

Summary of Findings

1 Aerobic power and work capacity are commonly reduced in patients with ankylosing spondylitis (AS), the major limiting factor being musculoskeletal deconditioning.

2 Despite an elevated ventilatory response to exercise when compared with controls, breathing reserve remains adequate and pulmonary gas exchange normal in patients with AS.

3 Relative to age-and gender-matched controls, heart rate response to aerobic uptake in AS patients is raised; however, other cardiocirculatory variables are appropriate to exercise level. Thus, the raised heart rate response to exercise reflects a lack of physical fitness among AS patients.

4 Relative to age-and gender-matched controls, patients with AS perceive a greater degree of leg fatigue on exertion, implying an element of muscular deconditioning.

5 During exercise, aerobic energy production in AS patients is supplemented by anaerobic processes earlier than in matched healthy individuals, indicating a relative lack of aerobic fitness. The resultant lactic acid accumulation may in part account for the greater degree of leg fatigue perceived among AS patients.

6 Relative to age-and gender-matched controls, patients with AS perceive a greater magnitude of exertional dyspnoea, corroborating the findings in the previous studies. However, dyspnoea is not the major symptom limiting exercise tolerance in AS.

7 The heightened perception of exertional dyspnoea, the impaired resting lung volumes, and the severity of chest restriction in AS are unrelated and represent seperate quantities which characterise the condition of patients with AS.

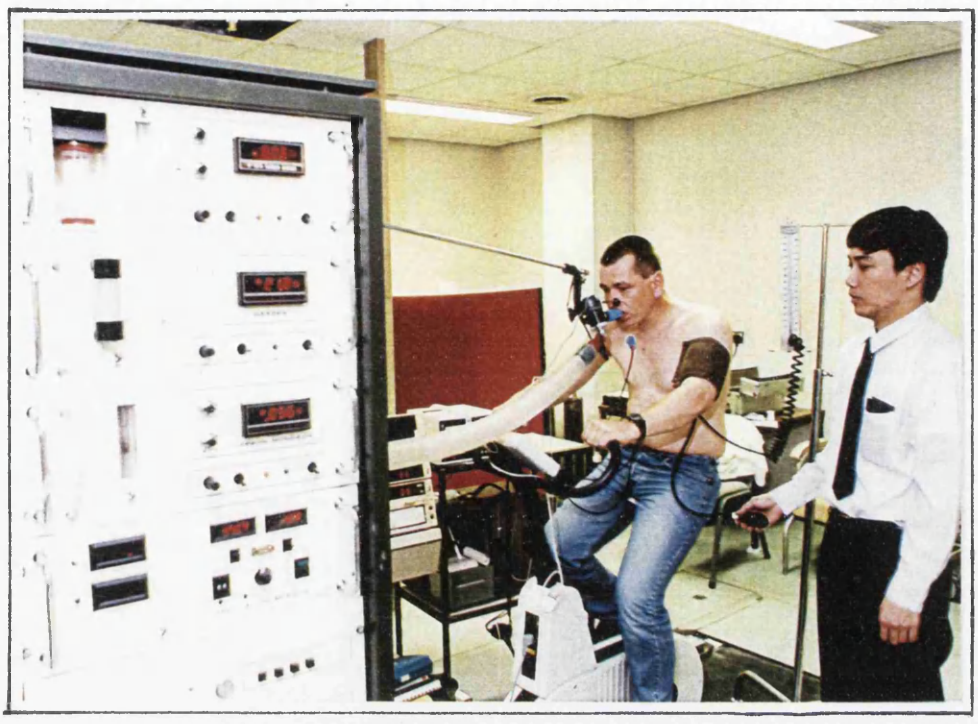
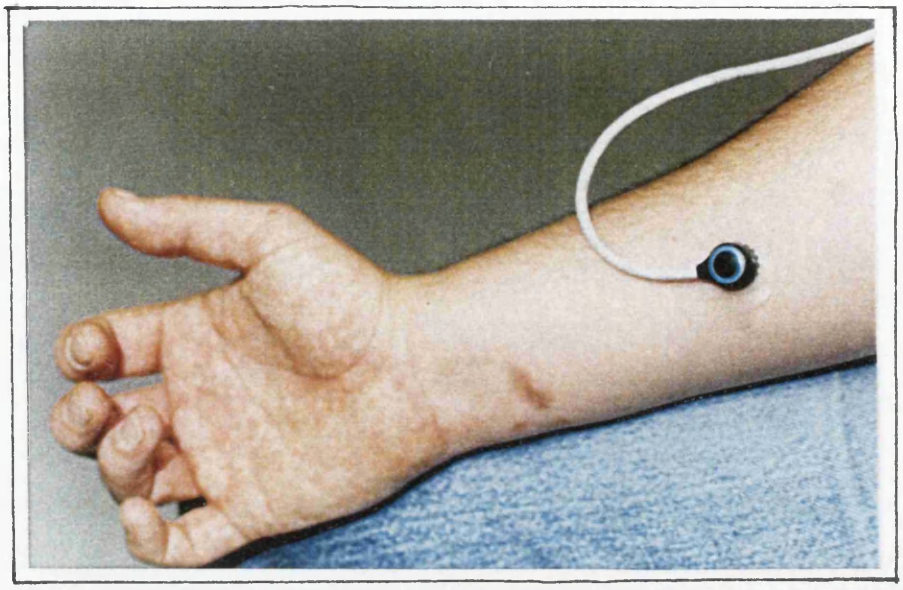


Figure 4.1 *Cardiopulmonary exercise testing. The subject cycles on a stationary, electrically-braked ergometer. An on-line ventilation and expired gas analyzer is seen on the left-hand side. Electrocardiogram and trans-cutaneous PO_2 and PCO_2 are continuously monitored. Blood pressure is manually measured at baseline and peak exercise.*

(With kind permission from the subject)

a)



b)

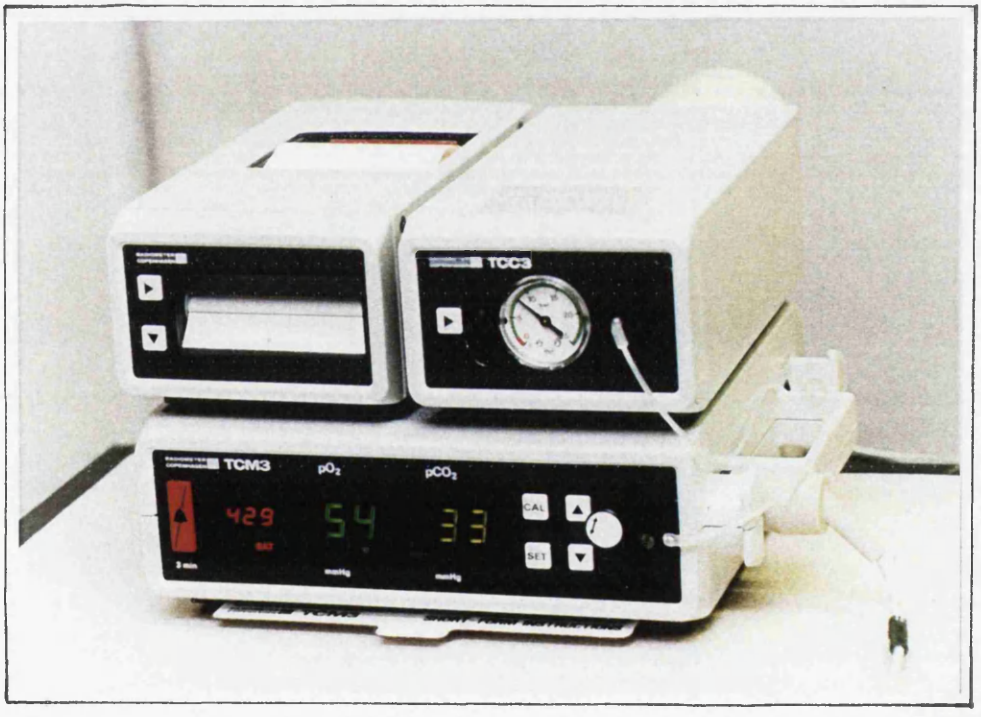


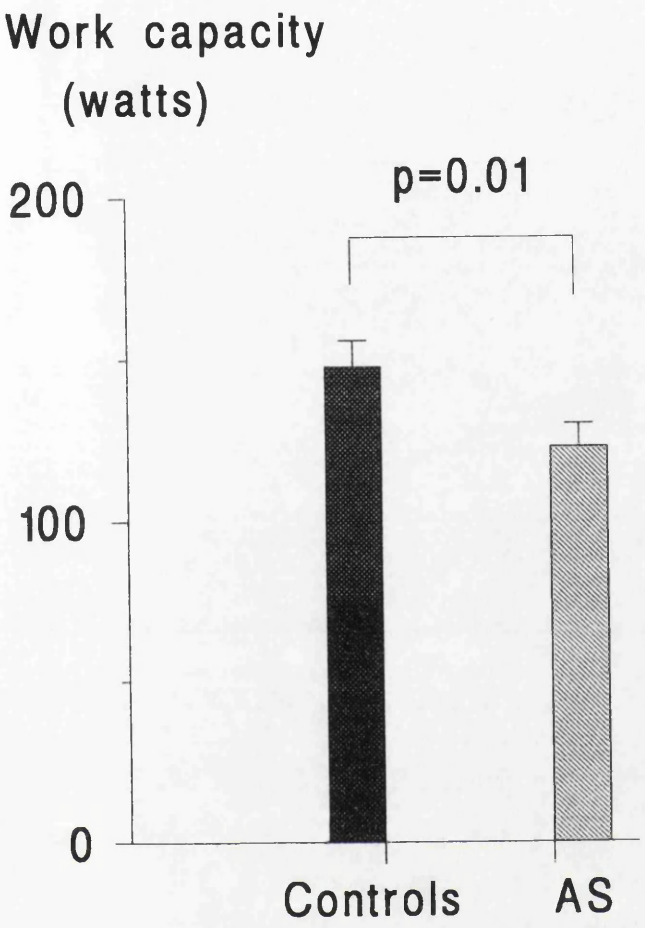
Figure 4.2 *a) A combined O_2 and CO_2 transcutaneous electrode, sited on the volar aspect of the forearm.*

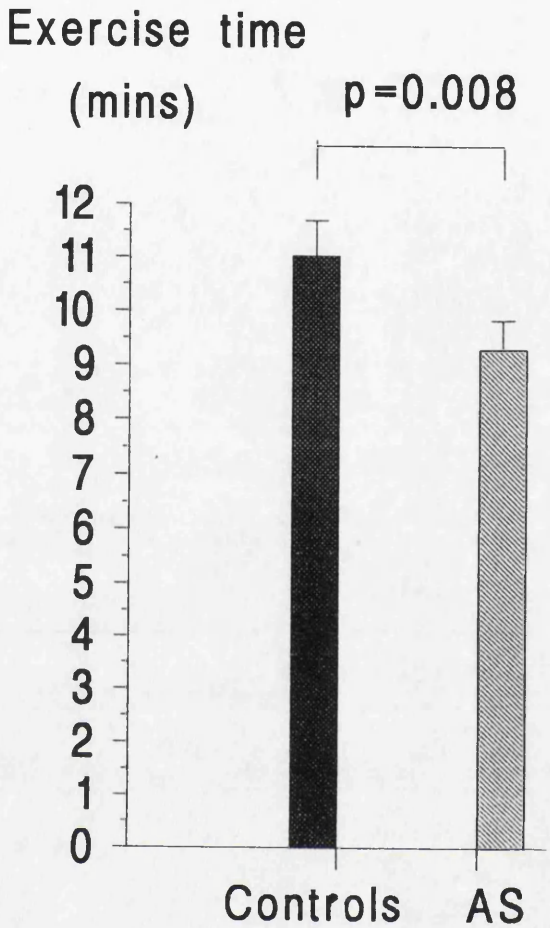
b) Transcutaneous PO_2 and PCO_2 calibration and monitoring units.

0	Nothing at all
0.5	Very very slight
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very very severe
10	Maximal

Figure 4.3 *Modified Borg scale for Rating of Perceived Exertion.*

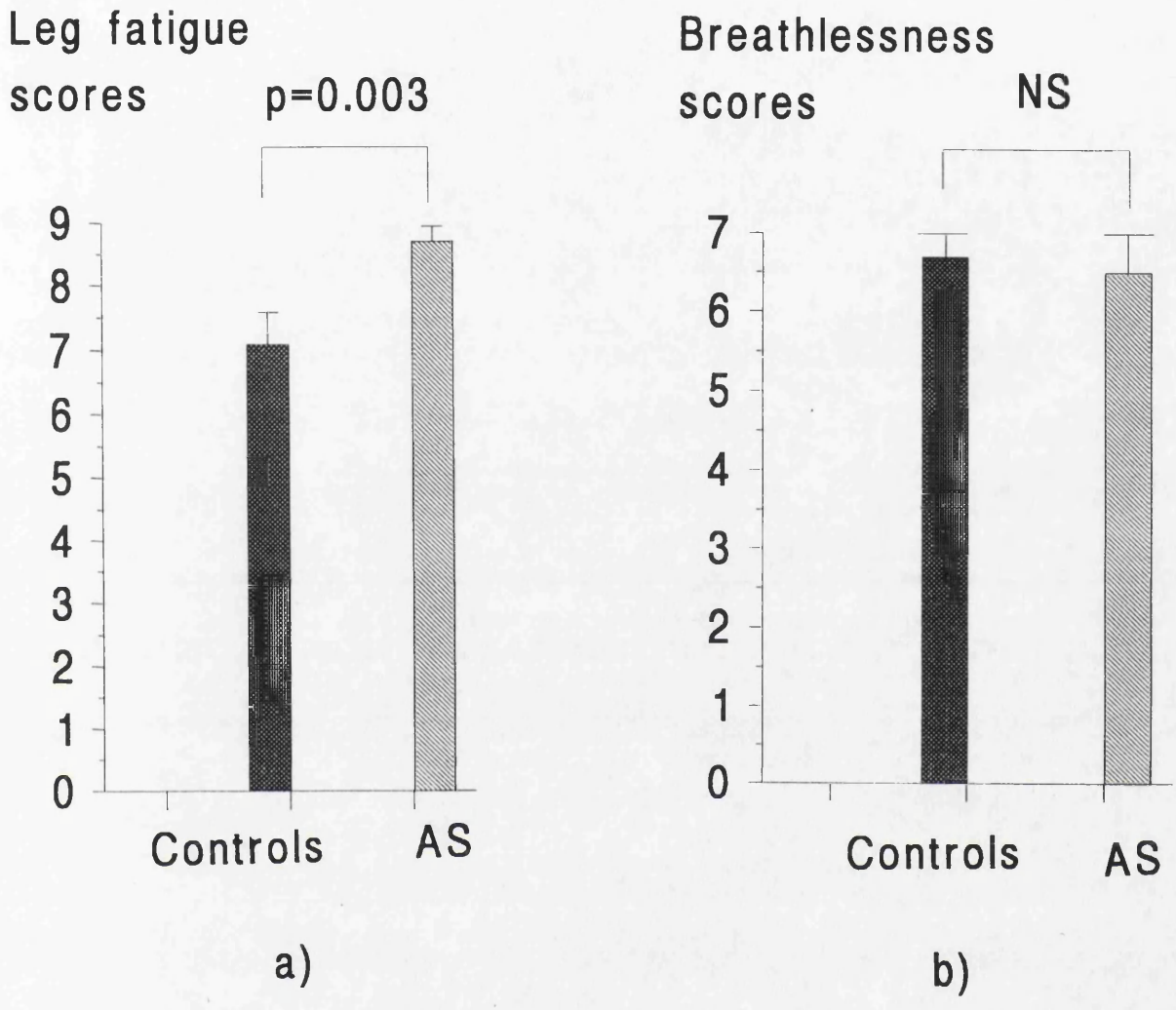
(From reference [114])





Figures 4.4 *Comparisons of a) Work capacity b) Total exercise time between 20 AS patients and 20 matched controls*

Bars represent SEM



Figures 4.5 *Comparisons of a) Leg fatigue scores b) Breathlessness scores between 20 AS patients and 20 matched controls*

NS = not statistically significant

Bars represent SEM

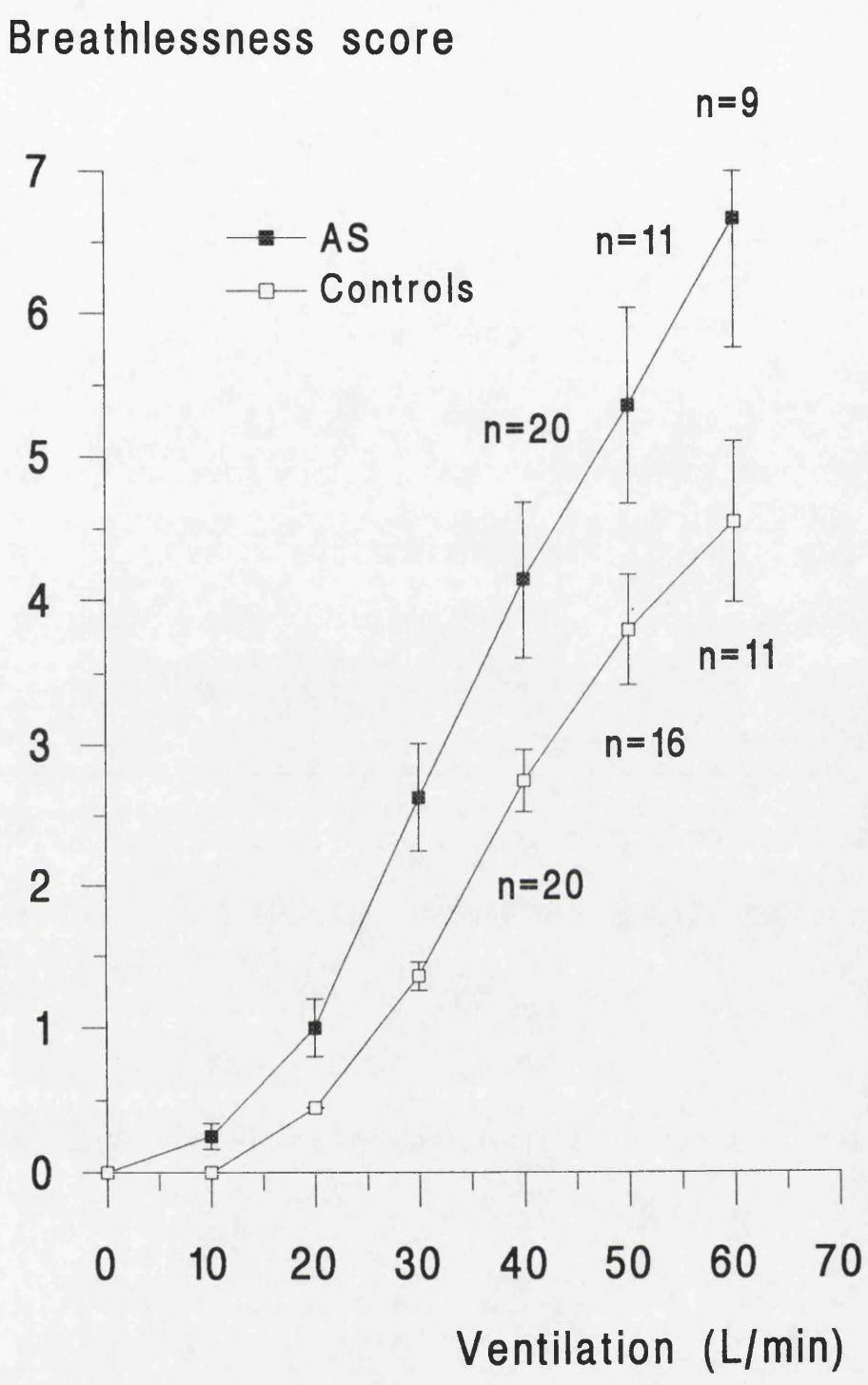


Figure 4.6 *Comparison of $\Delta BS/\Delta V_E$ between the AS and control subjects. Each square represents a mean of data from 20 subjects unless specified otherwise. Bars represent SEM.*

The mean slope of $\Delta BS/\Delta V_E$ was significantly steeper in the AS group ($p=0.01$)

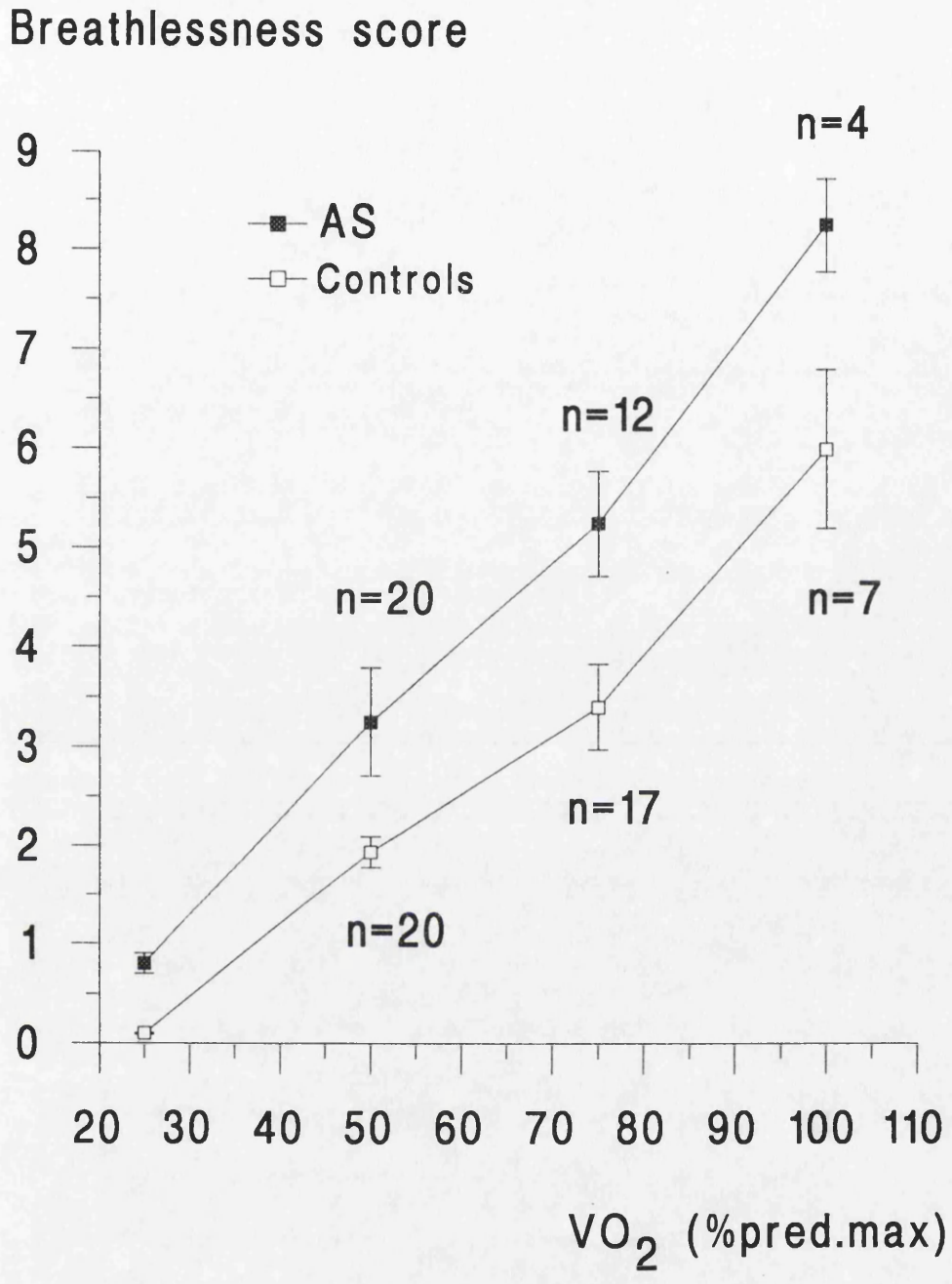
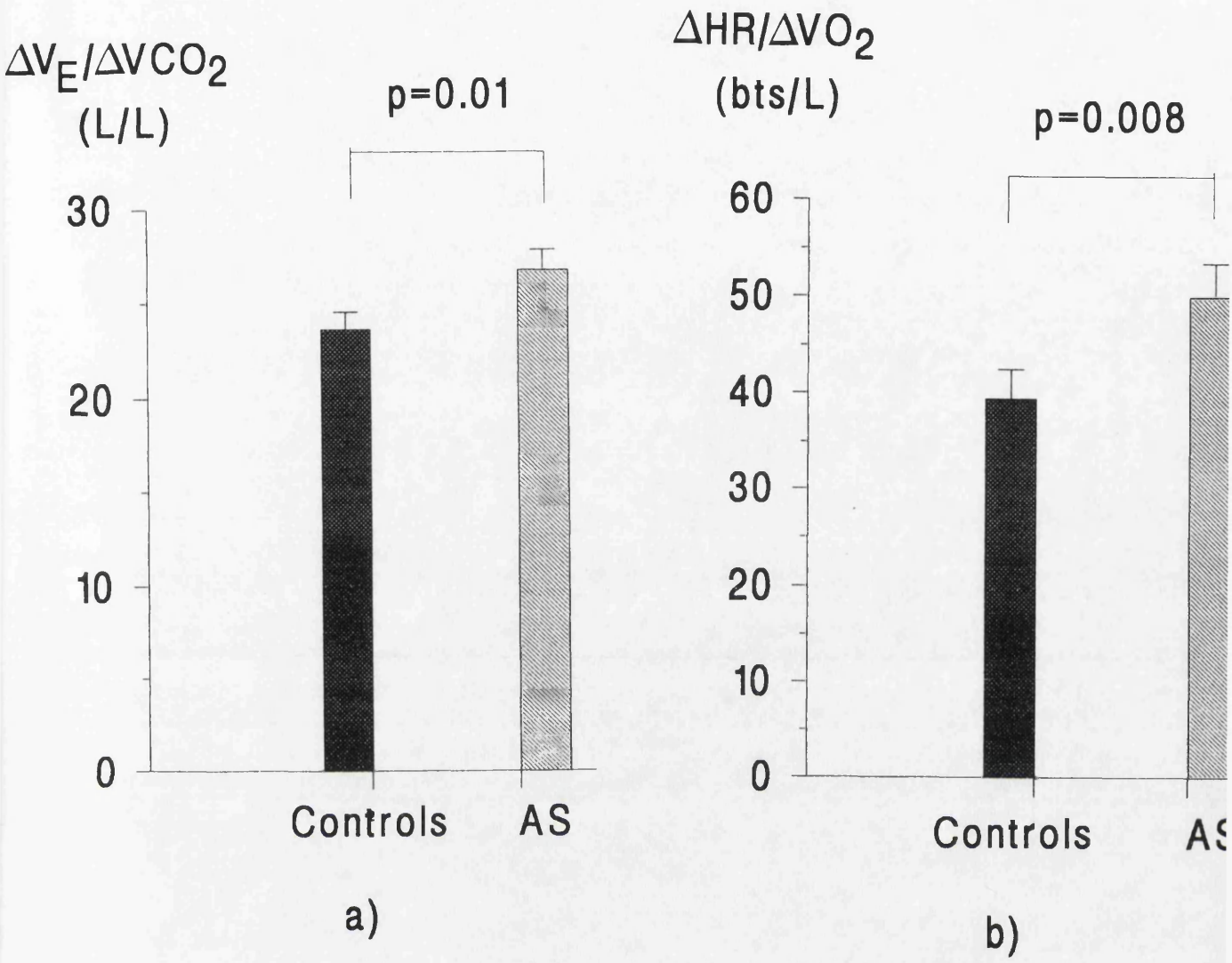


Figure 4.7 *Comparison of $\Delta BS/\Delta VO_2max$(expressed as % pred.max) between the AS and control subjects.*

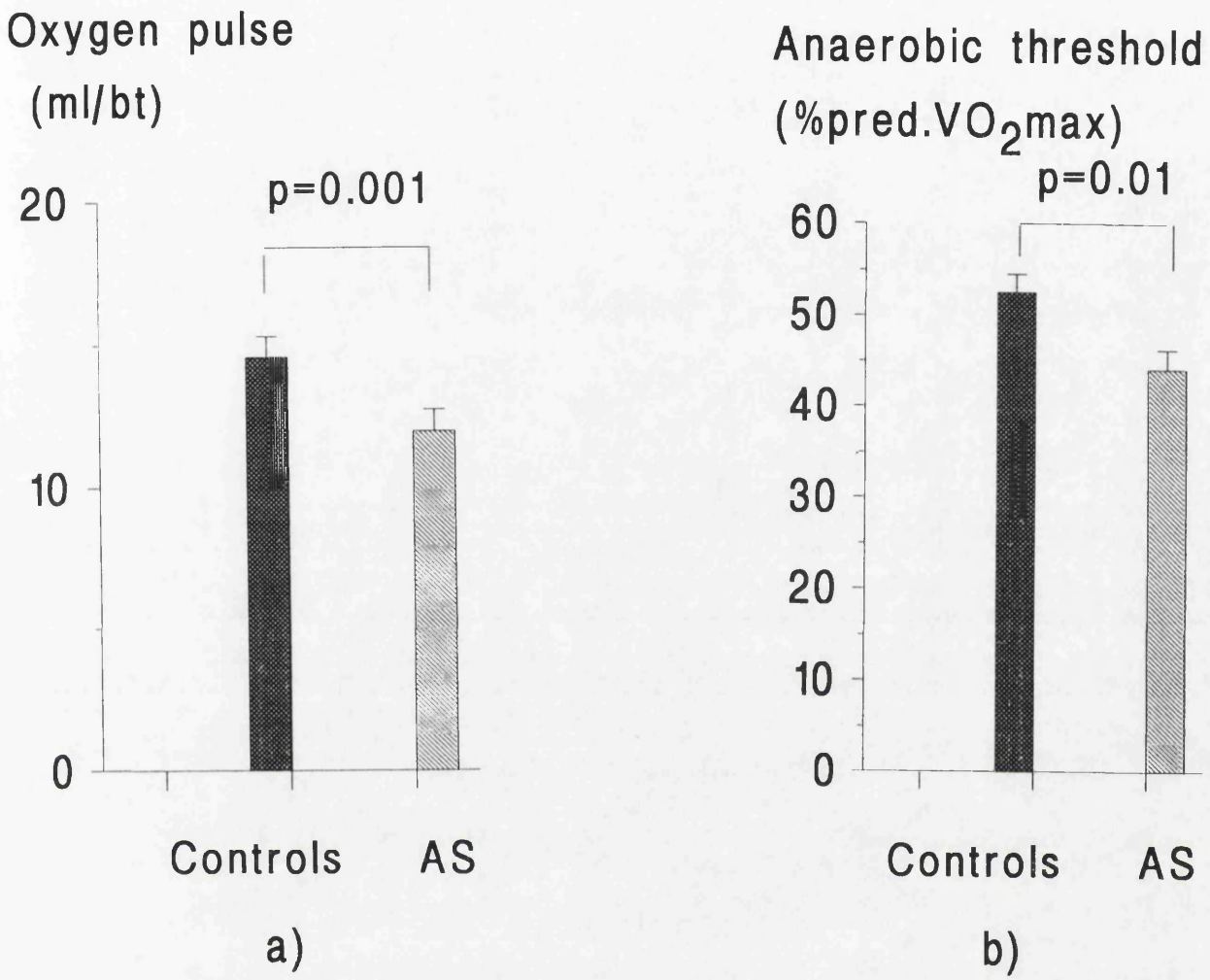
Each square represents a mean of data from 20 subjects unless specified otherwise. Bars represent SEM.

The mean slope of $\Delta BS/\Delta VO_2max$ was significantly steeper in the AS group ($p=0.01$)



Figures 4.8 *Comparisons of a) Ventilatory response b) Cardiac response to exercise between 20 AS patients and 20 matched controls*

Bars represent SEM



Figures 4.9 *Comparisons of a) Oxygen pulse at peak exercise and, b) Anaerobic threshold between 20 AS patients and 20 matched controls*

Bars represent SEM

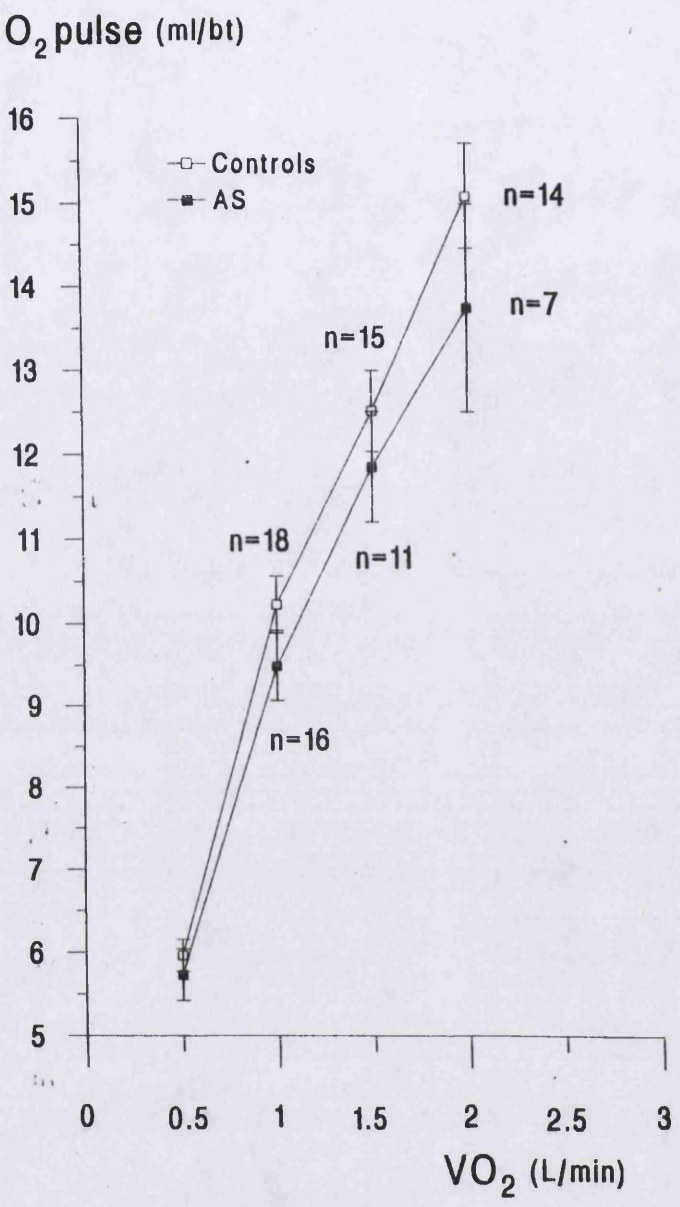


Figure 4.10 *Comparison of oxygen pulse at submaximal exercise between the AS and control subjects.*

Each square represents a mean of data from 20 subjects unless specified otherwise. Bars represent SEM.

Few subjects in each group attained VO_2 greater than 2.0 L/ min; accordingly, data points at VO_2 of 2.5 and 3.0 are not shown.

Table 4.1

Clinical characteristics and Pulmonary function data of 20 AS and 20 matched controls in the exercise study *

	Controls (n = 20)	**AS subjects (n=20)**
Age , yrs	46.4 (12.2)	46.5 (12.3)
Gender , male : female	13 : 7	13 : 7
Exercisers : Non-exercisers	9 : 11	13 : 7
Smokers : Non-smokers	7 : 13	9 : 11
Body mass index , $kg \cdot m^{-2}$	25.3 (2.7)	26.1 (4.6)
VC , % predicted	106 (18.9)	78 (12.0) #
FRC , % predicted	115 (21.7)	122 (38.6)
RV , % predicted	103 (25.1)	110 (30.1)
TLC , % predicted	104 (15.3)	86 (15.3) +
Raw , $kPa^{-1} \cdot sec^{-1} \cdot L^{-1}$	0.15 (0.05)	0.15 (0.04)
DLco , % predicted	not measured	98.0 (23.7)
MVV , $L \cdot min^{-1}$	133 (6.6)	106 (7.4) +

* Values are mean (SD)

+ $p = 0.001$

# $p < 0.001$

Table 4.2

Metabolic variables and Symptom scores at peak exercise *

	Controls (n=20)	AS subjects (n=20)
VO_2max, $L \cdot min^{-1}$	2.31 (0.12)	1.82 (0.13) #
VO_2max, $ml \cdot kg^{-1} \cdot min^{-1}$	33.1 (1.6)	25.2 (1.4) #
, % predicted	93 (3.7)	75 (3.9) #
Work capacity, watts	148 (8.2)	123 (7.1) ++
VCO_2max, $L \cdot min^{-1}$	2.54 (0.12)	2.00 (0.15) #
R	1.10 (0.01)	1.10 (0.02)
BS	6.7 (0.5)	6.5 (0.6)
LS	7.1 (0.5)	8.7 (0.3) #
$\Delta BS/\Delta WR$	0.043 (0.003)	0.054 (0.005) +
$\Delta BS/\Delta V_E$	0.115 (0.012)	0.147 (0.012) ++
$\Delta BS/\Delta VO_2$(% pred.max)	0.045 (0.003)	0.084 (0.009) #

* Values are mean (SEM)

+ $p = 0.03$

++ $p = 0.01$

# $p < 0.01$

Table 4.3

Cardiorespiratory variables at baseline *

	Controls n = 20	AS subjects n = 20
HR, bts·min^{-1}	73 (1.8)	78 (2.6)
BP systolic, mmHg	109 (3.0)	116 (2.8)
BP diastolic, mmHg	67 (2.1)	69 (1.8)
f, breaths·min^{-1}	14 (0.5)	16 (0.3)
V_T, L	0.41 (0.02)	0.45 (0.02)
V_E, L	5.74 (0.10)	7.2 (0.25)
$tcPO_2$, mmHg	89 (1.0)	88 (2.1)
$tcPCO_2$, mmHg	37 (0.9)	36 (0.7)
V_D/V_T	0.33 (0.02)	0.35 (0.01)
$P(A\text{-}a)O_2$,mmHg	12 (1.7)	15 (1.8)

* Values are mean (SEM)

Table 4.4

Respiratory variables at peak exercise *

	Controls (n=20)	AS subjects (n=20)
f , breaths·min^{-1}	30 (1.1)	35 (2.0) +
V_T , L	2.28 (0.11)	1.81 (0.13) #
$V_T$max/VC	0.50 (0.01)	0.51 (0.02)
V_E , L	68.1 (3.3)	63.2 (3.6)
$\Delta V_E/\Delta VCO_2$,L/L	23.7 (0.9)	26.8 (1.1) ++
BR , %	49 (2.2)	40 (2.0)
tcPO_2 , mmHg	94 (1.5)	91 (2.5)
tcPCO_2 , mmHg	41 (1.3)	39 (1.1)
V_D/V_T	0.19 (0.02)	0.22 (0.03)
P(A-a)O_2,mmHg	14 (1.4)	17 (2.4)

* Values are mean (SEM)

+ p = 0.03

++ p = 0.01

p = 0.003

Table 4.5

Cardiocirculatory variables at peak exercise *

	Controls (n=20)	**AS subjects (n=20)**
HRmax, bts·min^{-1}	161 (3.2)	153 (3.7)
, % predicted	92 (4.6)	85 (1.7)
BP systolic, mmHg	160 (3.0)	166 (6.8)
BP diastolic, mmHg	81 (2.0)	83 (2.4)
$\Delta HR/\Delta VO_2$, bts·L^{-1}	39.5 (3.0)	50.0 (3.5) ++
Oxygen pulse, ml·bt^{-1}	14.6 (0.7)	12.0 (0.8) #
, % predicted	120 (6.5)	95 (4.5) #
AT, L·min^{-1}	1.35 (0.05)	1.10 (0.06) #
, % pred VO_2max	52 (1.9)	44 (2.1) +

* Values are mean (SEM)

+ $p = 0.01$

++ $0.001 < p < 0.01$

$p = 0.001$

Chapter 5

Factors Influencing Aerobic Power among AS Patients

5.1 Introduction

The directly measured maximum oxygen uptake (VO_2max) is a highly reproducible measure of the individual's aerobic fitness. The VO_2max measures the capacity of the working muscles to utilise oxygen and thus reflects the integrated function of the oxygen transport system including the lungs and chest bellows, heart, blood and active muscles.

The exercise study in chapter 4 has confirmed that aerobic power in patients with ankylosing spondylitis (AS) is commonly curtailed. Although the ventilatory and heart rate responses to exercise were elevated among the AS patients, the main limiting factor appeared to be musculoskeletal deconditioning as reflected by a greater magnitude of leg fatigue perceived at peak exercise despite achieving a lower work capacity as compared with matched controls. Furthermore, the study in chapter 3 has revealed the presence of diminished respiratory muscle endurance among AS patients although the maximum respiratory muscle strength is relatively well-preserved.

Thus, exercise intolerance in AS patients may result from muscular as well as pulmonary impairment. However the relative contribution of these factors to reduction in aerobic power among AS patients has not been quantitively examined. Improved knowledge in this area would be of clinical importance both in understanding the pathophysiological basis of exercise limitation and in devising effective training/rehabili-

-tation strategies for sufferers from this condition.

The objectives of the present study were therefore to identify and determine the individual and additive influence of lung vital capacity, respiratory muscle strength and endurance, peripheral muscle strength, limited chest expansion, and reduced spinal mobility on aerobic power among AS patients.

5.2 Methods

5.2.1 Sample size determination & Subjects

Multiple regression analysis was used to assess the additive influence of various variables on VO_2max and the appropriate sample size was decided in advance. As a general rule, the number of explanatory variables in the regression model should not exceed the square root of the sample size.[123] Five variables were defined as explanatory variables of primary importance in the design stage of the study *(see below)*. Accordingly, a total sample size of 25 was considered necessary.

25 patients with definite AS were recruited as described in the previous studies. Exclusion criteria were as described in chapter 2.3.1. The majority of the subjects were those who participated in the exercise study (chapter 4). The subjects were classed as exercisers/non-exercisers as described in chapter 2.2.1. Subject characteristics are presented in Table 5.1.

5.2.2 Outcome variable

The outcome (response) variable in this study was maximum aerobic power

(VO_2max), corrected for body weight, and expressed in $ml \cdot kg^{-1} \cdot min^{-1}$. It should be emphasised that *capacity* denotes total energy available whereas *power* means energy output per unit of time.

5.2.3 Potential explanatory variables

Based on the findings in the previous studies, a number of physiological variables appeared to potentially influence VO_2max among AS patients. Five variables were considered to be of primary importance, namely, vital capacity, maximal inspiratory pressure, respiratory muscle endurance, chest expansion, and maximum strength of the quadriceps.

In addition, it would be of interest to explore the relations between VO_2max and clinical indices of the extent/activity of the disease, namely, wall-tragus distance, the range of thoraco-lumbar movement, and erythrocyte sedimentation rate (ESR). The effects of age, height, and lean body mass would also be examined. Furthermore, the influence of regular exercise on VO_2max would be evaluated.

5.2.4 Measurements

VO_2max was determined, using symptom-limited incremental cycle ergometry as described in chapter 4.2.

Vital capacity (VC), maximal static inspiratory pressure (MIP), respiratory muscle endurance time (Tlim), and chest expansion (CE) were measured as described in chapter 3.2.

The total range of thoraco-lumbar (TL) movement in the sagittal plane was measured, using a spondylometer and expressed as degrees(°) as described previously.[124] Wall-tragus distance was used as an index of thoracic kyphosis and expressed in cms.

5.2.5 Assessment of peripheral muscle function

Peripheral muscle function was assessed by measuring both muscle strength (knee extensors and hand grip) and amount (lean body mass).

Knee extensor strength

The force of a maximal voluntary contraction of the knee extensors was measured by the method described by Edwards *et al*[125](Figure 5.1). The subjects sat upright in an adjustable, straight-backed chair with the lower leg dependent and the knee flexed to 90°. Adjustable straps were positioned around their waist and over both thighs, to prevent excessive movement during the manoeuvre. A cuff was placed around the leg just proximal to the malleoli and attached horizontally to an electrical strain gauge (Cranlea & Co., Birmingham, UK) with a digital read out. The subjects performed 3 maximal voluntary contractions at approximately one minute intervals. The greatest peak force achieved was recorded. Peak torque was calculated from the product of force and the distance between mid knee joint and mid point of the lower leg strap, expressed in Newton-metre (N-m). A coefficient of variation of 4 % and a mean difference in strength of 6 % between the right and left leg have been noted.[126] Since the quadriceps femoris is the principal muscle engaged in knee extension,[127] the maximum force is abbreviated Qds for clarity of discussion.

Hand grip strength

Right hand grip strength was measured, using a hand-held dynamometer (Takei Company, Japan) with a digital read out. Measurement was made with the subjects standing, legs slightly apart, and arms extended downward. Peak grip strength was recorded from the maximum of three efforts separated by one-minute intervals and expressed in kgW.

Lean body mass (LBM)

LBM was calculated from the sum of skinfold thicknesses at four sites, namely, biceps, triceps, subscapular, and supra-iliac regions as described by Durnin *et al*[128]and expressed in kilograms. This method has been validated against "underwater weighing" technique and a high correlation coefficient (0.9) and a low intra-observer error(3.5%) have been found.[128]

5.2.6 Statistical methods

Descriptive data are presented as means, SD, and range. Single linear regression was used to assess the relationships between VO_2max and various variables. The additive influence of explanatory variables on VO_2max was examined, using forward stepwise regression analysis. Comparison of VO_2max between exercisers/non-exercisers was performed directly and after adjusting for age. Level of probability was calculated from F or partial F values, and statistical significance was assessed at 5 % level. The proportion of variance accounted for by each relationship is reported as R^2 (%), and adjusted for the expected chance prediction when the null hypothesis is true (adj.R^2).[123]

5.3 Results

The 25 AS subjects exhibited a wide range of functional impairment and degree of spinal mobility as shown by the data in Table 5.1. The mean VO_2max was 26.06 $ml \cdot kg^{-1} \cdot min^{-1}$(75 % predicted). 15 subjects were classed as exercisers and 10 as non-exercisers.

5.3.1 Factors influencing aerobic power in AS

The individual influences of the main explanatory variables on VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) were as follows :

	VC (L)	**MIP** (cmH_2O)	**Tlim** (s)	**CE** (cm)	**Qds** (N-m)
adj.R^2 (%)	12	11.8	0	0	46.9
F	4.29	4.21	0.49	0.25	22.16
P-value	0.05	0.05	0.49	0.62	< 0.001

The influences of the other explanatory variables on VO_2max were as follows :

	Hand grip (KgW)	**LBM** (kgs)	**Age**	**Height**	**Wall-tragus distance**	**TL mobility**	**ESR**
adj.R^2 (%)	23.5	0	10.7	0	0	0	0
F	8.35	0.17	3.87	0.57	0.67	0.07	0.05
P-value	0.008	0.68	0.06	0.45	0.42	0.79	0.82

Relationship of aerobic power to pulmonary function in AS

There was a weak relationship between VC (L) and VO_2max which accounted for 12 % of the total variance (p=0.05). The association was stronger after controlling for age, as described by the following expression :

1) $VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 16.4 - 0.17\ age\ (yr) + 2.33\ VC\ (L)$

[adj.R^2 19.6 %, F 3.92, p 0.03, n 25]

It can be seen that the aerobic power decreased with advancing age. The addition of LBM, Ht, CE, Wall-tragus distance, TL mobility or ESR did not improve the total variance explained.

VO_2max was also weakly related to MIP (adj.R^2 11.8 %, p 0.05). The relationship was stronger after adjusting for the difference in age, as expressed by the following equation :

2) $VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 28.1 - 0.16\ age\ (yr) + 0.07\ MIP\ (cmH_2O)$

[adj.R^2 17.9 %, F 3.63, p 0.04, n 25]

The addition of VC, LBM, Ht, CE, Wall-tragus distance, TL mobility or ESR did not improve the prediction of VO_2max based on MIP.

Tlim was not significantly related to aerobic power either directly or after allowing for the differences in age, VC, LBM, Ht, CE, Wall-tragus distance, TL mobility or ESR ($p > 0.05$).

Relationship of aerobic power to chest expansion in AS

There was no direct association between aerobic power and CE. However, the two variables became related at 10 % level once accounting for the difference in age, as expressed by the following model :

3) $VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 42.0 - 0.24\ age\ (yr) + 1.45\ CE\ (cm)$

[adj.R^2 12.3 %, F 2.68, p 0.09, n 25]

The addition of VC, MIP, LBM, Ht, Wall-tragus distance, TL mobility or ESR did not improve the total variance explained.

Relationship between aerobic power and peripheral muscle strength in AS

Qds and Hand grip strength were closely related to VO_2max, accounting for 46.9 % and 23.5 % of the total variance ($p < 0.001$ and p 0.008, respectively). The relation between Qds and VO_2max can be described as follows :

4) $VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 14.7 + 0.10\ Qds\ (N\text{-}m)$

[adj.R^2 46.9 %, F 22.16, $p < 0.001$, n 25]

The above relationship is also shown in Figure 5.2. Since Qds was the single variable which exhibited the strongest association with VO_2max, other variables were added to the regression model 4) in a stepwise fashion in order to try and explain the largest amount of the remaining variability in VO_2max.

LBM was the best second variable; the addition of LBM into the model further improved to total variance explained to 73 %, as expressed by the following equation :

5) $VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 27.8 + 0.17\ Qds\ (N\text{-}m) - 0.39\ LBM\ (kg)$

[adj.R^2 73 %, Residuals SD 3.42, F 33.48, $p < 0.001$, n 25]

The multiple regression data for the above model is presented in Table 5.2. The total variance explained improved only marginally after controlling for age, as described by the following expression :

6) $VO_2max(ml \cdot kg^{-1} \cdot min^{-1}) = 31.7 + 0.16Qds\ (N\text{-}m) - 0.37LBM\ (kg) - 0.08age\ (yr)$

[adj.R^2 74.5 %, Residuals SD 3.33, F 24.4, $p < 0.001$, n 25]

It can be seen that LBM was inversely related to VO_2max since the latter was expressed in $ml \cdot kg^{-1} \cdot min.^{-1}$ When expressed in $L \cdot min^{-1}$, VO_2max was positively related to Qds and LBM as following :

7) VO_2max ($L \cdot min^{-1}$) = 0.378 + 0.011 Qds (N-m) + 0.005 LBM (kg)

[adj.R^2 78.3 %, Residuals SD 0.29, F 44.2, $p < 0.001$, n 25]

The prediction of VO_2max based on Qds and LBM did not improve further with the addition of VC, MIP, CE, Ht, Wall-tragus distance, TL mobility or ESR (adj.R^2 = 71.9, 72.1, 72.1, 71.9, 72.2, 72.1, 70.0 % respectively).

Effect of regular exercise on aerobic power in AS

The exercisers(n=15) and non-exercisers(n=10) did not differ with respect to aerobic power when the VO_2max values were compared directly (p = 0.48, Mann-Whitney U test). However, the effect of regular exercise became apparent after accounting for the difference in age, as described by the following expression :

8) VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) = 35.9 - 0.26 age (yr) + 4.36 Exercise ,

where exercise is a binary variable (Non-exerciser = 0, Exerciser = 1).

[adj.R^2 17.2 %, F 3.49, p 0.04, n 25]

Hence, after adjusting for age, the mean VO_2max was 4.36 $ml \cdot kg^{-1} \cdot min^{-1}$ higher in the group classed as exercisers (p = 0.04).

5.3.2 Validity of the regression model

Multiple linear regression, like other statistical procedures, makes certain strong assumptions including :

i) Independence in the observations.

ii) Random scatter of the points about the best-fitting line.

iii) Constant variability about the best-fitting line for the values of the explanatory variables.

In the present study, each observation was made independently. The following plots can be used to verify the assumptions ii) and iii) :

a) Normal plot of the residuals. Residuals are the differences between the observed values and the fitted values. A Normal plot of the residuals can be used to check the overall fit and verify that the residuals have an approximately Normal distribution. As shown in Figure 5.3, the Normal plot of the residuals from the regression model 5) is very straight, and provides no reason to question the validity of the analysis.

b) Residuals plot against the fitted values. No pattern should be discernable in this plot. As shown in Figure 5.4, the variability of the residuals from the regression model 5) appears reasonably constant across the range of the fitted values.

In addition, the observed values and the fitted values derived from the regression were highly correlated ($r = 0.86$, $p < 0.001$), as shown in Figure 5.5.

5.4 Discussion

The results from the current studies must be interpreted in the context of the severity of patients studied. These AS subjects clearly exhibited at least moderately advanced disease, as evident by a mean chest expansion of 2.0 cm, a mean wall-tragus distance of 16.9 cm, and a mean spondylometric measurement of 51°. The clinical implications therefore apply to those with a moderately advanced stage of disease.

The present study revealed that aerobic power in AS patients, without cardiac

or pulmonary parenchymal disease, was closely related to peripheral muscle function. Pulmonary impairment and the severity of chest restriction appeared to influence aerobic power only weakly. These findings therefore elaborate the findings from the previous studies (chapters 3 and 4).

As expected, advancing age exerts a significant influence on several physiological variables including vital capacity. (eq.1) and respiratory muscle strength (eq.2). Furthermore, the effects of chest restriction, and regular exercise became evident only after controlling for the differences in age (equations 3 and 8, respectively).

As anticipated during the design stage of the study, significant relationships were found between aerobic power and most of the explanatory variables of primary importance with the exception of Tlim. As described in chapter 3.2, respiratory muscle endurance (RME) was assessed at 70 % of MIP and the duty cycle (Ti/Ttot) was kept constant at 0.4. The lack of association between VO_2max and RME may result from the different duty cycles adopted by the subjects during various stages of the incremental exercise test. Alternatively, this may reflect muscle specificity with the two manoeuvres. The respiratory muscles are mainly involved during RME testing whereas several groups of skeletal muscles are engaged during cycle ergometry.[127]

The body consists of two chemically distinct compartments, fat and fat-free(or lean body); the former is metabolically fairly inert.[129] Lean body mass (LBM) can be used as an index of muscle mass. During exercise, the demand on the oxygen transport system varies with the size of the active muscles. Hence, LBM exerts a significant influence on VO_2max, as evident in the equations 5, 6 and 7.

The present study emphasises the importance of assessing peripheral muscle

function when evaluating exercise intolerance. Peripheral muscle impairment has also been implicated as a contributor to disability in patients with idiopathic thoracic scoliosis[130]and cystic fibrosis.[131] Similarly, LBM has been shown to complement measures of pulmonary function in the prediction of disability in patients with chronic obstructive pulmonary disease.[132]

It is noteworthy that chest expansion and vital capacity were related to aerobic power with a relatively similar degree. The findings suggests that chest restriction in AS expresses its influence on VO_2max through a reduction in vital capacity. The weakness of the influence of chest restriction, even after accounting for age, may be explained by the well-recognised diaphragmatic compensation for the work of breathing.[74-75]

A number of methodological issues are worthy of discussion. Both the force of maximum voluntary contraction of the quadriceps(Qds) and hand grip strength were strongly related to aerobic power in the AS subjects. The former was selected as the prime candidate for the stepwise regression analysis as it is clearly more pertinent to the type of exercise under consideration, i.e. cycle ergometry.

Exercise usually involves both static and dynamic contractions.[30] The former type is measured by an isometric dynamometer, as used in this study. The latter can be assessed by an isokinetic dynamometer, which enables the control of angular velocity of the moving limb. While the latter type of facility has some advantages,[133]its use is confined within the province of few centres due to the exceptionally high cost.

No attempts were made in the present study to address the effect of difference in gender on aerobic power. This was because of the relatively small number of

subjects in each category (17 males, 8 females). It is well known that aerobic power is higher in the average male, largely due to a higher percentage of fatty tissue in the average female.[30]

It should be mentioned that the degree of thoracic kyphosis in this study was not measured by radiographic means; rather, it was reflected by the wall-tragus distance. However, the adverse effect of thoracic kyphosis *per se* on aerobic power has not been previously confirmed.

Although restricted thoraco-lumbar mobility is physically disadvantageous, the degree of TL mobility, as assessed by spondylometry, did not appear to influence aerobic power among the AS subjects. This may be explained by the nature of cycle ergometry, during which the trunk is essentially immobile.

The finding of significantly higher aerobic power, after controlling for age, in the exercisers group underpins the importance of physical activity in patients with AS. On the basis of the findings in the present study, interventions aimed at improving peripheral muscle function would be expected to improve aerobic power and exercise tolerance in this condition.

Summary of Findings

1 In line with the findings in the previous study (chapter 4), aerobic power was commonly reduced in the 25 patients with ankylosing spondylitis (AS).

2 Aerobic power in the AS subjects was mostly influenced by peripheral muscle strength, thus elaborating the findings in the previous studies. This finding strongly suggests that strategies to improve peripheral muscle strength would modify aerobic power in this condition.

3 Vital capacity and limited chest expansion influenced aerobic power only weakly in the AS subjects. The findings concur with the view that the diaphragm compensates well for the work of breathing in AS.

4 When taking into account the peripheral muscle strength, lean body mass further improved the prediction of aerobic power in AS.

5 The extent of thoracic kyphosis and the degree of thoraco-lumbar mobility did not appear to exert a significant influence on aerobic power in AS.

6 Aerobic power was significantly higher in the group classed as regular exercisers, thereby emphasising the importance of physical activity in patients with AS.

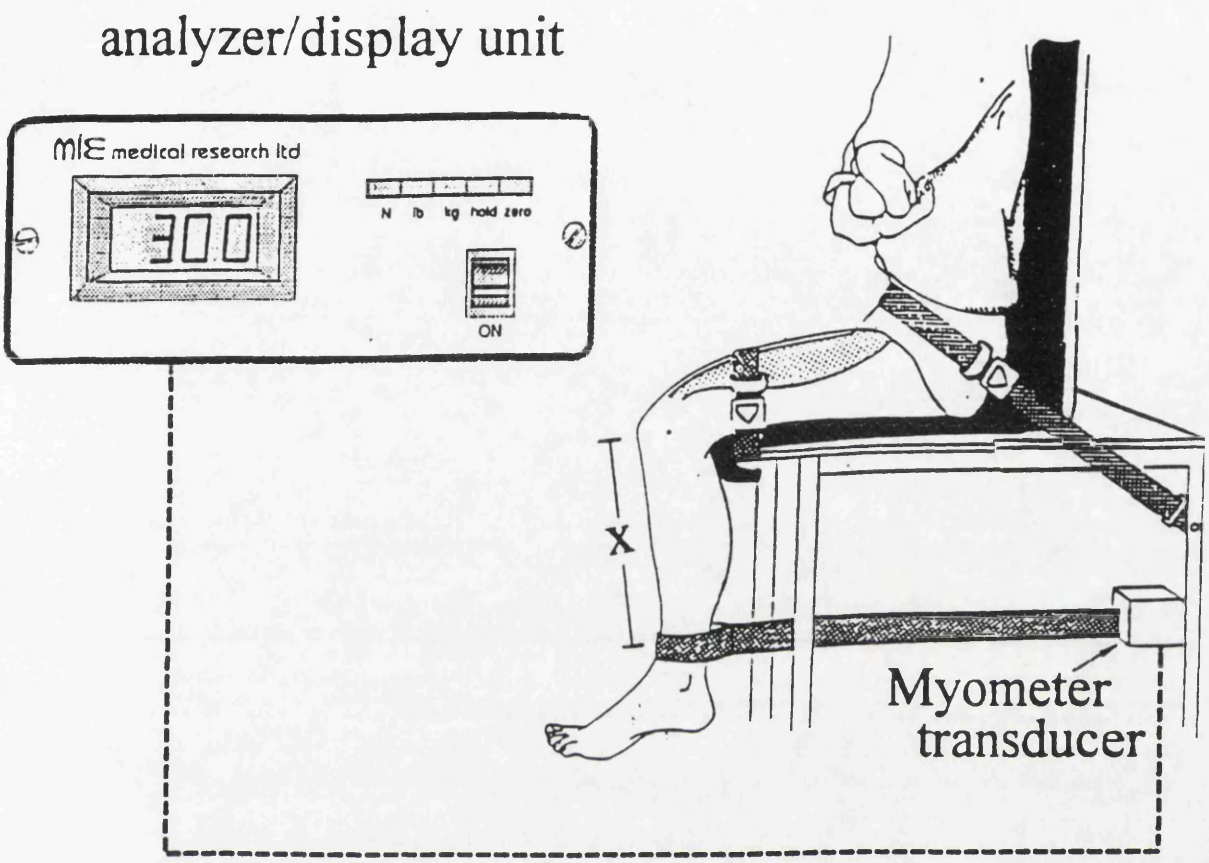
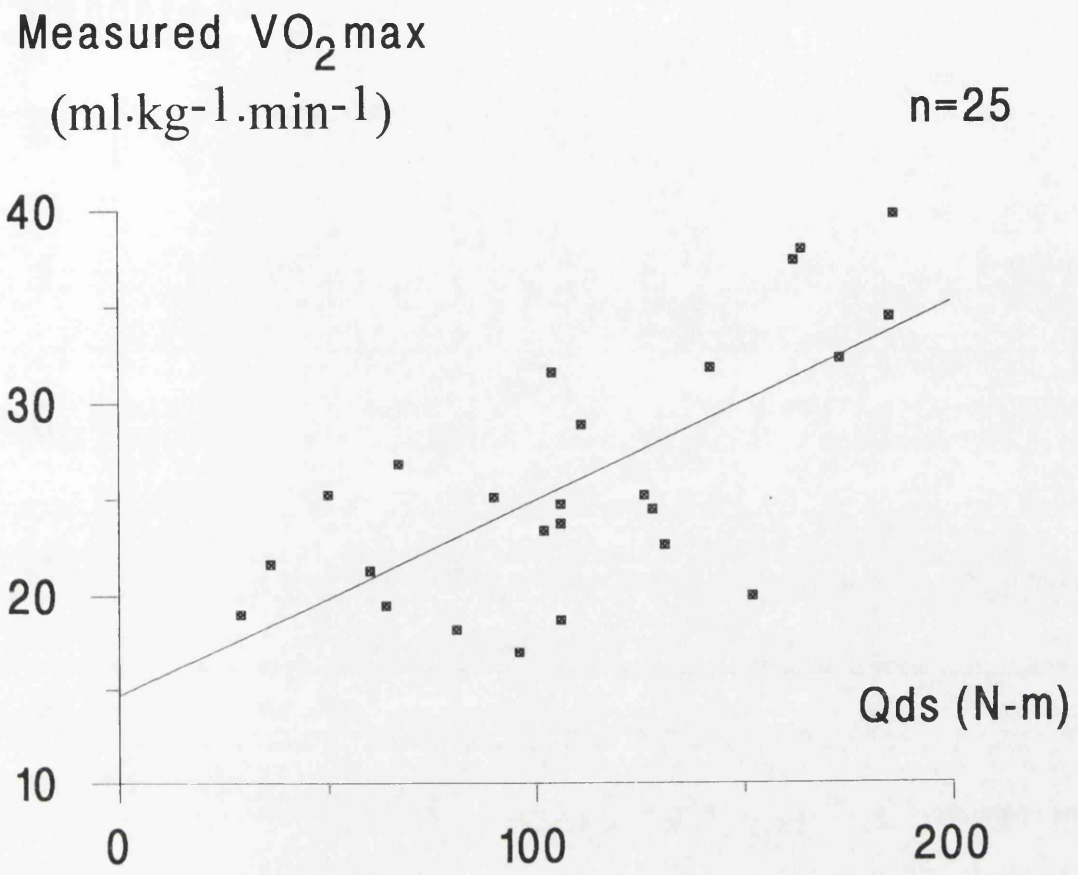


Figure 5.1 *Schematic illustration of the experimental set-up for the measurement of maximum isometric contraction of the quadriceps (Qds). X denotes the distance between the centre of force and the fulcrum of the knee joint.*

Qds = Maximum force × X (Newton-metre).

(Modified from reference 125)



VO_2max (ml·kg^{-1}·min^{-1}) = 14.7 + 0.10 Qds (N-m)

[adj.R^2 46.9 %, F 22.16, $p < 0.001$]

Figure 5.2 *Linear regression of VO_2max on the force of maximum isometric contraction of the knee extensors (Qds) in 25 AS patients.*

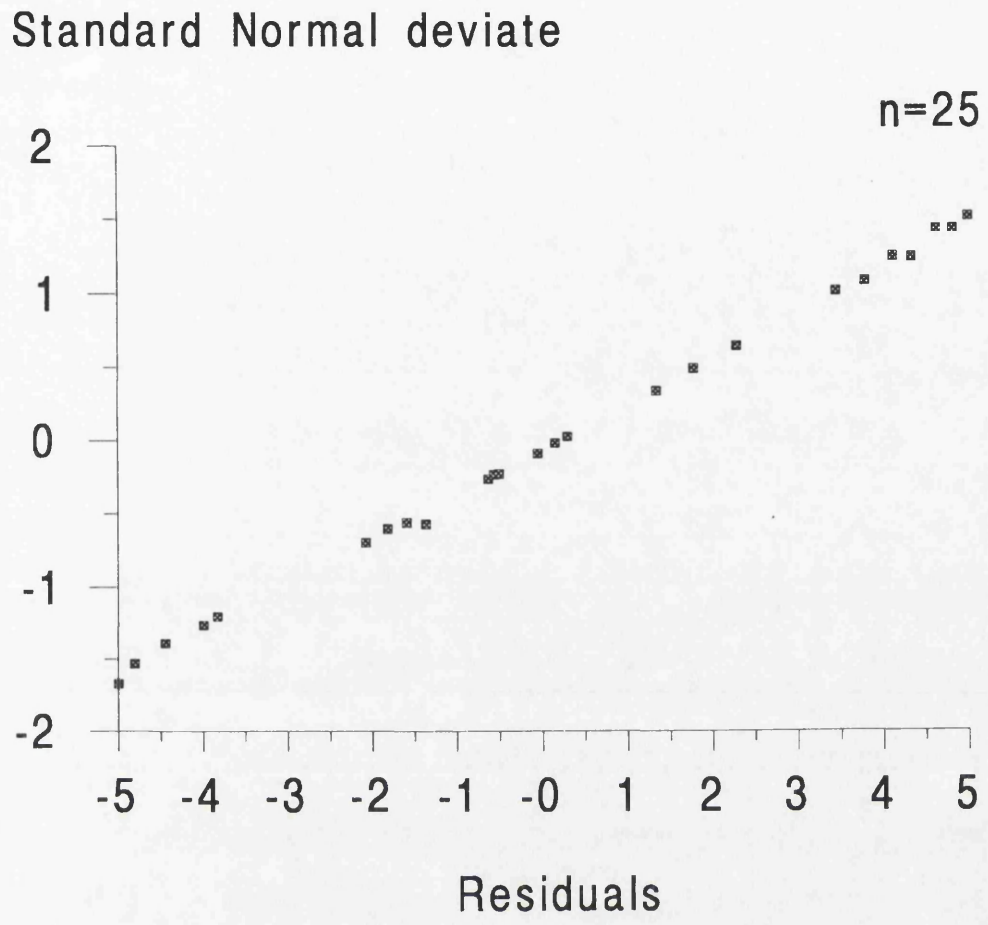


Figure 5.3 *Normal plot of Residuals from the regression model :*

$$VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 27.8 + 0.17\ Qds\ (N\text{-}m) - 0.39\ LBM\ (kg)$$

(derived from 25 subjects with ankylosing spondylitis).

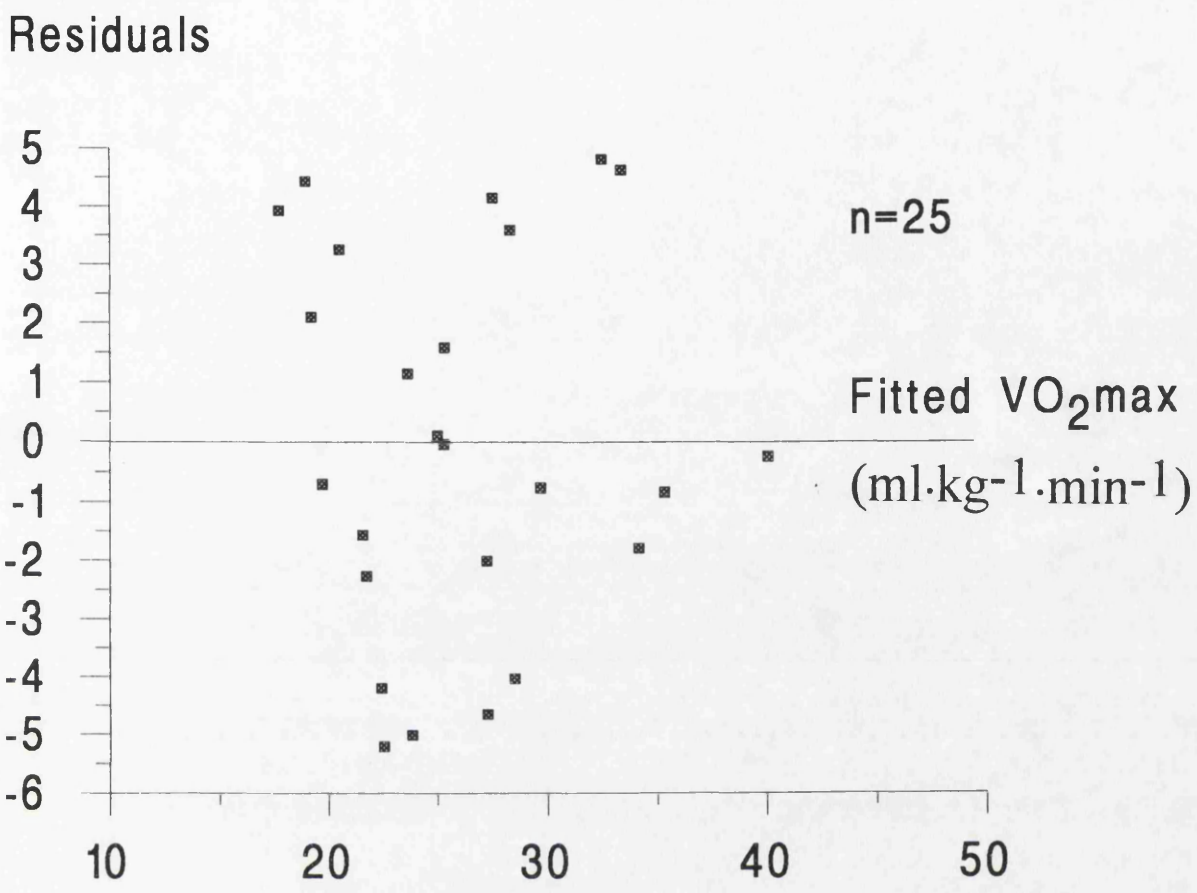


Figure 5.4 *Scattergram of Residuals vs Fitted VO_2max from the model :*

$$VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 27.8 + 0.17\ Qds\ (N\text{-}m) - 0.39\ LBM\ (kg)$$

(derived from 25 subjects with ankylosing spondylitis).

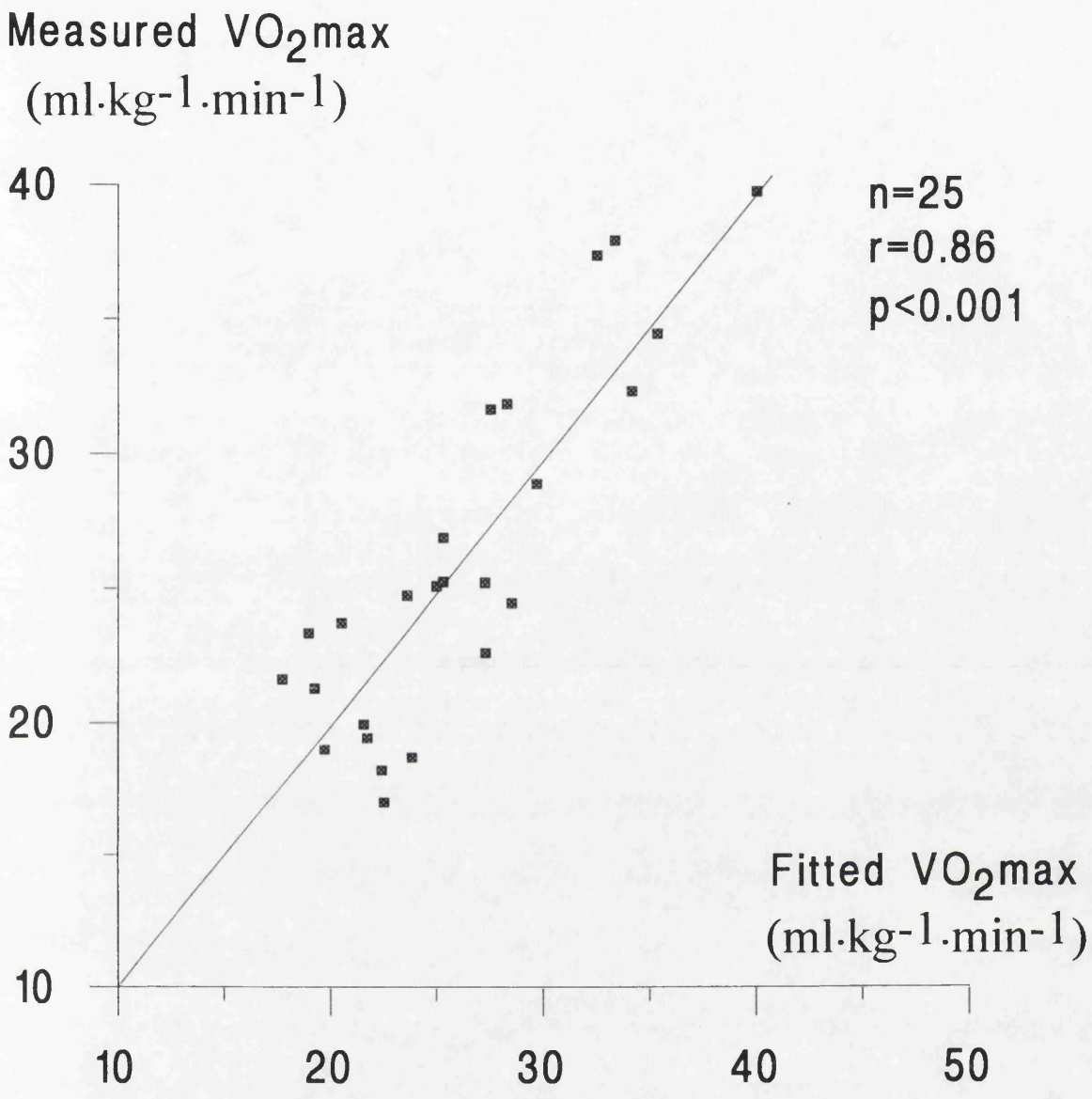


Figure 5.5 *Linear correlation between Measured vs Fitted VO_2max ,*

from the regression model :

$$VO_2max\ (ml \cdot kg^{-1} \cdot min^{-1}) = 27.8 + 0.17\ Qds\ (N\text{-}m) - 0.39\ LBM\ (kg)$$

The straight line represents the line of identity.

(derived from 25 subjects with ankylosing spondylitis).

Table 5.1

Clinical characteristics of 25 AS subjects

(17 males, 8 females; 15 exercisers, 10 non-exercisers)

	Mean	**SD**	**Range**
Age , yr	46.7	12.1	22 - 67
Height , m	1.66	0.08	1.47 - 1.80
LBM , kg	51.66	11.42	27.73 - 80.90
VO_2max, $ml \cdot kg^{-1} \cdot min^{-1}$	26.06	6.60	17.05 - 39.80
VO_2max, % predicted	75	17.6	48 - 110
VC , L	3.66	0.98	2.14 - 5.40
MIP , cmH_2O	83.6	31.0	37 - 148
Tlim , s	130	116	30 - 460
Chest expansion , cm	2.02	0.71	0.6 - 3.0
Qds , N-m	110	44.9	29 - 186
Hand grip strength , kgW	35.3	11.73	14 - 55.5
Spondylometry , °	51	17.7	20 - 86
Wall-tragus distance, cm	16.9	6.1	9.5 - 33
ESR , $mm \cdot 1^{st}hr^{-1}$.	19	14.4	1 - 58

Table 5.2

Stepwise regression of VO_2max on Qds and LBM *

Predictor	Coefficient	Stdev	t-ratio	P
Constant	27.804	3.281	8.48	<0.001
Qds	0.169	0.0208	8.14	<0.001
LBM	-0.396	0.0821	-4.83	<0.001

Analysis of variance :

Source of variation	Degree of freedom	Sum of squares	Mean squares	P
Regression on Qds	1	512.54	512.54	<0.001
Addition of LBM	1	273.67	273.67	<0.001
Residual	22	258.34	11.74	
Total	24	1044.55		

Residual SD = $\sqrt{11.74}$ = 3.42 $ml \cdot kg^{-1} \cdot min^{-1}$, F = 33.48.

Regression model :

VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) = 27.8 + 0.17 Qds (N-m) - 0.39 LBM (kg)

Chapter 6

Conclusions and Future Directions

The series of studies comprising this thesis have attempted to answer the questions posed in the first chapter regarding the factors influencing aerobic power and the mechanism (s) underlying exercise limitation among patients with ankylosing spondylitis (AS). In the following pages, the results of the foregoing studies will be pulled together and interpreted in the light of other recent studies in this field. Also, suggestions for further areas of study will be made. Before summarising the findings of importance in individual studies, several points require comment.

As indicated earlier in this thesis, the studied patients came from a tertiary, referral centre. This has inevitably resulted in a study of patients with more severe AS than would be claimed representative of a standard AS population. This is evident by a mean chest expansion of 2.0 cm and a narrow standard deviation of 0.7 cm. The results and clinical implications arising from the current studies therefore apply principally to patients with well established, moderately advanced disease.

With respect to the use of the term maximal aerobic uptake, it is defined as the highest oxygen uptake the individual can attain during exercise while breathing air at sea level.[30] To fit this definition, a plateau in the oxygen uptake during exercise has to be reached. However, this is not usually achieved since the subjects may cease exercising owing to various symptoms or external stimuli or, in some instances, poor

motivation. Therefore, the term maximal oxygen uptake (VO_2max) in this thesis refers to the highest oxygen uptake achieved during exercise to symptom limitation.

No claim should be made that aerobic power equates exercise power. Indeed, anaerobic processes play an increasingly greater role as the severity of exercise increases. Anaerobic power is indicative of a kind of work important in many common tasks. Although tests for measurement of anaerobic power have been described,[134-135] their clinical applications have been limited in view of the relative complexity of the methods. Aerobic power, on the other hand, can be measured relatively easily during exercise on a treadmill or cycle ergometer.

Since there is a lack of similar tool for direct measurement of anaerobic power, some sort of indirect means have to be applied when evaluating exercise power. Anaerobic threshold (AT), as employed in chapter 4, is one of such methods. The concept of AT is based on an exponential rise in blood lactate concentration when exceeding a certain rate of exercise/oxygen uptake. As outlined in chapter 1.3, AT can be detected by measuring blood lactate level or noninvasively by detecting a breaking point of pulmonary ventilation *versus* oxygen uptake. However, it is sometimes difficult to establish a well-defined 'point'. The work rate at which a nonlinear increase in ventilation occurs need not be the same exercise rate at which the lactate concentration rises.[30] Furthermore, there are individual variations in the highest lactate level which can be tolerated during prolonged exercise.[136] Nonetheless, AT provides important information as regards the individual's aerobic potential, and about the effect of training. The threshold concept, as such, however, rests on an unstable foundation.

The studies comprising this thesis commenced in **Chapter 2** with measurements

of the symptom of breathlessness, which is important in any studies such as these. The results are in contrast with the prevailing concept that AS patients rarely suffer from exertional dyspnoea. The subjects who took regular exercise experienced undue breathlessness less commonly than the non-exercisers. The finding of a greater magnitude of dyspnoea perceived during everyday activities among the AS patients in the oxygen cost diagram study substantiates the main finding from the initial survey. The findings thus confirmed the presence of perceived exertional dyspnoea among AS patients in subjective as well as numerical terms, and indicated the need for the subsequent physiological studies.

Chapter 3 examined the performance of the respiratory muscles in AS both in terms of maximal strength and endurance. The study provides no strong evidence that respiratory muscle strength, as indicated by maximal respiratory pressures, is reduced in AS. However, the inefficiency of the respiratory muscles in the AS patients became evident during sustained breathing at high inspiratory pressures. Furthermore, the elevated resting lung position adopted by the AS patients appeared to adversely affect respiratory muscle performance during work requiring high inspiratory pressures. The finding of impaired respiratory muscle endurance (RME) posed a crucial question as to its clinical significance in AS and called for the subsequent investigation into the possible role of impaired RME on exercise tolerance in this condition.

In **Chapter 4** attention was paid to a comprehensive assessment of exercise tolerance in AS. Furthermore, attempts were made to examine the possible link between exertional dyspnoea in AS, as evident from the studies in chapter 2, and altered lung subdivisions and chest restriction commonly found in this condition. Several

important findings emerged from this study. In agreement with the few previous studies,[40,41] effort tolerance and work capacity were substantially curtailed in the AS patients. The finding of a greater degree of leg fatigue perceived among the AS subjects suggested that musculoskeletal deconditioning was the main factor limiting exercise in the AS group.

While a comparatively higher ventilatory response to exercise was observed in the AS group, as compared with the controls, their V_{Emax}/ VCO_2 values were still within normal range. Furthermore, their breathing reserve remained adequate and no major gas exchange abnormality was found.

Although heart rate response to exercise in the AS group was raised, other cardiocirculatory variables were appropriate to exercise level. The findings were compatible with an element of cardiac deconditioning consequent to a relative lack of physical activity rather than cardiac disease. The interpretation of the findings thus agreed with the aforementioned view that peripheral deconditioning was the main factor causing exercise intolerance in the AS subjects.

The severity of breathing effort at an equivalent work rate or ventilation was found to be greater among the AS subjects, thus corroborating the findings in chapter 2 with respect to exertional dyspnoea. However, the magnitude of exertional dyspnoea was not related to impaired resting lung volumes or the degree of chest restriction, indicating that the three variables represent separate quantities which characterise the condition of patients with AS.

Another prominent finding emerged was the lower mean anaerobic threshold in the AS group, as compared with that of controls. This finding implies a relative lack

of aerobic fitness among the AS subjects. Furthermore, the resultant lactic acid accumulation may in part account for the greater degree of leg fatigue perceived among the AS subjects. However, in the absence of direct measurement of blood lactic acid the interpretation of this finding is speculative.

Apposite to the findings in chapter 4 is the findings from a recent study by Calin *et al.*[137] In part of the study, the investigators followed a random cohort of 60 AS patients over a 2-week period and found that fatigue was the main symptom in over 50 % of the subjects. The authors concluded that fatigue should be considered a major problem for patients with AS, worthy of further exploration in terms of both aetiology and therapy.

The results in chapters 3 and 4 suggested that peripheral muscles and/or respiratory muscles play an important role in reduction in aerobic power in AS. The final study in **Chapter 5** therefore attempted to quantitively determine the contribution of these factors to aerobic power in AS. The finding of a major influence of peripheral muscle strength on aerobic power in the AS subjects elaborated the results in chapter 4.

Little attention has focused on peripheral muscle function in AS. Based on limited available information, convincing evidence of involvement of skeletal muscles in AS is lacking.[79] Peripheral muscle deconditioning in AS therefore appears to result from disuse consequent to the chronic nature of the disease.

The finding of a weak influence of limited chest expansion on aerobic power in AS may be accounted for by the diaphragmatic compensation in this condition. A similar explanation may apply to the weak relationship between aerobic power and vital capacity.

Impaired respiratory muscle endurance did not appear to play a significant role in exercise intolerance in the AS subjects. Possible explanations for the lack of association between aerobic power and RME were given in the discussion in chapter 5.4.

Perceived exertional dyspnoea among AS patients is one of the issues addressed in this thesis. Although undue breathlessness was confirmed in chapter 2, various cardiorespiratory abnormalities did not account for exercise limitation in subsequent physiological studies. The undue breathlessness is therefore best interpreted as normal " physiological " breathlessness which is one component of perceived exertion and can be prominent in deconditioned patients.

A variety of deficits in lung function and exercise mobility are demonstrated in this thesis. However, it is not the deficits in lung function which are the cause of the loss of mobility but rather the vicious cycle of deconditioning which affects peripheral muscle thereby promoting gradual loss of mobility. The common assumption that breathlessness limits exercise performance where there are deficits in thoracic wall excursion is potentially unhelpful as it can deflect clinicians away from potentially effective musculo-skeletal rehabilitation.

Based on the results of the present studies, assessment of peripheral muscle function should form an important element in rehabilitation programme for AS patients. The findings suggest that strategies aimed at maintaining/improving peripheral muscle function are potentially beneficial to sufferers from this condition.

Peripheral muscle training, for example weight lifting, has been found valuable for improving exercise tolerance in patients with coronary artery disease[138]and chronic airflow limitation.[139] More recently, isolated exercise of specific muscle groups

(sequential muscle training) has been shown to improve muscle conditioning and tolerance of steady state submaximal exercise in patients with chronic obstructive airway disease.[80]

Ankylosing spondylitis is heterogeneous with patients across a wide range of severity of skeletal restriction. Recommendations upon effective rehabilitation options must be based on the type of patients being considered. It is nevertheless not a disadvantage of the current studies to have looked at patients with moderately advanced stage of AS. The results are also very likely to apply to those with milder end of the spectrum who may benefit most from improvement in mobility through systematic application of muscle conditioning.

However, patients with the most advanced chest restriction and ventilatory limitation may require different strategies for treatment other than simple peripheral muscle conditioning. Such a population may demonstrate an amplified reduction in repiratory muscle function and may benefit from respiratory muscle training.

ABBREVIATIONS

Respiratory variables

BR	Breathing reserve
BTPS	Body temperature and pressure, saturated with water vapour
DLco	Diffusing capacity of the lungs for carbon monoxide
f	Breathing frequency
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FRC / TLC	Functional residual capacity as a proportion of total lung capacity
15-sMVV	Maximal voluntary ventilation
$P(A\text{-}a)O_2$	Alveolar-arterial oxygen pressure difference
Palv	Alveolar pressure
PaO_2	Partial pressure of arterial oxygen
$PaCO_2$	Partial pressure of arterial carbon dioxide
pH	Blood pH value
Pm	Mouth pressure
R	Respiratory exchange ratio
Raw	Airways resistance
RV	Residual volume
RV / TLC	Residual volume as a proportion of total lung capacity
STPD	Standard temperature and pressure, dry
$tcPO_2$	Transcutaneous oxygen pressure

$tcPCO_2$	Transcutaneous carbon dioxide pressure
Ti	Inspiratory duration
TLC	Total lung capacity
Tlim	Respiratory muscle endurance time
Ttot	Duration of a complete breath
Ti / Ttot	Duty cycle, or inspiratory duration as a proportion of a total breath
VC	Vital capacity
VCO_2	Carbon dioxide production per minute (STPD)
V_D / V_T	Physiological dead space-tidal volume ratio
V_E	Expired minute ventilation (BTPS)
$\Delta V_E / \Delta VCO_2$	Ventilatory response to exercise
VO_2	Oxygen uptake per minute (STPD)
VO_2max	Symptom-limited maximum oxygen uptake

Haemodynamic variables

AT	Anaerobic threshold
BPdias	Diastolic blood pressure
BPsys	Systolic blood pressure
ECG	Electrocardiograph
HR	Heart rate
$\Delta HR / \Delta VO_2$	Heart rate response to exercise

Statistical notations

95 % CI	95 % confidence interval
SD	Standard deviation
SEM	Standard error of mean

Other variables

AS	Ankylosing spondylitis
BS	Breathlessness score (modified Borg scale)
CPX	Cardiopulmonary exercise
LBM	Lean body mass
LS	Leg fatigue score (modified Borg scale)
Qds	Force of the maximum voluntary contraction of the quadriceps

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APPENDIX A

Screening questionnaire for AS study (GRI, 1993) Date of interview .....

Name ..... Date of birth ...../...../.....

Address .....

Occupation .....

Instructions : Please tick the appropriate box, or write in the space provided when indicated.

1. For how long have you suffered from ankylosing spondylitis ? .....years.

2. What is the level of physical activity involved in your job or daily life ?

Light	
Moderate	
Strenuous	

3. Do you regularly take exercise or play sport ?

Yes	
No	

if " Yes " Please give details :

Type of exercise or sport 1....., approximately .....hours/week.

2....., approximately .....hours/week.

3....., approximately .....hours/week.

4. Do you ever get short of breath when walking with others of your own age, on level ground ?

Yes	
No	

5. Do you usually cough first thing in the morning ?

Yes	
No	

6. Do you usually cough like this on most days for as much as three months each year ?

Yes	
No	

7. Do you usually bring up spit or phlegm first thing in the morning ?

Yes	
No	

8. Do you usually bring up spit like this on most days for as much as three months each year ?

Yes	
No	

9. Do you smoke ?

Yes	
No	

10. How many cigarettes/cigars do you smoke per day ? .....per day

11. How long have you smoked ? .....years.

12. If you have ever smoked,

a. How long did you smoke for ? .....years.

b. How many did you smoke per day .....per day

c. When did you stop ? .....

13. Have you ever had : a. Heart trouble ☐

b. Bronchitis ☐

c. Asthma ☐

d. Pneumonia / Pleurisy ☐

e. Tuberculosis ☐

f. Other chest illnesses, please give details .....

14. Do you require regular medicines for any condition ?

Yes	
No	

if " Yes " please give details : a. What is the condition ? .....

b. What are the medicines? .....

15. Do you think you get tired more easily than other people ?

Yes	
No	

16. Has your physical fitness changed much in the past 5 years ?

Yes	
No	

if " Yes " , please indicate if your fitness is worse or improved

worse	
improved	

APPENDIX B

Presentations at scientific meetings on the studies relating to this thesis.

1. Influence of Altered Lung Subdivisions on Respiratory Muscle Performance in Patients with Ankylosing Spondylitis.

   P Riantawan, R Carter, R D Sturrock, S W Banham

   Oral presentations and discussions at the

   1 Scottish Rheumatology Club meeting, Glasgow, 28/ 05/ 94.

   2 Scottish Thoracic Society summer meeting, Perth, 24/ 06/ 94.

   Poster presentations at the

   1 European Respiratory Society annual congress, Nice, France,4/10/94.

   2 British Society for Rheumatology Heberden round, Bath, 22/09/94.

2. Factors Influencing Aerobic Power in Patients with Ankylosing Spondylitis.

   P Riantawan, R Carter, R D Sturrock, S W Banham

   Poster presentation and oral discussion at the

   British Thoracic Society summer meeting, Manchester, 1/ 07/ 94.

3. Exercise Limitation in Patients with Ankylosing Spondylitis

   P Riantawan, R Carter, R D Sturrock, S W Banham

   Poster presentation at the

   European Respiratory Society annual congress, Nice, France, 4/10/94.

APPENDIX C

Published abstracts on the studies relating to this thesis.

1. P Riantawan, S W Banham, R D Sturrock. Influence of altered lung subdivisions on respiratory muscle performance in patients with ankylosing spondylitis. ***Eur Resp J*** 1994; 7 (suppl 18): 343s.

2. P Riantawan, S W Banham, R D Sturrock. Exercise limitation in patients with ankylosing spondylitis. ***Eur Resp J*** 1994; 7 (suppl 18): 324s.

3. P Riantawan, R Carter, S W Banham, R D Sturrock. Factors influencing aerobic power in patients with ankylosing spondylitis. ***Thorax*** 1994; 49: 1076p.