THE ROLE OF EXERCISE TESTING IN CARDIAC DISEASE

by

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AUTHORS DECLARATION.

The author of this text was responsible for the research design of all the studies in this thesis. He carried out all the exercise tests with the help of medically qualified personnel when patients with heart failure were tested.

The author assimilated the data for all the studies and carried out the statistical analysis under the guidance of Mr. T. Aitchison of the Statistics Department, University of Glasgow.

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SUMMARY.

INTRODUCTION.

Breathlessness and fatigue are the characteristic symptoms of chronic heart failure (CHF). Their quantification during submaximal exercise may be of value in the evaluation of patient disability and the impact of drug treatment. Since these symptoms are commonly experienced during the submaximal levels of exercise involved in everyday activities, it was deemed appropriate to assess subjective scales during submaximal exercise and to compare physiological variables with these subjective scales to establish if any relationship existed between them.

Exercise testing in cardiology is commonplace and encompasses a variety of exercise protocols and subjects with wide ranging fitness capability. A new exercise protocol (STEXT protocol) has been developed which accommodates a wide range of fitness levels within a relatively short time period. Thus, it was considered appropriate to evaluate the symptomatic and physiological responses to this protocol.

This thesis is based on a series of studies which were designed to investigate the role of exercise testing in cardiology. The primary aims of the three studies reported in this thesis were to examine the reproducibility and (where appropriate) sensitivity to change of subjective scales for breathlessness and general fatigue. The sensitivity of the subjective scales was assessed using beta blockade to promote a sensation of breathlessness and general fatigue. In addition, an examination of a possible link between physiological variables and the subjective scales was carried out. The impact of beta blockade on physiological variables was also examined.

STUDY ONE.

A COMPARISON OF THE REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 AND LIKERT SCALES.

The main aims of this study were to:

1) assess which subjective scale if any, is most reproducible and sensitive to change in the assessment of symptoms.
2) determine the magnitude of the visit and therapy effects of the subjective scales and physiological variables
3) compare the subjective scales with the physiological responses to exercise.

Twenty three physically active male subjects (mean S.D. age 30.3. $\pm$ 6.5 years) were recruited. Gas collection was continuous throughout all exercise tests and heart rate was recorded every minute. The subjects were given an incremental VO_2 max test and a submaximal economy test so that relative intensities could be calculated. The subjects were studied on four occasions. Three subjective scales were used - (1) Visual analogue (VAS) (continuous scale) (2) Borg CR10 scale (12 fixed points) and (3) Likert scale 5 fixed points). Four identical submaximal tests were given (2 minutes at 60% VO_2 max and 6 minutes at 70% VO_2 max). Two tests were undertaken to assess reproducibility of scores obtained with each subjective scale. Two other tests were undertaken to assess sensitivity of each scale to a change in symptom perception. Here a double blind treatment with propranolol 80 mg (to increase the sensation of breathlessness and general fatigue during exercise) or matching placebo was given. All four tests were allocated using a Latin rectangle design and took place within 7 days of each other. The subjective scale scores were measured at 2, 6 and 8 minutes of exercise.

Reproducibility was defined as the proportion of total variance (i.e. between plus within subject variance) explained by the between subject variance given as a percentage. Sensitivity was defined as the effect of the active drug therapy over the variation within subjects.

RESULTS.

SUBJECTIVE SCALES.

Overall the VAS performed best in terms of reproducibility for breathlessness and general fatigue. For sensitivity the VAS was best for breathlessness and the Borg CR10 scale was most sensitive for general fatigue. e.g. the Table S1 shows the values for reproducibility and for sensitivity with 95% confidence intervals for each subjective scale for breathlessness at 6 minutes:

Table S1.

Reproducibility and Sensitivity with 95% Confidence Intervals for each Subjective Scale for Breathlessness at 6 minutes.

Scale	Reproducibility	Sensitivity
VAS	74% (59-86)*	2.7* (2.4, 3.0)
Borg CR10	42% (33-66)	2.0 (1.6, 2.4)
Likert	55% (38-80)	2.6 (2.2, 3.0)

* VAS significantly different from Borg CR10.

PHYSIOLOGICAL VARIABLES.

The VO_2 max (mean S.D.) of the subjects was 56.9 (4.9) $ml.kg^{-1}.min^{-1}$. On the placebo trial the relative percentage of maximum was 70.8%. A generalised linear model was used to examine if there were any systematic effects for the following: visit, within subject between subject and therapy effect. There were no significant differences among the "non therapy interventions". There were significant therapy effects for the following variables:

VE - after three minutes the active treatment was significantly higher than the other three "interventions".

VO_2 - the active treatment was significantly lower than the other three "interventions" until the last 2 minutes.

VCO_2 - in minutes 1 and 2 the VCO_2 was significantly lower than the other 3 "interventions" and at minute 8 was significantly higher than the other 3 "interventions".

Frequency of breathing - after 2 minutes the frequency of breathing was significantly higher than the other three "interventions".

Heart rate - heart rate was significantly lower for the active treatment compared with the other 3 "interventions" at all timepoints during exercise.

VE/VO_2 and VE/VCO_2 - the active treatment was significantly higher than the other 3 "interventions" for both these variables at all timepoints during exercise.

RER - the active therapy raised the RER at all timepoints throughout exercise compared with the other 3 "interventions".

Tidal volume - the only significant results were at 2 and 6 minutes when the active therapy was significantly higher than replicate 2.

RELATIONSHIP BETWEEN PHYSIOLOGICAL VARIABLES AND BREATHLESSNESS AND GENERAL FATIGUE.

It was decided that the best way to indicate which perception of symptom was best related to each physiological variable was to evaluate individual subject correlations based on all observations for each subject. Once these correlations were evaluated, the correlations across all the subjects was taken as an overall measure of the relationship between variables.

For VE, VO_2, VCO_2 and heart rate and all the subjective scales, correlations were above 0.9. For the other physiological variables, (apart from VE/VCO_2) and the subjective

scales, correlations were above 0.75. There was no significant difference in some physiological variables, (eg VE, VO_2, VCO_2 and frequency of breathing) between 6 and 8 minutes. Despite this stability in the physiological variables, the scores for the subjective scales increased. These findings suggest that there is not a direct association between the perception of symptoms and physiological variables.

CONCLUSION.

In conclusion, this study suggests that subjective scales can reproducibly measure symptoms during exercise and detect the effect of a drug intervention. The VAS and Borg CR10 scales appear to be the best subjective scales for this purpose. The active treatment had a lowering effect on heart rate and increased several respiratory variables including ventilation, frequency of breathing, RER and VCO_2 VE/VO_2, and VE/VCO_2 at some or all timepoints. At some timepoints VO_2 and VCO_2 were reduced. Some physiological variables had very high correlations with the subjective scales (breathlessness and general fatigue).

As the VAS and Borg CR10 scales performed best in this study, it was decided to evaluate the reproducibility of these scales in patients with chronic heart failure.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

A large number of exploratory tests were conducted to determine a range of appropriate relative intensities and to devise a method of selecting relative intensities. Thereafter, a pilot study was carried out.

CHF PILOT STUDY.

Six subjects with CHF (NYHA I & II) were studied. Each undertook 2 baseline maximal incremental treadmill tests. Submaximal tests were undertaken 1, 2, 4 and 6 weeks later. Each consisted of 6 minutes at 3 workrates (65%, 73% and 83% of peak VO_2). During each stage of the submaximal test, patients recorded their symptoms of breathlessness and general fatigue using computer automated VAS and Borg CR10 scales. Reproducibility was defined as the proportion of total variance (i.e. between plus within subject variance) explained by the between subject variance given as a percentage. Reproducibility coefficients for the three workrates are given in Table S2.

Table S2.
Reproducibility coefficients for the Visual Analogue (VAS) and Borg CR10 Scales (Breathlessness and General Fatigue) at three relative intensities.

Relative Intensity (% Peak VO_2)	Breathlessness VAS	Breathlessness Borg CR10	General Fatigue VAS	General Fatigue Borg
65%	78%	43%	55%	39%
74%	63%	65%	67%	60%
83%	82%	72%	81%	71%

There were no significant differences between the scales for breathlessness or general fatigue at any timepoint.

The subjective scales used were found to be as reproducible in patients with CHF as they were in treadmill familiar normal volunteers (see previous study). Reproducibility was best at higher workrates. Overall the VAS tended to be the more reproducible scale. The fairly prolonged procedure employed to determine appropriate workrates was considered to be a disadvantage. It was decided to use the VAS and Borg CR10 scales linked to a constant workrate treadmill protocol.

STUDY TWO.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE CHRONIC HEART FAILURE.

The aims of this study were to:

1) determine the reproducibility of VAS and Borg CR10 scales in CHF patients.
2) determine a method of establishing a constant workrate test which resulted in a symptom limited endpoint between 8 and 17 minutes and thus be of value in a clinical setting.
3) identify the relative intensities of the patients during the constant work rate test.
4) examine the relationship between the physiological variables and subjective scales during the constant work rate tests.

Ten patients with CHF (NYHA I&II) were studied. Based on 2 maximal incremental treadmill tests an individual protocol using a constant workrate at a submaximal intensity was derived using a diagrammatic aid. The projected treadmill time was between 8 and 17 minutes. Tests were carried out 1, 2 ,4 and 6 weeks after the maximal tests. Every two and a half minutes during the submaximal tests patients recorded their symptoms of breathlessness and general fatigue using computer automated VAS and Borg CR10 scales. Gas collection was continuous and heart rate was monitored at the end of each minute. Reproducibility was defined as the proportion of total variance (i.e. between plus within subject variance) explained by the between subject variance given as a percentage.

RESULTS.

SUBJECTIVE SCALES.

Table S3 shows the reproducibility coefficients with 95% confidence intervals for each subjective scale for breathlessness and general fatigue.

Table S3.
Reproducibility Coefficients and 95% Confidence Intervals for Visual Analogue and Borg Scales for Breathlessness and General Fatigue.

REPRODUCIBILITY.				
Breathlessness				
Time / Scale	2.5 Min	5.0 Min	7.5 Min	10.0 Min
VAS	82% (58,91)	83% (61,92)	68% (36,83)	66% (22,78)
Borg CR10	51% (16,73)	48% (13,70)	46% (11,69)	38% (-0.57)

General Fatigue				
Time / Scale	2.5 Min	5.0 Min	7.5 Min	10.0 Min
VAS	77% (51,89)	86% (66,93)	83% (60,92)	81% (48,82)
Borg CR10	51% (17,73)	77% (50,89)	64% (32,81)	46% (6,64)

Confidence intervals are in brackets beneath each estimate of reproducibility.

There were no significant differences between the scales for breathlessness and general fatigue at any timepoint.

PHYSIOLOGICAL VARIABLES.

The peak VO_2 (mean S.D) of the patients was 20.6 + (4.2.) $ml.kg^{-1}.min^{-1}$. The mean relative intensities for VO_2, VE and heart rate were 89.3%, 92.5% and 98.5%

respectively. The mean (S.D.) endurance time (seconds) for tests 1, 2 3 and 4 were 609 (159), 715 (218), 615 (295) and 713 (214) respectively. A reproducibility coefficient of 51% was calculated for endurance time for all constant workrate tests. This figure increased to 76% when the first test of subject 6 is excluded. Subject 6 increased his endurance time from 7 minutes to 17 minutes from test 1 to test 2.

RELATIONSHIP BETWEEN SUBJECTIVE SCALES AND PHYSIOLOGICAL VARIABLES.

The highest correlations were between heart rate and the subjective scales (around 0.8). Correlations for all the subjective scales and the respiratory physiological data (except VO_2) were not particularly good and indicate a fairly poor relationship between these variables.

CONCLUSION.

It can be concluded that, overall, the VAS tended to be more reproducible than the Borg CR10 scale over the four submaximal tests. The method of selecting the workrate for the submaximal test (to elicit an endurance time of between 8-17 minutes) was appropriate for most patients. The CHF patients exercised at very high relative intensities during the submaximal tests. The relationship between the respiratory physiological variables and the subjective scales was generally quite poor.

The use of the above exercise protocol with the VAS can offer a useful means of evaluating symptoms in CHF and potentially their response to treatment.

STUDY THREE.

AN EVALUATION OF THE STEXT PROTOCOL.

There is no common exercise protocol for all categories of cardiac patients. A protocol with an exponential rise in energy cost (STEEP) was devised to encompass the anticipated energy cost range of cardiac patients so that treadmill times did not exceed 15 minutes. The STEEP protocol was extended to 18 minutes to accommodate the anticipated higher fitness levels in a population study of 2000 West of Scotland normal subjects (MONICA Study). This extension was called the STEXT protocol. The STEEP protocol has also been adopted by a number of clinicians and researchers. It has also been proposed to use the STEXT protocol to evaluate drug treatment in a group of angina subjects. No evaluation of the reproducibility or sensitivity to change of the physiological variables or subjective scales has been undertaken.

It was decided to assess the STEXT protocol using a drug trial format i.e. the number and timing of the tests simulated a possible drug trial time scale and sequence of events. Propranolol was selected to induce an increase in the perception of breathlessness and general fatigue.

The main aims of this study were to:

1) assess which subjective scale (VAS or Borg CR10) if any, is decidedly more reproducible and sensitive to change in the assessment of symptoms.

2) determine the magnitude of the visit and therapy effects of the subjective scales and the physiological variables.

3) assess the reproducibility of maximal physiological values.

4) compare the subjective scales with the physiological responses to exercise.

Twelve healthy males (mean S. D.) (age 32.8 $\pm$ 8.9) who took part in regular exercise were recruited. The subjects performed a treadmill exercise test (STEXT) on 8 occasions. Pairs of tests were carried out (48 hours apart) at weeks 0, 2, 6 and 10. At weeks 6 and 10 subjects were given placebo or 80 mg of propranolol 12 and 2 hours before testing (to increase the sensation of breathlessness and general fatigue during exercise). During the test, subjective scales for breathlessness and general fatigue were presented using computer automated scales at 2 mins 10 seconds and every 2 minutes thereafter until the end of the test when the subjects responded to record their symptoms at maximum. VAS and Borg CR10 scales were used. Six subjects received a VAS/Borg CR10 sequence and six a Borg CR10/VAS order of presentation.

RESULTS.

SUBJECTIVE SCALES.

Reproducibility was defined as the proportion of total variance (i.e. between plus within subject variance) explained by the between subject variance given as a percentage. At the first two timepoints reproducibility was low for both scales for breathlesness and general fatigue. Thereafter, to maximum, reproducibility for breathlessness and general fatigue was generally between 75-85%. These values compare favourably with the previous study using steady state exercise with normal

subjects. There were no significant differences between the scales. The VAS and Borg CR10 scales were generally significantly sensitive between the fifth and seventh timepoints. Sensitivity ratios (treatment effect/variation within subjects) were low compared with the "steady state" study and ranged between 0.02 to 1.7. There were no significant differences between the scales for sensitivity.

MAXIMAL PHYSIOLOGICAL VALUES.

The VO_2 max (mean S.D.) of the subjects was 56.5 $\pm$ 5.8 ml.kg.$^{-1}$ min^{-1} . There were no differences among the 6 non-propranolol tests for the maximal physiological variables. Reproducibility coefficients ranged between 43% to 96%. Generally reproducibility was considered to be good. Examples of reproducibility coefficients were 79% for exercise time and 76% for VO_2 max. Both propranolol tests showed significant decreases for heart rate, VO_2 VCO_2 VE, and endurance time.

SUBMAXIMAL PHYSIOLOGICAL VARIABLES.

There was a therapy effect for the following variables:

VE - on the "active" therapy there was a significant decrease in VE at minute 8 and a significant increase in VE at minutes 14 and 15.

VO_2 - VO_2 was significantly decreased throughout the entire exercise protocol on the "active" therapy.

VCO_2 - VCO_2 was significantly lowered at minute 8 and significantly increased at minute 15 on the "active" therapy.

Frequency of breathing/tidal volume - frequency of breathing and tidal volume were significantly increased at minutes 14 and 15 on the "active" therapy.

Heart rate - heart rate was lowered throughout the entire exercise protocol on the "active" therapy.

VE/VO_2 - VE/VO_2 was significantly increased from minutes 10 - 15 on the "active" therapy.

VE/VCO_2 - VE/VCO_2 was significantly increased from minute 12-15 on the "active" therapy.

RER - RER was significantly raised at minute 1 and from minutes 10-15 on the "active" therapy.

RELATIONSHIP BETWEEN THE PHYSIOLOGICAL VARIABLES AND SUBJECTIVE SCALES.

The correlations for VE and VCO_2 were all over 0.8 for both the VAS and Borg CR10 scales (breathlessness and general fatigue). Apart from VE/VO_2 and VE/VCO_2 all other correlations were over 0.7.

CONCLUSION.

This study suggests that subjective scales can reproducibly measure symptoms during incremental exercise and detect the effect of drug intervention. It is concluded that maximal physiological variables were reproducible over a projected drug trial time period. The maximal physiological variables and the submaximal physiological variables were affected by the intervention of propranolol. VO_2 max, VCO_2 max, VE max, maximum heart rate and endurance time were among the variables significantly reduced after propranolol. For the latter submaximal stages of the test, there were significant increases in VE, frequency of breathing, tidal volume, VE/VO_2 and RER. On the "active" therapy, there was a significant decrease in VO_2 throughout the test with beta blockade. The relationship between some physiological variables and the subjective scales was good. The STEXT test could be used to evaluate aerobic fitness reproducibly.

CHAPTER 1
SECTION ONE.

INTRODUCTION

1.1.1. SYMPTOMS AND EXERCISE TESTS.

In most cardiac conditions patients have symptoms during exercise. Quantification of symptoms during exercise is therefore valuable in assessing both the patient's condition and the efficacy of drug intervention. Exercise testing has been applied to various categories of cardiac patients to help evaluate current status, predict prognosis and to monitor the effect of drug treatment.

In this thesis a series of studies were designed to investigate the role of exercise testing using subjective scales in the assessment of cardiac patients.

1.1.2. HEART FAILURE.

In pathophysiological terms Braunwald, (1988) describes heart failure as "an inability of the heart to deliver blood (oxygen) at a rate commensurate with the requirements of the metabolising tissues despite normal or increased ventricular filling pressures (or can only do so at the expense of increased ventricular filling pressures - 'diastolic dysfunction')". The underlying pathophysiology in chronic heart failure (CHF) is complicated and it is not surprising that many physicians find CHF difficult to define. However, CHF in most patients is associated with depressed systolic function of the left ventricle (LV) secondary to myocardial damage or necrosis which has resulted from myocardial infarction, infection, toxic, metabolic or idiopathic causes. The response of the body to heart failure involves a number of compensatory mechanisms which include LV hypertrophy and dilatation, changes to central hemodynamics, and neuroendocrine stimulation (a collective term for a variety of processes including activation of the renin-angiotensin system and the sympathetic nervous system leading to peripheral haemodynamic changes involving raised peripheral resistance and redistribution of blood flow).

Chronic heart failure is a relatively common condition in Western society and the prevalence of CHF continues to rise (McMurray et al; 1993). The prognosis of heart failure is poor, with around a 50% survival rate over a five year period. As CHF results from several factors, there is no single treatment for CHF. The introduction of a variety of new drugs has prompted renewed efforts to develop new techniques for the demonstration of drug efficacy and long term evaluation of patients.

The three main aims of therapy in chronic heart failure are to improve the quality of life by making the patient feel better, to enable the patient to be more active and to extend survival. While measurement of the effect on mortality is unambiguous, assessment of quality of life is more problematic. There is no obvious marker or gold standard by which changes in patient status can be readily and accurately assessed. Questionnaires have been used to assess the quality of life in several categories of cardiac patients with varied success.

1.1.3. EXERCISE TESTS.

Traditionally, cardiologists have used a maximum exercise tolerance test to:

1) categorise the severity of heart failure.
2) predict prognosis and provide information on the question of transplantation.
3) assess efficacy of treatment.

The reason for carrying out maximum exercise tests is the hope that CHF patients can attain a representative "maximum" which reflects the true limits of the cardiovascular system. However, the researcher is often uncertain that a CHF patient has in fact produced a maximum effort. Maximum tests are influenced by the motivation of the subject and the skill and experience of the test administrator. Some studies have highlighted the need to conduct several tests to establish a representative baseline for peak oxygen consumption (Elborn et al; 1990).

An added limitation to the use of maximal tests in the assessment of heart failure is the poor correlation between left ventricular function with exercise time and Peak VO_2. A possible explanation for this finding is that maximum oxygen uptake is limited not only by cardiac output but also by the delivery of oxygenated blood to the working skeletal muscles and the utilisation of oxygen by the working skeletal muscles. A further disadvantage of maximum tests in CHF is that they do not relate to the degree of activity in everyday life.

Attempts to circumvent these problems have included the measurement of respiratory gas exchange during exercise tests (Wasserman, 1990). However, the controversy surrounding the ventilatory threshold leaves its usage open to debate. The use of a respiratory exchange ratio (RER) value of 1.0 or an extrapolation to maximum using gas exchange measurements relies on the patient reaching a RER of 1.0 (Buller and Poole-Wilson, 1988). An exercise test which reflects the normal life of CHF patients and can evaluate symptoms, may be of great value in the long term monitoring of CHF patients. Many clinicians agree that some form of sub-maximal exercise test is desirable.

Since dyspnoea and general fatigue on exertion are limiting symptoms in CHF (Weber et al; 1986). It would be of great value to be able to quantify them in order to assess patient status and evaluate interventions. Previous research has demonstrated that different methods of testing have resulted in a variety of responses. While frusemide and captopril produced an increase in total treadmill time in a maximal test, frusemide had a more beneficial effect on some sub-maximal indices (Cowley et al., 1986). However, an appropriate test methodology involving sub-maximal exercise and subjective scales has yet to be established. Furthermore, the test protocol must be shown to be simple, reproducible and sensitive to change.

1.1.4. SUBJECTIVE SCALES AND SUBMAXIMAL TESTS.

A variety of scaling systems have been used to assess dyspnoea, perceived exertion and fatigue but it is unclear how the results of studies which have used one scaling system relate to possible use with CHF patients. Furthermore, the selection of work intensity for submaximal tests in CHF patients is a subject of intense debate. Some leading cardiologists have recognised the need for a sub maximal test which relates to everyday activities and is conducted within a "reasonable" timescale. However, they concede that there is little data relating submaximal performance to clinical status or information available on an appropriate submaximal intensity (Franciosa, 1984, Poole-Wilson, 1989a). Thus, it is important to establish which scales should be used to measure symptoms and to determine the intensity and duration of exercise which is most appropriate for evaluation of symptoms. Poole-Wilson, (1989a), on page 355 outlines the need for a "new" exercise test, "There is a need for a simple exercise test which can be used to evaluate symptoms of patients with chronic heart failure and to test the efficacy of new drugs as they become available. The test must be simple, cheap, reproducible and sensitive. Exercise tests which relate to everyday activities of patients appear promising."

1.1.5. ASSESSMENT OF THERAPEUTIC RESPONSE .

Studies involving the evaluation of therapeutic agents is commonplace in cardiology. These studies have incorporated a variety of exercise protocols and sometimes subjective scales are used. Therapeutic interventions often involve a run-in period and fairly extended periods of time between exercise tests. Thus, the evaluation of exercise tests and subjective scales should attempt to mirror the time scales and procedures of drug trials.

1.1.6. STEEP PROTOCOL.

A new exercise protocol, the STEEP protocol (Northridge et al; 1990) which is currently in use in a number of hospitals, has been included in the evaluation of therapeutic agents. In addition, this protocol is currently being used to assess cardiorespiratory fitness in a medical screening project in 2000 people in the West of Scotland. The STEEP protocol

has been extended to accommodate the anticipated wide range of fitness levels in a cross section of the population. The extended protocol has been called the STEXT protocol. No evaluation of this protocol has been carried out to date with the use of subjective scales. An appraisal of the protocol using two subjective scales under similar conditions to a drug trial would provide information on the reproducibility of measurement. In addition, the effect of beta blockade on exercise function could be used to measure sensitivity and therefore may indicate which subjective scale is more sensitive to intervention.

1.1.7. THESIS CONTENT.

This thesis has been subdivided into three parts:

PART ONE.

The reproducibility and sensitivity to change of three subjective scales in normals.

PART TWO.

Symptomatic and physiological responses to a submaximal exercise test in chronic heart failure patients.

PART THREE.

An evaluation of the STEXT protocol in normal subjects.

CHAPTER 2
SECTION ONE.

REVIEW OF LITERATURE

CHRONIC HEART FAILURE.

2.1.1. AETIOLOGY.

In the Framingham study hypertension was the major aetiological factor in 75% of CHF cases with coronary heart disease accounting for only 10% of cases (McKee et al; 1971). However, recent studies indicate that coronary artery disease is the major cause of CHF (Teerlink et al; 1991).

2.1.2. PREVALENCE.

The Framingham study reported that the incidence rate of CHF was 3 per 1000 for both sexes aged between 35-64 years and 10 per 1000 for those aged 65-94 years. (McKee et al; 1971). Using these figures it was calculated that there were 400,000 new cases in the USA in 1983. For the same year 2.3 million cases of CHF were estimated for the USA. In a survey of three London family general practices with a combined population of 30,204, 117 patients (0.4%) had CHF. The prevalence rate was only 0.06% for those under 65 years but increased to 2.8% for those over 65 years (Sutton,1990). The study of McMurray et al; (1993) demonstrated that CHF is an increasingly common and costly cause of admission to hospital in the U.K. The authors concluded that in-patient mortality was very high and that CHF is a major health problem.

2.1.3. MORBIDITY AND MORTALITY.

CHF is responsible for a dramatic impairment in the quality of life. Jessup, (1986) stated that CHF is characterised by general fatigue and dyspnoea which results in limited physical work capacity. Other problems associated with CHF are socio-economic limitations, emotional concerns and adverse side effects (Rector and Cohn, 1993). The Framingham study reported that the probability of dying within five years of onset of CHF was 62% for males and 48% for females (McKee et al; 1971). Several studies have

confirmed the poor prognosis for CHF patients and indicate higher mortality rates with increasing clinical severity (SOLVD, 1990; Gillum, 1990).

2.1.4. IMPLICATIONS.

Better treatment of patients who suffer from the clinical manifestations of CHD may increase the incidence of CHF. As the general population will become "older" and the incidence of CHF is associated with age, it is likely that the incidence of CHF will continue to rise.

2.1.5. PATHOPHYSIOLOGY.

Many complex and interrelated pathophysiological mechanisms are involved in CHF. Systolic impairment and/or diastolic dysfunction are characteristics of CHF. The inability of the left ventricle to contract with sufficient power to expel the venous return is often associated with the inability to relax with sufficient speed and adequate compliance during diastole to allow optimal filling (Braunwald, 1988). The consequences of ventricular dysfunction are an increase in ventricular volume, slower ventricular filling and a fall in ejection fraction. In CHF a number of adaptive mechanisms take place to maintain pump function. The development of hypertrophy is a common compensatory mechanism which is not well understood. Chronic pressure or volume overload on the ventricle results in myocardial hypertrophy and depresses contractility and performance of the heart. Myocardial hypertrophy is considered to be a compensatory process which normalises wall tension (Kiowski, 1989). Salt and water retention increases the circulatory volume. This leads to an increased filling pressure in the affected ventricle. The increased preload helps maintain cardiac performance. However, the adaptive mechanism are finite and adverse events produce the syndrome of chronic heart failure. Increased ventricular wall stress and myocardial oxygen consumption, reduced cardiac output and the stimulation of neuroendocrine responses are all unfavourable responses to heart failure. Cardiac output is reduced in CHF but blood flow to the brain and heart is maintained whereas blood flow to the skin, skeletal muscles and splanchnic regions is reduced. The compensatory mechanisms which result from the fall in output from the failing heart - some

vasoconstrictive and others leading to salt and water retention eventually become a major problem in themselves. A decrease in cardiac output promotes a response from the kidney which leads to an expansion of extracellular fluid volume and ultimately to circulatory congestion and oedema. A decline in cardiac output results in vasoconstriction which tends to maintain perfusion pressure but increases aortic impedance and eventually impairs ventricular function. It is suggested that the compensatory response seen in CHF is an ancient reflex with the purpose of maintaining blood pressure (Harris, 1987).

2.1.6. CENTRAL HEMODYNAMICS.

The three major determinants of stroke volume have traditionally been considered to be contractility, preload and afterload.

2.1.6. (a) CONTRACTILITY.

Physiologically, contractility refers to a muscle's ability to shorten independently of its end diastolic length and the load opposing shortening (and in vivo, heart rate). Decline in contractile function in CHF has been attributed to infarction or cardiomyopathic processes. However, it has been demonstrated that surviving muscle may show abnormal contractile responsiveness (Braunwald, 1988). Beta adrenoreceptor down-regulation may limit the normal inotropic response to catecholamines (Hammond, 1993). A variety of other abnormalities may also be responsible for injury or even destruction of normal muscle and thus contribute to reduced cardiac function. Reductions in the maximal velocity of shortening of unloaded myocardium and a decrease in the development of maximal isometric force are characteristics of depressed cardiac performance (Braunwald, 1988).

2.1.6. (b) PRELOAD.

The preload is determined by end diastolic fibre length and end diastolic volume (EDV). The principal variable which influences EDV is the rate of venous return to the heart. An increase in the end diastolic volume will enhance the contractile potential of the ventricle according to the Frank Starling mechanism (i.e. lengthening of the sarcomeres to an

optimal level of thick and thin element overlap enhances contraction). The extracellular fluid volume expansion, venoconstriction, a reduced venous capacity and a decreased ventricular compliance contribute to an increased preload in CHF. In CHF, the left ventricular function curve is depressed which results in little increase in cardiac output despite an increase in preload. Pulmonary oedema occurs when end diastolic pressure reaches a critical level.

2.1.6. (c) AFTERLOAD.

The load applied after the onset of muscle contraction is referred to as the afterload. The afterload is primarily influenced by the aortic pressure during ejection. Increases in aortic pressure raises the level of the afterload. Stroke volume is inversely proportional to the afterload - an increase in aortic pressure produces a decrease in stroke volume. Aortic impedance is largely determined by systemic vascular resistance but other factors which include large artery compliance and blood viscosity also have a bearing on aortic impedance. In CHF small changes in afterload can have a marked effect on cardiac output. Unlike the normal ventricle, a small increase in systemic vascular resistance can cause a marked decrease in cardiac output whereas a slight fall in afterload can greatly increase cardiac output. When there is a marked reduction in contractility, and no preload reserve is available, any increase in afterload results in a significant decrease in the velocity of shortening (Katz, 1987).

2.1.7. NEUROENDOCRINE RESPONSE.

Impaired ventricular function and the associated fall in cardiac output results in a relative hypoperfusion of various organs which prompts a neuroendocrine response. This neuroendocrine response incorporates a variety of processes and includes the activation of the renin-angiotensin-aldosterone system (RAA), the sympathetic nervous system, vasopressin, atrial natriureic factor (ANF) and prostaglandins (Poole-Wilson, 1989b). The main aims of the neuroendocrine response are the maintenance of blood pressure by constriction of the systemic arteries and veins and an expansion of blood volume (Van Gilst and De Graeff, 1990). Abnormal baroreflex function may be responsible for much

of the neurohumoral activation (Marin-neto et al; (1991). The increase in blood volume is brought about by the retention of salt and water as a result of increased aldosterone secretion and stimulation of the antidiuretic hormone. Higher circulating concentrations of angiotensin II contribute to excessive vasoconstriction of the peripheral arteriolar resistance vessels and those and increase in afterload. In addition, vasoconstriction is augmented by an increase in vascular resistance as a result of increased salt and water retention. Angiotensin II (a potent sodium retainer) is a powerful stimulus to adrenal secretion of aldosterone, leading to salt retention. The above vasoconstrictor mechanisms are countered to a certain extent by ANF and vasodilator prostaglandins which tend to lower vascular resistance and promote salt and water excretion. It is important to stress that a significant considerable part of the neuroendocrine response is as a result of diuretic therapy and not CHF per se (Goldsmith et al; 1989).

2.1.8. SYMPATHETIC NERVOUS SYSTEM.

A major compensatory mechanism in CHF is an increase in sympathetic activity as evidenced by increased plasma concentrations and urinary excretion of norepinephrine (Richards, 1989). Increased sympathetic drive augments myocardial contractility. Enhanced sympathetic activity moves the Starling curve upward and to the left and thereby increases the rate and force of each cardiac contractionat any fibre length. Increased sympathetic activity also results in an increase in cardiac output and peripheral perfusion. Desensitisation of vessels and the myocardium to agonists is a characteristic of CHF (Colucci et al; 1989).

2.1.9. RAISED PERIPHERAL RESISTANCE.

Increased peripheral resistance and changes in the distribution of the cardiac output at rest and during exercise characterise CHF. Alteration in the distribution of the cardiac output and increased peripheral resistance cannot be solely attributed to a neuroendocrine response. Changes within the microvasculature of the endothelial cells or smooth muscle are associated with a reduction in blood flow to skeletal muscle during exercise. Vascular

"stiffness" is increased by vessel wall sodium content and arterial compliance is reduced (Poole-Wilson, (1989b).

2.1.10. PERIPHERAL HAEMODYNAMICS AND REGIONAL BLOOD FLOW.

Alterations in cardiac output distribution and increased peripheral resistance are implicated in the reduced muscle blood flow during exercise which result in decreased exercise performance, general fatigue and dyspnoea. The kidney does not receive an adequate blood flow which leads to fluid retention.

2.1.11. SKELETAL MUSCLE ABNORMALITIES.

A variety of skeletal muscle abnormalities have been described in CHF. Alterations in fibre type, changes in muscle metabolism and muscle enzyme activity and reductions in muscle strength and endurance have been found (Drexler, 1992). A lowered rate of muscle protein synthesis in the early stages of heart failure and an increased rate of protein breakdown in the advanced stages of CHF have been reported.

2.1.12. THE LUNGS.

The lower ejection fraction which characterises CHF results in an increased pressure and volume in the pulmonary arteries and veins. The pulmonary capillary volume and total lung water are also increased. These changes result in large discrepancies in the ventilation perfusion ratio in the lung.

2.1.13. TREATMENT.

The main aims in the treatment of heart failure are:

1) relief of symptoms.
2) reduction in the incidence of morbid events.
3) increase in longevity.

The pharmacological treatment of heart failure has traditionally centred on two areas:

1) the use of diuretics and vasodilator drugs to reduce salt and water retention, and unload the heart (Van Zweiten, 1990).

2) enhancement of cardiac contractile force with the use of inotropic drugs.

Diuretic treatment is the most effective drug which provides symptomatic relief for CHF patients. Diuretics act by promoting renal excretion of salt and water and by blocking tubular reabsorption of sodium and chloride. Diuretics and sodium restriction result in the activation of the renin angiotensin system which promotes the formation of angiotensin (a potent vasoconstrictor) and an increase in afterload.

ACE Inhibitors (ACEIs) (eg captopril, enalapril) have a number of effects including a lowering of systemic vascular resistance, increased cardiac output, decreased blood pressure, improved renal perfusion and an increase in blood flow to exercising skeletal muscle. ACEIs have been shown to be effective in prolonging life in patients with all grades of heart failure, and increase exercise tolerance (Firth, 1988). The increase in exercise capacity is delayed until after some weeks of therapy, and is believed to be the result of an increase in skeletal muscle blood flow following vasodilation (Riegger, 1991).

Positive inotropic drugs strengthen the contractile force of the heart independent of load alterations (Schlepper et al; 1989). Digoxin is an inotropic drug which inhibits sodium-potassium ATPase; Intracellular sodium is exchanged for extracellular calcium. These higher intracellular levels of calcium allow increased binding of contractile proteins actin and myosin resulting in enhanced contractility. Digoxin enhances baroreceptor function and decreases sympathetic nervous system activity which results in an increased limb blood flow (Braunwald, 1988).

Dobutamine is a selective agonist of the beta 1 receptor which increases intracellular cyclic AMP which results in increased calcium availability for contraction. Amrinone and milrinone are phosphodiesterase inhibitors which inhibit phosphodiesterase and therefore

prevent the breakdown of cyclic AMP, the accumulation of which results in increased contractility.

Several types of vasodilators (eg. hydralazine, flosequinan) are potential therapeutic agents used in heart failure. Flosequinan causes both arterial and venous dilatation while hydralazine has a predominantly arterial effect. Arteriolar vasodilators reduce the after-load which results in an increased cardiac output. Alpha adrenergic blockers (eg prazosin) and direct smooth muscle relaxants (eg hydralazine) are examples of arteriolar vasodilators. Venodilators (eg isosorbide mononitrate) reduce pre-load by reducing venous return and lead to a fall in pulmonary arterial pressure. It might be expected that an increased cardiac output and a concomitant decrease in systemic vascular resistance would result in a reduction in symptoms. However, haemodynamics at rest, during exercise or during acute drug therapy have been shown not to give an accurate prediction of the patients' symptomatic response. While some vasodilator s have been shown to alter haemodynamics acutely, a lack of chronic response has been attributed to the development of drug tolerance .

A few drugs which have a simultaneous inotropic effect and vasodilator effect and are termed inodilators. Dopamine and dopexamine are examples of inodilator drugs which improve contractile performance by the stimulation of cardiac beta and possibly alpha 1-adrenoreceptors. Stimulation of dopaminergic receptors in the blood vessels and the kidney cause vasodilation and enhanced renal perfusion. Dopamine is not such an effective inotrope as dobutamine but the selective action of dopamine on dopaminergic receptors enhances renal perfusion.

2.1.14. CLINICAL MANIFESTATIONS.

Appropriate methods are necessary to enable the clinician to evaluate the efficacy of treatment on patient symptoms.

2.1.15. CLASSIFICATION OF CHF PATIENTS

Peak $V0_2$ has been used to assess functional status of CHF patients but is not routinely used in hospitals as measurement of peak VO_2 is expensive, time consuming and requires experienced personnel. The New York Heart Association (NYHA) classification system (Braunwald, 1988) has been used to classify the severity of CHF by assessing the severity of symptoms experienced in everyday life. The assessment criteria rely heavily on the physician's subjective appraisal of how compromised the patient is and relate how the patient's symptoms correspond to "ordinary activity". The severity of heart failure is usually graded to the level of physical activity at which breathlessness and general fatigue appear. Cowley et al; (1991) have described the NYHA scale as an attempt to quantify a clinical description but concluded that it is a crude measure of disability and that a much better way of measuring patients' functional ability is to use some form of exercise test.

The value of the NYHA classification has been questioned due to the subjectivity of measurement and limited reproducibility of measurement (Smith, 1985, Goldman et al; 1982). Furthermore, the NYHA lacks the sensitivity to detect small but clinically important changes (Van den Broek et al; 1992). As the NYHA classification system categorises patients on a subjective impression of the degree of functional compromise, it may be that a decrease in physical activity may be interpreted as an improvement because the new activity level could result in fewer symptoms being reported (Goldman et al; 1982).

Traditionally assessment of therapy effects has centred around clinical measures. The limitations of these measures have been recognised and quality of life assessment has emerged as an important outcome measure. Eriksson et al; (1988) have reported that quality of life measures demonstrated that CHF patients on drug treatment were more adversely affected than those who were not treated. The results from a study entitled "Quality of Symptom Control - The Patient Perspective", suggest that the physician may not fully appreciate the actual impact that CHF has on a patient's lifestyle. Brice, (1993)

has found that there are differences between patient, physician and spouse perspectives on the impact of heart failure. He indicated that physicians appear to focus on the symptoms of heart failure, which many patients tend to avoid provoking through adjustments in lifestyle and restriction of everyday activities.

Weber et al; (1984) classified CHF patients according to the peak VO_2 attained in an exercise test. This stratification has been shown not to correspond with the NYHA classification and it is doubtful if the severity of cardiac dysfunction can be assessed by an incremental exercise test.

Limitations in the current tests employed to classify CHF patients and monitor changes in status highlight the need for other tests to be developed.

CHAPTER 2
SECTION TWO

SYMPTOMS IN CHRONIC FAILURE.

2.2.1. BREATHLESSNESS AND FATIGUE IN CHF.

Dyspnoea and fatigue characterise CHF. The causes of these symptoms are multiple and may be interrelated. CHF patients have a peak $V0_2$ of less than 25 $ml.kg^{-1}. min^{1}$ (Franciosa et al; 1979). Thus, participation in normal daily activities may force them to function so close to maximum that fatigue results. Lipkin et al; (1986a) have shown that the symptom which ultimately terminated exercise was dependent on the type of exercise protocol employed. In a "fast" protocol, all subjects stopped exercising as a result of breathlessness whereas in a "slow" protocol 23 out of 25 subjects terminated the exercise due to fatigue. The sensation of breathlessness was associated with a higher ventilation, peak lactate and a lower pH during the "fast" protocol compared with the "slow" protocol.

A variety of abnormalities which may affect exercise capacity and have a bearing on symptoms in CHF patients have been reported. An examination of these abnormalities may provide information on how these factors relate to general fatigue and breathlessness.

2.2.2. HAEMODYNAMIC FACTORS.

Attempts have been made to explain the severity of symptoms by examining exercise capacity and haemodynamic variables. Cardiac output is chronically reduced in CHF at rest and exercise. The inability to increase cardiac output to meet O_2 requirements has been cited as the reason for the decrease in physical work capacity and a possible reason for fatigue in CHF (Weber et al; 1986). A poor relationship has been found between indices of systolic ventricular function, symptomatic status and exercise capacity (Franciosa etal; 1981). Szlachcic et al; (1985) showed no association between the change in ejection fraction from rest to peak exercise and exercise capacity. Correlations between

indices of left ventricular function and exercise capacity have been consistently low, ranging from -0.10 to 0.24 (Myers and Frolicher, 1991).

Right ventricular ejection fraction (RVEF) has been shown to correlate with exercise capacity (Baker et al; 1984). This finding suggested an important role of the RV in determining the exercise capacity of CHF patients. There is evidence of an interaction between right and left ventricles in LV dysfunction. Baker and her colleagues speculate that RV overload displaces the interventricular septum into the LV which alters the geometry and distensibility of the LV. In a recent study with 109 patients, Deedwania et al; (1993) found that LVEF and RVEF were poor predictors of exercise tolerance. The authors suggested that earlier studies that showed RVEF to be have a good correlation with exercise tolerance, could be explained by the fact that there were few subjects in these studies.

Abnormal pulmonary haemodynamics is a characteristic of CHF. Exercise capacity has been increased in some but not all studies which have lowered pulmonary and right sided cardiac pressures by chronic pharmacological means (Massie et al; 1984). Furthermore, pulmonary arterial hypertension resulting from backward transmission of elevated left heart and pulmonary capillary pressures may lower RV function.

2.2.3. NEUROHUMORAL ABNORMALITIES.

Reduced exercise capacity in CHF can be partly attributed to abnormalities in neurohumoral mechanisms. Although catecholamine concentrations are thought to be higher in CHF, it may be there is a reduced sympathetic response during exercise (Francis, 1987). Reduced beta receptor density and sensitivity have been shown in CHF and contribute to the chronotropic incompetence (Collucci et al; 1989). Baroreceptor reflex changes have been observed in animals with heart failure which may also contribute to chronotropic incompetence and lowered systolic pressure during exercise which may be linked to peripheral perfusion abnormalities (Higgens et al; 1972) .

2.2.4. PERIPHERAL ABNORMALITIES, BLOOD FLOW ABNORMALITIES.

Abnormalites of the peripheral circulation have been cited as one of the major causes of fatigue in CHF. It has been demonstrated that CHF patients have a greater than normal exercise A-VO_2 difference which has been interpreted as a compensatory response to reduced skeletal muscle blood flow. It has been shown that in CHF patients, the exercising muscle has a more rapid depletion of creatine phosphate and a decrease in pH compared with normals (Wilson et al; 1985). Impairment of blood flow to the exercising muscle is one possible reason for this response which would result in an imbalance between energy requirements and oxygen substrate delivery.

Although A-VO_2 difference was greater in CHF patients than normals, Rubin et al; (1982) found that peak VO_2 was 40% lower which indicated that despite the higher A-VO_2 difference this compensatory measure was inadequate to make up for the reduced blood flow. The Rubin and Brown, (1984) study and others (Wilson et al; 1984) suggest that the reduced exercise capacity in CHF is mainly due to limited oxygen availability to the skeletal muscles. Zelis and Flaim (1982) found that the more severe the CHF, the greater the impairment of regional distribution in cardiac output in CHF. Wilson et al; (1984) showed that CHF patients stopped exercising because of fatigue when skeletal muscle underperfusion reached a critical level and that this level of exercise intolerance was a direct function of the degree of impairment of skeletal muscle blood flow. The reduced skeletal muscle perfusion is one possible reason for the lower exercise capacity in CHF as a close relationship has been established between the early onset of anaerobic metabolism, metabolic acidosis and impaired work capacity in CHF patients (Sullivan et al; 1989). Cowley et al; (1986) found a significant correlation between the maximum exercise duration of CHF patients and calf blood flow after exercise and at rest. In addition, the CHF patients had a higher VE and decreased VO_2 compared with controls which is suggestive of an earlier onset of anaerobic metabolism.

A number of reasons for impaired skeletal muscle blood flow have been suggested but the underlying mechanisms remain unclear. Arterial vasodilation during exercise has been shown to be lower in CHF relative to normals (Zelis and Flaim, 1982). It is thought that sodium and water retention is implicated in this impaired vasodilatory response (Zelis and Flaim, 1982). Sullivan et al; (1989) found that a lower proportion of the cardiac output was delivered to the skeletal muscles during exercise in CHF patients compared with normals. Even although the cardiac output was reduced, the CHF patients maintained a normal mean arterial pressure as a result of a higher than normal vascular resistance. Conversely, Wilson et al; (1986) concluded that there was no vasodilatory abnormality. Wilson et al; (1986) reported that reduced arterial blood pressure response in patients was the most likely mechanism responsible for underperfusion in nonedematous patients. A reduction in sympathetic drive and vasoconstrictor tone in CHF patients during exercise have been suggested reasons for arterial hypotension and skeletal muscle underperfusion (Wilson et al; 1993). Excessive sympathetic tone in CHF could impair vasodilation during exercise. However, it has been shown that acute blocking of alpha adrenergic tone does not always produce an increase in leg blood flow. Increases in plasma angiotensin as a result of renin-angiotensin-aldosterone stimulation has several effects including a probable increase in sodium and water content in the vascular walls and a resultant increase in vascular "stiffness."

The deconditioned state in CHF has been implicated in the reduced skeletal muscle blood flow (Sinoway et al; 1988). Chronic high flow states may promote endothelial changes which result in a facilitated release of endothelial derived relaxing factor whereas the opposite has been shown in CHF (Miller et al; 1986, Kaiser et al; 1988). Poole-Wilson et al; (1989b) stated that the cause of the increased resistance in vessels supplying the limbs is unknown. They cited the example of the changes in forearm resistance after heart transplantation (Sinoway et al; 1988) which does not return to normal for at least 4 weeks and concluded that changes are not directly linked to central haemodynamics. Some

studies indicate that peripheral vessels are deconditioned. After 4-6 months of aerobic training CHF patients showed an increase in peak leg blood flow and a fall in leg vascular resistance with no change in mean arterial pressure (Sullivan et al; 1988). These findings suggest an increase in vasodilatory capacity and/or a decrease in sympathetic vasoconstrictor activity.

2.2.5. SKELETAL MUSCLE ABNORMALITIES.

The impairment of nutritive flow to the exercising muscle is not the only possible cause of fatigue in CHF. Indeed, Wilson et al; (1993) found in their study that a substantial number of patients developed exertional fatigue due to skeletal muscle abnormalities rather than due to a reduction in skeletal muscle blood flow. Sullivan et al; (1990) concluded that intrinsic abnormalites in skeletal muscle have a potentially important role in the development of early lactic acidosis and fatigue. They showed that CHF patients' skeletal muscle abnormalities included fibre atrophy, a decrease in the percentage of type one fibres, an increase in type two fibres and a decrease in oxidative enzymes. A metabolic abnormality whereby skeletal muscle oxidative enzymes may be significantly reduced could be responsible for a reduced exercise capacity (Drexler et al; 1987) and may occur as a result of deconditioning (Cohen-Solal, 1989). Similarly, skeletal muscle atrophy and the associated muscle weakness may have a role in fatigue in CHF (Poole-Wilson and Buller, 1988). Histological abnormalities have been shown in the quadriceps muscles of CHF patients which have been related to reduced strength levels compared with normals (Lipkin et al; 1986a). The 'early' recruitment of fast twitch fibres during exercise in CHF patients would result in the production of lactate at a lower workrate in CHF patients.

The lower pH and increased levels of inorganic phosphate in the exercising skeletal muscle observed in some CHF patients compared with normals are likely causes of fatigue in CHF patients (Massie et al; 1987), Wiener et al; 1986). Significantly, the CHF patients with lower pH values at submaximal exercise were found to be the more symptomatic patients. Massie et al; (1987) concluded that intracellular pH may be a major determinant

of fatigue. Astrand and Rodahl, (1986) discussed the possibility that hydrogen ions alter the binding of calcium ions to muscle regulatory proteins and therefore reduce the contractile force. They hypothesise that a decrease in pH could reduce the myofibrillar ATP ase activity which would decrease the rate of ATP turnover and cross bridge cycling. CHF patients have a reduced work capacity and for a given workrate will be working closer to maximum and initiate anaerobic metabolism at a lower workload than normals.

2.2.6. DISPROPORTIONATE INCREASE IN VENTILATION.

Reduced skeletal muscle blood flow and the resultant muscle underperfusion promotes anaerobic glycolysis which leads to intramuscular lactate accumulation and lactate release into the blood (Karlson and Jacobs, 1982). Reddy et al; (1988) found that light isometric forearm exercise in CHF patients represented an anaerobic contraction with lactate production. They concluded that the subsequent increase in $C0_2$ production was responsible for a disproportionate increase in minute ventilation during recovery which may partly account for the perception of breathlessness in CHF patients. Other possible reasons for an increased blood lactate level in CHF patients during exercise include the possibility of early recruitment of fast twitch fibres and reduced liver blood flow resulting in diminished hepatic metabolism. Lipkin et al; (1986a) concluded that the sensation of breathlessness was associated with a rapid rise in plasma lactate concentration and a fall in pH. Compared with a "slow" exercise protocol, they found greater plasma lactate levels during a "fast" protocol which coincided with a higher level of breathlessness. The sensation of breathlessness was accompanied by increases in VE during the "fast" protocol which may indicate that breathlessness is linked to VE. Thus, the sensation of breathlessness was associated with an increase in plasma lactate levels and a fall pH stimulating a hyperventilatory response. This apparently plausible explanation for breathlessness and fatigue does not necessarily imply a cause and effect. Patients with McArdle's syndrome cannot produce lactate yet demonstrate a non linear increase in ventilation (Hagberg et al; 1989). Recently, it has been suggested that increased plasma potassium levels could result in a disproportionate increase in ventilatory drive via the

carotid bodies which are potassium sensitive (Busse et al; 1991, Paterson et al; 1990). Exercise is associated with a rapid increase in plasma potassium. Barlow et al., (1994) showed that the exercise induced rises in arterial plasma potassium and VE at given submaximal workrates were greater in CHF than subjects with normal LV function. The authors concluded that the close correlation between VE and potassium supported the hypothesis that potassium may serve as a humoral signal in the drive to breathe. Wilson et al; (1988) used dichloroacetate to decrease lactate formation by increasing pyruvate oxidation. The findings from this study suggest that intramuscular lactate is not responsible for muscular fatigue as there was no change in exercise capacity between the control situation and the dichloroacetate administration. Thus, it is possible to decrease blood lactate levels without enhancing muscle perfusion. The authors postulated that the production of the diprotonated acidic form, of inorganic phosphate (H_2PO_4) may cause muscular fatigue. Wilson et al; (1988) also noted that respiratory gases did not change despite changes in blood lactate. Thus, the possible linkage between changes in blood lactate levels and ventilation appear to have limitations.

2.2.7. "EXCESSIVE" VENTILATION.

During exercise CHF patients demonstrate increased ventilation (termed "excessive ventilation" by Rubin and Brown, 1984) compared to normals. The size of this abnormality is closely linked to the degree of chronic heart failure (Weber et al; 1982). Weber et al; (1982) have shown that as peak VO_2 declines in CHF patients, the ventilation rate for any given work rate becomes higher. Fink et al; (1986) confirmed that excessive ventilation responses are frequent in CHF and reported that the $VE/VC0_2$ ratio (at a VCO_2 of 1 litre per minute) ranged from 27-71 and exceeded the 33 or less observed in non-CHF individuals. They found that the VE/VCO_2 ratio did not correlate with peak exercise pulmonary artery wedge pressure.

VCO_2 is closely related to VE in normals and CHF patients. However, in CHF patients, the slope of the VE/VCO_2 relationship is increased and the slope correlates with the

decrease in peak VO_2 (Buller and Poole-Wilson, (1990). Furthermore, the same authors have found that for any given rate of CO_2 production the respiratory rate is higher in CHF patients. Poor lung compliance may contribute to the increased respiratory rate. This occurs with the accumulation of interstitial fluid and may activate the (J) receptors which may cause tachpynoea and promote the sensation of breathlessness (Karlsberg et al; 1979). However, there is a poor relationship between decreased lung compliance and the degree of dyspnoea (Paintal, 1969). Furthermore, only small increases in pulmonary blood volume and pulmonary extravascular fluid have been found with CHF patients (Hayward and Knot, 1955). Franciosa et al; (1984) found exercise intolerance in CHF patients was associated with an increase in pulmonary capillary wedge pressure. They suggested that therapeutic interventions might decrease symptoms by lowering wedge pressures. The findings of Lipkin et al; (1986a) suggest that a high pulmonary capillary wedge pressure is not the major factor associated with the sensation of breathlessness in CHF. They found that there was no difference in the maximum pulmonary capillary wedge pressure at the end of "slow" and "fast" protocols but the patients reported a much higher incidence of breathlessness during the "fast" protocol. Thus, symptoms were altered by changing the protocol but the pulmonary capillary wedge pressure remained the same. Furthermore, Fink et al; (1986) found that an acute decrease in intrapulmonary pressures with vasodilator or inotropic therapy did not decrease exercise ventilation during exercise in CHF patients. In a comparison of pulmonary artery pressure changes during maximal treadmill and cycle exercise and daily activities, Gibbs et al; (1990) found that symptoms and pulmonary artery pressure during treadmill and cycle exercise were not the same as during every day activities. The main symptom which limited maximal exercise was breathlessness.

2.2.8. DEAD SPACE.

Rubin and Brown, (1984) postulated that VE is increased in CHF during exercise by two mechanisms:

1) the fraction of dead space/tidal volume is increased, decreasing ventilatory efficiency and requiring greater VE to maintain eucapnia.

2) alveolar hyperventilation.

Both factors combine to increase ventilatory equivalents for O_2 and CO_2. Rubin and Brown, (1984) have postulated that the increase in alveolar ventilation may be as a result of elevated venous pressures stimulating pulmonary receptors which trigger hyperventilation but they concede that it is likely that metabolic acidosis promotes hyperventilation by stimulating peripheral chemoreceptors. It has been suggested that ventilation perfusion mismatch could explain the increase in ventilation in CHF patients (Rubin et al; (1982) i.e. areas of high perfusion and low ventilation (ie. increase in physiological shunting) and areas of normal ventilation but low perfusion (ie. increased dead space ventilation). It has been shown that dead space is increased in CHF patients. Total physiological dead space consists of the anatomical component (conducting airways) and alveolar dead space ie. the alveoli which are ventilated and not perfused. While anatomical dead space is not increased in absolute terms, Weber et al; (1982) have postulated that anatomical dead space is increased relatively in CHF patients as increased respiratory rates at smaller tidal volumes could be a contributory factor. Sullivan et al; (1988) concluded that the increase in VE was due to elevations in the dead space/tidal volume (Vd/Vt) ratio and was not related to lactate production or increased pulmonary vascular pressures. Sullivan et al; (1988) found that cardiac output was inversely related to Vd/Vt and VE/VCO_2 and they postulated that decreased lung perfusion may accentuate ventilation perfusion mismatching and increased pulmonary dead space. They also reported no differences in VE/VCO_2, Vd/Vt or alveolar ventilation/volume of CO_2 produced (Va/VCO_2) in patients with normal wedge pressures versus patients with increased pressures.

Weber et al; (1982) have shown that for any given rate of CO_2 production, CHF patients demonstrate a higher respiratory rate. The greater the decrease in peak VO_2 the higher the respiratory rate for any given workrate. The increased respiratory rate may result in a

greater respiratory effort to ventilate the dead space. Buller and Poole-Wilson, (1990) concluded that two thirds of increase in ventilation in CHF patients was due to an increase in physiological dead space ventilation and a significant ventilation perfusion mismatch. The cause of the increased alveolar ventilation is unknown. Buller and Poole-Wilson, (1990) attributed the other third increase in ventilation to changes in breathing pattern. Sullivan et al; (1988) have shown that the primary mechanism for an increased respiratory rate in CHF is an abnormal increase in physiological dead space per breath. They have postulated that an abnormally low cardiac output results in a ventilatory perfusion mismatch.

2.2.9. ARTERIAL OXYGEN SATURATION.

A fall in arterial oxygen saturation might be expected if a respiratory limitation was implicated in the reduced work capacity in CHF. Several studies have shown that arterial oxygen desaturation is normal in CHF patients (Rubin et al ;1982). Mancini et al; (1991) confirmed the ventilatory abnormalities associated with CHF (i.e.increased ventilation and respiratory rate compared to normals) but noted that there was respiratory muscle deoxygenation which may be due to respiratory muscle underperfusion. Mancini et al; (1991) reported that there was no arterial oxygen desaturation but concluded that breathlessness in CHF may be partly as a result of respiratory muscle undeperfusion.

CHAPTER 2
SECTION THREE.

USE OF EXERCISE TESTS IN CHRONIC HEART FAILURE.

2.3.1. REASONS FOR EXERCISE TESTS.

Exercise testing in CHF has been widely used for a variety of reasons;

1) to indicate the functional capacity of patients.
2) to predict prognosis.
3) to assess drug intervention.
4) to categorise the severity of heart failure.

The assessment of CHF patients has usually been carried out using incremental protocols to a symptom limited maximum. Assessment of CHF patients using a maximum test has problems:

1) some patients stop before a "true maximum" has been reached.
2) it has been shown that exercise time can be increased by giving encouragement.
3) if a maximum test is used, at least two tests should be performed as a single test will probably underestimate exercise capacity (Elborn et al: (1990).
4) it has been suggested that maximum tests do not simulate everyday life (Cowley et al; 1991).

2.3.2. WHICH TEST? WHAT FOR?

While exercise testing is widely used to evaluate CHF patients, there is no agreement on the most appropriate protocol. In addition, there is no consensus on the interpretation of the results. Gibbs et al; (1991) have shown that walking and stair climbing elicit different

haemodynamic responses to maximum tests and concluded that this may restrict the use of maximum tests in the assessment of CHF patients.

Problems associated with maximum tests have led to attempts to circumvent some of these difficulties. Weber and Janciki, (1985) concluded that the severity of heart failure could be graded by the appearance of anaerobic metabolism (by examining mixed venous lactate levels during incremental exercise). They found that the anaerobic threshold as determined by mixed venous lactate showed a good correlation with non invasive ventilatory values. Lactate levels were very reproducible. They concluded that the anaerobic threshold (AT) (lactate and ventilatory) may be useful markers of severity of heart failure.

The use of the ventilatory threshold (VT) has been explored as a cardiorespiratory measure but has limitations. A variety of criteria have been used to determine VT and various methods have resulted in different values (Cohen Solal et al; 1991). Cohen Solal et al; (1991) examined the use of VT using 5 different graphical methods to determine VT. They found that VT could only be determined between 72-88% in CHF patients using the 5 methods and concluded that the reproducibility of VT was less than the peak VO_2 in the same group of CHF patients. However, using the V slope method Pina et al; (1990) compared the detection of VT using four different protocols in CHF patients and concluded that the VT was more reproducible and effort independent than peak VO_2. The authors referred to a reproducibility to within $\pm$ 7% and did not mention any problems with the detection of VT. In CHF patients, Metra et al; (1990) found that peak VO_2, lactate threshold (LT) and VT were related to each other but significantly the VT could only be found in 77% of the patients tested. If there is an association between VT and LT it would be expected that lactate and ventilatory markers would correspond, this has not always been the case (Spurway, 1992). It has been shown that VT correlates more closely with K^+ accummulation than lactate (Busse et al., 1991). The LT has been shown to be a sensitive marker of training status in athletes. Blood flow influences the removal of

lactate and the uptake of lactate by the liver. Irregularities in blood flow in CHF may influence the LT so that blood lactate measurement may not reflect the production in exercising muscles. Thus, the use of AT (VT and LT) may have limitations in CHF.

2.3.3. SUBMAXIMAL EXERCISE TESTS.

In recognition of the inappropriateness of maximal tests to everyday life, researchers have attempted to use submaximal tests to evaluate CHF patients. For example, an attempt has been made to measure how long a patient can exercise at 70% of maximum (Poole-Wilson, 1989a). Personal experience of this method has shown that exercise times can exceed 30 minutes. Thus the excessive timescale makes this approach impractical. Cowley et al; (1991) compared a Bruce and a sub-maximal protocol in CHF patients. They found that with treatment that the constant work rate test showed a much greater percentage increase than the Bruce protocol. They concluded that a fixed sub-maximal workrate may be better to assess exercise tolerance in CHF as peak VO_2 is difficult to attain. Van Baak et al; (1991) used a sub-maximal workrate on a cycle ergometer to evaluate the use of enalapril on hypertensives. However, the mean exercise time was over 50 minutes making this timescale unaccetpable for clinical use. Koch and Broustet, (1993) used a constant workrate sub-maximal test (two stages under the maximal stage in a 10 watts per minute incremental maximal test) to assess training effects in CHF patients. The mean exercise times were 10 minutes (pre-training) and 19 minutes (post training). The standard deviations of around 14 minutes in both tests indicates a wide range of endurance times.

2.3.4. WALKING TESTS.

Some researchers have used a self paced walk test to evaluate CHF patients. Two types of test have been described. One where experimenters have measured how long a patient can walk in a certain length of time eg. 6 minute walk test. (Lipkin et al; (1986b) investigated the use of a six minute walking test in CHF patients. Patients were asked to walk as far as possible in 6 minutes in a 20 metre "shuttle" corridor test. All subjects preferred the corridor test to a maximal treadmill test. The authors concluded that the 6 minute test was

a simple objective guide to disability and of particular value in assessing patients with severe CHF. A marked limitation in this test is its inability to discriminate between patients with mild heart failure and normal subjects. A corridor walk test where the time taken to walk a fixed distance is measured is another form of walk test (Cowley et al; 1986). The patient controls the pace during a timed corridor test but it is difficult to monitor physiological variables. There is the possibility of distraction and pace judgement may prove to be difficult. Furthermore, patients have been asked to adjust their speed to slow, normal and fast and assessment made on their responses to these descriptions. This methodology would appear to have limitations as the meaning of this approach is unclear.

Guyatt et al (1985) compared a variety of functional tests including incremental tests, a 6 minute walk test and they administered functional status questionnaires. They concluded that the 6 minute walk was reproducible and reported that none of the functional status measures were as reproducible as the 6 minute walk. Cowley et al; (1991) are critical of standard 6 or 12 minute tests as they are symptom limited.

Parameshwar et al; (1989) measured the distance walked on a self powered treadmill and concluded that this method was simple, self paced and avoided the problems of congestion associated with corridor tests. The authors stated that this test has the sensitivity to detect change. However, the fact that the subject must hold on to the support rails would invalidate this test as it is not possible to standardise the workrate.

2.3.5. EXERCISE TESTS - THE FUTURE?

Cowley et al; (1991) considered the best marker of a patient's symptomatic impairment was the amount of exercise carried out in daily activities, and indicated that step counting with body-borne pedometers may be a useful method of monitoring daily activities. This method does not detect pace fluctuations or changes in symptoms.

Guyatt et al; (1985) have suggested that an ideal measure of function in CHF should be highly reproducible, reflect physiological function and be closely related to the patient's ability to cope with the demands of daily living. Undoubtedly the best indicator of exercise tolerance in CHF must be how it relates to every day activities.

Weber and Janicki, (1985) considered that any submaximal test which lacks objective and quantitative endpoints would appear to have limited use in CHF. Poole-Wilson, (1989a) concluded in his review of exercise testing in CHF that "there is a need for a simple exercise test which can be used to evaluate symptoms of patients with CHF and to test the efficacy of new drugs as they become available." He advocated that the test must be simple, cheap, reproducible and sensitive. In addition, he stressed the need for tests which relate to everyday life.

Treadmill exercise, no matter the protocol involves the patient in a learning process to become familiar with the apparatus and surroundings. Thus, it has been suggested that some form of free walking test may provide a better indicator of functional capacity. However, a treadmill test has several merits in the evaluation of CHF patients: Most patients can be quickly familiarised with the apparatus. Walking is a natural activity and part of daily activity. Exercise testing allows the experimenter to relate the patient's sensation of breathlessness and general fatigue to physiological markers. A treadmill in a laboratory enables the experimenter to establish a controlled and reproducible environment and allow for a direct comparison with previous tests, unlike a corridor test or a self powered treadmill which depend on the pace setting of the subject. It seems sensible to assess patients during walking and not cycling as walking is common to all.

A treadmill test which relates to daily activities can measure symptoms has a defined endpoint and is reproducible would be of great benefit in the evaluation and monitoring of CHF patients.

Thus, the concept of two forms of exercise test for CHF patients seems plausible. A submaximal test which measures symptoms and a maximal test which predicts prognosis and measures functional capacity. Both types of test would be valuable in the assessment of drug intervention.

2.3.6. THE QUEST FOR THE "BEST" TEST.

It is important that the clinician is able to gain the patient's own perception of symptoms rather than the impression of an "external observer". Exercise testing can give the clinician the opportunity to assess symptoms in a stable environment. Furthermore, with monitoring of respiratory gases, it should be possible to study any relationship, if any, between the sensation of breathlessness and objective measures of respiration.

In recognition of a need for a new test an attempt was made to establish a protocol which was sub-maximal but had an end point within a reasonable period of time, included an assessment of symptoms, was reproducible and could be easily applied to a clinical setting.

Several CHF patients were given a sub-maximal test at 70% of peak VO_2. However, some subjects were able to continue at 70% peak VO_2 for over 30 minutes. A second strategy involved the selection of the sub-maximal workrate by adopting the workrate at a ventilatory threshold. However, this method sometimes produced treadmill times in excess of 30 minutes.

Experimentation with workrates around 80% peak VO_2 produced (in some instances) treadmill times between 8 and 17 minutes but not in all cases. Therefore, it was decided that it was not feasible to calculate an appropriate workrate which would result in an "acceptable" exercise duration time.

A pilot study (see Appendix A for details) was conducted to determine which subjective scale (VAS and Borg CR10) was more reproducible during submaximal exercise in CHF patients. After two maximal tests the subjects performed a submaximal "trial" test which consisted of 6 minute stages. The subjects started at 60% peak VO_2 and progressed in approximately 10% peak VO_2 increments to a symptom limited endpoint. Based on the findings of the test the subjects were given 3 submaximal workrates during which they were asked to record their perceptions of breathlessness and general fatigue at various timepoints during the test. The subjects performed four tests at weeks 1,2 4 and 6 to examine the reproducibility of the scales.

The results of this pilot study demonstrated that both scales showed good reproducibility at the highest of the three submaximal workrates. Despite the attainment of a reproducible tests clinicians in the hospital considered that the methods employed had some limitations. A trial submaximal test was needed to establish the appropriate range of submaximal workrates. In addition, in most instances there was no symptom limited endpoint i.e. the subjects were stopped by the experimenter at the end of 18 minutes.

It was decided to once again attempt to find a method of selecting a submaximal workrate which would give a "subject limited" endpoint. Experimentation suggested that it was possible to determine an appropriate workrate by selecting 80% of the predicted maximum oxygen cost of the higher workrate attained by the subject during the two maximal incremental tests.

A study was undertaken to establish if this procedure would result in a test which would be simple, could be used to evaluate symptoms and be reproducible. The aim of this study was to evaluate the use of a submaximal test with a symptom limited end point and to measure symptoms in patients with chronic heart failure.

CHAPTER 2
SECTION FOUR

THE STEEP TEST.

2.4.1. THE STEEP TEST.

A variety of exercise protocols are used in cardiology but no single protocol is appropriate for a wide range of patients' exercise capacity. A new protocol (STEEP TEST - Standardised Exponential Exercise Protocol) was devised by Northridge et al; (1990). This new exercise protocol consists of 15 one minute stages and is based on exponential rather than linear increments in workrate. The test begins with a low workrate and because it uses small, frequent increments in energy cost it is suitable for even severely limited patients. Nevertheless it is designed to induce cessation of exercise in cardiac patients within 15 minutes so that boredom and fatigue are not the limiting factors. As the STEEP protocol has very small energy cost increments every minute, it is hypothesised that the STEEP protocol may reflect a range of every day activities and energy costs. Thus, the STEEP protocol may be useful in evaluating symptoms encountered in every day life and may provide an easier method of assessing symptoms than the lengthy procedure of devising a relative intensity from a submaximal test and a maximum test. The STEEP protocol may have the advantage of providing meaningful submaximal information and maximal values in the one test. The STEEP protocol has been used in a number of hospitals and has been adopted to evaluate the effect of drug therapy in a number of drug trials. A limitation of the test is that normals with a relatively high VO_2max score can exceed the highest workrate on the STEEP protocol.

2.4.2. STEXT PROTOCOL.

As the STEEP protocol has been readily accepted by patients and clinicians, it was decided to use the protocol in a study (MONICA) which involved screening of 2000 men and women between the ages of 25-74 years in the West of Scotland. Exercise

testing, blood pressure, lipid profile and echocardiography were included in the test battery. It was necessary to extend the protocol by three stages to accommodate the anticipated high scores from fit young people. The extension of the protocol to a maximum of 18 minutes would have a number of advantages:

It was anticipated that the STEEP extension protocol (STEXT) would be suitable for all subjects in the MONICA study. The West of Scotland population could be categorised into aerobic fitness levels according to the STEXT protocol. Comparison of aerobic fitness levels and coronary risk factors could be made.

While the STEXT protocol has been adopted by the MONICA project more information is required about this protocol. The reproducibility of the maximal values has not been established. The possible use of subjective scales with this protocol has not been investigated. Drug trials normally have a "run in" period to establish representative baseline levels. A possible sequence of tests (involving the STEXT protocol) for a drug trial in patients with stable angina has been proposed. Patients will undergo two tests within 48 hours of each other at weeks 0, 2, 6 and 10. No drug therapy will be administered in the first 4 tests. At weeks 6 and weeks 10, a comparison of drug therapy will be made.

Thus, it was decided to evaluate the STEXT protocol using normals and adhering to the proposed timescale for a patients' study to determine the reproducibility of the physiological variables and subjective scales (Borg CR10 and VAS). No intervention would be made in the first four tests but "therapy" with beta blockers and placebo at weeks 6 and 10 would provide information on the sensitivity to change of the subjective scales.

CHAPTER 2
SECTION FIVE.

SUBJECTIVE SCALES.

2.5. SUBJECTIVE SCALES.

Many studies rely on subjective measures to evaluate outcomes including quality of life, dyspnoea and fatigue. Major debate has centred around the selection of the optimal response options. Guyatt et al; (1987) referred to several studies and concluded that different methods of presenting response options have produced consistently high correlations with each other. However, selection of an outcome measure must be related to its ability to detect clinically important change even if the change is small (Kirshner and Guyatt, 1985). Responsiveness of different scales can be examined by comparing outcome measures in the same trial. A number of subjective scales have been used to measure response options. The choice of subjective scale includes the Visual Analogue Scale (VAS), Likert scale, the Borg 6-20 scale and the Borg Category Ratio Scale (Borg CR10).

2.5.1. VISUAL ANALOGUE SCALE.

The VAS scale consists of a straight line labelled at either end. The subject is asked to respond by registering on the line to indicate his perception of a symptom (eg breathlessness). One end is labelled "none" and the other "very severe" and a title heading depending on the variable being measured (for example, with a breathlessness heading for breathlessness). The scale is scored from 0-100 but this subdivision into numbers is not visible to the subject.

2.5.2. LIKERT SCALE.

A Likert scale is a multi-item scale with verbal descriptors of feelings. For example, a four point Likert scale relating to pain - no pain, a little pain, moderate pain, a great deal of pain.

2.5.4. BORG SCALES.

In 1962 Borg produced a 21 point category rating scale for perceived exertion. This scale was established by taking the fairly close relationship between heart rate and perceived exertion into account. In 1970, Borg devised a 15 point category scale (Borg 6-20 scale). The change to the 15 point scale included changing some of the verbal anchors and the mid-point was lowered. The Borg 6-20 scale has been used to assess subjective rating of perceived exertion. Astrand and Rodahl, (1986) state that this scale can be modified to give a rating of general fatigue, leg fatigue and dyspnoea. In 1982 Borg developed a category ratio scale. This scale consists of a vertical scale labelled 0-10 with verbal anchors of progressively increasing perceived sensation. The scale range is from 0-10. Using the Borg CR10 scale, perceived exertion was shown to increase exponentially when related to exercise. Borg stated in 1982 that the new scale may be appropriate for determining other subjective symptoms eg breathing difficulties.

2.5.3. COMPARISONS OF SCALES.

Comparison of some subjective scales has included the magnitude of between-subject variability, test-retest reliability and the strength of relationship with other measures. The visual analogue scale (VAS) has been considered to be able to detect small clinically important change and therefore be highly responsive (Scott and Huskisson, 1977). However, (Guyatt et al; 1987) concluded that there is little evidence to support this contention. For example, a four point Likert scale and the VAS were compared in a trial to measure pain ratings. The results of this study were inconclusive (Guyatt et al; 1987). It has been shown that subjects found a 7 point Likert scale easier to use than a VAS in a quality of life assessment in patients with respiratory disease. The subjects needed more training time to understand the VAS. Guyatt et al; (1987) stressed that time may not be available in a clinical setting to educate patients in the use of the VAS. Guyatt et al; (1987) considered that the Likert 7 point scale has an added advantage over the VAS in that a change in a 7 point scale seems easier to grasp than a change of 10 or 20 mm in a

VAS scale. They concluded that there was no difference in the responsiveness between the Likert 7 point scale and the VAS. Guyatt et al; (1987) have stated that the Likert 7 point scale is easier to administer than the VAS. They concluded that clinicians intuitively grasp the Likert scale results. Thus, Guyatt and his colleagues recommended the use of the Likert scale. They conceded that results from a quality of life study may not be generalizable to other areas including symptoms. They recommended that other studies are undertaken with other outcome measures in different patient groups.

2.5.5. THE NEED FOR MORE RESEARCH.

The paucity of information on the comparison of response outcomes involving breathlessness and general fatigue makes investigation in this area desirable. Clearly a weakness of subjective scales is the unavoidable subjectivity. However, it is important to establish which scale if any, is reproducible and sensitive to change when the symptoms of breathlessness and general fatigue are assessed.

CHAPTER 2
SECTION SIX.

BREATHLESSNESS (DYSPNOEA).

2.6.1. BREATHLESSNESS (DYSPNOEA).

Dyspnoea has been difficult to evaluate because it is a subjective sensation which may or may not correlate with physiological measurements. There is no generally accepted definition of dyspnoea.

Dyspnoea according to Comroe, (1966) is "difficult, laboured breathing, uncomfortable breathing". Other workers have defined dyspnoea as "an uncomfortable awareness of breathing" (Mahler et al; (1984). Wasserman and Casaburi, (1988) described dyspnoea as "feeling breathless, air hunger" and they state that this symptom is experienced by normal people and patients. "The common experience of an uncomfortable need to breathe" (Adams et al; 1985a), "discomfort in the act of breathing" (Killian, 1988) and "an uncomfortable need to breathe" (Wilson and Jones, 1989) are examples of the various definitions used to define breathlessness.

Normal healthy individuals experience breathlessness which is usually experienced in association with an increase in ventilation but other potential links with breathlessness have not been clearly established.

2.6.2. VENTILATORY CONTROL MECHANISMS DURING EXERCISE.

Exercise results in an increase in cellular oxygen requirement and an increase in CO_2 production. In an incremental exercise test VE, VO_2 and VCO_2 increase linearly to around 60% of a normal persons VO_2 max. Above this value VE shows a disproportionate increase compared with VO_2. VE and VCO_2 both rise more steeply above the "breakpoint" in VE. This increased ventilatory drive has been attributed to metabolic acidosis. During exercise, VCO_2 increases as the intensity becomes greater and VE must

increase to keep the arterial PCO_2 ($PaCO_2$) constant. The increased levels of VE at the higher intensities is considered to be related to the buffering of lactic acid by bicarbonate and the increase in hydrogen ion concentration resulting in a lower arterial bicarbonate following the buffering reaction. During moderate work $PaCO_2$ stays fairly constant due to the increase in VE but, as the VE increases more quickly the $PaCO_2$ falls (Wasserman, 1978). The control of breathing during exercise is considered to be an amalgam of several factors. It has been suggested that neurogenic stimuli from the cerebral cortex or the active limbs result in the initial abrupt increase in VE at the start of exercise. Artificially induced increases in blood flow through canine hearts have resulted in an immediate increases in VE similar to the VE response at the onset of exercise (Wasserman et al; 1974). It has been speculated that chemoreceptors play the most important role in the overall regulation of VE. The precision with which arterial blood gases and acid-base balance are regulated makes this suggestion plausible (Wasserman and Carraburi, 1988).

2.6.3. DYSPNOEA PRODUCING STIMULI.

There are a variety of possible stimuli to breathing and hence dyspnoea. Several studies have reported that during exercise in normals that there is a linear relationship between VE and dyspnoea. Dyspnoea producing stimuli are integrated through the central nervous system. However, the location of the dyspnoea producing stimuli are unknown.

2.6.4. CHEMICAL VENTILATORY STIMULI AND DYSPNOEA - HYPERCAPNIA.

In a study using normals Lane et al; (1987) monitored the perception of dyspnoea while the subjects breathed inspired air in which the CO_2 content was varied in an oscillatory pattern. Subjects were asked to copy the CO_2 breathing pattern without allowing the PC02 to change. The subjects did not experience dyspnoea. The authors concluded that the perception of dyspnoea did not arise from the mechanical act of breathing alone but must involve input from the chemoreceptors as well. In their review, Adams and Guz (1991) concluded that experiments do not support the role of hypercapnia per se as a cause

of breathlessness but they suggest that the degree of reflex activation of VE whether by exercise or CO_2 is a major factor in determining the intensity of breathlessness.

2.6.5. HYPOXIA.

Progressive hypoxia is associated with increasing levels of breathlessness compared with exercise at equivalent levels of VE (Ward and Whipp, (1989), Chronos et al; (1988). Adams and Guz (1991) suggested that afferent activity from the peripheral chemoreceptors may have direct access to the sensory cortex and that the effect of hypoxia may be particularly noticeable in the time lag between the degree of reflex ventilatory activation of the respiratory centres and the resulting ventilatory response.

2.6.6. PULMONARY RECEPTORS AND DYSPN0EA.

Two lung reflexes which stimulate ventilation are thought to contribute to the sensation of dyspnoea and lie in the pulmonary vagus nerves. The inhibitory Hering-Breuer reflex takes place when the pulmonary stretch receptors fire during inspiration. This reflex operates in man only at increased tidal volumes. It has been suggested that J recptors are stimulated by distortion of the interstitial space of the lung. It is believed that disease states (eg. pneumonia) cause tachpnoea by stimulating the J receptors (Adams and Guz, 1991).

2.6.7. LENGTH TENSION.

Campbell and Howell (1963) postulated that dyspnoea arises because there is a mismatch between the demand for breathing and the effort required to achieve it. Campbell and Howell, (1963) hypothesised that tension to breath is appropriate to the tidal volume. When a resistance is imposed, there is a transient decrease in tidal volume which causes stimulation of muscle spindles within the respiratory muscles resulting in an increase in respiratory motor neurone output so that greater tension is produced. Thus tidal volume is maintained but with a greater muscle tension. Campbell and Howell, (1963) postulated that the alteration in the length/tension ratio is responsible for the sensation of

breathlessness being detected. The fact that reflexly stimulated increases in VE result in a perception of breathlessness but increases in volitional VE do not, appears to invalidate the length/tension theory.

2.6.8. CENTRAL RESPIRATORY COMMAND AND BREATHLESSNESS.

It has been suggested that the perception of breathlessness shares the same neurophysiological lanes as the sensation of muscular effort. Furthermore, the sensation of breathlessness comes mainly from the sensing of central nervous system activity and not from specific peripheral receptors (Adams and Guz, (1991)

2.6.9. METHODS OF ASSESSING BREATHLESSNESS.

Clinical interviews are a common method of assessing breathlessness. Interpretation of the responses is difficult as the answer may depend on several factors including the current level of physical activity, the subject's tolerance level, the intensity (energy cost of the task), the prevalence or otherwise of other symptoms, the accuracy of reporting distance and recall. In recognition of the problems associated with the assessment of breathlessness, questionnaires have been developed to categorize patients according to their symptoms reported during a variety of activities. For example, a five point scale has been used to assess breathlessness in daily activities (Medical Research Council, 1966). This five point scale has limitations as it is too insensitive to detect meaningful differences and gives little information on the intensity of the sensation. The scoring system of Mahler et al; (1984) has three different categories "functional impairment", "magnitude of task" and "magnitude of effort". This approach has many theoretical advantages including the offer of many responses by the patient. However, Adams and Guz, (1991) concluded that there is no evidence that the Mahler scale and its finer categorisation has any clear advantage over the five point grading system of the Medical Research Council, (1966).

2.6.10. EXERCISE TESTS.

The use of predetermined workrates (eg cycle ergometer) and the measurement of respiratory variables with concomitant assessment of the patient's symptoms provides the opportunity to compare physiological data with symptoms and both of these responses over time in a standardised environment. Criticisms of exercise tests include the unsettling feeling that many patients report. As a result, corridor walk tests have been used to provide a simple reproducible test which gives an objective index of functional impairment, but does not offer comparison between physiological and symptomatic data.

It is clearly important to be able to assess symptoms and be able to relate them to physiological data.

2.6.11. TERMINOLOGY TO DESCRIBE THE SENSATION OF BREATHLESSNESS.

The fact that there is no universally accepted definition of breathlessness has resulted in the use of a variety of terminology by researchers to describe the sensation of breathlessness. The description of breathlessness has varied greatly and may explain the different results in some studies. Some researchers have asked subjects to measure breathlessness without attempting to define the sensation (O'Neil et al; 1986). Other studies have employed a variety of terminology including "difficult" (Mahler et al; 1987) or "effort" in breathing (Killian et al; 1984). Several groups have referred to the "uncomfortable" nature of the sensation of breathlessness (Wilson and Jones, 1989). Wilson and Jones, (1991b) asked normals to differentiate between intensity and distress of breathlessness. They found that the mean intensity scores were greater than distress scores and that there was no common pattern between intensity and distress. They concluded that different elements of breathlessness could be identified and selectively measured depending on the wording used. These findings support Comroe's suggestion that breathlessness is not a unitary measure and stress that subjects are able to differentiate

between some aspects of breathlessness. The findings of Simon et al; (1989) support the contention that breathlessness is multidimensional in nature. Simon et al; (1989) studied 30 normals and induced breathlessness using 8 different stimuli. The subjects were asked to choose descriptions of their sensation(s) from a questionnaire listing 19 descriptors. Using cluster analysis the investigators were able to look for relationships among the descriptors and identify natural groupings. They found that subjects could distinguish different sensations of breathlessness and they reported an association between certain descriptor groups and stimuli. They concluded that the term breathlessness may encompass a variety of sensations and may not be a single physiological mechanism.

The literature indicates that breathlessness is a multi-dimensional sensation. Thus, it seems reasonable to speculate that the wording of instructions to subjects will influence how they respond to questions on their perception of breathlessness.

2.6.12. MEASUREMENT OF BREATHLESSNESS - VISUAL ANALOGUE SCALES.

Visual analogue scales (VAS) were first used to assess the sensation of pain and sedation but for more than a decade they have been used to assess the perception of breathlessness in normals and patients. Using the VAS in a group of six healthy males, Stark et al; (1981) quantified breathlessness during treadmill walking. They showed that VE and breathlessness scores increased and both values returned to resting levels during recovery. A paired t-test showed they there was no significant difference between VE or VAS scores between test 1 and test 2 which were one week apart. In 4 subjects sensitivity of the VAS was tested by using inspiratory resistances which resulted in an increased level of breathlessness for a given level of VE.

Later, Stark and his colleagues (1982) examined the reproducibility of the VAS in chronic bronchitis and emphysema patients. The patients visited the laboratory three times to allow for a familiarisation period and two identical treadmill tests 5 days apart. They

concluded (despite no statistical back-up) that the relationship between breathlessness scores and VE generally showed adequate within subject reproducibility. Using five asthmatic patients to test sensitivity, Stark et al; (1982) gave the patients a bronchodilator to promote a reduction in breathlessness. They found that in 3 subjects improvement could be clearly detected by the VAS scale, but cautioned that reproducibility could not be invariably attained. Stark et al; (1982) concluded that the assessment of breathlessness in patients was generally reliable and that responses are modified by drug intervention. The authors stressed that the patients in their study were selected for their cooperation and understanding. They cautioned that unselected subjects may use the VAS in an unreliable way. The authors advised that patients should undergo checks to ensure that the VAS is being used in a meaningful way.

Stark et al; (1983) examined the relationship of breathlessness and VE in 6 normals during a sub-maximal treadmill test of three two minute stages. On two different occasions two tests 90 and 130 minutes apart were given, one in the presence of and the other in the absence of inspiratory resistance. Using analysis of variance in accordance with the factorial design the authors reported high reproducibility. In the presence of a respiratory resistance, VE was slightly depressed but a significantly greater sensation of breathlessness was reported in relation to VE with the respiratory resistance.

Adams et al; (1985a) examined the reproducibility of the VAS over a time interval ranging from a day to one year. The subjects (34 males and females) were divided into groups and given a variety of "treatments" including hypercapnia and hypoxia and steady state exercise on a cycle ergometer. Statistics were conducted using a t-test and the relationship was clarified by linear regression analysis. The authors concluded that the reproducibility of the VAS when related to VE was independent of the nature of the ventilatory stimulus. Reproducibility was as good after one week ($r= 0.95$), as one day ($r= 0.95$) but was less good after one year ($r= 0.64$).

Despite the fact that it has been shown that VE is not directly related to breathlessness many studies have compared the relationship between VE and subjective scales. The relationship between VE and breathlessness is not fixed but is related to how breathlessness is induced. Adams et al; (1985b) have shown that breathing 15% O_2 caused an increase in breathlessness (using VAS) before an increase in VE was noted.

VAS scores have been shown to increase independently of VE during the fourth to sixth minute of steady state exercise (O'Neil et al; 1986). O'Neil et al; (1986) examined the response of 6 subjects to two steady state cycle exercise bouts and a progressive cycle test. Both sets of tests were repeated over a period of two days. A paired t-test showed that there was no significant difference in VAS and VE in the progressive test. Despite no change in heart rate, VE VCO_2 or VO_2 in the steady state protocol, the VAS was significantly increased at 6 minutes compared with 4 minutes. The authors concluded that breathlessness is not simply a sensing of VE achieved. This conclusion may be somewhat simplistic as it is unclear as to what is happening to individuals in these analyses. In addition, Wilson and Jones, (1989) have shown that subjects perceived a higher level of breathlessness relative to VE throughout the second half of an identical protocol over a two part test using VAS and Borg CR10 scales.

Muza et al; (1990) examined the "sense of effort" in breathing in chronic obstructive pulmonary disease (COPD) patients 3-5 times. The 6 subjects performed a progressive maximal test on a cycle with 1 hour between tests 1 and 2 and 1-10 days between tests 2 and 3. Tests 4 and 5 were carried out two weeks after the third test. The VAS correlated linearly with VE in all trials ($r= 0.98$) and when converted to common units correlated closely with the Borg Category scale ($R= 0.99$). Using z scores Muza et al; (1990) found that the VAS had almost twice the resolution of the Borg category scale. This finding suggests that the VAS may be almost twice as sensitive an indicator of a change in breathlessness than the Borg category scale. Muza et al; (1990) speculated that the

difference in the resolution may be due to the stated boundary present in Borg category scale. They considered that the subjects were constrained by the apparent maximum in the Borg category scale.

Research has shown that subjects use the VAS scale in an individual way and that only meaningful comparisons are those conducted on within subject basis (Stark and Guz). Debate has centred on whether the VAS should be anchored. One group of researchers has established a maximum point by using a short bout of strenuous exercise (Stark et al; 1981). Others have produced reproducible results without anchoring (Guz et al; 1981). A major repeatable difference between how individuals rate breathlessness has been reported using the VAS scale. One possible reason may be that individuals may interpret the meaning of the upper limit of VAS differently. Adams and Guz, (1991) recommended that the use of a reference point based on general experience is probably the best strategy for long term studies. In his review of breathlessness and VAS scales Stark, (1988) concluded that a proportion of patients appear to be unable to use VAS scales in a meaningful way. He recommended that clinical studies should incorporate tests to determine how well the VAS is used in a specific group.

2.6.13. MEASUREMENT OF BREATHLESSNESS - BORG CR10 SCALE.

Wilson and Jones (1991a) investigated the reproducibility of breathlessness scores on 7 occasions over 40 weeks in 7 healthy subjects during cycle exercise. The authors used an incremental cycle protocol and showed that the mean VE measured at each work rate did not differ significantly in any of the 7 tests. There was no significant difference between the mean Borg scores (compared with a given level of VE) for 5 out of the 7 tests. They found that the mean Borg scores at week 3 and week 6 were significantly lower than some other time points but they concluded that despite the downward trend at week 3 and week 6 there was no pattern in the change over time. They considered that the duration without testing between consecutive tests had no effect on reproducibility. The slope of the

analysis included analysis of variance and co-variance. It was concluded that the Borg CR10 scale provided a reliable technique for studying the sensation of breathlessness over extended time periods.

2.6.14. MEASUREMENT OF BREATHLESSNESS - COMPARISON OF VAS AND BORG CR10 SCALES.

It has been shown that VAS and Borg CR 10 scales correlate closely with VE during exercise in patients and normals. Wilson and Jones, (1989) compared the reproduciblity of VAS and Borg CR10 scales in 10 normals during cycle exercise using a test re-test design . Tests were 2-6 weeks apart and consisted of a progressive increase to 105 watts and a gradual return to zero load.

Wilson and Jones used the slope of the relationship of VE/breathlessness to compare tests and reported that the relationship was slightly higher in the second half of the test. They performed repeatability comparisons on the slope of the relationship as it was felt that VE would relate more closely to breathlessness than to workrate. Scores on both scales were lower in the second test compared with the first with the mean Borg CR10 score 16% lower and the VAS 27% lower. The authors reported a large inter-subject variation in the relationship between minute ventilation and breathlessness scores and a good correlation between the VAS and Borg CR10 scales. They suggested that the Borg CR10 scale appeared to have greater stability than the VAS and correlated slightly better with VE than the VAS. They reported that the Borg CR10 scale was used over a narrower range than the VAS and speculated that this result may be due to the effect of the verbal descriptors on the Borg CR10 scale which may have imposed a certain threshold of sensation intensity which had to be exceeded before proceeding to the next digit or it may be that "fit" subjects did not use the upper part of the scale. Descriptors may also increase preferential use of certain digits. The Borg CR10 scale has an in-built ratio bias with a tendency to restrict scores to the lower half of the scale. The midway point is labelled severe. The VAS has no constrictors. Wilson and Jones, (1989) favoured the Borg CR10

scale as they found it to be slightly more reproducible than the VAS and it correlated more with VE. However, they speculated that the VAS might be better because it has potentially a larger number of scoring levels whereas the Borg CR10 scale has only 12 levels and the subjects in their study used only 6. The limited range on the Borg scale may have contributed to the higher reproducibility compared with the VAS. However, the Borg CR10 scaling system forces subjects into preordained limits. The VAS offers greater potential for identifying small changes but this may depend on the study design and analysis.

Wilson and Jones; (1991a) mentioned one study (Jones et al; 1984) where the reproducibility of the VAS was so low that analysis of the results could not be undertaken and they recommended that the long term reproducibility should be confirmed before studies of long duration are attempted.

2.6.15. SUMMARY.

In principle, the VAS offers greater potential for identifying very small changes but this may depend on study design. Referring to the VAS and the Borg CR10 scales Adams and Guz, (1991) concluded that any differences between the scales was more theoretical than real.

CHAPTER 2
SECTION SEVEN.

GENERAL FATIGUE.

2.7.1. GENERAL FATIGUE.

General fatigue is a general term which may be applied to a variety of situations and may range from a slight feeling of tiredness to outright exhaustion. General fatigue need not arise directly from the subject's immediate exercise history: alternatively it can be a symptom of a disease or be psychological in nature, being associated with a lack of motivation or lack of interest. Christensen, (1960) has defined physical fatigue as a state of disturbed homeostasis which may result in subjective and objective symptoms. Linkage of symptoms with physiological variables may be possible in some instances. For example, high intensity exercise which results in high lactate levels correlates highly with subjective symptoms of fatigue. However, this relationship will not be present in prolonged work at low or moderate intensities. The area of fatigue and contributory factors to fatigue will vary depending on the type of and length of the exercise bout. In low intensity exercise (less than 50% VO_2 max) fatigue is often determined principally by factors which influence the CNS including pain, discomfort, dehydration, and changes in transmitter precursors. At intensities between 60-90% VO_2 max fatigue is associated with depleted stores of muscle glycogen. Endurance performance is closely related to the pre-exercise muscle level of glycogen (Costill and Hargreaves, 1992). At even higher intensities, the metabolic end products (i.e. lactate, H^+, Pi and ADP) accumulate and are associated with fatigue (Sahlin, 1992).

There is agreement that the possible causes of fatigue are multifactorial in nature. Sustained physical activity can result in fatigue which may be explained by central (impairment is located in the CNS) and peripheral (impairment is found in the peripheral nerve or contacting muscle) mechanisms (Sahlin, 1992).

2.7.2. CENTRAL FACTORS.

Amongst the mechanisms contributing to central fatigue is hypoglycaemia which has long been known to impair the function of the CNS (Costill and Hargreaves, 1992). NH_3 increases with exercise and might also impair CNS function (Mutch and Bannister, 1983). Endurance exercise raises the free plasma concentration of tryptophan which can increase the entry of tryptophan into the brain raising the brain level of 5-hydroxytryptamine which is linked to central fatigue (Newsholme et al, 1992). The more apparently psychological factors of motivation, discomfort and pain are also, of course, recognised as being considered to be extremely important in central fatigue (Sahlin, 1992).

2.7.3. PERIPHERAL FACTORS.

Fatigue has been described as a fall in power output during a period of activity (Lannergen et al, 1992). Muscle contraction varies in a number of ways including the mode of stimulation, the type of contraction, the frequency, intensity duration, and type of muscle. Thus, it is not surprising that the site and causes of peripheral fatigue may vary. Fatigue does not appear to be as a consequence of low ATP levels as studies have shown that there is only a small decrease in ATP in fatigued muscle and that force generation is virtually independent of ATP in the range of concentrations found in normal and fatigued muscles (Jones and Round, 1990). A decrease in intracellular pH resulting from glycolysis and H^+ accumulation has been shown to produce a decrease in force production. Possible mechanisms for this decrease in force production include interference with the interaction of myosin and actin and a fall in the affinity of troponin for Ca^{2+} (Jones and Round, 1990). A fall in pH cannot be the only cause of fatigue as McArdle's patients demonstrate an increase in pH during exercise but fatigue easily. Accumulation of Pi which also inhibits cross bridge activity (Cook and Pate, 1985) is one of the mechanisms which could operate in these patients. Slowing of relaxation is a further feature of acutely fatigued muscles. This implies decreased cross bridge detachment speed which is another phenomenon which could be brought about by a decrease in ATP or increased ADP but the concentrations of these in the normal fatigued muscle are unlikely to produce the

observed slowing. Instead, increased H^+ is thought to slow the cross bridge cycle. Changes in phosphorus metabolites lead also to a decreased uptake of Ca^{2+} in the sarcoplasmic reticulum (Cady et al, 1989) which could further contribute to the slowing of relaxation. A slower relaxation has been attributed to a reduced rate of cross bridge cycling and not slowed Ca^{2+} handling (Westerblad and Allen, 1993).

Decreased Ca^{2+} release has been shown to contribute to fatigue. The importance of the fall in Ca^{2+} release for the decrease in tension has been confirmed by Westerblad and Allen, (1991) who showed a concomitant recovery of both force and Ca^{2+} when caffeine was applied. Yet another mechanism operative at least during high frequency stimulation, is a loss of membrane excitability leading to a reduced force. The two factors implicated in the reduced membrane potential are the large K^+ fluxes from the working muscle resulting in high extracellular concentrations and the possibility of a metabolic change affecting the membrane characteristics, the result of which could have an influence on the rate at which the membrane Na^+ K^+ transport mechanism acts to redress the ionic balance. K^+ concentrations have been shown to be very high in the T-tubules so that they are unable to convey the action potential, the consequence is a decreased Ca^{2+} release, hence reduced force (Jones and Round, 1990). The above relates to short term fatigue mechanisms. A causal relationship between the depletion of intramuscular glycogen stores and fatigue in endurance exercise has been shown (Bergstrom and Hultman, 1967).

It used to be believed that transmission failure at the neuromuscular junction was another operative factor in physical fatigue (Stephens and Taylor, 1972). However, Bigland - Ritchie et al, (1982) have been unable to find any evidence for neuromuscular junction failure even in the most likely case of sustained maximal isometric contraction. There is also no indication of neuromuscular transmission failure in "total body" dynamic exercise (Spurway et al, 1987).

2.7.4. MEASUREMENT OF SUBJECTIVE RESPONSES TO EXERCISE - PERCEIVED EFFORT/PERCEIVED FATIGUE.

In measuring subjective responses to exercise, Rejeski, (1981) considered that there may be a need to distinguish between perceived effort (short term work) and perceived fatigue (long term work). He stated that it is necessary to take into account the duration of the task. Borg, (1962) stated that "short term" work on the cycle ergometer, during which time muscular force appears to be important, and that it may be convenient for healthy persons to speak of perceived or apparent force, effort, exertion or pedal resistance". However, for exercise involving a fairly long duration, Borg (1962) advised that it may be more appropriate to "speak of perceived exertion, laboriousness or fatigue....". Borg attempted to differentiate between short and longer term work by considering that the latter relates more to the length of exercise time and stress that is placed on the circulation. Pollock et al; (1984) referred to the studies of Borg (1978) and Skinner et al; (1973a) when they stated that "the RPE scale has been shown to be a valid indicator of the level of physical exertion ("relative fatigue)". When Pollock et al; (1984) quoted instructions to subjects (page 191), they stated, "By perceived exertion we mean the total amount of exertion and physical fatigue". They explained that participants should not focus on any one problem but, "on a general fatigue". Thus, these authors perceived a strong linkage between general fatigue and RPE. While there may be a relationship, it is possible to argue that these two concepts are not necessarily the same. It is possible to be "fatigued" and not make an effort or make a considerable effort and not be fatigued. Maresh and Noble, (1984) defined perceived exertion as a method to determine the sensations (feelings) experienced during exercise. They debated whether the sensation should be described as the effort expended eg. the perception of increased resistance or as the physiological response resulting from the effort. The authors prefer the latter.

Enoka, (1988) considered the task of carrying a suitcase for a long period when he described fatigue. He stated that at some point it will become more and more difficult to

hold the suitcase and the individual will have to try harder to do so. Finally, the individual will be unable to hold the suitcase. Enoka emphasised two conditions:

1) the increasing difficulty.

2) the impossibility that is ascribed to the concept of fatigue.

Fatigue is considered to be a series of adaptations which occur during a sustained effort and not one single happening. Fatigue has subjective (ie. difficulty) and objective (ie. impossibility) components. Enoka described fatigue "as a progressive increase in the effort required to exert a desired force and the progressive inability to maintain this force in sustained or repeated contractions". He stated that assessment of the difficulty of a task can be made by the psychophysical phenomenon known as sense of effort- "a relative subjective measure of the effort". Borg, (1962) conceded that the subjective perception of effort, exertion and fatigue is very difficult to define in a general way.

2.7.5. MEASUREMENT OF FATIGUE i.e. PERCEPTION OF FATIGUE.

"Fatigue" and "perceived exertion" have been used interchangeably by some researchers (Tesch, 1985, Gullestad et al; 1989). Many studies have used subjective scales to compare drugs, particularly beta blockers. It appears that "heavy" submaximal exercise i.e. at and above 70% Vo_2 max is associated with increased effort and fatigue (Tesch, 1985).

Some studies have used subjective scales to measure fatigue even although the timescale of the test has been fairly short. The word, "fatigue" has been used to monitor fatigue in patient groups and in normals. Dargie et al; (1991) compared two beta blockers (atenolol and celiprolol) using a VAS scale during submaximal exercise. They found that the normal male subjects recorded a significantly higher level of fatigue with atenolol and celiprolol compared with placebo. Gullestad et al; (1989) used a Borg 6-20 scale to assess subjective perception of fatigue. The aim of the study was to compare the effects of the opiod receptor antagonist naxolone and the non-selective beta blocker timolol on exercise performance and the subjective perception of fatigue. The 8 males (24-35 years) cycled for 30 minutes at a steady state. Thereafter, the workrate was increased every 2 minutes to

exhaustion. Timolol lowered physical work capacity and increased the perception of fatigue whereas naloxone had no effect on physical work capacity or fatigue. Lees et al; (1987) compared two beta blockers in 10 male hypertensives. During an incremental bicycle exercise to exhaustion the investigators used a Borg 6-20 scale to measure fatigue. Despite variable effects on heart rate, the subjective perception of fatigue during exercise was the same for all treatments including placebo.

The author has been unable to find any studies which examined the reproducibility of subjective scales assessing general fatigue. However with regard to rate of perceived exertion Carton and Rhodes, (1985) have shown that RPE scales are reliable and independent of exercise intensity involving various protocols. The authors have reviewed the relationship between physiological stimuli and RPE. For example, they stressed that while heart rate and RPE may be correlated, this relationship does not imply a causal relationship. A variety of stimuli have been proposed as making contributions to perception of effort. Morgan et al; (1976) used hypnosis to investigate the peripheral and metabolic contribution to effort perception. Hypnotic suggestion of uphill work resulted in an increase in effort ratings despite the fact that heart rate and VO_2 remained stable. In the exercise treatment, increases in RPE were in tandem with VE. Several studies have examined the role of VE and frequency of breathing on RPE. Noble et al; (1973) reported that VE and frequency of breathing were the best predictors of RPE. Other studies have reported correlations between VE and frequency of breathing and RPE between 0.52 and 0.94.

2.7.6. SUMMARY.

It may be important to distinguish between subjective exertion and subjective fatigue. The assessment of fatigue in a patient population can be of great value. It is important to establish if general fatigue can be measured reproducibly and if a change a patient status can be monitored using scales which assess the subjective perception of general fatigue.

CHAPTER 2
SECTION EIGHT.

OVERVIEW OF RATIONALE AND AIMS.

2.8. OVERVIEW OF RATIONALE AND AIMS.

Three studies are described in this thesis. All the studies have investigated the perception of symptoms (breathlessness and general fatigue) during exercise. While there are some common aims, other aims are specific to each study.

2.8.1. STUDY ONE: THE REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 AND LIKERT SCALES

This study was carried out to determine which, if any, of three subjective scales was most reproducible and most sensitive to change during submaximal exercise. Normal healthy volunteers were used as it was felt that the findings of this study could be applied to a patient population. Submaximal exercise was selected as it was proposed that submaximal tests would be applied to a patient population.

2.8.2. STUDY TWO: SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

The two best scales from Study One were used to assess the symptomatic responses during submaximal exercise of CHF patients. The main aims of this study were:

1) to examine the reproducibility of subjective scales in CHF.
2) to establish appropriate relative intensities which CHF subjects could sustain for a reasonable length of time and elicit symptoms.
3) to examine the feasibility of establishing a method of determining the length of a submaximal test with an endpoint within a clinically acceptable time (i.e. 8-17 minutes).

4) to determine the reproducibility of the endurance time of the submaximal tests.

2.8.3. STUDY THREE : AN EVALUATION OF THE STEXT PROTOCOL.

The STEXT protocol has been developed to cater for subjects with a wide range of aerobic fitness. It was deemed appropriate to assess the reproducibility and sensitivity to change of subjective scales using this protocol. In addition, it was important to measure the reproducibility of the maximum physiological responses.

2.8.4. COMMON AREAS.

As beta blockade was given to the subjects (in Studies One and Three) to promote a feeling of breathlessness and general fatigue, it was deemed appropriate to quantify the effect of beta blockade on the physiological variables. As exercise testing is carried out on an on going basis in cardiology, it was considered appropriate to quantify the visit/learning/familiarisation effects for the subjective scales and physiological variables in all three studies. Comparison of the visit and therapy effects would give an indication of the possible value of monitoring patients over a period of time and evaluating the therapy effect.

Linkage of the perception of symptoms to physiological variables could be of value in the treatment of patients. Thus, an aim in all three studies was to compare the relationship between the responses to the subjective scales and the physiological variables.

CHAPTER 3
SECTION ONE.

METHOD

REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 AND LIKERT SCALES.

3.1.1. SUBJECTS, RESEARCH DESIGN, EQUIPMENT AND SUBJECTIVE SCALES.

3.1.2. SUBJECTS.

Twenty three healthy male volunteers aged 30.3±4 years (mean S.D.) participated in this study. All took regular exercise, were familiar with treadmill testing and gave informed consent to this study which had been approved by the West Ethical Committee.

3.1.3. RESEARCH DESIGN.

3.1.3.(a) PRELIMINARY TESTS.

Subjects reported to the laboratory at the same time of day. A submaximal economy profile was established for each subject using at least three four-minute periods of treadmill exercise. After 30 minutes rest, each subject then undertook a symptom limited maximal treadmill test to measure VO_2 max. Depending on submaximal performance, either a "Lamb Normal Subject Treadmill Protocol" or "Lamb Athlete Treadmill Protocol" was used for this test so that treadmill time was around 10 minutes (Lamb, 1984). This time period has been shown to be optimal for eliciting maximal oxygen uptake values (Buchfuhrer et al; 1983).

3.1.3.(b) SUBMAXIMAL TESTS.

The results of the symptom limited maximal test and the submaximal economy profile were used to devise a standardised submaximal exercise protocol for each individual. This consisted of an initial workrate of 60% VO_2 max, increasing after 2 minutes to 70% VO_2 max which was maintained for a further six minutes.

3.1.4. EXPERIMENTAL PROTOCOl.

3.1.4.(a) VISITS/TREATMENTS.

Each subject attended the exercise laboratory on four occasions at intervals of one week. The order of visits was randomised according to a Latin rectangle design. The visits were termed "Reproducibility One" (R1), "Reproducibility Two" (R2), "Placebo"(P) and Active" (A), i.e. propranolol. On visits R1 and R2 no medication was administered. On the other two occasions propranolol 80 mg or matching placebo was taken 12 hours and 2 hours before the exercise test. To test sensitivity, subjects were randomised to receive either propranolol or matching placebo prior to two tests (see below). Propranolol was given as an intervention known to increase the perception of breathlessness and general fatigue.

3.1.5. SYMPTOM SCALES.

During each test, symptom scales (see below) were administered at 1 minute 30 seconds, 5 minutes 30 seconds and 7 minutes 15 seconds. Two different scales were used at each timepoint. Each scale was used twice at each timepoint, i.e. once to measure breathlessness and once to measure general fatigue. In other words, a total of 12 symptom scores were recorded during each exercise test. The presentation of scales was alternated i.e. VAS/other and other/VAS. Twelve subjects were randomised to the Likert scale/VAS group and 11 to the Borg CR10 scale/VAS group. The symptom of breathlessness was always measured before general fatigue.

3.1.6.(a) EQUIPMENT - TREADMILL, ECG AND GAS ANALYSIS.

Marquette MAC2 treadmill and ECG console were used. Heart rate was monitored throughout all tests and recorded during the last 10 seconds of each minute in all tests. Expired air was collected using a Hans Rudolph 2700 valve with a mouthpiece which was attached by tubing to the metabolic cart. All subjects wore a noseclip. Expired gases were analysed using a Beckman Metabolic Cart (Classic Exercise Model System 2).

Before each test the oxygen and carbon dioxide sensors were calibrated with standard gas mixtures. Volume was calibrated using the procedures outlined by the Beckman instruction manual. Gas collection and analysis were continuous and respiratory values for every 30 seconds were given on a print-out.

3.1.6.(b) EQUIPMENT - SUBJECTIVE SCALES.

Each scale was administered by a computer (BBC Master) and displayed on a colour television screen placed at eye level in front of the subject while he exercised on the treadmill. The subject recorded his response by means of finger controls (see below) and the information was stored in the computer. An audible prompt was given each time a new scale appeared on the screen. On each occasion the subjects had to move the lever before the cursor appeared on the screen, i.e. before any score was displayed (thus the previous score was not displayed when the new scale was presented). Equipment details are given in Appendix B.

3.1.7. SUBJECTIVE SCALES

3.1.7.(a) VISUAL ANALOGUE SCALE.

The VAS scale (see Appendix F) consisted of a horizontal line. The word "none" was placed at one end (left) of the scale and the word "very severe" at the other (right). A sliding lever allowed the subject to move the light cursor horizontally in either direction along the scale. Once the subject had chosen the desired score, he pressed a button to record this in the computer. At this point another scale was displayed.

3.1.7.(b) BORG CR10 SCALE.

This consisted of a vertical line labelled 0-10 with verbal descriptors at fixed points on the scale (see Appendix F). Using the lever and button described above, the subject selected and recorded his chosen score.

3.1.7.(c) LIKERT SCALE.

This consisted of five boxes placed vertically with verbal descriptors adjacent to each (see Appendix F). The score was selected and recorded as described above.

3.1.7.(d) USE OF SCALES.

A demonstration of the use of the scales was given before the maximal test and each subject was given an opportunity to practise using the finger controls. To enable subjects to appreciate the range of scales, they were asked to record scores for breathlessness and general fatigue at the end of their symptom limited maximal test. Two symptoms were measured with the scales. Subjects were given the following instructions before each of the submaximal tests.

3.1.7.(e) BREATHLESSNESS.

Breathlessness was described as, "breathless", out of breath, air hunger, unable to breathe enough". Subjects were told, "Based on these descriptions, quantify your sensation of breathlessness by referring to your common experience of "an uncomfortable awareness of breathing. Avoid simply observing an increase in breathing - think of "an uncomfortable need to breathe". Disregard other sensations like leg fatigue or general fatigue."

3.1.7.(f) GENERAL FATIGUE.

General fatigue was described as "overall tiredness and overall fatigue". "Based on these descriptions and by referring to your common experience of general fatigue you are asked to quantify your sensation of general fatigue. Disregard other sensations like leg fatigue and breathlessness."

CHAPTER 3
SECTION TWO.

METHOD

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

3.2.1. SUBJECTS, RESEARCH DESIGN, EQUIPMENT, SUBJECTIVE SCALES.

3.2.2. SUBJECTS.

Ten male subjects aged 59.9 $\pm$ 7.9 years (mean S.D.) gave informed consent to participate in the study. All subjects had chronic heart failure (NYHA 1 and 2) and all were taking some form of diuretic. All subjects gave informed consent to this study which had been approved by the West Ethical Committee.

3.2.3. RESEARCH DESIGN.

The subjects performed two maximal exercise tests (see Appendix C). From the longer of the two tests a submaximal workrate was calculated using a diagrammatic aid (see Appendix D). The subjects performed four submaximal tests at weeks 1,2,4 and 6 after the second maximal test.

3.2.3.(a) PRELIMINARY EXERCISE PROTOCOLS.

Subjects reported to the laboratory at the same time of day and with the same timing of medication on each occasion. Subjects underwent two maximal incremental treadmill tests at least four days apart. Before the maximal test the subjects were familiarised with the treadmill and the use of the subjective scales (see below). The subjects performed an incremental test (see Appendix C). At the end of the test the subjects were asked to quantify their perception of breathlessness and general fatigue.

3.2.3(b) CONSTANT WORKRATE TEST.

The predetermined speed and gradient were set on the treadmill using a diagrammatic aid (see Appendix D). Calculation of the work rate was carried out using 80% of the predicted oxygen cost of the stage attained in the longer of the two incremental tests. Calculation was based on the ACSM, (1986) equations. This procedure results in a workrate approximately two stages below that attained in the incremental protocol and allows for subjects who only manage a few seconds into a stage or almost complete a stage.

3.2.4. CONSTANT WORKRATE METHOD.

Subjects reported to the laboratory at the same time of day and with the same timing of medication on each occasion. The subjects' feet were placed on the side of the treadmill. At a given signal the subject walked on the treadmill and held on to the support bars for a few seconds until he had gained balance. Thereafter the subject walked without support. The subjects were asked to continue for as long as possible. At the end of the test the subjects were asked to state the reason(s) why they had stopped exercising.

3.2.5. SYMPTOM SCALES.

During each test, symptom scales (see below) were administered every two and half minutes. Each scale was used twice at each time point i.e. to measure breathlessness and general fatigue. The symptom of breathlessness was always measured before general fatigue.

3.2.6.(a) EQUIPMENT - TREADMILL, ECG AND GAS ANALYSIS.

During all tests expired air was collected using a Hans Rudolph 2700 valve with a mouthpiece which was attached by tubing to the metabolic cart. All subjects wore a noseclip. Respiratory variables were determined during exercise by an automated gas analysis system (Beckman metabolic measurement cart; classic exercise model system 2). Before each test the oxygen and carbon dioxide sensors were calibrated with a standard

gas mixture containing 16% oxygen 4% carbon dioxide and 80% nitrogen. Volume was checked using standard procedures. Gas collection and analysis were continuous and respiratory values for every 30 seconds were given on a print-out. A marquette MAC2 treadmill and ECG console were used. Heart rate was taken from the electrocardiogram during the last 10 seconds of each minute.

3.2.6.(b) EQUIPMENT - SUBJECTIVE SCALES.

Each scale was administered by a computer (BBC Master) and displayed on a colour television screen in front of the subject while he exercised on the treadmill. The subject recorded his response by means of finger controls and the information was stored in the computer. An audible prompt was given each time a new scale appeared on the screen. On each occasion the subjects had to move the lever before the cursor appeared on the screen i.e. before any score was visible (thus the previous score was not displayed when the new scale was presented).

3.2.7. SUBJECTIVE SCALES.

The scales had a heading of either breathlessness or general fatigue. The following scales were used:

3.2.7(a) VISUAL ANALOGUE SCALE.

The visual analogue scale (see Appendix F) consisted of a horizontal line. At the left hand side of the scale the word "none" was labelled and at the far right the word "very severe" was placed. Subjects indicated their level of breathlessness or general fatigue by moving the lever on the treadmill which adjusted the line on the TV monitor. Once the subject had chosen the desired score, he pressed the button to record this in the computer. At this point another scale appeared.

3.2.7.(b) BORG CR10 SCALE.

The Borg CR10 scale (see Appendix F) consisted of a vertical scale labelled 0-10 with verbal descriptors at various numbers on the scale. Operation of the lever on the treadmill allowed the subjects to select the appropriate number.

3.2.7.(c) USE OF SCALES.

Subjects were randomly assigned to a VAS/Borg CR10 or a Borg CR10/VAS sequence of presentation. The subjects were introduced to the subjective scales between the treadmill familiarisation and the first maximal test. Firstly, the subjects were shown how to operate the scales and they were given the opportunity to practise using the finger controls. The subjects were allowed to practise until they could carry out the procedures with no difficulty. To enable the subjects to appreciate the range of the scales, they were asked to record scores for breathlessness and general fatigue at the end of the incremental tests. Subjects were given the following instructions before each of the constant workrate tests.

3.2.7.(d) BREATHLESSNESS.

Breathlessness was described as:

"breathless, out of breath, air hunger, unable to breathe enough".

Subjects were told:

"Based on these descriptions, quantify your sensation of breathlessness by referring to your common experience of "an uncomfortable awareness of breathing." Avoid simply observing an increase in breathing - think of "an uncomfortable need to breathe". Disregard other sensations like leg fatigue or general fatigue".

3.2.7.(e) GENERAL FATIGUE.

General fatigue was described as "overall tiredness", overall fatigue". "Based on these descriptions and by referring to your com mon experience of general fatigue you are asked to quantify your sensation of general fatigue. Disregard other sensations like leg fatigue and breathlessness.

The subjects again practised with the scales and were asked to think about the range of the scales and their past experience in relation to breathlessness and general fatigue.

The subjects were asked if they understood the instructions. It was suggested to the subjects that zero on the scales may relate to their feelings at rest and at the upper end of the scales, subjects were asked to think of previous experiences which may relate to the upper ranges of the scales. It was also suggested to them that their perception of sensations at the end of the maximum tests may help them with their judgement of the range of the scales. Any questions from the subjects were answered.

During the constant workrate test the subjects were asked to respond to the scales when they appeared on the TV monitor.

CHAPTER 3
SECTION THREE.

METHOD.

AN EVALUATION OF THE STEXT PROTOCOL.

3.3.1. SUBJECTS, RESEARCH DESIGN, EQUIPMENT AND SUBJECTIVE SCALES

3.3.2. SUBJECTS.

Twelve healthy male volunteers (aged 32.8±8.9) (mean S.D.) who were regular exercisers gave informed consent to participate in the study which had been approved by the West Ethical Comittee.

3.3.3. RESEARCH DESIGN.

Subjects underwent two tests within 48 hours of each other at week 0 (Timepont 1), week 2 (Timepoint 2), week 6 (Timepoint 3) and week 10 (Timepoint 4). Tests were conducted at the same time of day. Subjects reported to the laboratory three hours fasted. Subjects were asked to exercise as long as possible and to indicate when they could no longer continue. At weeks 0 and 2 there was no intervention. At weeks 6 and 10 subjects were given a placebo or 80 mg of propranolol which were taken 12 hours and 2 hours before testing. Propranolol was given to promote sensations of breathlessness and general fatigue. At week 6, six subjects were given placebo first, and 48 hours later propranolol. At week 10, the same six subjects were given propranolol first and placebo 48 hours later. The other six subjects were given the opposite order of drug administration. Six subjects were given a VAS/Borg CR10 order of presentation and six subjects a Borg CR10/VAS order.

3.3.4. TEST PROTOCOL.

Subjects reported to the laboratory at the same time of day. The subjects performed the STEXT protocol (see Apendix E). The subjects were asked to continue on the treadmill as

long as possible and to signal when they wanted to stop. When the signal was given, the treadmill was slowed to an appropriate walking pace and the subjects recorded their responses to the scales at maximum exercise.

3.3.5. SYMPTOM SCALES.

Symptom scales (see below) appeared on the TV monitor every 2 minutes (ie. the scales appeared on the TV monitor 10 seconds into the third stage and every two minutes thereafter) and at maxmium. Each scale was used twice at each timepoint, i.e. to measure breathlessness and general fatigue. Six subjects were given a VAS/Borg CR10 combination and six subjects were given a Borg CR10/VAS order of presentation. The symptom of breathlessness was always measured before general fatigue.

3.3.6.(a) EQIUPMENT - TREADMILL AND GAS ANALYSIS.

A Marquette MAC2 and ECG console were used for the treadmill test. Heart rate was monitored by ECG continuously and recorded during the last 10 seconds of each one minute stage. Expired air was collected using a Hans Rudolph 2700 valve with a mousepiece which was attached by tubing to the metabolic cart. All subjects wore a noseclip. Respiratory variables were determined during exercise by an automated gas analysis system (Beckman metabolic measurement cart; classic exercise model system 2). Before each test the oxygen and carbon dioxide analysers were calibrated with a standard gas mixture containing 16% oxygen and 4% carbon dioxide and 80% nitrogen. Volume was checked using standard procedures and analysed using a Beckman Metabolic Cart. Gas collection and analysis were continuous and a print-out of respiratory variables was given every 30 seconds.

3.3.6.(b). EQUIPMENT - SUBJECTIVE SCALES.

The VAS and Borg CR10 scales are shown in Appendix F. A description of the scales is given in Section 3.1.7. Each scale was administered by a computer (BBC Master) and displayed on a colour television screen in front of the subject while he exercised on the

treadmill. The subject recorded his response by means of finger controls and the information was stored in the computer. An audible prompt was given each time a new scale appeared on the screen. On each occasion the subjects had to move the lever before the cursor appeared on the screen, i.e. before any score was dislayed (thus the previous score was not displayed when the new scale was presented). Equipment details are given in Appendix B.

3.3.7. SUBJECTIVE SCALES.

3.3.7.(a) USE OF SCALES.

Before Test 1 a demonstration of the use of the scales was given. Subjects were introduced to the scales and shown how to operate the lever system which adjusted the scale on the TV monitor and the button which recorded the score. After the subjects were familiar with the operation of the scales, the subjects were read the instructions outlined below. Thereafter the subjects again practised with the scales and were asked to think of the range of the scales and how the scales applied to their common experience of breathlessness and general fatigue. The subjects were asked if they understood the instructions. Any questions from the subjects were answered. The subjects were asked to respond to the scales when they appeared on the TV monitor throughout the exercise period and as soon as possible after the end of the test. Two symptoms were measured with the scales. Subjects were given the following instructions before each of the tests.

3.3.7.(b) BREATHLESSNESS.

Breathlessness was described as "breathless, out of breath, short of breath, air hunger, unable to breathe enough". Subjects were told "Based on these descriptions, quantify your sensation of breathlessness by referring to your common experience of an uncomfortable awareness of breathing. Avoid simply observing an increase in breathing - think of "an uncomfortable need to breathe, disregard other sensations like general fatigue and tired legs."

3.3.7.(c) GENERAL FATIGUE.

General fatigue was described as "overall tiredness, overall fatigue." "Based on these descriptions and by referring to your common experience of general fatigue you are asked to quantify your sensation of general fatigue. Disregard other sensations like breathlessness and leg fatigue."

CHAPTER 4.

STATISTICAL TREATMENT OF DATA.

4.1.1. OVERVIEW OF THE STATISTICAL ANALYSIS PLAN.

Three separate studies are reported in this thesis. An attempt has been made to standardise the statistical treatment of the data to allow for consistency of approach and a meaningful comparison of the data to take place. However, as the designs of the three studies differ, a consistent approach throughout was not possible and statistical treatment and presentation of data varies slightly among the studies. With such a wide ranging data set many different forms of analysis could be conducted but statistical analysis was limited to answer the most pertinent questions. The key questions arising through all three studies were:

1) what is the more (most) reproducible subjective scale?
2) which is the more (most) sensitive subjective scale to change?
3) what is the magnitude of the visit and therapy effects in the studies involving a therapy effect?
4) what is the relative magnitude of the visit effect?
5) how strong is any relationship between the subjective scales and the physiological variables?

The statistical approach to answering these questions is described in the remainder of this chapter.

4.1.2. GENERALISED LINEAR MODEL.

The basis for most of the analysis is in the form of Generalised Linear Models (GLMS) where an additive model attempts to describe the composition of each measurement of each variable. For example, taking data from the "The comparison of VAS, Borg CR10 and Likert scales", minute ventilation is measured on subject i (i=1 to 23 in this case) at timepoint j (j=1, 2 or 3 here corresponds to 2, 6 and 8 minutes respectively), for visit k

(k=1, 2, 3 or 4 here), with intervention l (l=1 for no beta blocker and l=2 if the subject is on the beta blocker). The GLM assumes that the minute ventilation on this subject averages to the grand mean

plus an effect for subject i*

plus an effect of timepoint j*

plus an effect for visit k*

plus a beta blocker effect l*

plus random/natural/error variation

*all effects are relative to the grand mean and simply measure differences from the grand mean (i.e. sum to zero).

NOTES.

1) The grand mean is effectively the average minute ventilation, in this case, over all subjects, timepoints, visit and the presence /abscence of the beta blocker.

2) Formally the subject effect is treated as a RANDOM effect in the sense that interest lies not in the specific subjects involved in the study but in the overall variability BETWEEN subjects. The between subject variability estimated through the GLM is used as the basis of the measure of reproducibility of the variable under consideration.

3) The last term in the model is assumed to have zero mean and a constant standard deviation across all subjects, timepoints etc and behave as if from a normal distribution. For each variable, all the data for all subjects, timepoints etc. is used in a least squares procedure to estimate all the above effects (i.e. subject, timepoint, visit and beta blocker). As far as was possible all possible two-way interactions among these effects were checked and found to be non significant.

   The output from the least squares procedure contains point estimates of all possible effects together with estimated standard errors of these effects which give some indication of the significance of the effects themselves.

The first stage in the analysis is a series of hypothesis tests in the form of an analysis of variance (ANOVA) table to investigate separately any subject, timepoint, visit and therapy effects.

Formally, a significance test is carried out of each null hypothesis that there are no differences at all among the levels of the effect under consideration (eg. of the null hypothesis that there are no significant differences across four visits). These are reported in the form of an ANOVA table and significance is based on a 5% level.

Any of these effects which subsequently prove to be significant at the 5% level are then followed up using a Bonferroni multiple comparisons procedure. For example, if some variable produced a significant visit effect, then the Bonferroni multiple comparisons procedure would attempt to identify exactly where any such differences lay. Bonferroni multiple comparisons procedures involve the PAIRWISE comparison of all possible levels of the effect under consideration (eg. in a study with four visits and a significant visit effect all 6 possible pairwise comparisons of the visits would be made). This procedure retains the probability of any spurious significant results at the same 5% significance level as the ANOVA.

4.1.3. THE CONCEPT OF THE REPRODUCIBILITY COEFFICIENT.

The reproducibility of each variable in turn was quantified as the proportion of the total variance (i.e. between subject plus within subject variance) explained by the between subject variance. Appropriate estimates of these were obtained using a generalised linear model incorporating visit, intervention, timepoint and subject effects. In effect, this means that the subject differences are pooled to produce an estimate of the between subject variance while the residual sum of squares is the basis for the estimate of the within subject variance. For example, if the between subject variance was 278 and the within subject variance was 63, the reproducibility coefficient would be 82% i.e. 278/(278+63) as a percentage. A score of 100% would signify perfect reproducibility (i.e. no within subject variability at all).

Conservative (i.e. at least ninety five percent) confidence intervals were calculated for the reproducibility coefficients of VAS, Borg CR10 and Likert scales for breathlessness and general fatigue to investigate differences between any two scales.

To illustrate the interpretation of a reproducibility coefficient, an example using a population with a VO_2 max ranging between 50 -70 $ml.kg^{-1}$ min^{-1} is given. A reproducibility coefficient of 80% would imply that the observed measurement of VO_2 max for any individual whose "true" VO_2 max was 55 $ml.kg^{-1}$ $.min^{-1}$. could be measured between 50 and 60 $ml.kg^{-1}$ $.min^{-1}$. This is in effect because a reproducibility coefficient of 80% corresponds to the between subject standard deviation being twice that of the within subject standard deviation. Further, a reproducibility coefficient of 90% corresponds to the corresponding ratio of between to within standard deviations being three.

4.1.4. THE CONCEPT OF THE SENSITIVITY COEFFICIENT.

Sensitivity was defined as the ratio of the estimated effect of the active drug over the placebo divided by the estimated within subject standard deviation. Ninety five percent confidence intervals for the sensitivity were used to determine if there was a significant "intervention" effect. For example, taking the data from "The comparison of VAS, Borg CR10 and Likert scales", ninety five percent confidence intervals were used to determine if there was a significant beta blocker effect i.e. the active treatment was significantly different from the other "interventions" (R1, R2 and placebo).

The reason why this measure of sensitivity was chosen was to allow assessment of the effect of the intervention on an INDIVIDUAL not on a group basis. For example, a sensitivity ratio of 1.5 for a particular intervention means that the effect of the intervention is to change the average level of the variable by one and half times the variability in the measurement seen across (within) any individual. Thus, sensitivity ratios under one would

be considered to be of limited value as the change in the variable is not very different from the variability in the measurement seen across (within) any individual.

4.1.5. STATISTICAL METHODS FOR THE LINK BETWEEN THE SYMPTOMATIC SCALES AND PHYSIOLOGICAL VARIABLES.

The relationship between each symptomatic scale and physiological variable is complicated as it may be influenced not only by differences among subjects but also by the effects of any therapy, intervention or indeed the cumulative effect of exercise through the effect of time into a test itself.

Accordingly, to provide as simple a summary as possible of such relationships it was decided that the best way to indicate which perception of symptom was best related to each physiological variable was to evaluate correlations based on all observations for each subject. The correlation summarised the following:

a) INDIVIDUAL VISIT CORRELATIONS correlations between the pairs of all measurements (subjective scales and physiological variables) for each individual were calculated for each of the visits in each study.

b) POOLED INDIVIDUAL VISIT CORRELATION the correlations for all visits were combined to give a pooled correlation for each individual.

c) ESTIMATED POOLED CORRELATION (OVERALL GROUP CORRELATION) a pooled overall correlation for each pair of relationships was calculated i.e. the pooled correlations for each subject were combined to give an overall pooled correlation.

It is assumed that any effect of therapy or time into the test within an individual merely pulls out both the scale and physiological variable in the same direction for any visit.

4.1.6. PRESENTATION OF RESULTS.

As some tables have a great deal of information in them, it was decided to miss out the units of measurement in some instances. If units are not included, the units used are those outlined in Appendix G.

CHAPTER 5
SECTION ONE.

REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 SCALES AND LIKERT SCALES.

RESULTS SECTION OF THE SUBJECTIVE SCALES.

5.1.1. THE DESIGN AND AIMS OF THE STUDY.

SUMMARY OF THE DESIGN OF THE STUDY.

Twenty three subjects took part in the study. Each subject had a maximal test and a submaximal economy test to enable relative intensities to be calculated for four subsequent submaximal tests (of 8 minutes duration) at 70% VO2max. Two tests (R1 and R2) were given to assess reproducibility of scores obtained with each subjective scale and two other tests were undertaken to assess the sensitivity of each scale to a drug intervention. Here a double blind treatment with a beta blocker (to increase the sensation of breathlessness and general fatigue during exercise) or a matching placebo was given.

Three subjective scales were used to assess breathlessness and general fatigue - (1) visual analogue (VAS) (continuous scale) (2) Borg CR10 scale (12 fixed points) and (3) Likert scale (5 fixed points). Each subject had symptomatic assessment at 2, 6 and 8 minutes. Subjects were given either a VAS/Borg CR10 or a VAS/Likert combination. A range of physiological variables were monitored continuously and recorded every minute.

THE MAIN AIMS OF THE STUDY.

These were to:

1) compare the reproducibility and sensitivity to change of visual analogue, Borg CR10 and Likert scales.
2) determine the magnitude of the visit and therapy effects of the subjective scales and physiological variables.

3) investigate the relationship between the subjective scales and the physiological variables for the FOUR submaximal tests of 8 minutes duration at 70% VO_2max.

5.1.2. RESULTS OF SUBJECTIVE SCALES.

5.1.3. STATISTICAL METHODS FOR THE SUBMAXIMAL TESTS - THE SYMPTOMATIC SCALES.

For each separate scale at each timepoint (i.e. 2, 6, and 8 minutes), a generalised linear model was used to investigate possible systematic differences among the four "interventions" (i.e. the test, re-test, the placebo treatment and the active treatment), as well as any systematic learning or visit/familiarisation effects across the four visits. The model also included components of variability due to between subject variation and due to within subject variation.

5.1.4. AN ILLUSTRATION OF THE RAW DATA FOR THE SUBMAXIMAL TESTS.

An impression of how the scales were used by the subjects is given in Figures 5.1-5.6. which show the ranges for the three scales for breathlessness and general fatigue for all four "interventions". The VAS and Likert scales are used over a much wider range than the Borg CR10 scale. The highest score on the Borg CR10 scale was five (general fatigue) and therefore only half of the scale was actually used whereas the corresponding proportion of the scales used for the other two scales was 80%. Examination of Figures 5.1-5.6. shows that the scores on the active visit tend to be higher than the other three "interventions" which show little difference from each other. The plots suggest that the scales in the three "non intervention" tests are reproducible. Subjects scored in an individualistic way i.e. despite exercising at the same 70% of VO_2 max, there was a wide range of values among the subjects for the subjective scales.

5.1.5. MEASUREMENT OF BREATHLESSNESS.

REPRODUCIBILITY.

The estimated reproducibility coefficients for the three scales at the three different timepoints are shown in Table 5.1. At all three timepoints there is a clear tendency for the VAS to be better than the other two scales i.e. to have higher reproducibility. At minute six the VAS was significantly higher than the Borg CR10 scale.

SENSITIVITY.

The VAS and Likert scale tend to be more sensitive to change than the Borg CR10 scale (see Table 5.2). At minutes six and eight the VAS is significantly higher in sensitivity than the Borg CR10 scale.

5.1.6. MEASUREMENT OF GENERAL FATIGUE.

REPRODUCIBILITY

Reproducibility tended to be better for the VAS than the other two scales but there were no statistically significant differences (see Table 5.1).

SENSITIVITY.

The Borg CR10 scale was significantly better than the Likert scale at 6 and 8 minutes and, perhaps surprisingly, better than the VAS at 6 minutes (see Table 5.2).

5.1.7. VISIT AND THERAPY EFFECTS FOR MINUTE 8.

As it was considered to be unwieldy to compare visit and therapy effects for all three timepoints, minute 8 was selected to provide a detailed and representative example of visit and therapy effects. An important issue here is to establish if the visit effect was as substantial as any therapy effect as this would raise major questions over the effective use of such a test protocol in clinical practice.

Using a GLM, point estimates were produced for the visit and therapy effects of each subjective scale separately. Table 5.3 shows the estimated visit and therapy effects for both breathlessness and general fatigue respectively. It is important to remember that these estimated effects are all relative to the grand mean (i.e. in the sense that all four visit effects sum to zero). If the ANOVA test of a visit effect proved significant for the particular variable under question, a Bonferroni based multiple comparisons procedure was used to assess where significant differences, if any, lay.

BREATHLESSNESS.

The VAS showed significant visit effects decreasing through the four visits. Formally, visit 3 was significantly lower than visit 1 and visit 4 was significantly lower than any other visit (in simple terms, visit 1 was 3.9 units on average ABOVE the grand mean while visit 4 was 5.6 units BELOW the grand mean producing a significant fall of 3.9+5.6 = 9.5 units in he VAS on average across allindividuals for visit 1 to 4). For the Likert scale the visit 4 value was significantly lower than the other three visits. There was no visit effect for the Borg CR10 scale.

ALL scales showed a SIGNIFICANT therapy effect. The therapy effect was MUCH HIGHER than any visit effects for all the scales.

GENERAL FATIGUE.

The VAS showed significant visit effects, again decreasing through visits. Formally, visit 2 and 3 were significantly lower than visit 1 and visit 4 was significantly lower than the other 3 visits. Visit 1 for the Borg CR10 scale was significantly higher than the other three visits which were not significantly different from each other. The Likert scale showed no significant visit effect.

ALL scales showed a SIGNIFICANT therapy effect. Again the therapy effects were much HIGHER than any of the visit effects.

5.1.8. SUMMARY.

REPRODUCIBILITY.

These results showed that the VAS tended to be consistently more reproducible than the Borg CR10 and Likert scales at all timepoints for breathlessness and general fatigue. At minute six the VAS was significantly so compared to the Borg CR10 scale for breathlessness. No clear pattern emerged when a comparison was made between the Borg CR10 and Likert scales.

SENSITIVITY.

For breathlessness, the VAS was the best scale at pulling out the intervention effect relative to the within subject variability whereas the Borg CR10 scale was best for general fatigue.

VISIT AND THERAPY EFFECTS.

Some scales did demonstrate a visit effect but the magnitude of the visit effect was small compared with the therapy effect which was always substantial.

CHAPTER 5
SECTION TWO.

RESULTS OF THE PHYSIOLOGICAL VARIABLES.

REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 SCALES AND LICKERT SCALES.

5.2.1. STATISTICAL METHODS FOR THE FOUR SUBMAXIMAL TESTS - THE PHYSIOLOGICAL VARIABLES.

A generalised linear model (GLM) was applied to the data to include the possible effects of visit, therapy, subject and natural (or error) variability. A Bonferroni multiple comparisons procedure was used to assess where the significant differences, if any, lay for any visit and/or therapy effect respectively. The variables investigated were VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VCO_2, VE/VO_2, tidal volume and respiratory exchange ratio (RER).

5.2.2. SOME COMMENTS ON THE RAW DATA FOR THE PHYSIOLOGICAL VARIABLES.

5.2.2.(a) AEROBIC POWER AND RELATIVE INTENSITY.

The mean VO_2 max of the subjects was 56.9 $ml.kg^{-1}.min^{-1} \pm 4.7$. During the placebo test, the mean percentage VO_2 max was 70.8% Thus, the targeted value of 70% VO_2 max was achieved.

5.2.2.(b) AN ILLUSTRATION OF THE SUBMAXIMAL RAW DATA.

It was considered to be unnecessary and unwieldy to illustrate all of the physiological raw data. Figure 5.7 provides a flavour of the physiological data and shows VE for all subjects for each of their four visits for the four submaximal tests. Scores on the active therapy appear to be higher than the other three "interventions". In the three "non active" treatments there is a suggestion that a steady state has been achieved between 6 and 8 minutes. For some subjects on the active therapy VE continues to rise from 6 to 8 minutes.

5.2.3. AN ANALYSIS OF THE EFFECT OF "INTERVENTION" THROUGH THE TEST.

In this section the main area of interest is the magnitude of change at each minute into the test of each of the physiologial variables due to the intervention of the beta blocker (i.e. the magnitude of the therapy effect through the test). Figures 5.8-5.16 display the point estimates of those variables where a significant therapy effect was found (i.e. VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, VE/VCO_2, tidal volume and RER). It must be remembered that the therapy effects are all relative to the grand mean and these sum to zero. There were no significant differences among the three "interventions," R1, R2 and placebo for any physiological variable but in general there were substantive and significant effects on the active therapy. The "bars" attached to each highest letter in the figures denote one pooled standard error of the therapy effects for each timepoint.

VENTILATION.

The active treatment was significantly HIGHER than the other three treatments after 3 minutes (Figure 5.8).

VO_2

The active treatment was significantly LOWER than the other three treatments until the last 2 minutes (Figure 5.9).

VCO_2

There was a complex pattern to the active therapy effect. The only significant differences were at 1, 2 and 8 minutes. At minutes 1 and 2 the active therapy was significantly LOWER than all the non-intervention treatments which at 8 minutes was significantly HIGHER (Figure 5.10).

FREQUENCY OF BREATHING.

After 2 minutes the frequency of breathing was significantly HIGHER for the active treatment compared with the other three "interventions" (Figure 5.11).

HEART RATE.

The major effect was a significantly LOWER heart rate at all timepoints for the active treatment compared with the other "interventions" (Figure 5.12).

VE/VO_2

The active treatment was always significantly HIGHER than the other three "interventions" (Figure 5.13).

VE/VCO_2

The pattern for the active treatment was exactly the same as for VE/VO_2 with the active drug always HIGHER than the other three "interventions" (Figure 5. 14).

TIDAL VOLUME.

The therapy effect showed no consistent pattern except that the active treatment tended to produce the lowest values for tidal volume. The only significant results were achieved at 2 and 6 minutes with the active treatment LOWER than replicate 2 (Figure 5.15).

RER.

For all eight timepoints the active therapy was HIGHER than the other three "interventions" (Figure 5.16).

5.2.4. THE RELATIVE MAGNITUDE OF ANY VISIT EFFECT.

The aim of this section was to determine how any visit effect compared in magnitude to the therapy effect. Again it was considered unnecessary to examine this relationship over all three timepoints. Minute 8 was selected to give an in depth examination of the visit and therapy effects. Table 5.4 shows the visit and therapy effects for the physiological variables at minute 8. The values given are in relation to the grand mean. A Bonferroni based multiple comparisons procedure was used to assess where significant visit differences, if any, lay.

Only VE, frequency of breathing and VE/VCO_2 produced significant VISIT effects among the physiological variables, although VO_2 was close to the significance borderline.

However, the pattern across almost all the physiological variables was the same in the sense that the variable was highest at visit 1 and decreased through the remaining three visits. For example, for VE, the average fell from visit 1 to visit 4 by 2.99+2.08 =5.07 which in this case proved significant.

As discussed in the previous section there were significant THERAPY effects for all variables apart from VO_2 and tidal volume.

For the variables with significant visit effects (i.e. VE, frequency of breathing and VE/VCO_2), the therapy effect was much greater than the visit effect. Indeed for all the physiological variables the visit effects were of much lesser magnitude than the therapy effect. Thus it is reasonable to conclude that the therapy effect can be easily identified and is much more substantial than any learning/familiarisation effect.

5.2.5. SUMMARY.

The active treatment had a lowering effect on heart rate and increased several respiratory variables including VE, frequency of breathing, RER, VCO_2, VE/VO2, and VE/VCO_2 at some or all timepoints. At some timepoints VO_2 and VCO_2 were reduced. It is concluded that the therapy effect is much more substantial than any learning/familiarisation effect.

CHAPTER 5
SECTION THREE.

REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 SCALES AND LICKERT SCALES.

RESULTS OF THE RELATIONSHIP BETWEEN PHYSIOLOGICAL VARIABLES AND THE SUBJECTIVE SCALES.

5.3.1. WHY? HOW?

If a relationship exists between a physiological variable and a symptomatic scale a strong correlation would be evident. Any strong relationship may be of value in the assessment and treatment of symptoms during exercise. It was decided that the best way to indicate which perception of symptom was the best related to each physiological variable was to evaluate individual subject correlations based on all observations for each subject across all timepoints.

An explanation of how the correlations were calculated is given in Section 4.5.

5.3.2. A VISUAL IMPRESSION OF THE RELATIONSHIP BETWEEN THE SUBJECTIVE SCALES AND VE.

A flavour of the relationship between the subjective scales and the physiological variables is given by taking the VAS (breathlessness) and VE and displaying these variables in the following examples. For minutes 2, 6 and 8, Figure 5.17 shows the VE/VAS (breathlessness) relationship for subject 4 for all four tests. Figure 5.18 shows the VE/VAS (breathlessness) relationship for all subjects for all tests. Both figures suggest that there is a marked increase in VE and VAS (breathlessness) from timepoint 1 to timepoint 2. Figure 5.18 suggests that VE is fairly stable for many subjects between 6 and 8 minutes but for some subjects, the VAS (breathlessness) score increases from 6 to 8 minutes.

5.3.3. CORRELATIONS.

A visual impression of "correlations" of one subjective scale and physiological variable is given in Figure 5.19. Figure 5.19 gives the correlations for VE and VAS (breathlessness) for:

1) individual visit correlations for each subject.
2) pooled individual correlations.
3) estimated pooled correlation (overall group correlation).

For some subjects, eg 1, 12, 22 and 23, the individual visit correlations are very close together whereas other subjects showed a wide range of individual visit correlations eg 9, 13, 14 and 21.

The overall group correlations, the pooled individual correlations and the minimum and maximum individual visit correlations for VAS, Borg CR10 and Likert scales (breathlessness and general fatigue) and VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2 VE/VCO_2 tidal volume and RER are shown in Table 5.5.

There were high overall group correlations for all the subjective scales and VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, tidal volume and RER. For VE, VO_2, VCO_2 and heart rate and all the subjective scales overall pooled correlations were above 0.90. For the other physiological variables (apart from VE/VCO_2) and the subjective scales, the overall group correlations were above 0.75. The overall group correlation for all scales and VE/VCO_2 were very low. A wide range in the minimum and maximum (individual and pooled) visit correlations was found for all the subjective scales and the physiological variables.

5.3.4. TIME EFFECT- COMPARISON OF THE CHANGES IN SUBJECTIVE SCALES AND PHYSIOLOGICAL VARIABLES FOR MINUTES 2, 6 and 8.

A comparison of the responses to the subjective scales and physiological variables was made to investigate any relationship between the changes in scores. If it could be

demonstrated that there was no increase in some physioloical variables (i.e. a steady state had been attained) but the scores for the subjective scales increased, it could be concluded that the perception of symptoms changed despite no difference in some physiological markers. The variables investigated were all the subjective scales and the following physiological variables, VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, VE/VCO_2 and tidal volume.

Using the output from the GLM, point estimates for time effects were obtained. A Bonferroni multiple comparisons procedure were used to determine if there were differences among the timepoints (see Table 5.6).

For all three timepoints, all three subjective scales were significantly different at each timepoint except for Likert (breathlessness) which showed no change between timepoint 2 and timepoint 3. The differences between 6 and 8 minutes were 3.8 for the VAS (breathlessness). For VAS (general fatigue) the difference between 6 and 8 minutes was 3.2. The Borg CR10 (breathlessness) scale was significantly higher (0.25) at 8 minutes compared with 6 minutes. On the Borg CR10 (general fatigue) scale the 8 minute score was 0.22 higher than the 6 minute score. On the Likert (general fatigue) scale the 8 minute value was 0.24 higher than the 6 minute value.

There were significant differences for all the physiological variables between timepoint 1 and 2. For VE, VO_2, VCO_2, frequency of breathing, VE/VO_2, VE/VCO_2 and tidal volume there were no differences between timepoints 2 and 3. Between timepoints 2 and 3 there was a significant increase in heart rate of 3.1 $beats.min^{-1}$.

Table 5.7 gives an example of the respiratory values and heart rate at 6 and 8 minutes for the placebo test. There were no significant differences among the variables. Thus it can be said that a steady state had been attained in the placebo test. A one way analysis of variance and 95% confidence intervals showed that in the "active" treatment, there was a

significant increase in VE of 4.1 litres.min^{-1} 0.1 litres.min^{-1} in VO_2, 0.06 litres.min^{-1} in VCO_2 and 1.5 beats.min^{-1} in heart rate between 6 and 8 minutes.

5.3.5. SUMMARY.

These findings indicate that there is a very good correlation between the subjective scales and VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, tidal volume and RER. Examination of the data from timepoint 2 to 3, showed that on almost all occasions, the perception of breathlessness and general fatigue increased despite the fact that there was no change in a range of physiological variables.

Table 5.1

Reproducibility coefficients and 95% Confidence Intervals for Breathlessness and General Fatigue for Visual Analogue, Borg CR10 Scales and Likert Scales.

REPRODUCIBILITY.			
Breathlessness			
Time / Scale	2 Min	6 Min	8 Min
VAS	59% (45-76)	74%* (59-86)	78% (66-89)
Borg CR10	55% (39-78)	42% (33-66)	50% (36-76)
Likert	50% (36-76)	55% (39-80)	76% (55-90)

General Fatigue			
Time / Scale	2 Min	6 Min	8 Min
VAS	63% (50-78)	69% (55-82)	78% (66-89)
Borg CR10	45% (33-72)	63% (42-83)	66% (45-85)
Likert	45% (36-72)	50% (36-76)	55% (39-80)

* VAS significantly higher than Borg CR10.

Confidence intervals are in brackets beneath each estimate of reproducibility.

Table 5.2

Sensitivity co-efficients and 95% Confidence Intervals for Visual Analogue, Borg CR10 and Likert Scales.

SENSITIVITY.			
Breathlessness			
Time Scale	2 Min.	6 Min.	8 Min.
VAS	1.3 (1.0, 1.6)	2.6* (2.3, 2.9)	2.7* (2.4, 3.0)
Borg CR10	1.3 (0.9, 1.7)	2.0 (1.7, 2.4)	2.0 (1.6, 2.4)
Likert	1.4 (1.0, 1.8)	2.2 (1.8, 2.6)	2.6 (2.2, 3.0)

* VAS significantly higher than Borg CR10

General Fatigue			
Time Scale	2 Min.	6 Min.	8 Min.
VAS	1.7 (1.4, 2.0)	2.1 (1.8, 2.4)	2.4 (2.1, 2.7)
Borg CR10	1.6 (1.2, 2.0)	2.9*+ (2.5, 3.3)	3.0* (2.6, 3.3)
Likert	1.6 (1.2, 1.9)	2.0 (1.6, 2.4)	2.0 (1.7, 2.4)

* Borg CR10 significantly higher than Likert.
\+ Borg CR10 significantly higher than VAS.

Confidence intervals are in brackets beneath each estimate of reproducibility.

Table 5.3

Visit and Therapy Effects for the Subjective Scales for Minute 8.

Visit / Scale	1	2	3	4	P Value for Visit Effect	Standard Error of Visit Effect	Therapy Effect (All Significant)
VAS Breathlessness	3.9 a	2.5 ab	-0.8 b	-5.6 c	0.003	1.4	19.8
VAS General Fatigue	5.3 a	-0.9 b	0.4 b	-4.8 c	0.001	1.5	19.0
Borg Breathlessness	0.30 a	0.15 a	-0.12 a	-0.33 a	0.09	1.6	1.26
Borg General Fatigue	0.32 a	0.07 b	-0.18 b	-0.21 b	0.04	0.12	1.43
Likert Breathlessness	0.16 a	0.16 a	-0.02 a	-0.3 b	0.016	0.09	0.93
Likert General Fatigue	0.32 a	-0.14 a	-0.04 a	-0.14 a	0.10	0.14	1.03

A common symbol (.e.g a) denotes visits are in common (i.e. no statistically significant difference).

Table 5.4

Visit and Therapy Effects for the Physiological Variables for Minute 8.

Visit / Scale	1	2	3	4	P Value for Visit Effect	Standard Error of Visit Effect	Therapy Effect (All Significant)
VE (litres.min^{-1})	2.99 $_a$	-0.07 $_{ab}$	-0.84 $_b$	-2.08 $_b$	0.02	1.0	11.0
VO_2 (litres.min^{-1})	0.07 $_a$	0.03 $_a$	-0.01 $_a$	-0.09 $_a$	0.054	0.04	-0.04
VCO_2 (litres.min^{-1})	0.02 $_a$	-0.001 $_a$	0.02 $_a$	-0.04 $_a$	0.72	0.03	0.11
Frequency of Breathing (breaths.min^{-1})	1.57 $_a$	0.05 $_b$	-0.35 $_b$	-1.27 $_b$	0.01	0.51	7.6
Heart Rate (beats.min^{-1})	2.65 $_a$	-0.37 $_a$	-1.05 $_a$	-1.23 $_a$	0.14	1.2	-44.7
VE/VO_2	0.45 $_a$	-0.19 $_a$	-0.19 $_a$	-0.07 $_a$	0.58	0.33	4.2
VE/VCO_2	0.92 $_a$	0.11 $_b$	-0.46 $_{bc}$	-0.57 $_c$	0.001	0.23	3.0
Tidal Volume (litres)	-0.02 $_a$	-0.02 $_a$	0.004 $_a$	0.04 $_a$	0.31	0.025	-0.06
RER	-0.02 $_a$	-0.02 $_a$	0.01 $_a$	0.03 $_a$	0.09	0.001	0.06

A common symbol (.e.g $_a$) denotes visits are in common (i.e. no statistically significant difference)

Table 5.5 **Correlations for the Subjective Scales and Physiological Variables.**

The Estimated Overall Pooled Correlation, the Minimum and Maximum Pooled Individual Visit Correlations and the Minimum and Maximum Individual Visit Correlations for all Subjective Scales and Physiological Variables.

	Visual Analogue Scale		Borg CR10 Scales		Likert Scales	
	Breathlessness	General Fatigue	Breathlessness	General Fatigue	Breathlessness	General Fatigue
VE	0.95 0.75 0.99 0.01 1.00	0.94 0.58 0.99 -1.00 1.00	0.92 0.77 0.99 0.42 1.00	0.90 0.17 0.97 0.57 1.00	0.94 0.81 1.00 0.58 1.00	0.92 0.69 1.00 0.26 1.00
VO_2	0.95 0.79 0.98 -0.12 1.00	0.95 0.69 0.99 -0.99 1.00	0.92 0.77 1.00 0.31 1.00	0.93 -0.06 0.98 -0.46 1.00	0.95 0.83 1.00 0.50 1.00	0.92 0.63 1.00 0.33 1.00
VCO_2	0.94 0.80 0.99 -0.16 1.00	0.94 0.72 0.99 -1.00 1.00	0.92 0.76 0.99 0.34 1.00	0.92 0.07 0.99 -0.52 1.00	0.95 0.88 1.00 0.56 1.00	0.92 0.64 1.00 0.35 1.00
Frequency of Breathing	0.85 -0.94 0.98 -1.00 1.00	0.81 -0.90 1.00 -1.00 1.00	0.79 -0.92 0.98 -1.00 1.00	0.80 -0.72 0.97 -0.99 1.00	0.77 -0.73 0.99 -1.00 1.00	0.80 -0.64 0.99 -0.99 1.00
Heart Rate	0.95 0.60 0.99 -0.70 1.00	0.95 0.57 0.99 -0.99 1.00	0.92 0.78 0.99 0.45 1.00	0.92 0.56 0.98 -0.76 1.00	0.95 0.77 0.99 0.50 1.00	0.92 0.33 0.98 0.08 1.00
Tidal Volume	0.88 0.34 0.99 -0.96 1.00	0.89 0.22 0.99 -0.99 1.00	0.88 0.62 0.99 -0.96 1.00	0.89 0.26 0.98 -0.53 1.00	0.89 0.61 0.98 -1.00 1.00	0.80 0.08 0.97 -1.00 1.00
R.E.R.	0.91 0.53 0.99 -0.54 1.00	0.91 0.42 0.99 -1.00 1.00	0.90 0.73 0.99 0.37 1.00	0.89 0.18 1.00 -0.55 1.00	0.93 0.59 1.00 -0.64 1.00	0.86 0.32 1.00 -0.75 1.00
VE/VO_2	0.91 0.52 0.98 -0.90 1.00	0.89 0.43 0.99 -0.99 1.00	0.89 0.66 0.98 0.89 1.00	0.88 0.13 0.98 -0.89 1.00	0.90 0.50 0.99 -0.25 1.00	0.85 -0.24 0.99 -1.00 1.00
VE/VCO_2	0.03 -0.94 0.96 -0.43 0.94	0.17 -0.97 0.99 -0.39 0.92	-0.15 -0.93 0.84 -1.00 1.00	-0.15 -0.93 0.67 -1.00 1.00	0.01 -1.00 0.91 -1.00 0.99	0.06 -0.96 0.96 -1.00 1.00

An example of how the data is presented is given for VE and VAS breathlessness. The estimated overall pooled correlation is 0.95. Minimum and maximum pooled individual visit correlations

Table 5.6

Time Effects for Subjectivie Scales and Physiological Variables.

Variable / Time	2	6	8	P Value for Time Effect	Standard Error
VAS Breathlessness	-11.8 a	4.0 b	7.8 c	P< 0.001	0.8
VAS General Fatigue	-11.2 a	4.0 b	7.2 c	P< 0.001	1.0
Borg CR10 Breathlessness	0.83 a	0.29 b	0.54 c	P< 0.001	0.08
Borg CR10 General Fatigue	-0.74 a	0.26 b	0.48 c	P< 0.001	0.07
Likert Breathlessness	-0.67 a	0.28 b	0.39 b	P< 0.001	0.05
Likert General Fatigue	-0.64 a	0.20 b	0.44 c	P< 0.001	0.06
VE (litres.min^{-1})	-12.0 a	5.46 b	6.6 b	P< 0.001	0.5
VO_2 (litres.min^{-1})	-0.35 a	0.16 b	0.19 b	P< 0.001	0.02
VCO_2 (litres.min^{-1}	-0.48 a	0.24 b	0.24 b	P< 0.001	0.02
Frequency of breathing (breaths.min^{-1})	-2.4 a	1.0 b	1.4 b	P< 0.001	0.3
Heart Rate (beats.min^{-1})	-11.3 a	4.6 b	6.7 c	P< 0.001	0.6
VE/VO_2	-1.5 a	0.6 b	0.9 b	P< 0.001	0.02
VE/VCO_2	0.31 a	-0.33 b	0.02 b	P< 0.009	0.12
Tidal Volume (litres)	-0.25 a	0.12 b	0.13 b	P< 0.001	0.01
RER	-0.069 a	0.036 b	0.033 b	P< 0.001	0.004

A common symbol (e.g. a) denotes visits are in common (i.e. no statistically significant difference).

Table 5.7

Respiratory Variables and Heart Rate at Minutes 6 and 8 for the Placebo Test.

	MINUTE	
	6	8
VO_2 ($ml.kg^{-1}.min^{-1}$)	40.43±5.4	40.25±5.5
VCO_2 ($litres.min^{-1}$)	2.62±0.48	2.60±0.44
VE ($litres.min^{-1}$)	66.96±12.9	66.98±13.1
RER	0.895±0.06	0.897±0.06
Tidal Volume (litres)	2.27±0.41	2.28±0.42
Frequency of Breathing ($breaths.min^{-1}$)	30.52±6.8	30.4±7.5
Heart Rate ($beats.min^{-1}$)	154.6±13.8	156.8±13.8

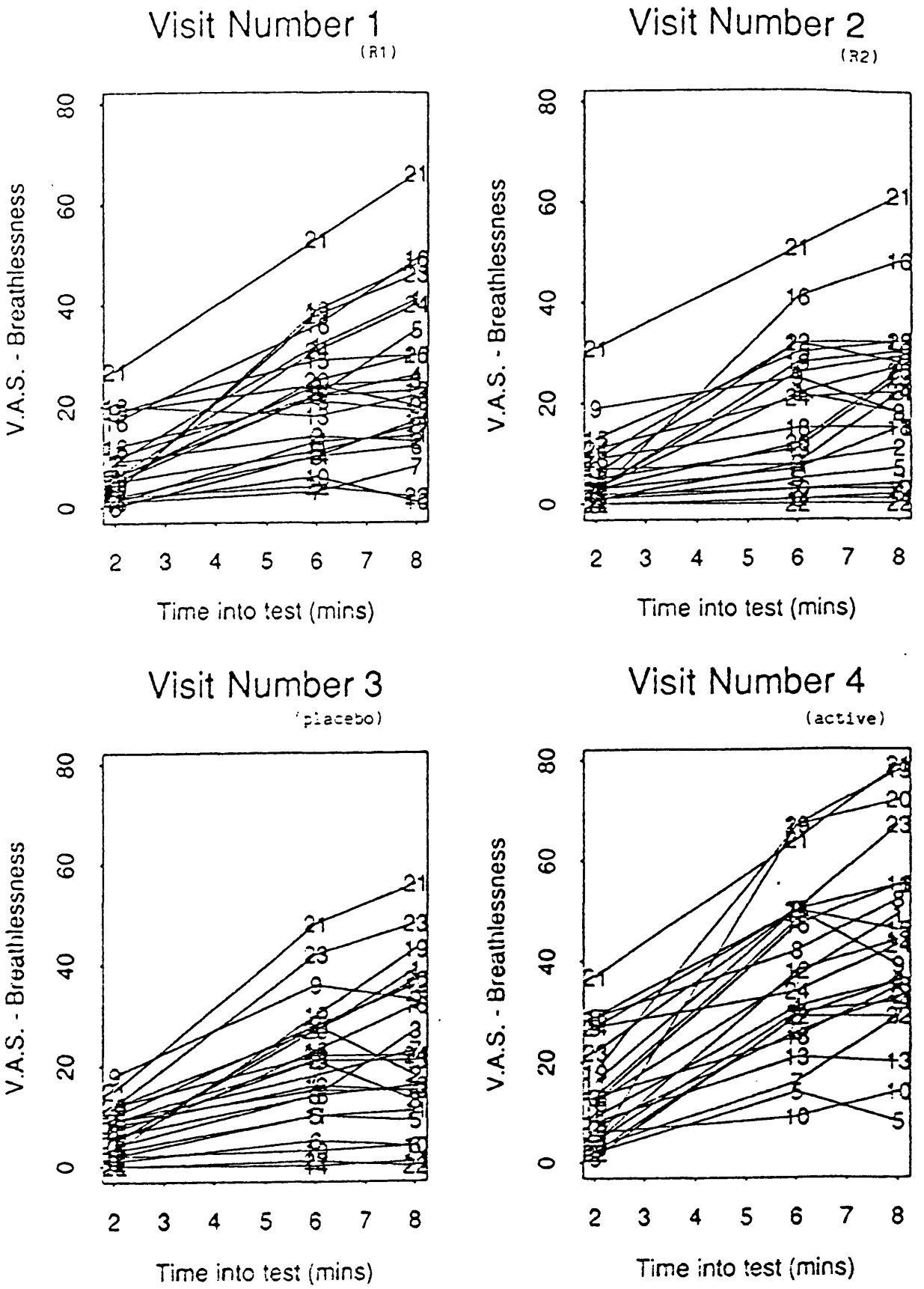


Fig 5.1

VAS breathlessness for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23.

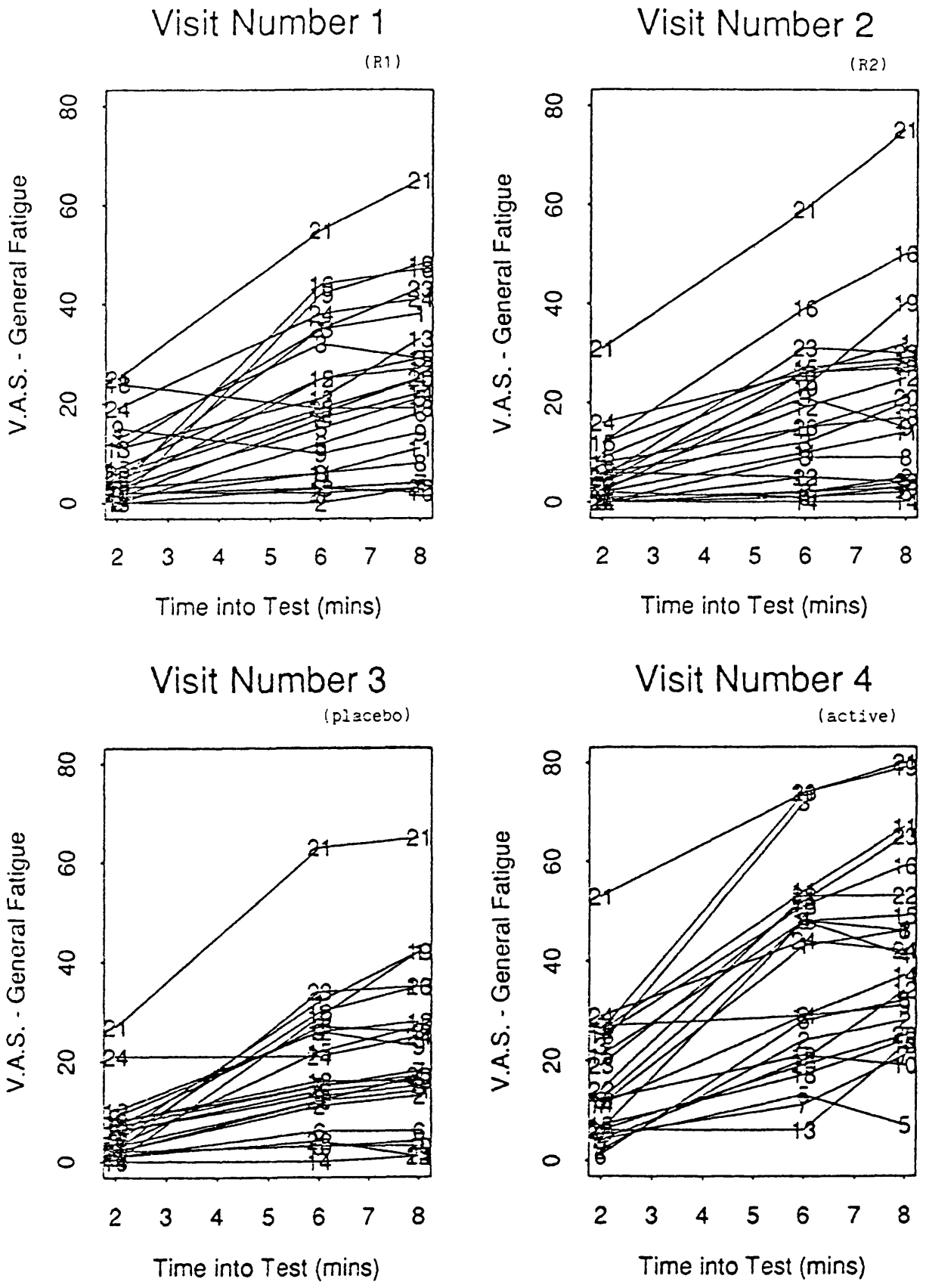


Fig 5.2
VAS general fatigue for the four submaximal tests (R1, R2, Placebo and active) labelled by subject numbers 1-23.

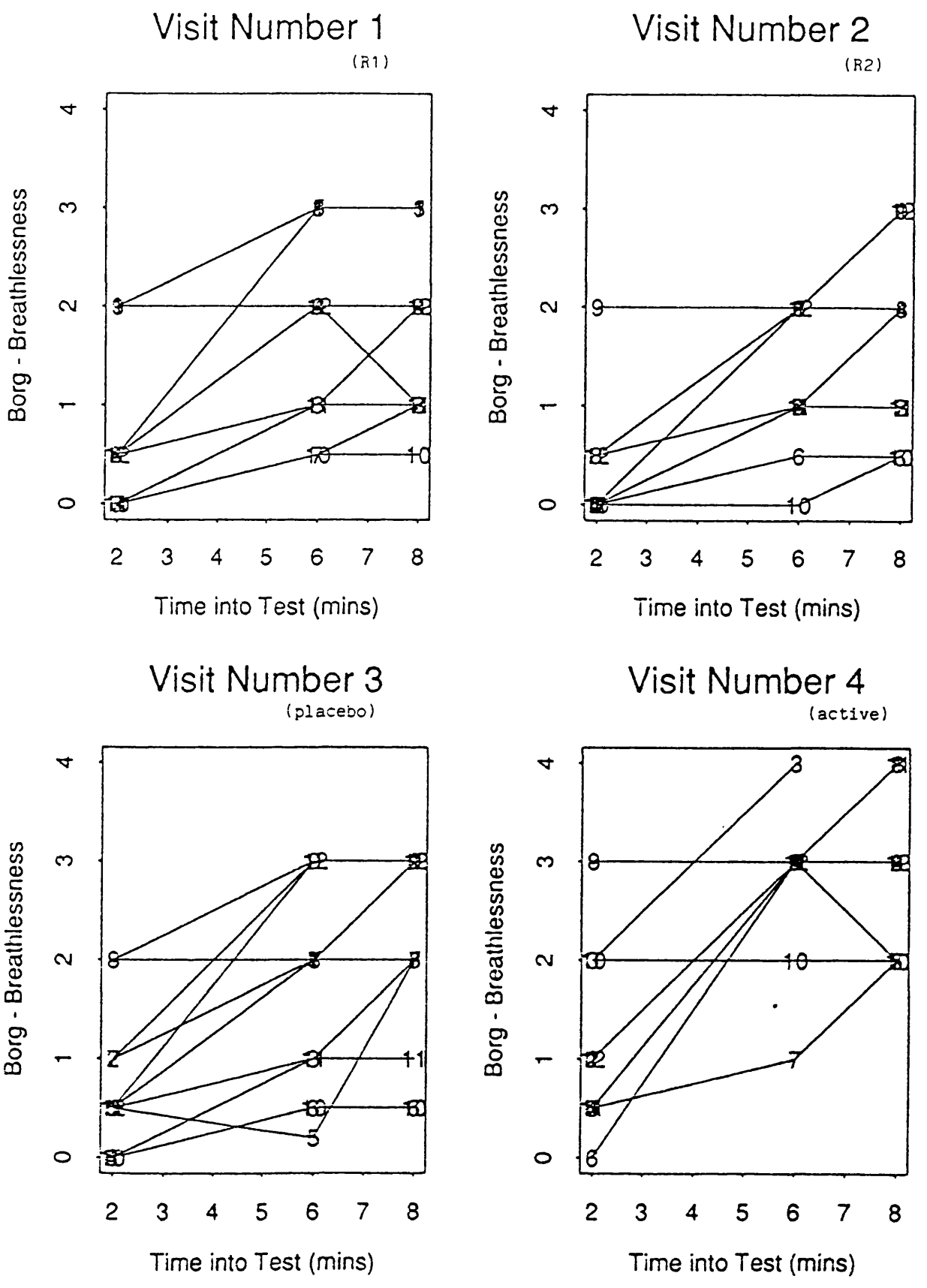


Fig 5.3

Borg CR10 breathlessness for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23.

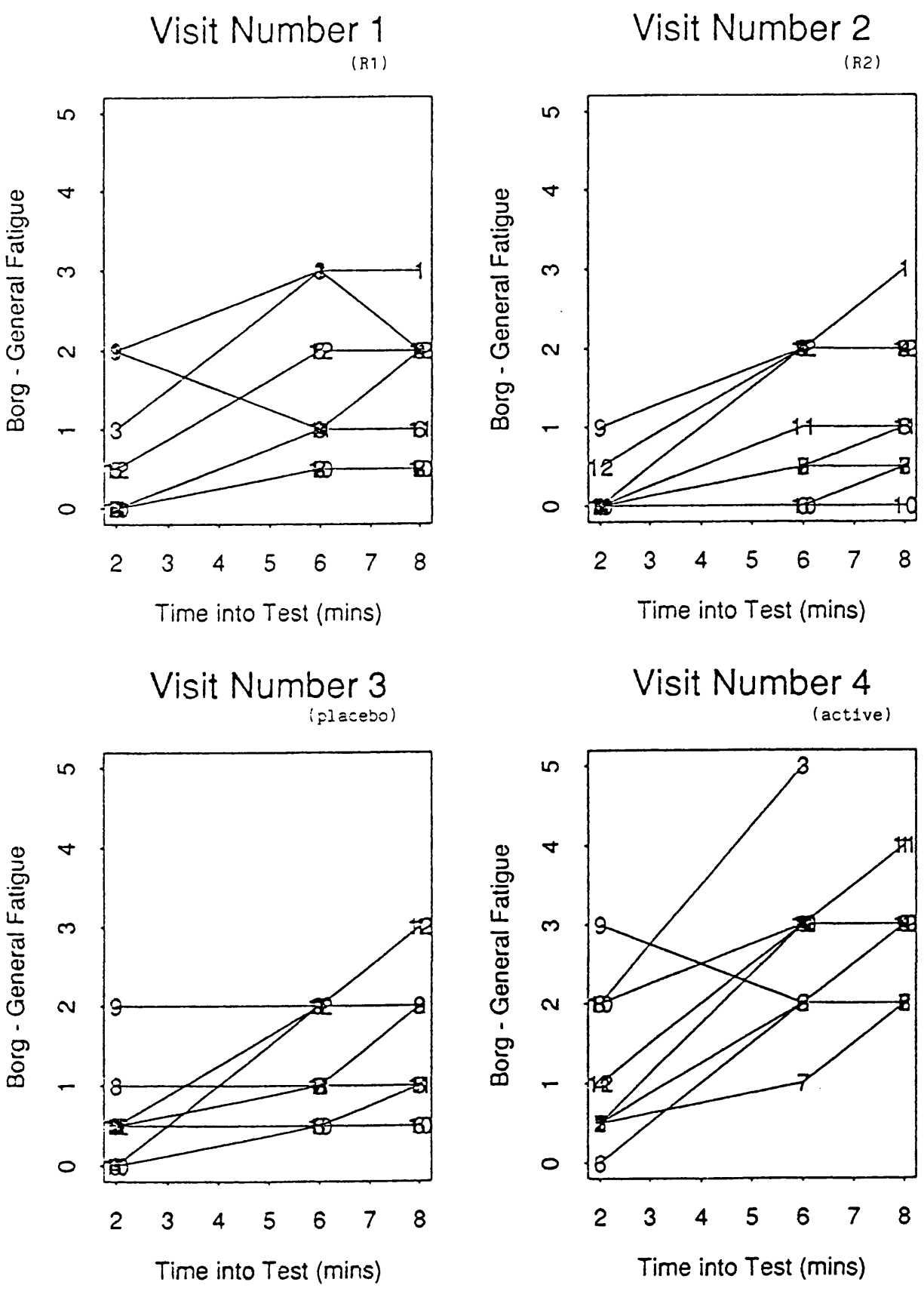


Fig 5.4

Borg CR10 general fatigue for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23.

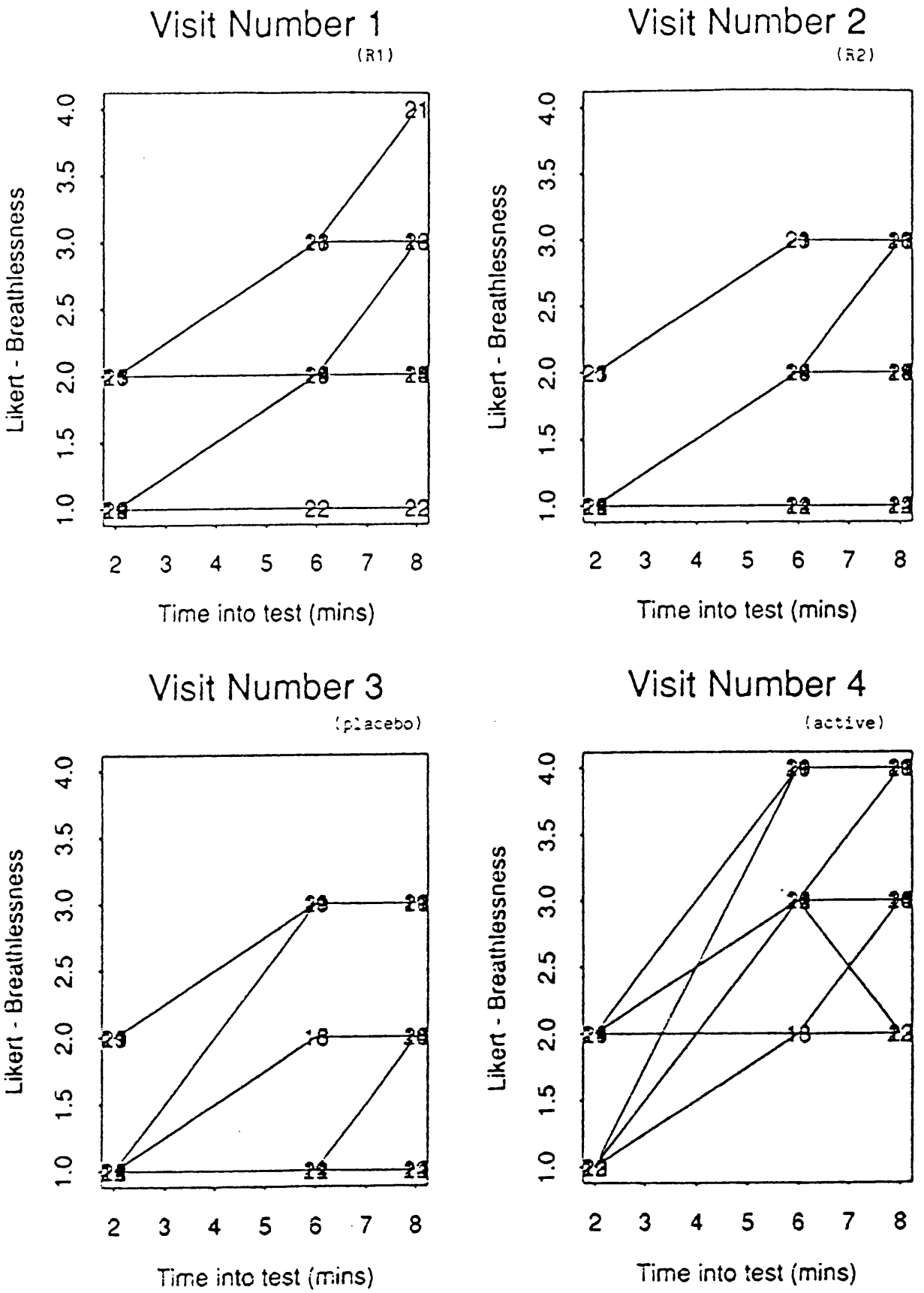


Fig 5.5

Likert breathlessness for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23.

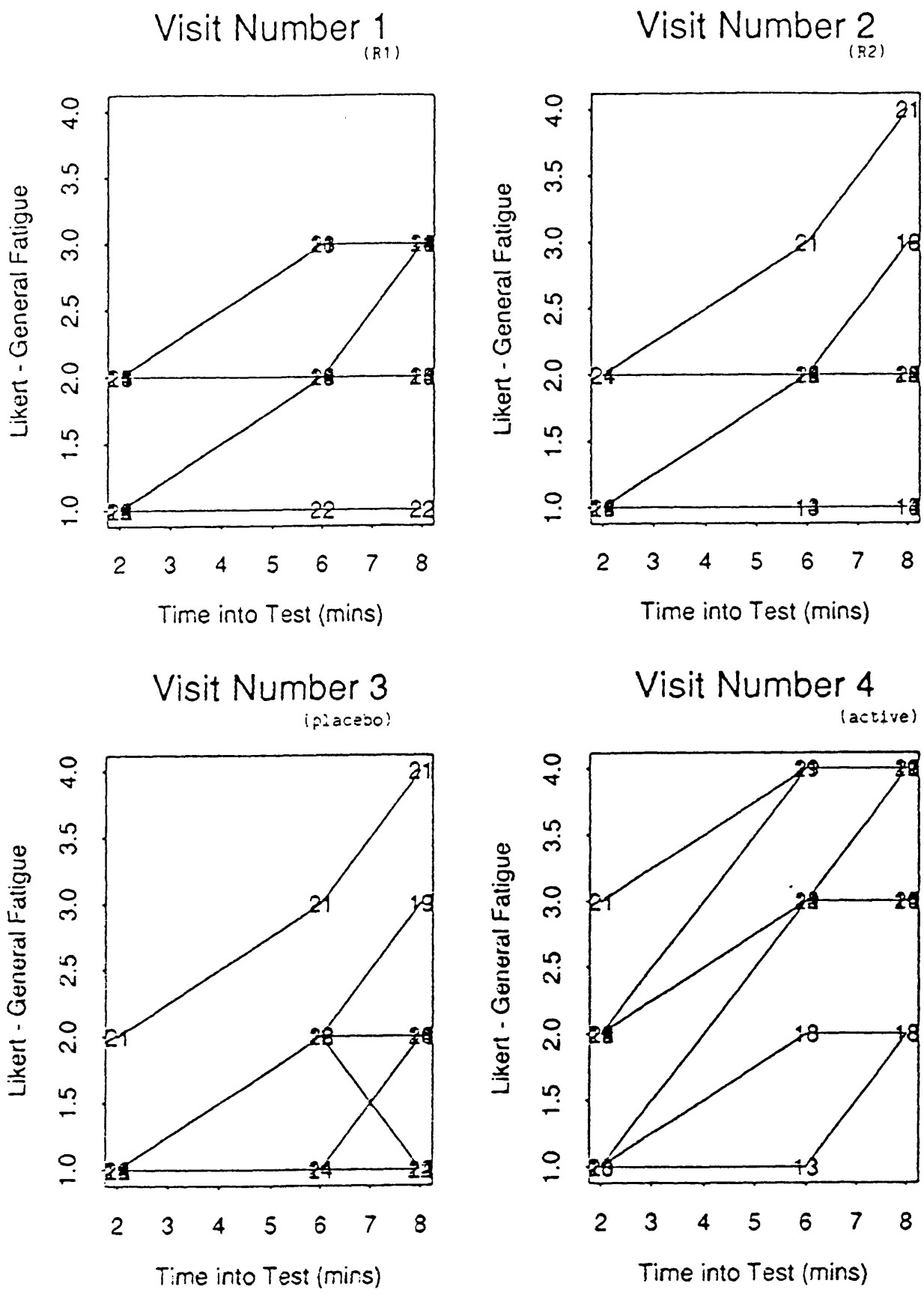


Fig 5.6

Likert general fatigue for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23.

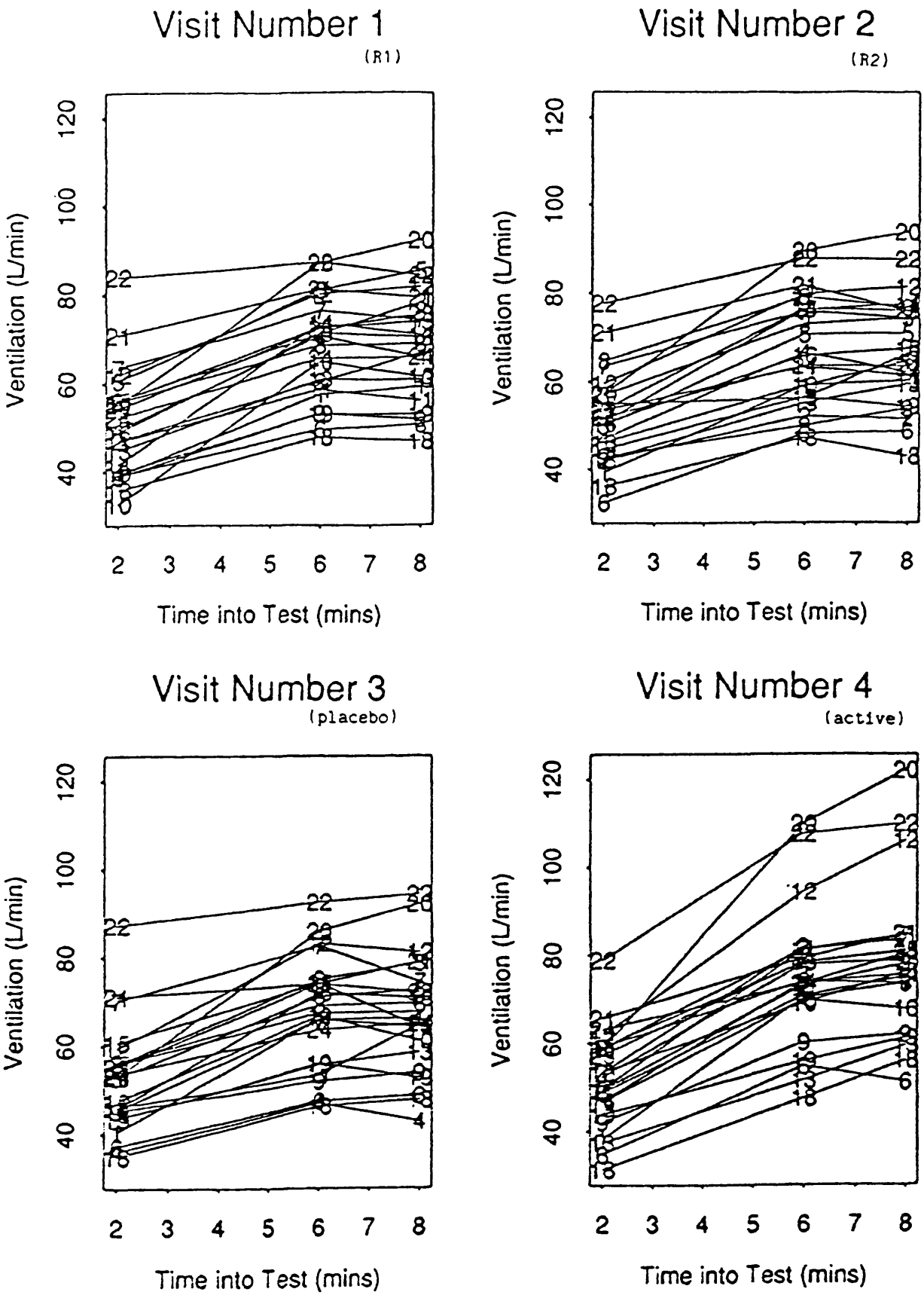
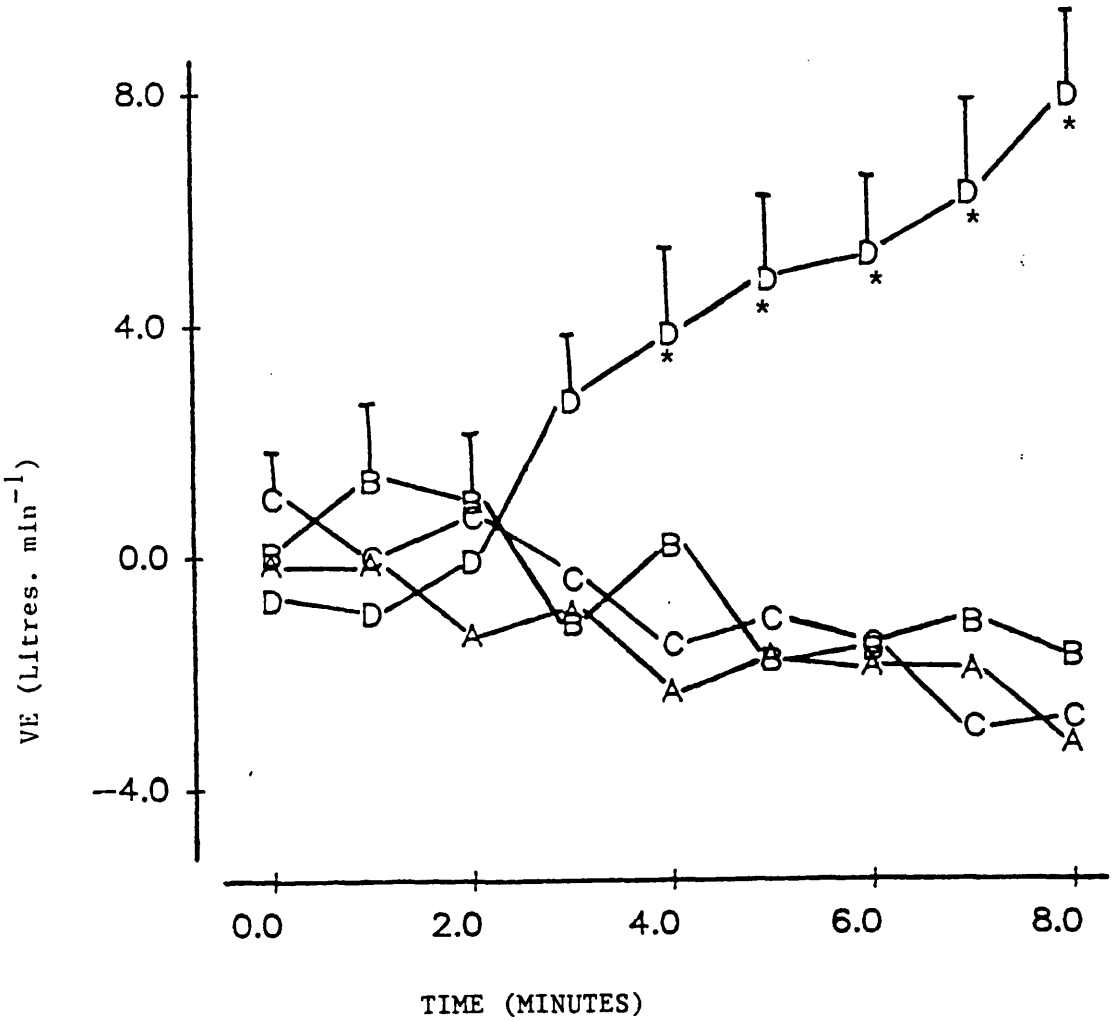


Fig 5.7

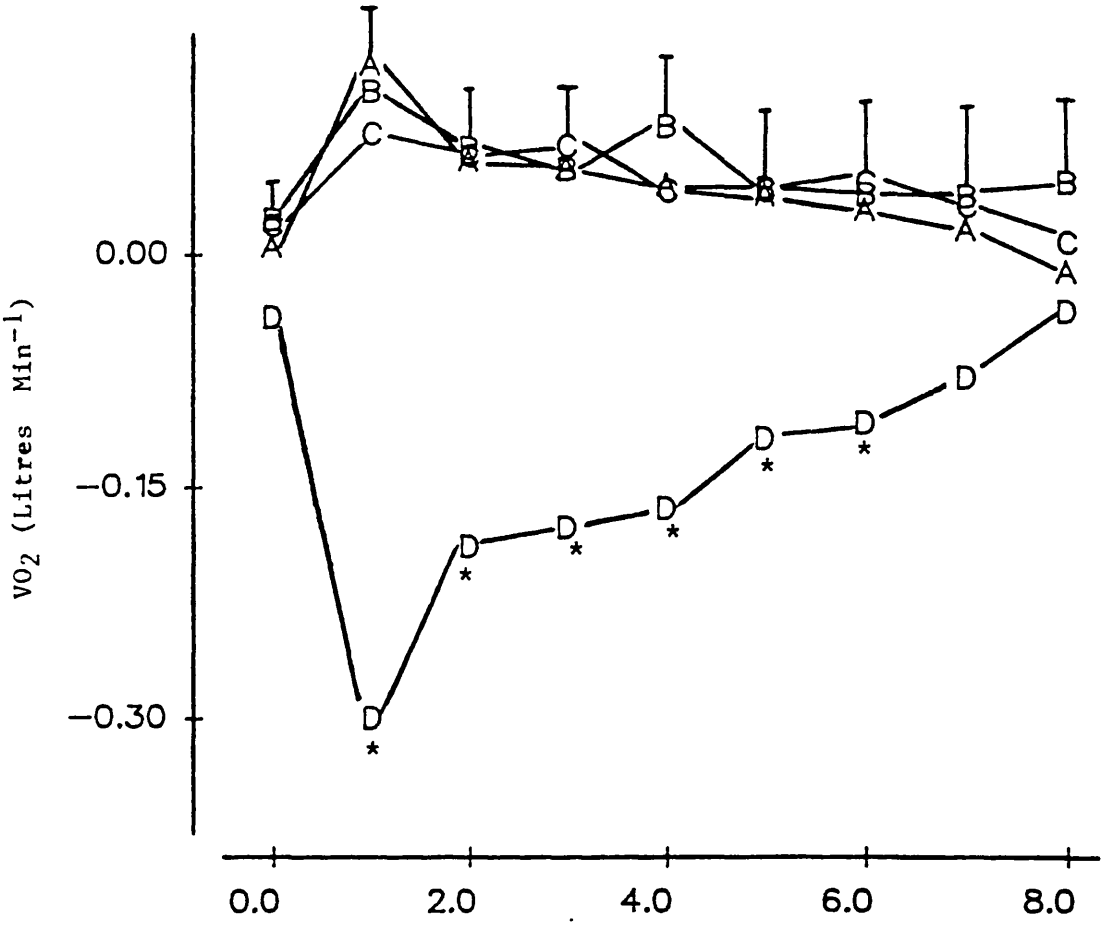
Minute ventilation for the four submaximal tests (R1, R2, placebo and active) labelled by subject numbers 1-23



* Denotes Significant Therapy Effect

FIG 5.8
Therapy effects for minute ventilation

A: R1 B: R2 C: PLACEBO D: ACTIVE

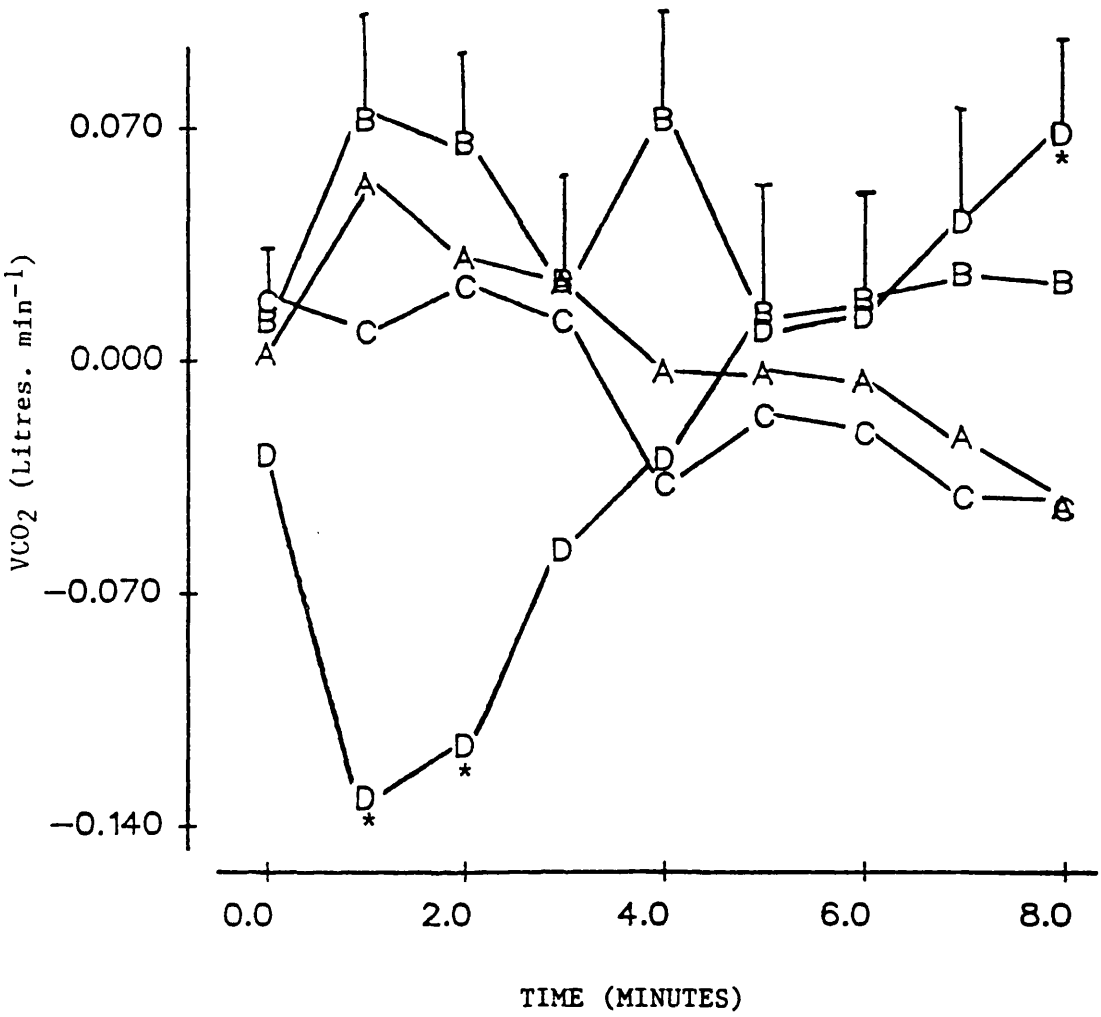


* Denotes Significant Therapy Effect

FIG 5.9

Therapy effects for volume of oxygen consumed

A: R1 B: R2 C: PLACEBO D: ACTIVE

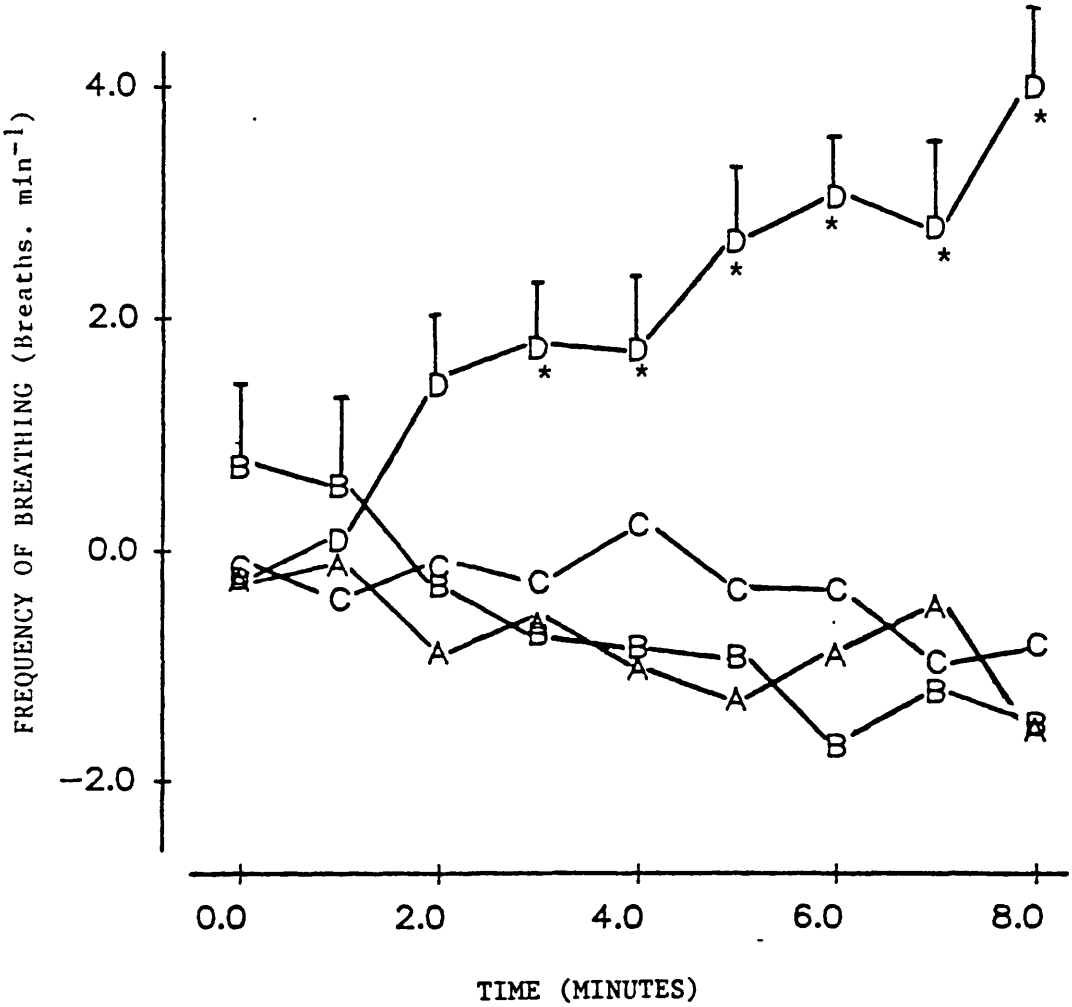


* Denotes Significant Therapy Effect

FIG 5.10

Therapy effects for volume of carbon dioxide produced

A: R1 B: R2 C: PLACEBO D: ACTIVE

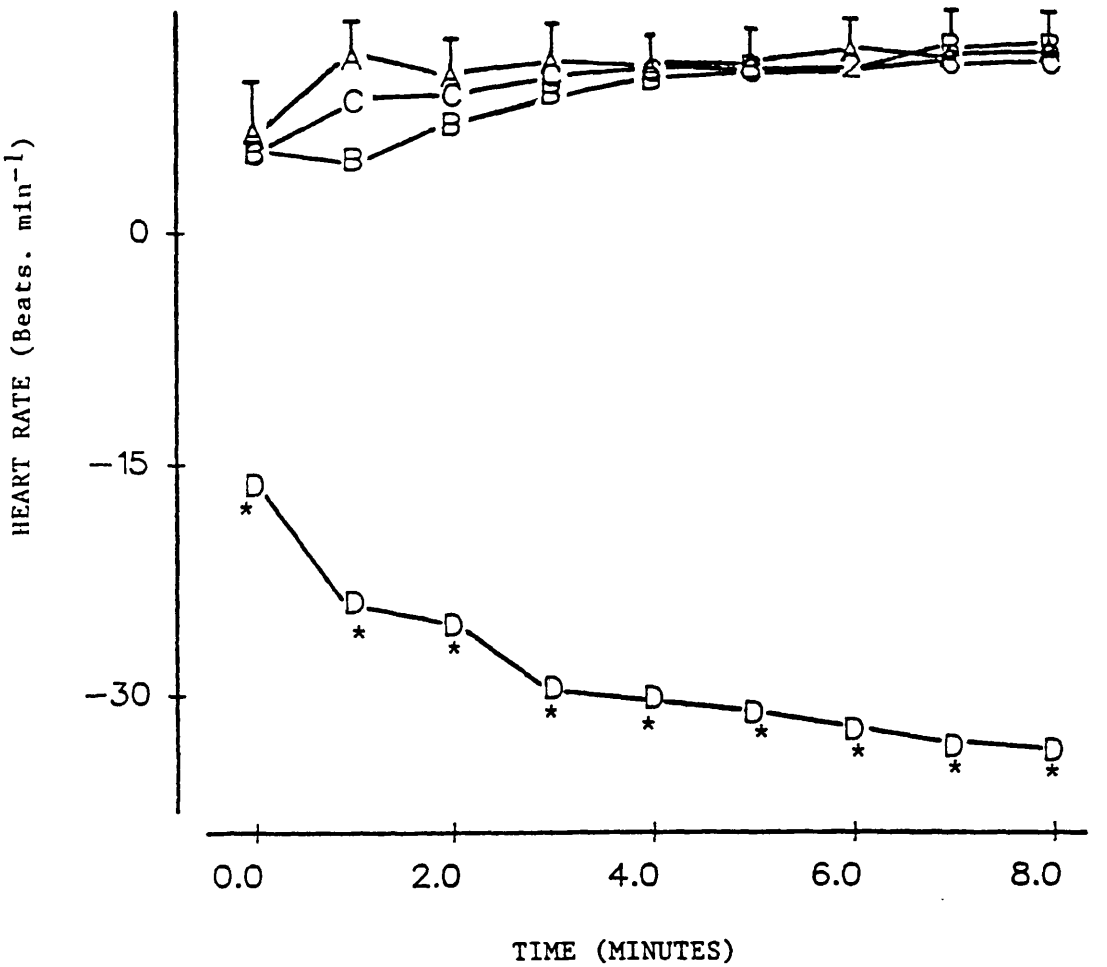


* Denotes Significant Therapy Effect

FIG 5.11

Therapy effects for frequency of breathing.

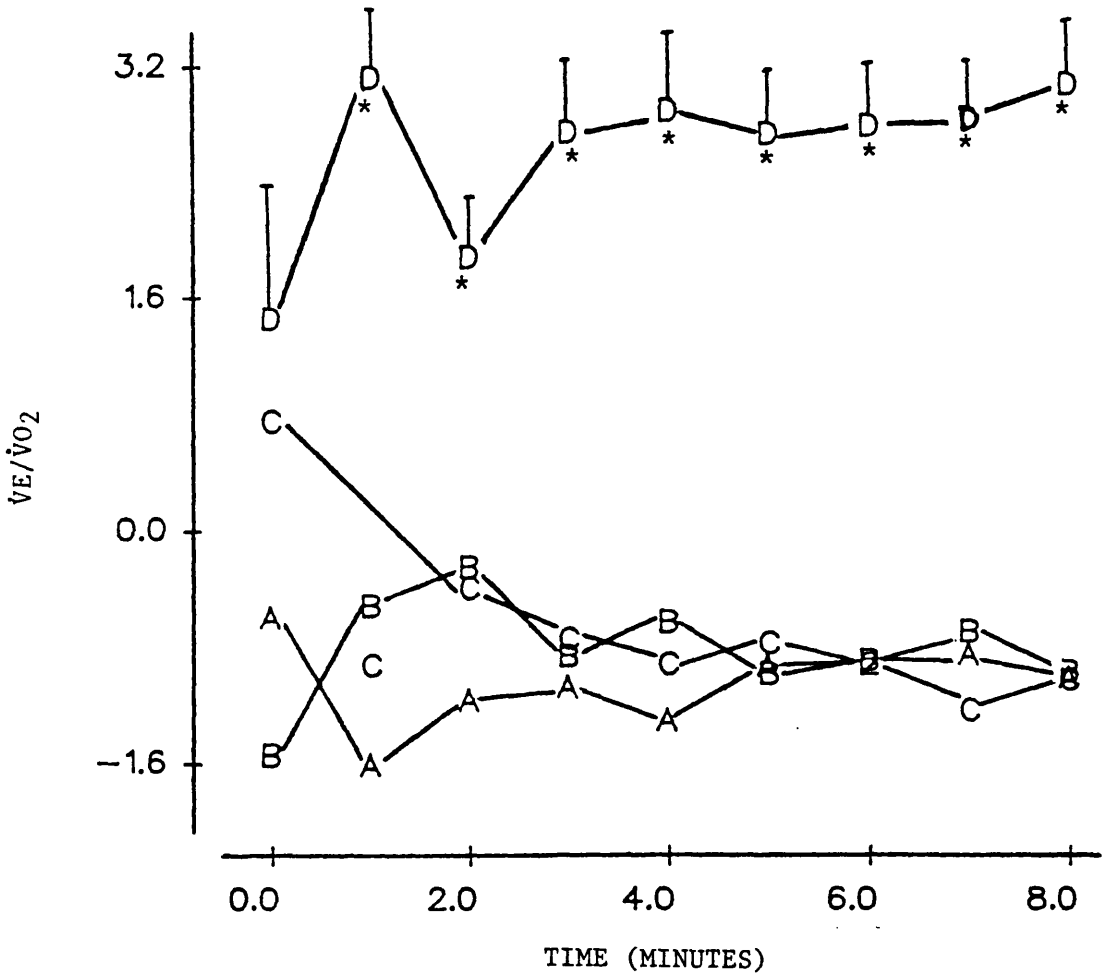
A: R1 B: R2 C: PLACEBO D: ACTIVE



* Denotes Significant Therapy Effect

FIG 5.12

Therapy effect for heart rate

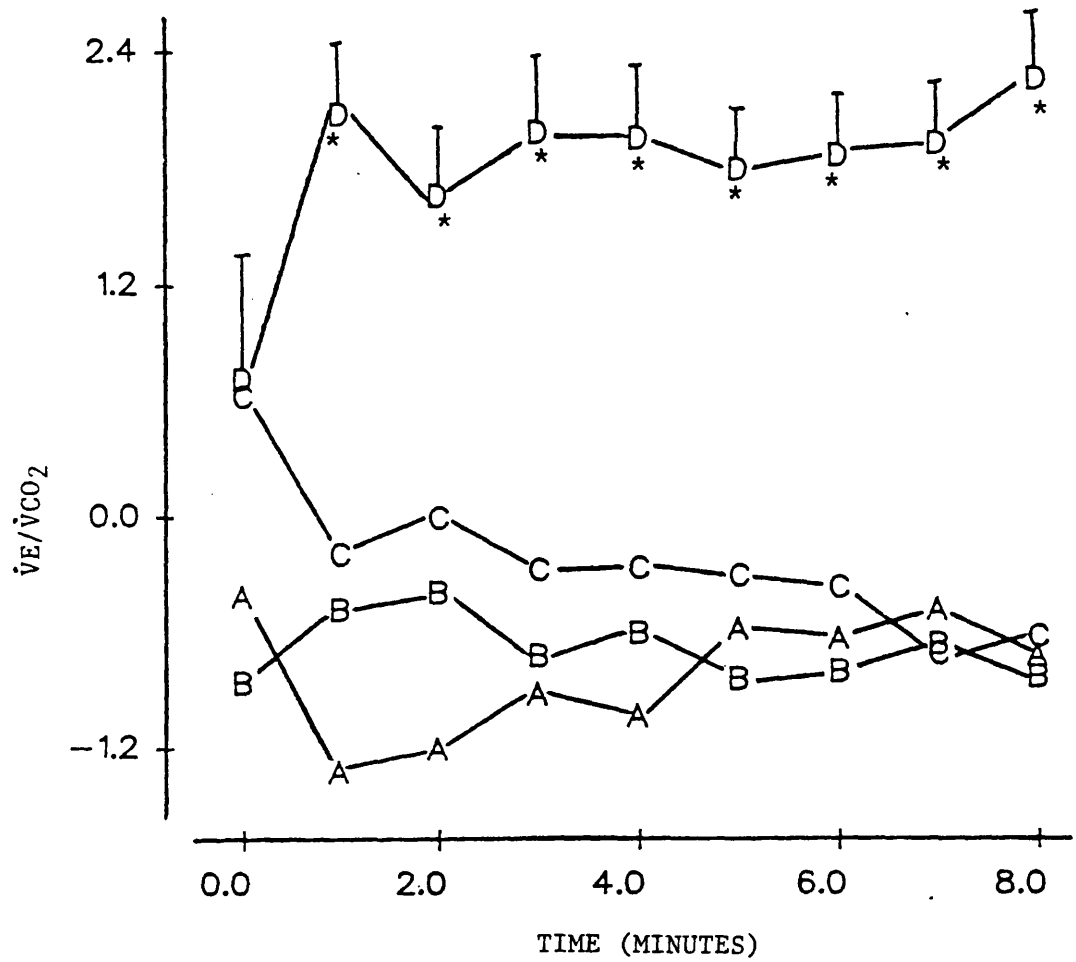


* Denotes Significant Therapy Effect

FIG 5.13

Therapy effect for VE/VO_2

A: R1 B:R2 C: PLACEBO D: ACTIVE

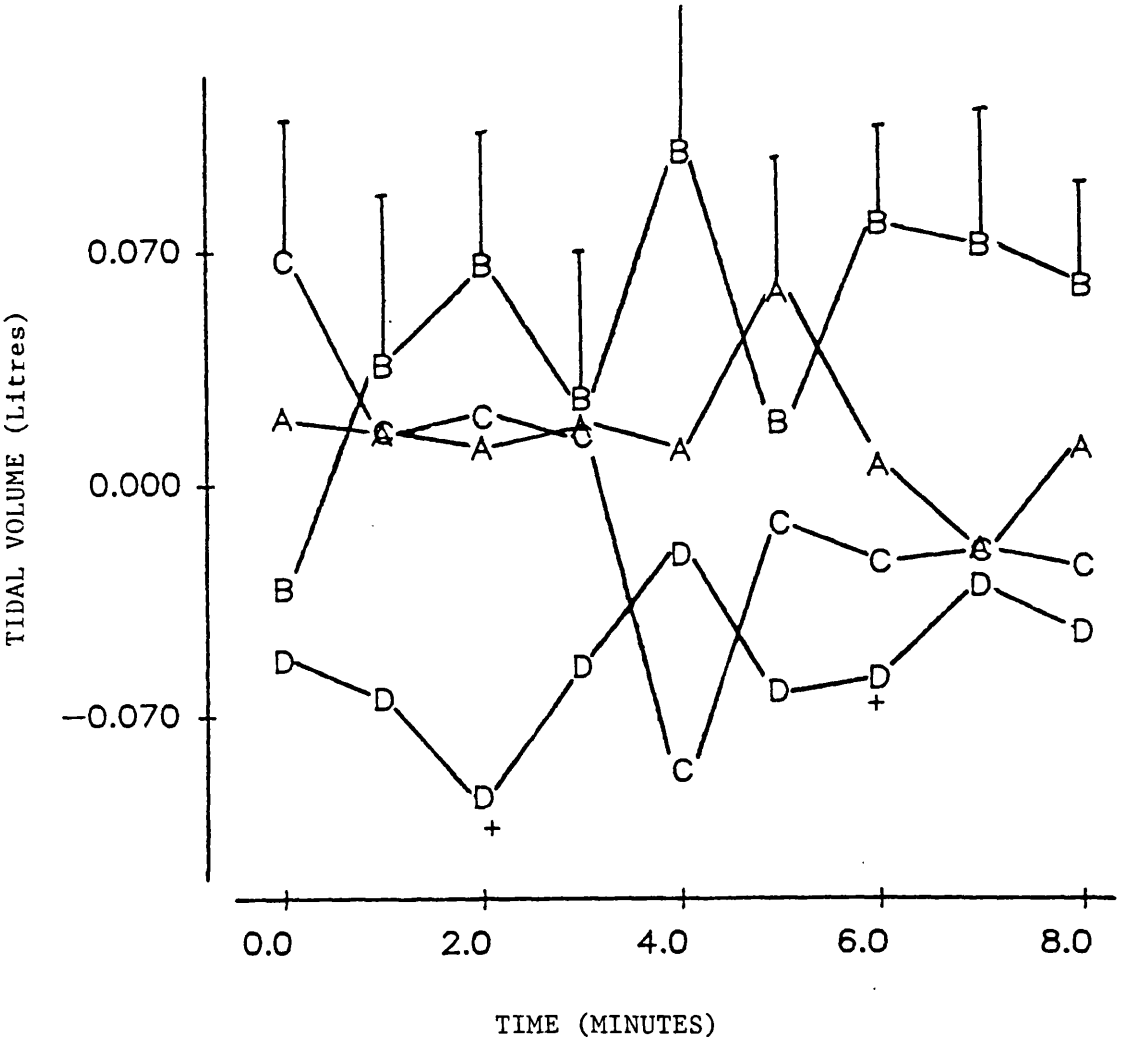


* Denotes Significant Therapy Effect

FIG 5.14

Therapy effects for VE/VCO_2

A: R1 B: R2 C: PLACEBO D: ACTIVE

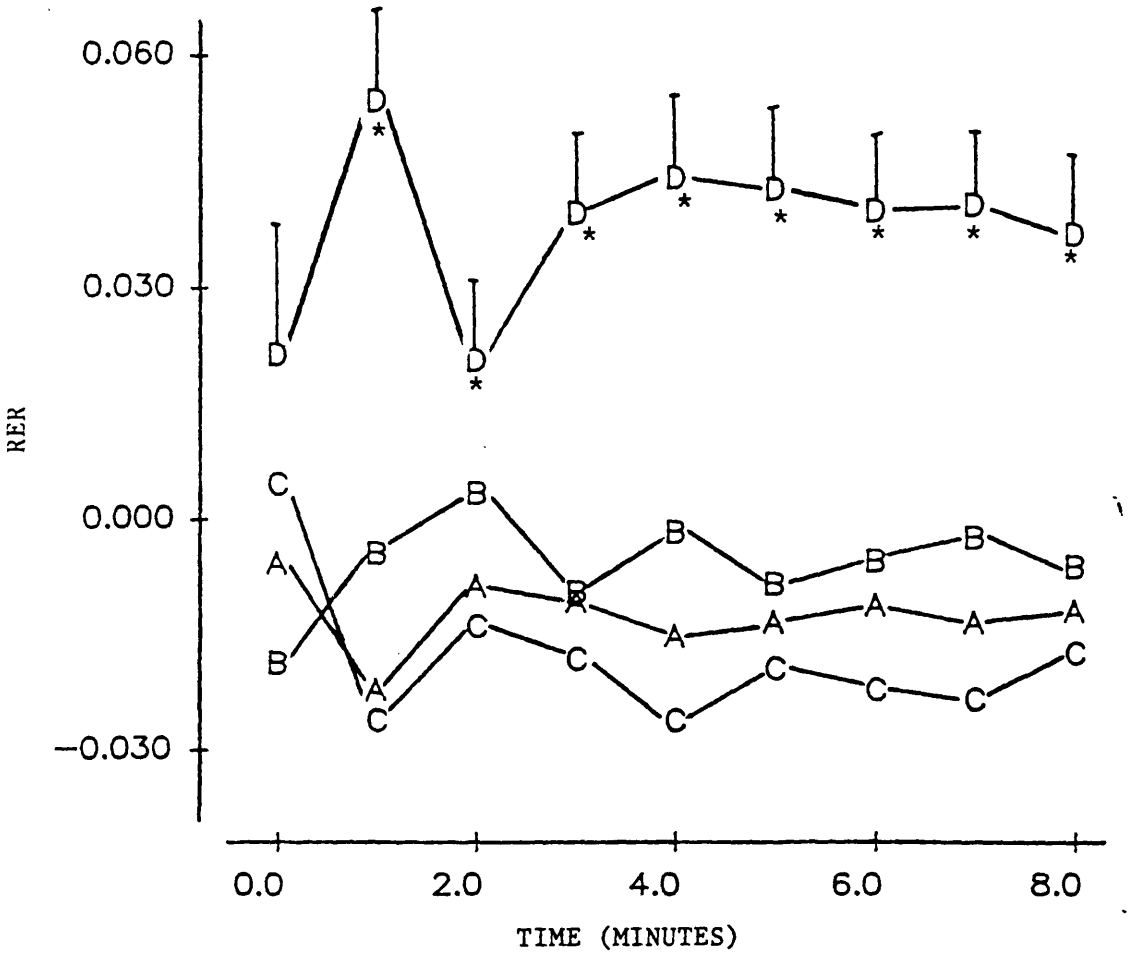


+ Active Treatment Is Significantly Lower Than Replica 2.

FIG 5.15

Therapy for tidal volume

A: R1 B: R2 C: PLACEBO D: ACTIVE



* Denotes Significant Therapy Effect

FIG 5.16

Therapy effects for RER

A: R1 B: R2 C: PLACEBO D: ACTIVE

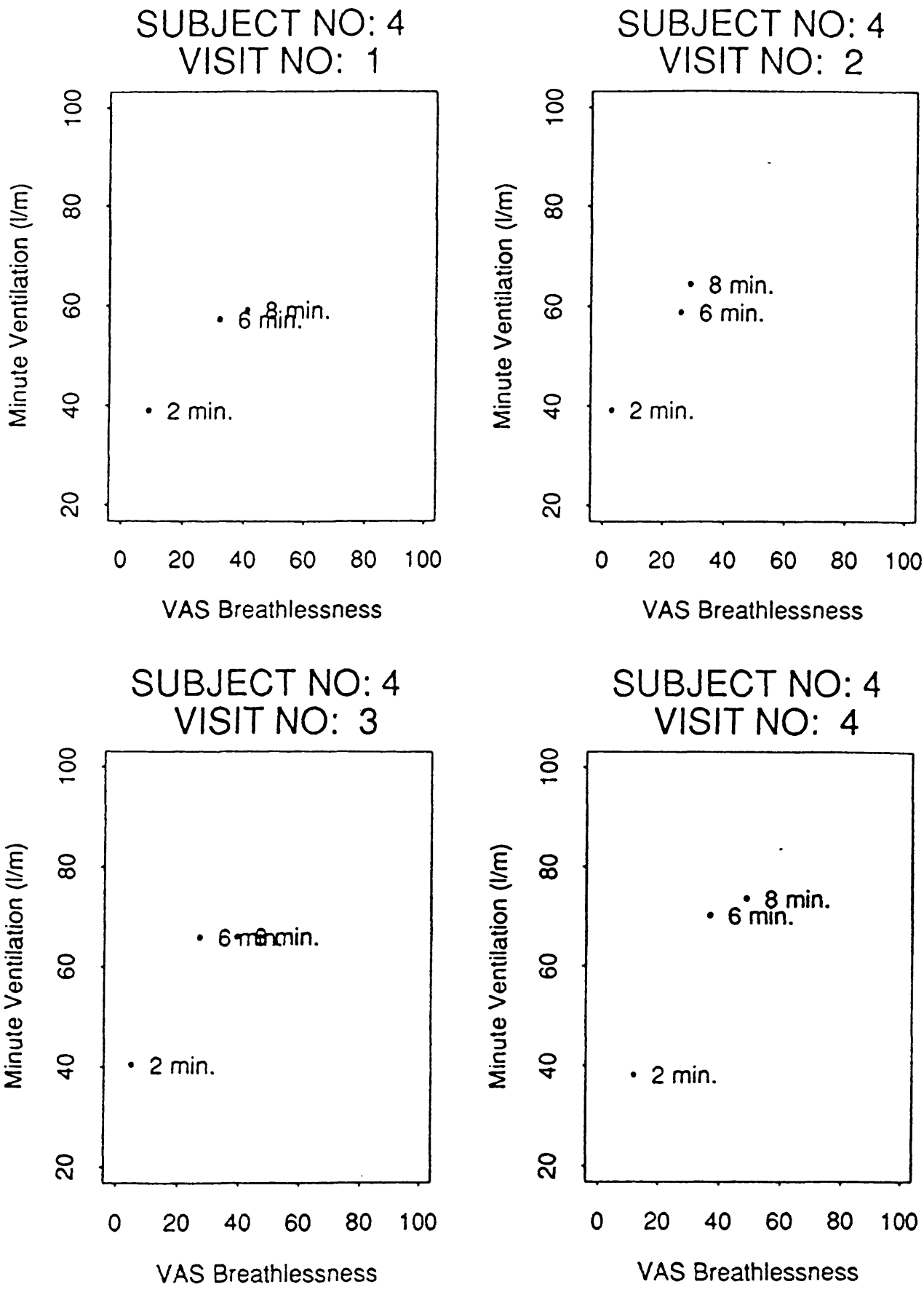


FIG 5.17

The VE/VAS breathlessness relationship for subject 4 for all tests

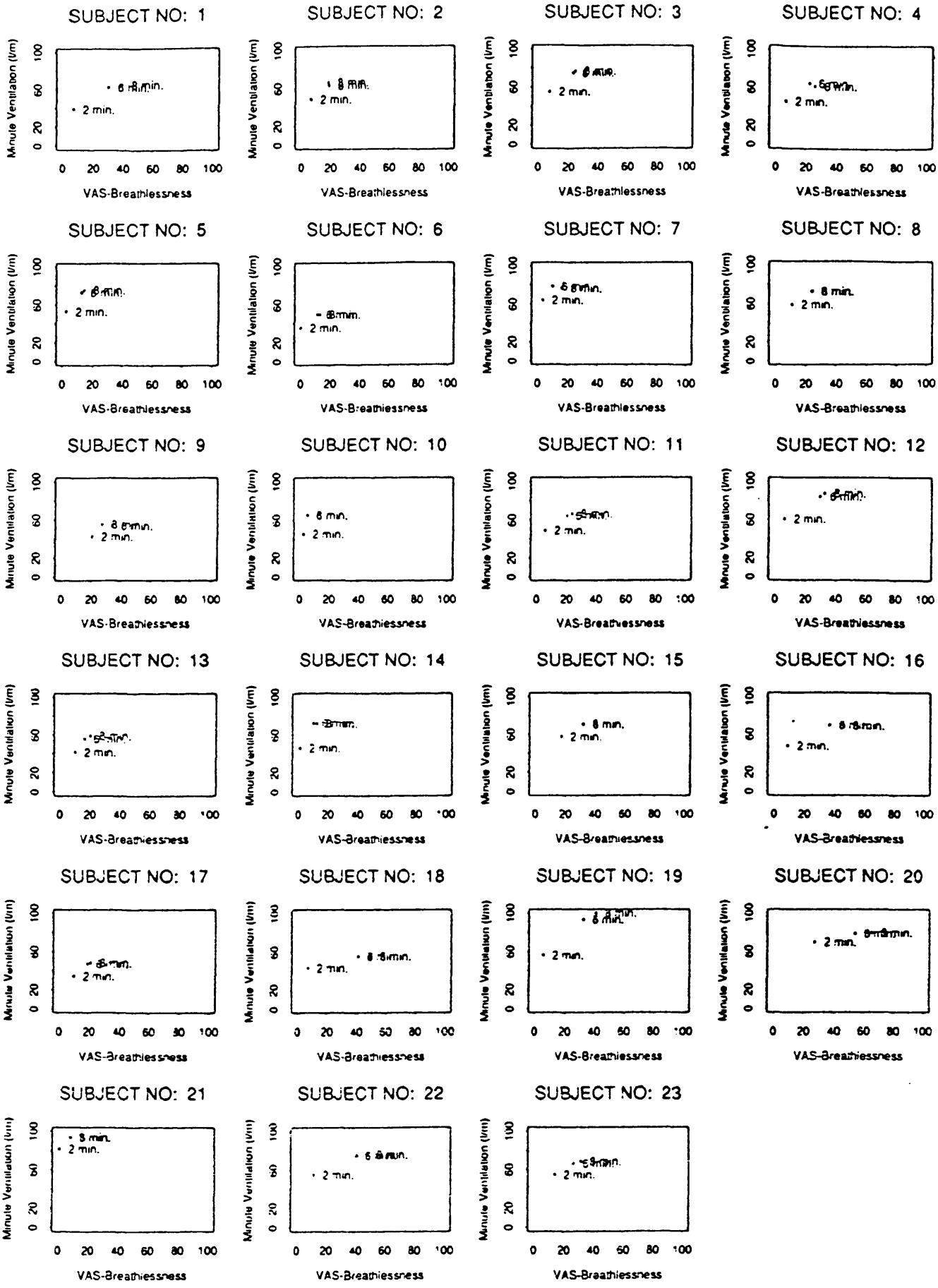


FIG. 5.18
VE/VAS Breathlessness relationship for all subjects for all tests.

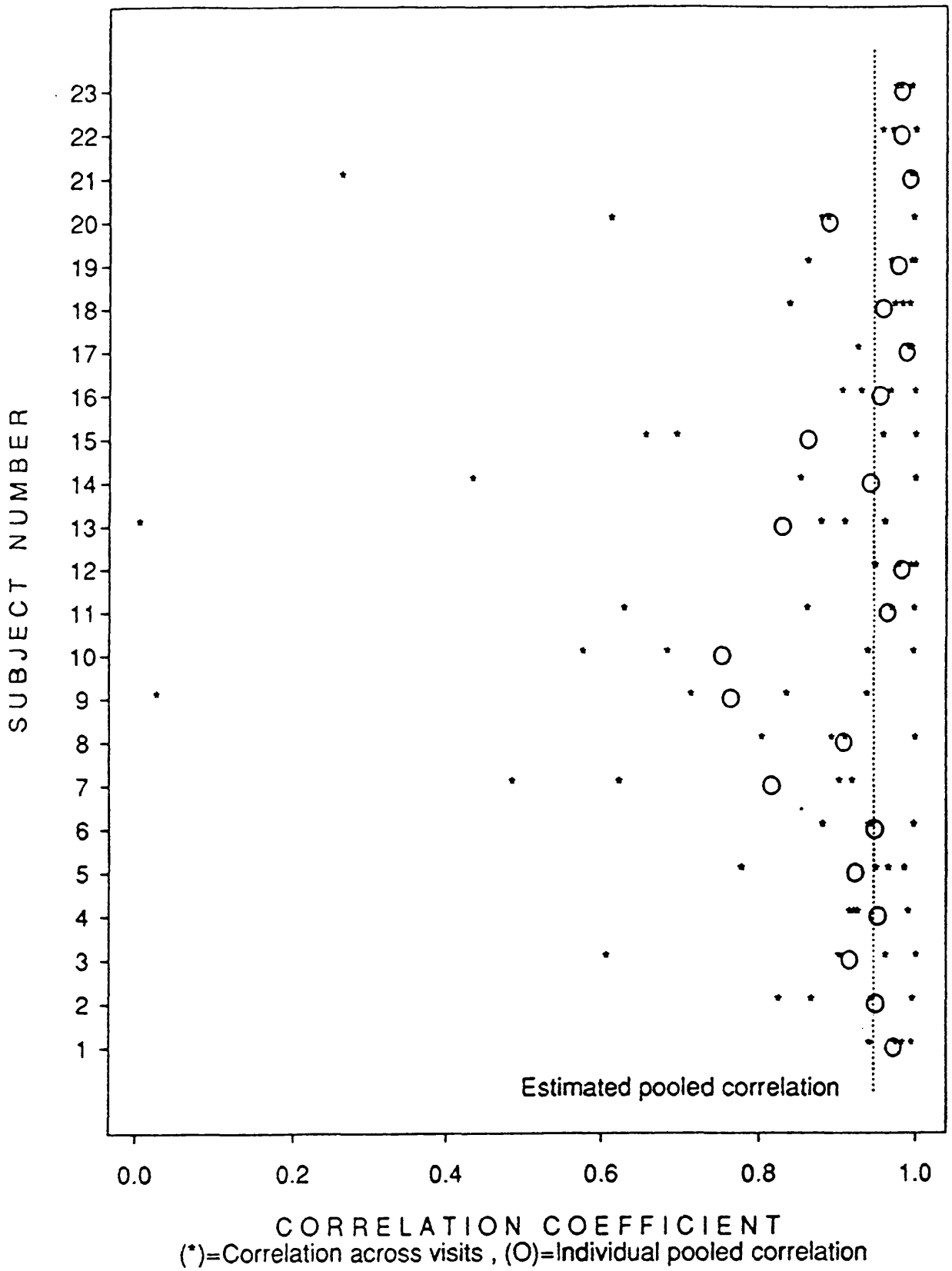


FIG 5.19
The correlations for VE and VAS breathlessness.

i) Individual visit correlation for VE and VAS breathlessness.
ii) Individual pooled correlation.
iii) Estimated pooled correlation.

CHAPTER 6
SECTION ONE.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

RESULTS OF THE SUBJECTIVE SCALES.

6.1.1. DESIGN AND AIMS OF THE CHF STUDY.

SUMMARY OF THE DESIGN OF THE CHF STUDY.

Ten patients with chronic heart failure underwent two maximal incremental tests followed by four submaximal (constant workrate) symptom limited tests at weeks 1, 2, 4 and 6. Two subjective scales were used - (1) visual analogue (VAS) (continuous scale) (2) Borg CR10 scale (12 fixed points) to measure breathlessness and general fatigue. During the submaximal tests, scales were used to measure the symptoms of breathlessness every 2.5 minutes. A variety of physiological variables were measured at each minute throughout the tests.

THE MAIN AIMS OF THE CHF STUDY WERE TO:

1) Compare the reproducibility of the visual analogue and Borg CR10 scales.
2) Determine the reproducibility of the submaximal tests.
3) Assess the relative intensity at which the subjects work during the submaximal test.
4) Investigate the relationship between the subjective scales and physiological variables.

6.1.2. RESULTS FOR THE SUBJECTIVE SCALES.

6.1.3. STATISTICAL METHODS FOR THE SUBMAXIMAL TESTS.

Statistical analysis was limited to the first four timepoints i.e. 2.5, 5.0, 7.5 and 10 minutes as there were insufficient data after 10 minutes to allow for meaningful analysis. A generalised linear model (GLM) was applied to the data to include the possible effects of visit, subject, time and natural (or error) variability.

6.1.4. AN IMPRESSION OF THE RAW DATA FOR THE SUBMAXIMAL TESTS.

An impression of how the scales were used is given in Figures 6.1. to 6.4. which show the ranges for both scales for breathlessness and general fatigue.

These figures highlight that the scales are used in a highly individualistic way. For example, subject 1 tends to score very low for all scales for all tests, whereas subject 7 scores high throughout all scales for all tests. The figures show that the scales were used over a wide range throughout the four timepoints.

6.1.5. THE REPRODUCIBILITY OF THE SUBJECTIVE SCALES.

The estimated reproducibility coefficients for VAS and Borg CR10 for the first four timepoints are given in Table 6.1. For both breathlessness and general fatigue the reproducibility of the VAS was clearly higher than the Borg CR10. Ninety-five percent confidence intervals, however, showed that there were no significant differences between the scales. For the VAS (breathlessness), the reproducibility appeared to decrease through time into the test (i.e. the coefficients were lowest at 7.5 and 10 minutes).

In general, reproducibility was better for the VAS on general fatigue than on breathlessness.

6.1.6. THE IMPORTANCE OF ANY VISIT EFFECTS.

Using a GLM, the visit effect was investigated only for timepoint three (i.e. 7.5 minutes) as it was deemed unnecessary and impractical to examine the visit effects for all timepoints. Table 6.2 shows that there was no visit effect for any subjective scale at this timepoint.

6.1.7. THE CONSISTENCY OF THE SYMPTOMATIC SCALES IN THE MAXIMAL INCREMENTAL TESTS.

As part of the protocol leading up to the above four submaximal tests, two maximal incremental tests were carried out at least four days apart. The symptomatic scores for breathlessness and general fatigue measured at the end of each of these two tests were

compared to determine if the subjects had reassessed their perception of symptoms after the experience gained in the first test. Table 6.3 shows the peak values for breathlessness and general fatigue for the VAS and Borg CR10 for these two incremental maximal tests. All scales were used over a very wide range. For example, in test 2 for general fatigue, the ranges were 15-80 and 1-7 for the VAS and Borg CR10 scales respectively. Table 6.4 shows the mean differences and 95% confidence intervals for the differences between tests. There were no significant differences for any scale.

6.1.8. SUMMARY OF THE SUBJECTIVE SCALES DATA.

For breathlessness and general fatigue, the VAS consistently had higher reproducibility coefficients than the Borg CR10 scale which, however, did not reach statistical significance. The scales were used over a wide range at maximum in the incremental tests and during the constant workrate tests. There were no significant visit/familiarisation effects in the incremental and constant workrate tests.

CHAPTER 6
SECTION TWO.

RESULTS FOR THE PHYSIOLOGICAL VARIABLES.

6.2.1. STATISTICAL TREATMENT FOR THE SUBMAXIMAL TESTS.

A generalised linear model was applied to the data to include the possible effects of visit, subject and natural (or error) variability. A Bonferroni multiple comparisons procedure was used to assess where the significant differences, if any, lay. The variables investigated were VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, VE/VCO_2 and tidal volume.

6.2.2. RAW DATA.

6.2.2.(a) THE MAXIMAL VALUES OF THE PHYSIOLOGICAL VARIABLES FROM THE MAXIMAL INCREMENTAL TESTS.

The maximal values for the two incremental tests were investigated for two major purposes:

1) To allow comparison with other studies.
2) To determine if there was any learning/familiarisation effect across the two tests.

Table 6.5 gives the peak values for VO_2, VCO_2, VE, RER, frequency of breathing, tidal volume and heart rate and endurance time for the two maximal tests. Table 6.6. shows the mean differences and 95% confidence intervals for the differences between the two test results for each of the physiological variables. Only for VE was the test 1 score significantly higher than the test 2 score. There was a tendency for VO_2 and VCO_2 to be lower on test 2. Only two of the test 2 Peak VO_2scores were higher than test 1.

6.2.2.(b) AN ILLUSTRATION OF THE RAW DATA FOR THE PHYSIOLOGICAL VARIABLES ON THE SUBMAXIMAL TESTS.

It was considered unnecessary to illustrate all the physiological data from the constant workrate tests. Figure 6.5 provides a flavour of the physiological data and shows VE for

all subjects for each of the four visits and each of the submaximal tests. The VE scores look to be consistent for all subjects for the four tests.

6.2.3. VISIT EFFECT FOR THE PHYSIOLOGICAL VARIABLES.

Timepoint 3 (i.e. 7.5 minutes) was selected to give examples of possible visit effects since the data were somewhat sparse at 10 minutes. Table 6.7 shows that there were no visit effects for any physiological variable at 7.5 minutes.

6.2.4. ENDURANCE TIME.

6.2.4.(a) RAW DATA FOR ENDURANCE TIME.

The endurance times for all four submaximal constant workrate tests for all subjects are illustrated in Figure 6.6, while the mean and standard deviation for the four tests are given in Table 6.8. Figure 6.6 suggests that the endurance times were relatively stable. However, subject 6 showed a large increase in endurance time from Test 1 to Test 2.

6.2.4.(b) VISIT EFFECT FOR ENDURANCE TIME.

A reproducibility coefficient of 51% was estimated over all tests. This figure increased to 76% when the first test of subject 6 was excluded. Subject 6 increased his endurance time from 7 minutes on Test 1 to 18 minutes on Test 2. There were no significant visit effects for endurance time.

6.2.5. RELATIVE PERCENTAGES FOR THE CONSTANT WORKRATE TESTS.

The relative percentages for VE, VO_2, and heart rate during the final minute of the constant workrate test are given in Table 6.9. Values are the overall mean for all tests and relative to the higher score for each individual in the two maximal incremental tests. The mean relative intensities for VO_2, VE and heart rate were 89.3%, 92.5% and 98.5% respectively. For VE and heart rate, the ranges show that the values attained in the constant workrate tests were sometimes higher than the values reached in the maximal incremental tests.

6.2.6. SUMMARY.

A decrease in VE in Test 2 was the only significant difference in any physiological variable in the incremental tests. There were no significant visit/familiarisation effects in any physiological variable or endurance time in the submaximal constant workrate tests. During the constant workrate tests the subjects worked close to the maximum they attained in the incremental tests.

CHAPTER 6
SECTION THREE.

RESULTS OF THE RELATIONSHIP BETWEEN THE PHYSIOLOGICAL VARIABLES AND THE SUBJECTIVE SCALES FOR BREATHLESSNESS AND GENERAL FATIGUE.

6.3.1. WHY? HOW?

If a relationship exists between a physiological variable and a symptomatic scale, a strong correlation would be evident. Any strong relationship may be of value in the assessment and treatment of symptoms during exercise.

It was decided that the best way to indicate which perception of symptom was best related to each physiological variable was to evaluate correlations based on all observations for each subject, where possible, over the first four timepoints.

An explanation of how the correlations were calculated is given in Section 4.1.5.

6.3.2. A VISUAL IMPRESSION OF THE RELATIONSHIP BETWEEN THE SUBJECTIVE SCALES AND VE.

A flavour of the relationship between the subjective scales and the physiological variables is given by graphically showing the relationship between VE and the VAS (breathlessness). Figure 6.7 gives an example of the relationship between VE and VAS (breathlessness) for subject 9 for all four tests. Figure 6.8 shows the VE/VAS (breathlessness) relationship for all subjects for all tests. There is an inconsistent pattern among the subjects. The VE for some subjects, eg 3, 9, and 10, looks fairly stable but the VAS (breathlessness) score rises throughout the 10 minute period. For subject 8, VE rises between 5 and 7.5 minutes with little change in VAS (breathlesness) during this time.

6.3.3. CORRELATIONS.

A visual impression of "correlations" for one subjective scale and physiological variable is given in Figure 6.9. Figure 6.9 gives the correlations for VE and VAS (breathlesness) for:

1) individual visit correlations for each subject.

2) pooled individual correlations.

3) estimated pooled correlations (overall group correlations)

The individual visit correlations for subject 5 are very similar whereas the individual visit correlations for subjects 1 and 7 show a wide range. The pooled individual correlation for subject 1 is very poor.

The overall group correlations, the pooled individual correlations and the minimum and maximum individual correlations for the VAS and Borg CR10 scales (breathlessness and general fatigue) and each of VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2 VE/VCO_2 and tidal volume are given in Table 6.10. The highest overall group correlation for each subjective scale is with heart rate. Correlations for all four scales were around 0.80. For VO_2, there was a good overall group correlation (0.78) with VAS (breathlessness and general fatigue) whereas for the Borg CR10 scales the correlations were around 0.67 with VO_2. Perhaps surprisingly, VE and frequency of breathing had overall group correlations of around 0.6 with the subjective scales. The overall group correlations for VE/VO_2, VE/VCO_2 and tidal volume and the subjective scales were low and for RER the correlations for all scales were very low.

There were no meaningful differences among the subjective scales i.e. similar correlations were found for each subjective scale with each physiological variable. The only slight difference between the scales was for VO_2 where correlations with the VAS were 0.78 and Borg CR10 scale were around 0.67. A wide range in minimum and maximum pooled pooled individual correlations and individual visit correlations across individuals was found for all the subjective scales and the physiological variables.

6.3.4. TIME EFFECT- COMPARISON OF THE CHANGES IN SUBJECTIVE SCALES AND PHYSIOLOGICAL VARIABLES FOR TIMEPOINTS 1, 2 AND 3.

An examination of the differences of the subjective scales and physiological variables was made to determine the association between the subjective scales and the physiological variables over time (see Table 6.11.). Time effects were calculated for the subjective

scales and the physiological variables to examine the change in values over time. Using the output from the GLM, point estimates for time effects were obtained. A Bonferroni multiple comparisons procedure was used to assess where significant differences if any, lay. The variables investigated were the VAS and Borg CR10 scales and the following physiological variables, VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, VE/VCO_2 and tidal volume.

6.3.4.(a) SUBJECTIVE SCALES - TIME EFFECT.

Apart from VAS (breathlessness) between timepoint 2 and timepoint 3, there was a significant difference at all timepoints i.e. scores increased for all scales over time.

6.3.4.(b) PHYSIOLOGICAL VARIABLES - TIME EFFECT.

VE.

For VE, there was a significant INCREASE in scores to timepoint 3. VE decreased from timepoint 3 to 4. There was no difference between timepoints 2 and 4.

VO_2

There was a significant INCREASE in VO_2 between timepoints 1, 2 and 3. Timepoint 4 was significantly LOWER than the other three timepoints.

VCO_2

VCO_2 INCREASED significantly from timepoint 1 to 2 and decreased between timepoint 2 and 3 with timepoint 4 LOWER than timepoint 3.

FREQUENCY OF BREATHING.

Frequency of breathing INCREASED significantly over the first three timepoints but DECREASED from timepoint 3 to 4.

HEART RATE.

Heart rate INCREASED significantly over ALL four timepoints. There was no difference between timepoints 3 and 4.

VE/VO_2

The VE/VO_2 ratio INCREASED significantly from timepoint 1 to 2 and remained stable thereafter.

VE/VCO_2 .

The VE/VCO_2 ratio remained the SAME throughout.

TIDAL VOLUME.

Tidal volume was significantly LOWER at timepoint 1 compared to timepoint 3.

The decreases in some variables between timepoints 3 and 4 can be explained by the smaller number of subjects at timepoint 4 compared to timepoint 3.

6.3.5 SUMMARY.

These findings indicate that at all timepoints the perception of breathlessness and general fatigue increased apart from the VAS (breathlessness) between timepoints 2 and 3. In several instances, there was a concomitant change in physiological variables (eg VE, frequency of breathing and heart rate). The highest correlations were between heart rate and the subjective scales (around 0.80). Correlations for all the subjective scales and the respiratory physiological data (except VO_2) were not particularly good and indicate a fairly poor relationship between these variables.

Table 6.1.

Reproducibility Coefficients and 95% Confidence Intervals for Visual Analogue and Borg Scales for Breathlessness and General Fatigue.

REPRODUCIBILITY.

Breathlessness				
Time Scale	2.5 Min	5.0 Min	7.5 Min	10.0 Min
VAS	82% (58,91)	83% (61,92)	68% (36,83)	66% (22,78)
Borg CR10	51% (16,73)	48% (13,70)	46% (11,69)	38% (-0.57)

General Fatigue				
Time Scale	2.5 Min	5.0 Min	7.5 Min	10.0 Min
VAS	77% (51,89)	86% (66,93)	83% (60,92)	81% (48,82)
Borg CR10	51% (17,73)	77% (50,89)	64% (32,81)	46% (6,64)

Confidence intervals are in brackets beneath each estimate of reproducibility.

Table 6.2.

Visit Effects at the Third Timepoint for the Subjective Scales.

Scale \ Visit	1	2	3	4	P Value for Visit Effect	Standard Error of Visit Effect
VAS Breathlessness	3.3 [a]	-0.2 [a]	1.5 [a]	-4.6 [a]	0.51	3.2
VAS General Fatigue	3.8 [a]	-0.3 [a]	0.9 [a]	-4.4 [a]	0.35	2.9
Borg Breathlessness	0.34 [a]	0.03 [a]	-0.004 [a]	-0.37 [a]	0.52	0.30
Borg General Fatigue	0.16 [a]	-0.06 [a]	0.17 [a]	-0.27 [a]	0.54	0.22

A common symbol (e.g. [a]) denotes visits are in common (i.e. no statistically significant difference).

Table 6.3

Peak Values for Breathlessness and General Fatigue using Visual Analogue and Borg CR10 Scales (Mean, S.D. and Range) for the Incremental Tests.

	VAS		Borg CR10	
	Breathlessness	General Fatigue	Breathlessness	General Fatigue
Test 1	60.7±19.0	54.5±12.7	4.4±1.7	3.5±1.1
	(32-87)	(28-74)	(2-7)	(2-5)
Test 2	65.4±23.9	51.3±22.5	5.0±2.0	3.9±1.6
	(22-99)	(15-80)	(2-9)	(1-7)

Table 6.4

Mean Differences and Ninety-Five Percent Confidence Intervals for the Differences Between the Test 1 and Test 2 Incremental Tests for Visual Analogue and Borg CR10 Scales for Breathlessness and General Fatigue.

Variable	Mean	S.D.	95% Confidence Interval
VAS (Breathlessness)	4.7	18.3	-18, 8
VAS (General Fatigue)	-3.2	22.1	-13, 19
Borg (CR10 (Breathlessness)	0.6	1.78	-1.9, 0.7
Borg CR10 (General Fatigue)	0.4	1.90	-1.8, 1.0

Mean values are the Test 1 values minus the Test 2 values.

Table 6.5

Peak Mean Values (Mean, S.D.) for Test 1 and Test 2 (Incremental Tests) for $V0_2$, $VC0_2$, VE, RER, Frequency of Breathing, Tidal Volume Heart Rate and Endurance Time.

	VO_2 ($ml.kg.^{-1}min.^{-1}$)	VCO_2 ($litres.min^{-1}$)	VE ($litres.min^{-1}$)	Frequency of Breathing. ($breaths.min^{-1}$)
Test 1	20.6± 4.6	1.72±0.52	62.6±17.7	36.9±10.6
Test 2	18.8± 4.2	1.51±0.50	53.9±17.1	34.2± 8.7
	RER	Tidal Volume (litres)	Heart Rate ($beats.min^{-1}$)	Endurance Time (Seconds)
Test 1	1.02±0.11	1.71±0.30	139±23.4	909.3±158
Test 2	0.97±0.14	1.59±0.40	137.3±22.5	868.7±148

Table 6.6.

Mean Differences and Ninety Five Percent Confidence Intervals for the Differences Between Incremental Test 1 and Test 2 for the Physiological Variables.

Variable	Mean	S.D.	95% Confidence Interval.
VO_2 (litres.min^{-1})	-0.14	0.28	-0.01, 0.4
VCO_2 (litres.min^{-1})	-0.25	0.38	-0.01, 0.5
VE (litres.min^{-1})	-8.68	10.38	1.3, 16.1*
Frequency of Breathing (breaths.min^{-1})	-2.73	4.08	-0.2, 5.7
Heart Rate (beats.min^{-1})	-2.50	1.09	-5.3, 10.3
RER	-0.066	0.13	-0.1, 0.2
Tidal Volume (litres)	-0.127	0.26	-0.1, 0.3
Endurance Time (Seconds)	-40.6	215	-194, 113

* Significantly different.

Mean values are the Test 1 values minus the Test 2 values.

Table 6.7.

Visit Effects at the Third Timepoint for the Physiological Variables.

Visit / Variable	1	2	3	4	P value for Visit Effect	Standard Error of Visit Effect.
VE (litres.min^{-1})	0.73 a	-0.08 a	1.46 a	-0.65 a	0.61	1.11
VO_2 (litres.min^{-1})	-0.01 a	-0.02 a	0.04 a	-0.01 a	0.54	0.027
VCO_2 (litres.min^{-1})	-0.007 a	-0.012 a	0.039 a	-0.020 a	0.53	0.027
Frequency of Breathing (breaths.min^{-1})	0.15 a	0.80 a	0.17 a	0.48 a	0.58	0.64
Heart Rate (beats.min^{-1})	-2.44 a	-1.75 a	3.74 a	0.45 a	0.40	2.4
VE/VO_2	-0.36 a	0.69 a	0.12 a	-0.45 a	0.81	0.83
VE/VCO_2	-0.62 a	0.55 a	0.08 a	-0.01 a	0.89	0.87
Tidal Volume (litres)	-0.029 a	0.053 a	0.032 a	-0.056 a	0.09	0.031
RER	0.0048 a	0.0048 a	0.0020 a	-0.0116 a	0.35	0.02

A common symbol (e.g. a) denotes visits are in common (i.e. no statistically significant difference).

Table 6.8

Endurance times (Mean, S.D. minimum and maximum for the four constant workrate tests in seconds.

TEST	MEAN	S.D.	MINIMUM	MAXIMUM
1.	609	159	395	942
2.	715	218	492	1009
3.	706	295	407	1272
4.	754	214	542	1295

Table 6.9

Relative percentages for VO_2 , VE and heart rate during the final minute of the constant work rate test. (Values are the overall mean for all tests and relative to the higher score for each individual in the two maximal incremental tests.

Variable	Mean	Median	S.D.	Range
VO_2	89.3	91.4	7.3	80.1-99.1
VE	92.5	88.4	13.9	73.7-123.0
Heart Rate	98.5	99.7	3.7	91.4-102.3

Table 6.10 **Correlations for the Subjective Scales and Physiological Variables.**

The Estimated Overall Pooled Correlation, the Minimum and Maximum Pooled Individual Visit Correlations and the Minimum and Maximum Individual Visit Correlations for all Subjective Scales and Physiological Variables.

	Visual Analogue Scale		CR10 Scales	
	Breathlessness	**General Fatigue**	**Breathlessness**	**General Fatigue**
VE	0.64 -0.11 1.00 -1.00 1.00	0.66 -0.26 0.95 -1.00 1.00	0.56 -0.32 0.99 -1.00 1.00	0.63 0.12 0.96 -1.00 1.00
VO_2	0.79 -0.37 1.00 -1.00 1.00	0.78 -0.62 0.98 -1.00 1.00	0.67 -0.62 0.99 -1.00 1.00	0.66 -0.33 0.95 -1.00 1.00
VCO_2	0.54 -0.16 1.00 -1.00 1.00	0.58 -0.32 0.94 -1.00 1.00	0.43 -0.36 0.98 -1.00 1.00	0.50 0.01 0.98 -1.00 1.00
Frequency of Breathing	0.62 0.08 0.99 -0.86 1.00	0.66 -0.07 0.97 -0.89 1.00	0.59 -0.03 1.00 -0.95 1.00	0.63 0.06 0.90 -0.93 1.00
Heart Rate	0.84 -0.34 0.98 -0.99 1.00	0.83 -0.59 0.96 -0.96 1.00	0.83 -0.49 0.98 -0.76 1.00	0.77 -0.67 0.99 -0.76 1.00
Tidal Volume	0.34 -0.45 0.96 -1.00 1.00	0.34 -0.44 0.86 -1.00 1.00	0.22 -0.47 0.93 -1.00 1.00	0.29 -0.46 0.99 -1.00 1.00
R.E.R.	0.13 -0.54 0.94 -0.96 1.00	0.17 -0.69 0.87 -1.00 1.00	0.02 -0.50 0.90 -0.99 1.00	0.13 -0.48 0.97 -0.98 1.00
VE/VO_2	0.42 -0.52 0.99 -0.94 1.00	0.41 -0.51 0.92 -0.92 1.00	0.36 -0.63 0.99 -0.96 1.00	0.45 -0.56 0.97 -0.94 1.00
VE/VCO_2	0.44 -0.68 0.86 -1.00 1.00	0.38 -0.75 0.88 -1.00 1.00	0.46 -0.79 0.91 -1.00 1.00	0.49 -0.50 0.92 -1.00 1.00

An example of how the data are presented is given for VE and VAS breathlessness. The estimated overall pooled correlation is 0.64. Minimum and maximum pooled individual visit correlations are -0.11, 1.00 Minimum and maximum individual visit correlations are -1.00, 1.00

Table 6.11

Time Effects for Subjective Scales and Physiological Variables.

Timepoint	1	2	3	4	Time Effect	Standard Error
VAS Breathlessness	-16.6 $_a$	-3.1 $_b$	6.1 $_b$	13.5 $_c$	P<0.001	1.5
VAS General Fatigue	-13.7 $_a$	-2.7 $_b$	5.4 $_c$	11.0 $_d$	P<0.001	1.4
Borg CR10 Breathlessness	-1.6 $_a$	-0.3 $_b$	0.4 $_c$	1.5 $_d$	P<0.001	0.15
Borg CR10 General Fatigue	-1.3 $_a$	-0.2 $_b$	0.4 $_c$	1.1 $_d$	P<0.001	0.12
VE (litres.min $^{-1}$)	-5.7 $_a$	0.8 $_b$	3.9 $_c$	1.0 $_b$	P<0.001	0.9
VO_2 (litres.min $^{-1}$)	-0.1 $_a$	0.0 $_b$	0.5 $_c$	-0.4 $_d$	P<0.001	0.02
VCO_2 (litres.min $^{-1}$)	-0.11 $_a$	0.30 $_b$	0.07 $_c$	-0.26 $_d$	P<0.001	0.02
Frequency of Breathing (breaths.min $^{-1}$)	-1.79 $_a$	-0.67 $_b$	1.83 $_c$	0.63 $_d$	P<0.001	0.36
Heart Rate (beats.min $^{-1}$)	-8.3 $_a$	-0.4 $_b$	3.4 $_c$	5.3 $_c$	P<0.001	1.0
VE/VO_2	-1.67 $_a$	0.47 $_b$	1.35 $_b$	-0.15 $_b$	P<0.009	0.57
VE/VCO_2	-0.80 $_a$	-0.49 $_a$	0.63 $_a$	0.66 $_a$	P<0.194	0.46
Tidal Volume (litres)	-0.05 $_a$	0.01 $_{ab}$	0.06 $_b$	-0.02 $_{ab}$	P<0.01	0.03

A common symbol (e.g. $_a$) denotes visits are in common (i.e. no statistically significant difference).

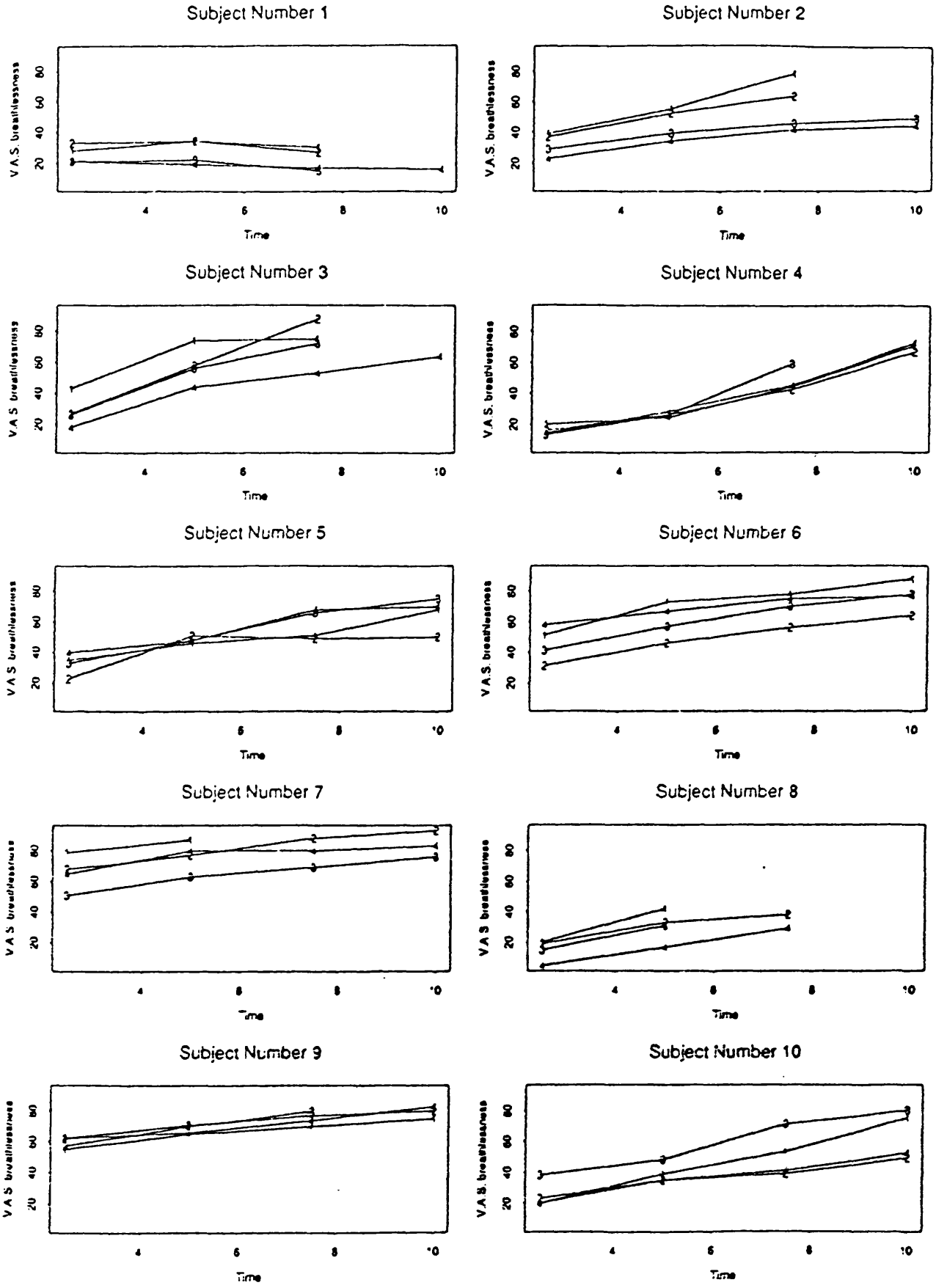


Fig 6.1

VAS breathlessness for the four submaximal tests (labelled by subject numbers 1-10)

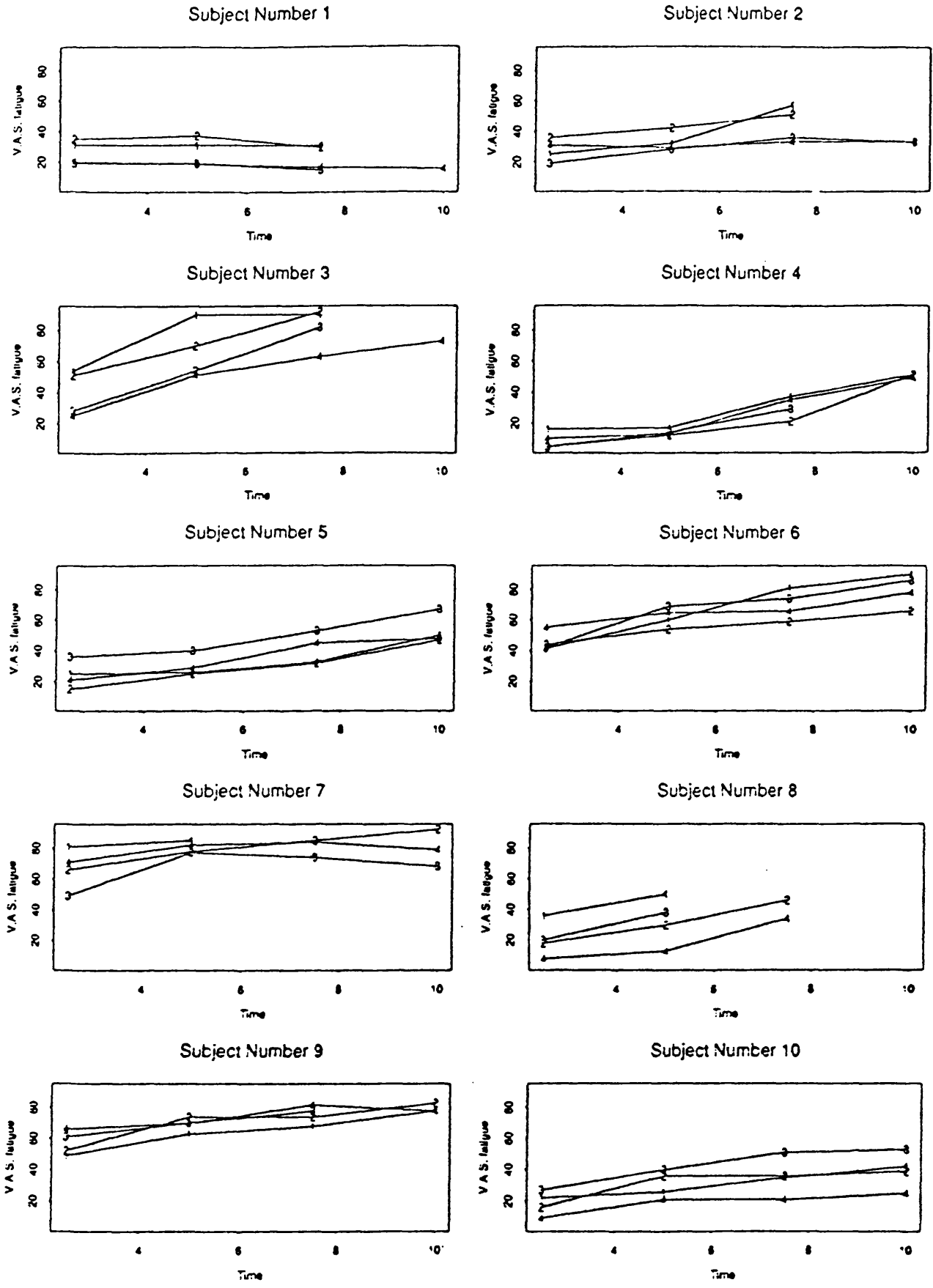


Fig 6.2

VAS general fatigue for the four submaximal tests
(labelled by subject numbers 1-10)

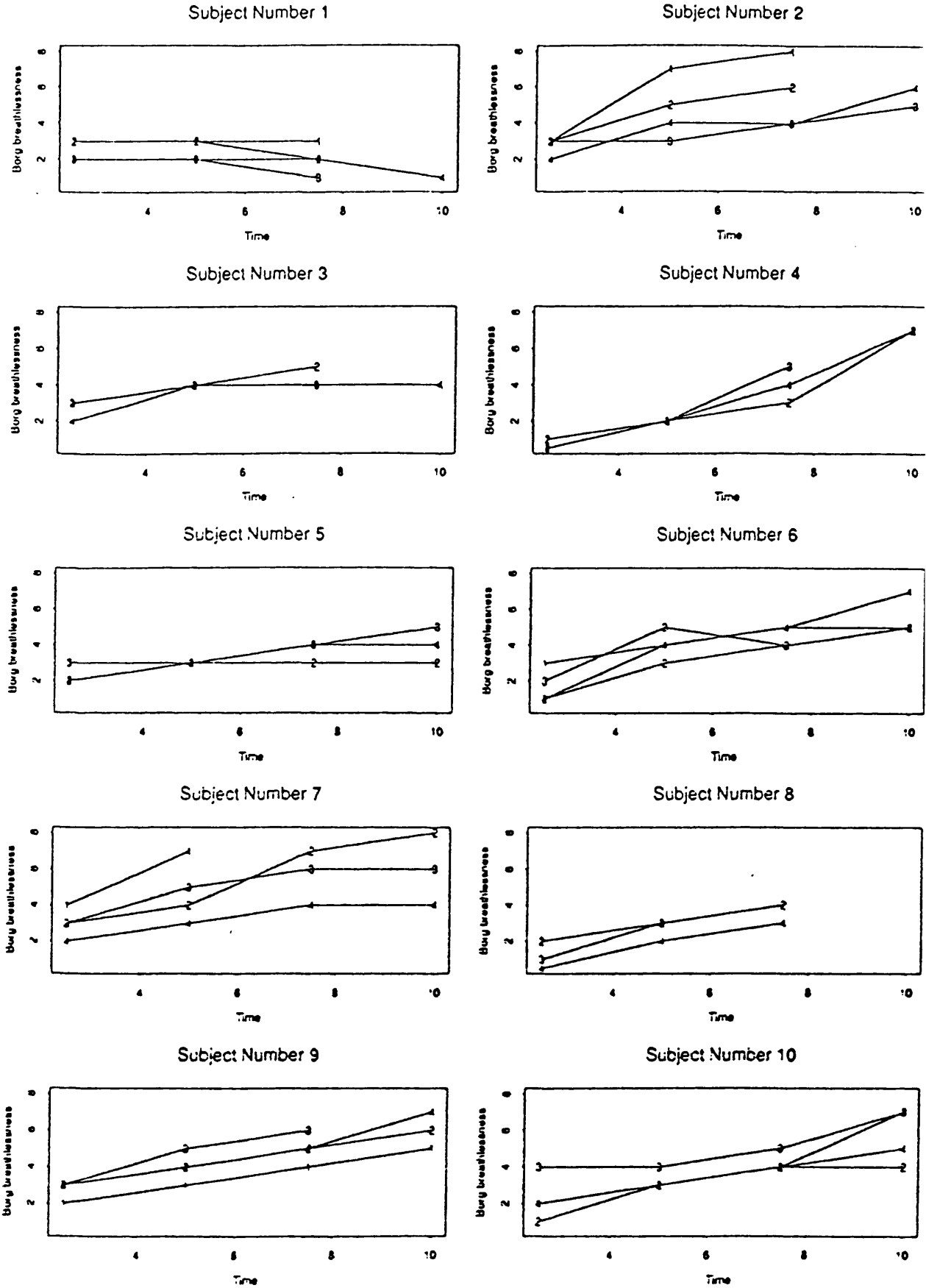


FIG 6.3

Borg CR10 breathlessness for the four submaximal tests (labelled by subject numbers 1-10)

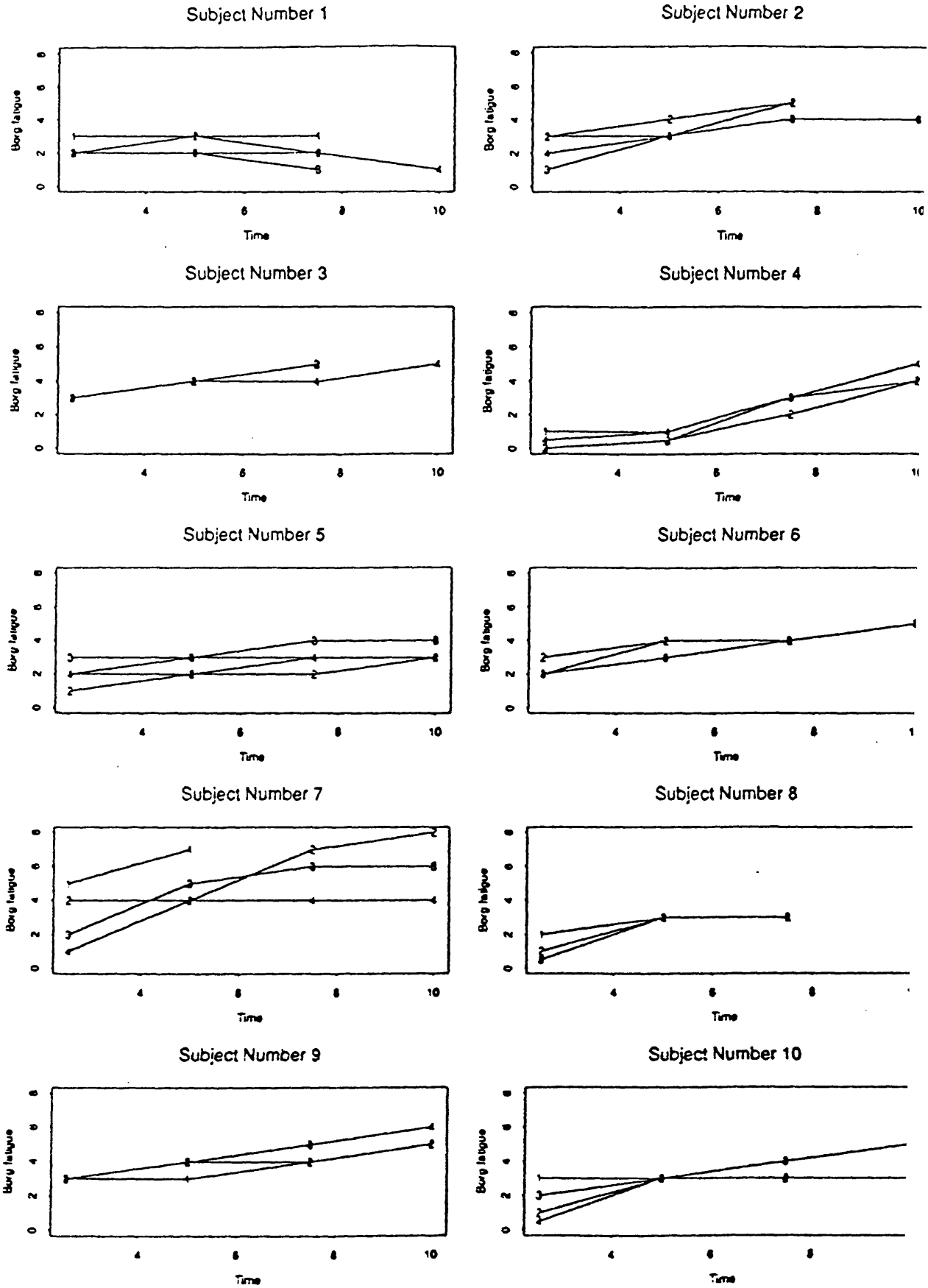


FIG 6.4

Borg CR10 general fatigue for the four submaximal tests (labelled by subject numbers 1-10)

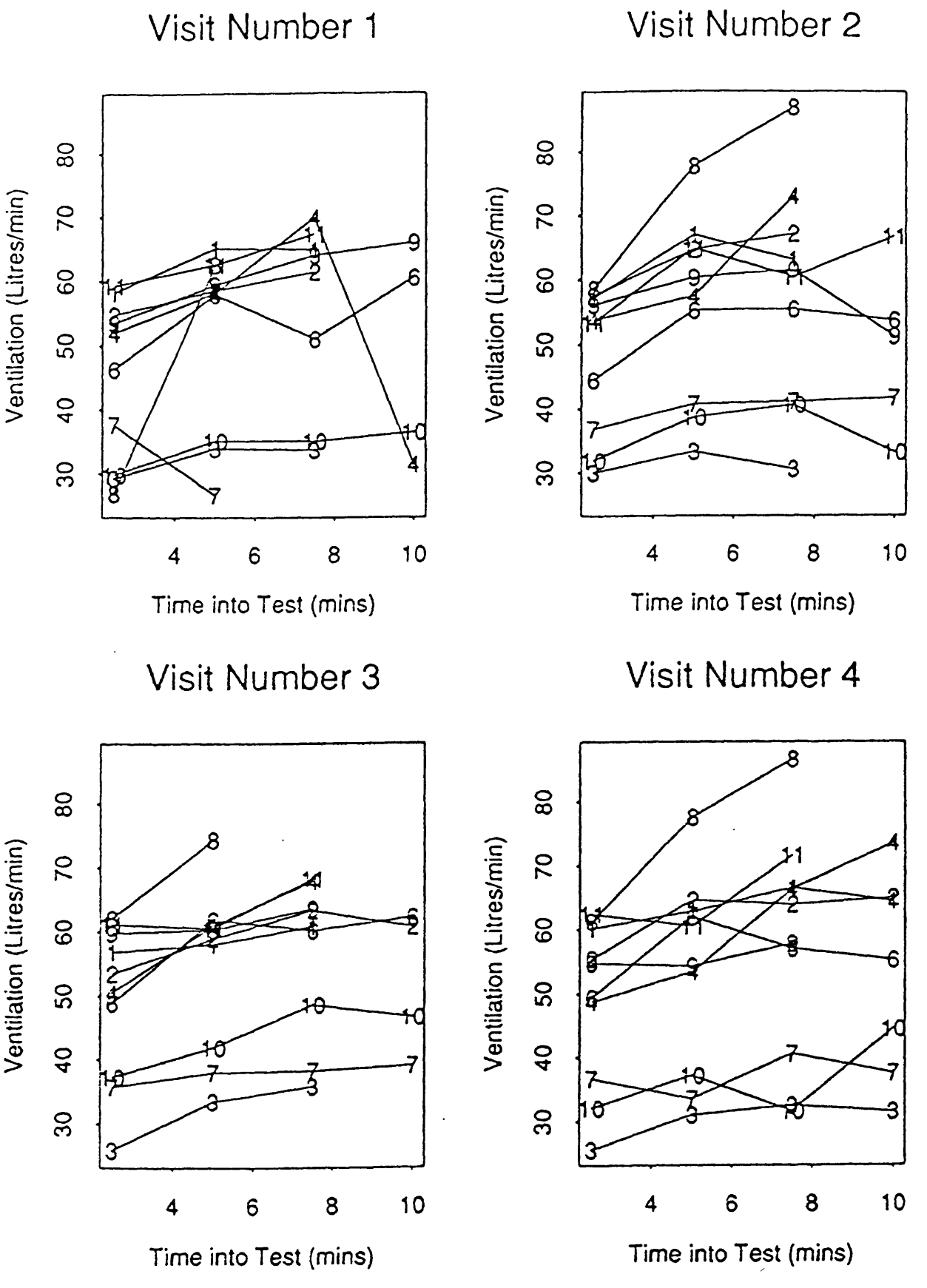


Fig 6.5

Minute ventilation for the four submaximal tests
(labelled by subject numbers 1-10)

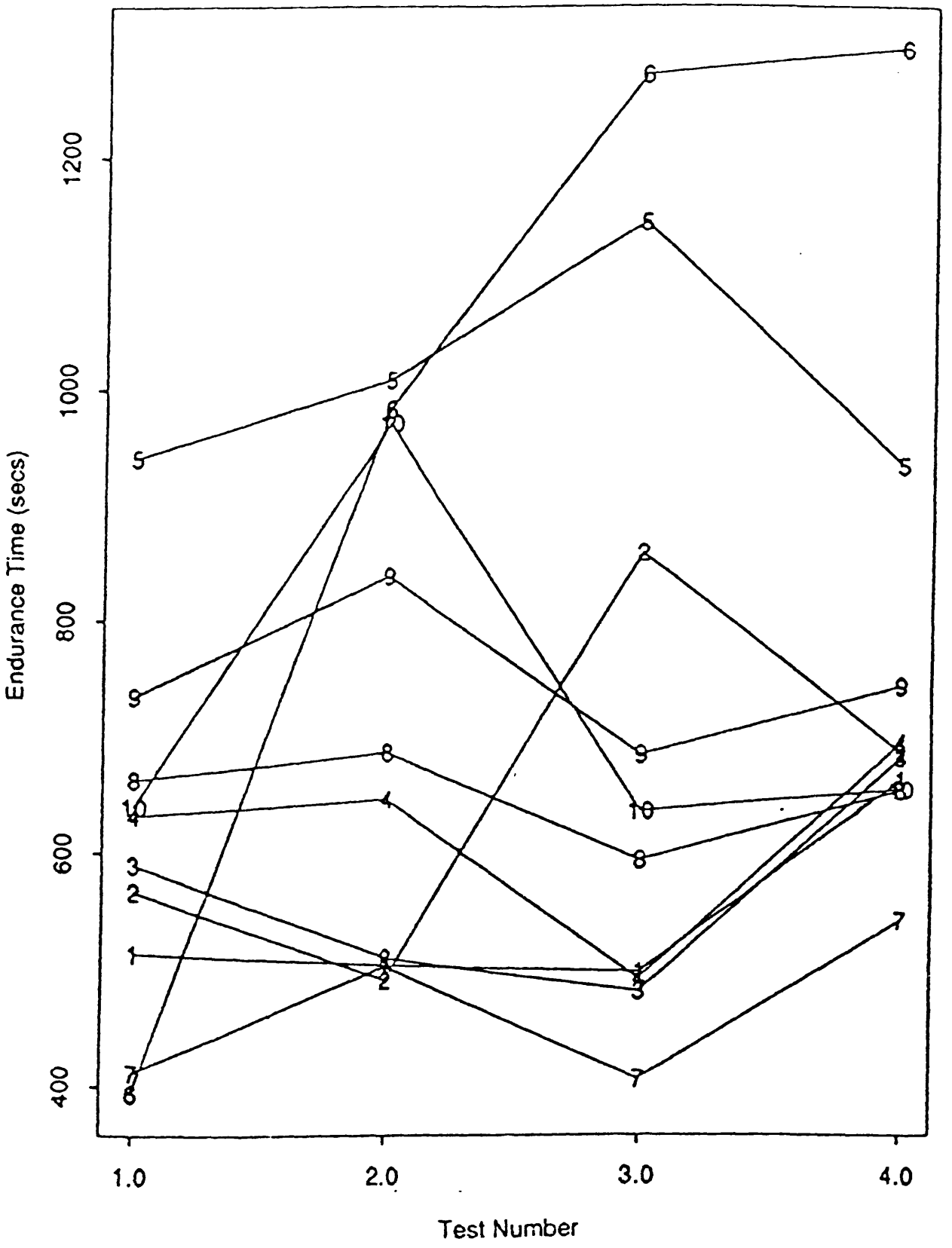


FIG 6.6

Endurance times for the four submaximal
(labelled by subject numbers 1-10)

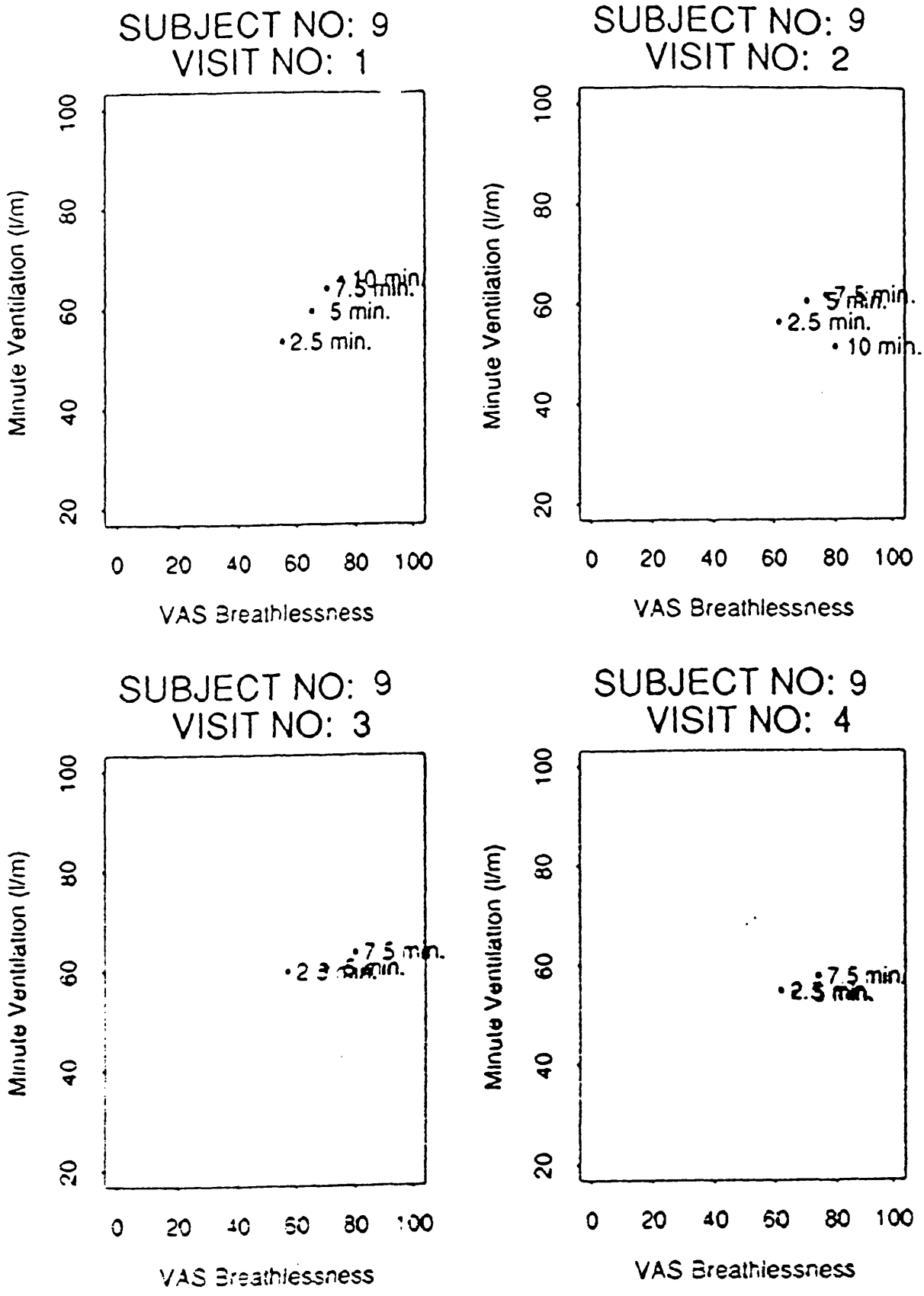


FIG 6.7

The VE/VAS breathlessness relationship for subject 9 for all tests

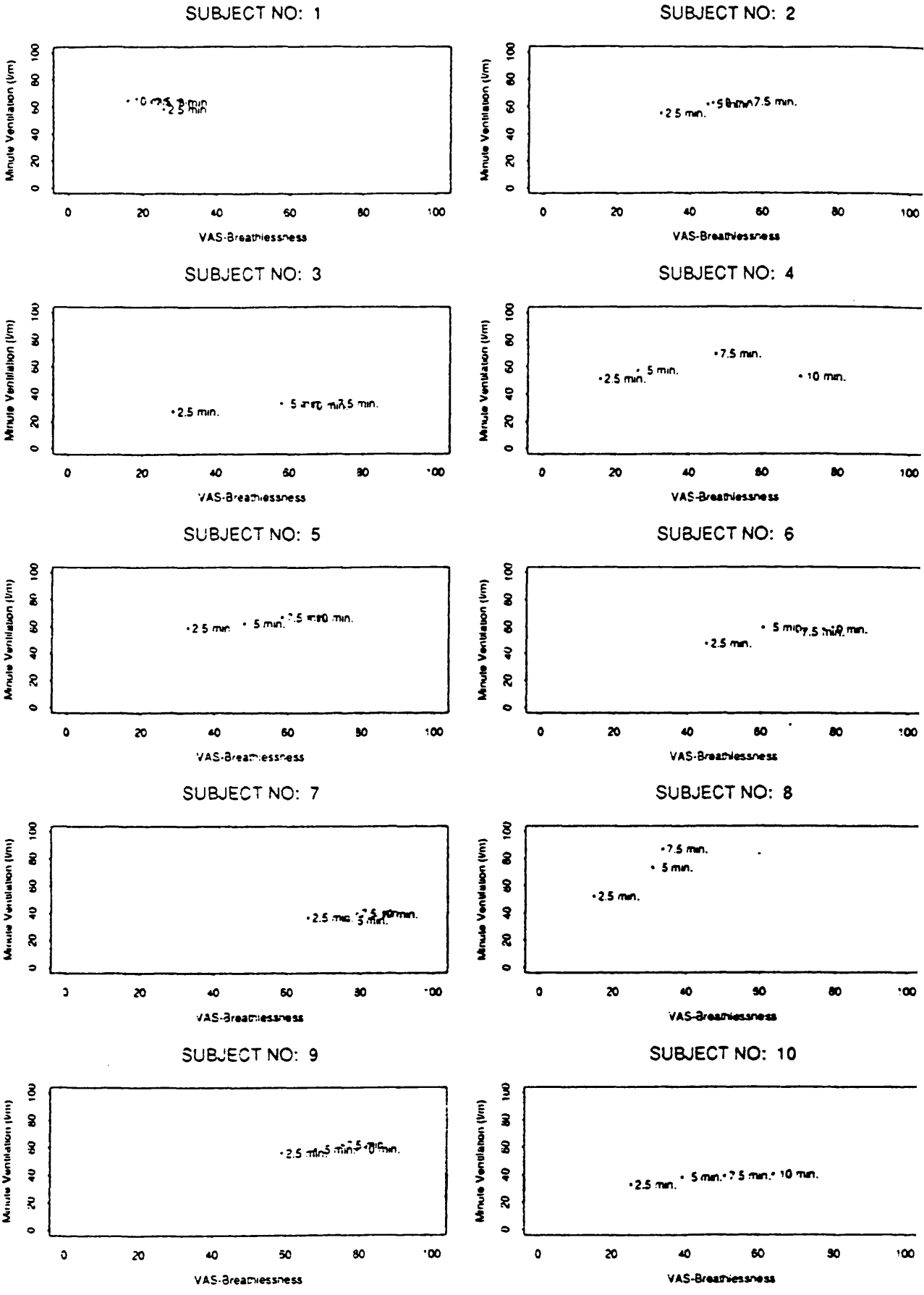


FIG 6.8

The VE/VAS breathlessness relationship for all subjects for all tests

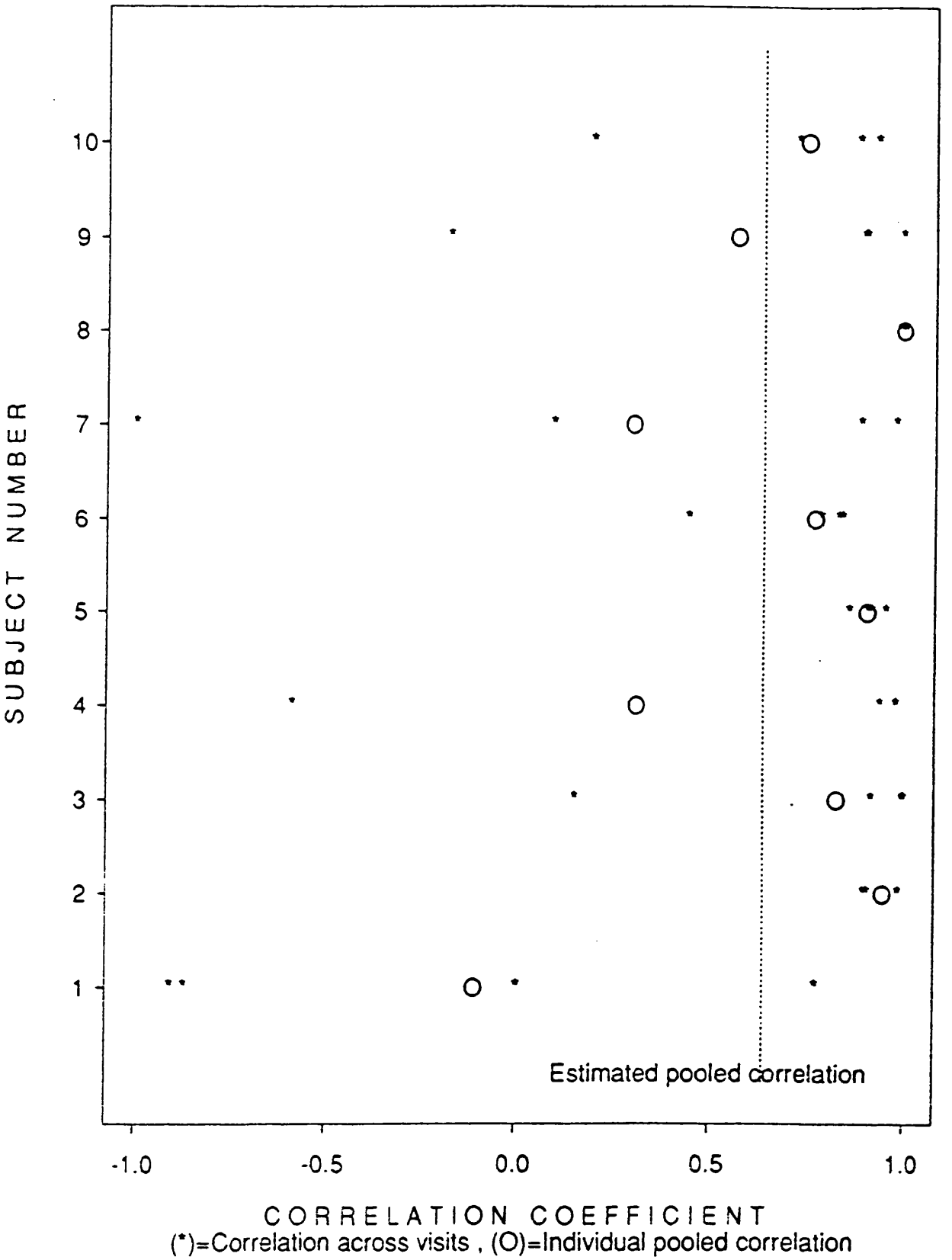


FIG 6.9
The Correlations For VE And VAS Breathlessness

i) Individual visit correlation for each subject
ii) Individual pooled correlation
iii) Estimated pooled correlation

CHAPTER 7
SECTION ONE.

AN EVALUATION OF THE STEXT PROTOCOL.

RESULTS OF THE SUBJECTIVE SCALES.

7.1.1. DESIGN AND AIMS OF THE STUDY.

SUMMARY OF THE DESIGN OF THE STUDY.

Twelve male subjects took part in the study. Each subject underwent eight exercise tests using the STEXT protocol. The subjects were asked to exercise for as long as possible and to indicate when they could no longer continue. Subjects underwent two tests within 48 hours of each other at weeks 0, 2, 6 and 10. At weeks 0 and 2 there was no intervention. At weeks 6 and 10 subjects were given a beta blocker (propranolol) or placebo. Propranolol was given to promote a perception of breathlessness and general fatigue. At week 6, six subjects were given placebo first and 48 hours later propranolol. At week 10 the same six subjects were given propranolol first and placebo second. The other six subjects were given the opposite order of drug administration. Six subjects were given a VAS/Borg CR10 scale order of presentation and six subjects a Borg CR10/VAS order. Scales appeared on the TV monitor every 2 minutes (starting at 2 minutes 10 seconds) for breathlessness and general fatigue using VAS and Borg CR10 scales.

The main aims of the STEXT protocol study were to:

1) Compare the reproducibility and sensitivity to change of VAS and Borg CR10 scales.
2) Determine the magnitude of the visit and therapy effects on the subjective scales and physiological variables.
3) investigate the relationship between the subjective scales and physiological variables.

7.1.2. RESULTS FOR THE SUBJECTIVE SCALES.

7.1.3. STATISTICAL METHODS.

It is important to note that the STEXT protocol includes submaximal and maximal data incorporated into one test. For each scale at each timepoint a generalised linear model was used to investigate possible systematic learning effects, differences among the tests and treatment differences. The model also included components of variability due to between subject variation and within subject variation. Minute 15 was selected to examine in detail any systematic visit/learning effect.

7.1.4. AN IMPRESSION OF THE RAW DATA FOR STEXT TESTS.

An impression of how the subjective scales were used is given in Figures 7.1-7.4 which show data from 7 minutes onwards because there was little movement in the scales in the early stages of the tests. Figures 7.1-7.4 show that all scales were used over a wide range for most subjects. For all four scales, subject 11 consistently scored low. Subject 5 did not rate general fatigue "high" on any test. Subjects 9 and 12 did not use the upper ranges in any of the scales in any of the tests. The scores from subject 8 showed the greatest variability and he rated breathlessness and general fatigue much more highly than the other subjects throughout the tests.

7.1.5. MEASUREMENT OF BREATHLESSNESS.

REPRODUCIBILITY.

The reproducibility of VAS was low at 3 minutes (48%) but increased to 83% at 9 minutes and was stable at around 82% to maximum (see Table 7.1). The Borg CR10 was very low at 3 minutes (23%), increased to 77% at 7 minutes and was relatively stable thereafter. There were no significant differences between the scales.

SENSITIVITY.

The sensitivity ratios and confidence intervals for VAS and Borg CR10 scales are shown in Table 7.2. For the VAS the 95% confidence intervals showed that at minutes 5 and 7 the sensitivity ratio was not significantly different from zero whereas it was at 3 minutes

and from 9 to 15 minutes. For the Borg CR10 scale there was only a significant therapy effect from 11-15 minutes. Examination of the 95% confidence intervals showed that there was an overlap at all timepoints between the scales and suggests no real difference between the scales. Analysis of the sensitivity for the maximum values is not given as it was considered that the values would be misleading. There was no sensitivity effect at maximum and in fact a reversal of the sign. This finding may be explained by the fact that the subjects perceived that they were exercising at maximum (during the active therapy) despite the fact that their endurance time was reduced.

7.1.6. MEASUREMENT OF GENERAL FATIGUE.

REPRODUCIBILITY.

At minute 3 the reproducibility ratio for the VAS was 35% and by minute 9 increased to 84% with little change to maximum (see Table 7.3). For the Borg CR10 scale the reproducibility ratio was 26% at minute 3 and increased to 83% at minute 11 and remained relatively stable thereafter. There were no significant differences between the scales.

SENSITIVITY.

The sensitivity ratios and confidence intervals for the VAS and Borg CR10 scales are given in Table 7.4. For the VAS and Borg CR10 scales, the sensitivity ratio was significantly increased from minutes 9-15. There were no significant differences between the scales. Analysis of the sensitivity for the maximum values is not given for the reasons outlined above.

7.1.7. INVESTIGATION OF THE RELATIVE EFFECTS OF VISIT AND THERAPY.

An examination of the differences in the subjective scales attributed to the visit and therapy effects was made for minute 15. It was considered to be unrealistic to compare the visit and therapy effects over all timepoints. Using the output from the GLM, point estimates were obtained for visit and therapy effects. A Bonferroni based multiple

comparisons procedure was used to assess where significant differences, if any, lay. All scales showed a marked therapy effect which was generally much higher than the visit effect. The visit effect was most marked in the first two or three tests.

BREATHLESSNESS.

There were no significant differences among Tests 2-8 for the VAS. Test 1 was significantly lower than tests 3-8. Tests 5 and 6 were 17 and 14 units respectively, higher than Test 1 and the therapy effect for VAS was 12 units. Thus, the therapy effect for VAS was less than the visit effect (see Table 7.5) between Test 1 and Tests 5 and 6.

There were no significant differences for the Borg CR10 scale among tests 2-8. Test 1 was significantly lower than tests 3-8. On average Tests 5-7 were 1.5 units higher than Test 1 and the therapy effect was 1.24. As for the VAS, the therapy effect was less than the visit effect between Test 1 and Tests 5-7.

These findings suggest that the subjects reassessed their perception of breathlessness on both scales after Test 1 i.e. the subjects rated breathlessness higher after Test 1. Thus, it is advisable to include a "run in" period of at least two visits to allow for stabilisation of scores before any intervention is attempted.

GENERAL FATIGUE.

For the VAS there were no significant differences among tests 2-8. Test 1 was lower than tests 3-8. The therapy effect was much higher than any visit effect.

For the Borg CR10 scale there were no significant differences among tests 2-8. Test 1 was significantly lower than tests 5-8 (see Table 7.5). The therapy effect was much higher than any visit effect.

7.1.8. SUMMARY.

There was no clear or consistent difference between the VAS and Borg CR10 scales in terms of reproducibility and sensitivity. All scales showed a visit effect in the sense that generally the scores for Test 1 were much lower than the other tests. From Test 3 to Test 8 scores tended to be quite stable. Care has to be taken in the use of this protocol when breathlessness is assessed as it has been shown that the visit effect between Test 1 and the latter tests is greater than the therapy effect. Thus, it is advisable to incorporate a "run-in" period when breathlessness is assessed using this protocol.

CHAPTER 7
SECTION TWO.

AN EVALUATION OF THE STEXT PROTOCOL. RESULTS OF THE PHYSIOLOGICAL VARIABLES.

7.2.1. STATISTICAL METHODS.

A generalised linear model (GLM) was used to investigate possible visit, therapy, subject and natural (or error) variability. A Bonferroni multiple comparisons procedure was used to assess where the significant differences, if any, lay.

7.2.2.(a) AN IMPRESSION OF THE MAXIMAL RAW DATA.

It was considered unnecessary and unwieldy to illustrate all the physiological raw data. An example of the maximal data is given in Figure 7.5 which shows the VO_2 max scores for all subjects for all 8 tests. For technical reasons it was not possible to obtain representative maximum respiratory variables for subject 8 on Test 3. The impact of beta blockade can be clearly seen. There is a marked decrease in scores on two occasions for all subjects between tests 5-8.

7.2.2.(b) AN IMPRESSION OF THE SUBMAXIMAL DATA.

Figure 7.6 provides a flavour of the physiological data and shows VE for all subjects for all 8 tests. VE looks very reproducible apart from early in the tests for subjects 7 and 9. The increases in VE with beta blockade in the latter stages of the test is not particularly noticeable as the scale is very small.

7.2.3.(a) MAXIMAL VALUES - THE EFFECT OF BETA BLOCKADE.

Table 7.6 shows the maximum mean values for VE, VO_2, VCO_2, VE, frequency of breathing, heart rate, tidal volume, RER and endurance time for all eight tests. For clarity of presentation, the data were arranged as follows - at the third timepoint (i.e. tests 5 and 6) the placebo and active treatment scores have been combined so that test 5 refers to the placebo and test 6 refers to the active treatment. Similarly, at timepoint 4, test 7 is the placebo, and test 8 the active treatment. The output from the GLM showed that under beta

blockade there were significant differences between the beta blockade and non beta blockade tests for VE, VO_2, VCO_2, frequency of breathing, heart rate, tidal volume and endurance time. All these variables showed a significant decrease under beta blockade. There were no significant visit effects.

Reproducibility was calculated for the maximal physiological values (see Table 7.7). Reproducibility coefficients were high for all variables EXCEPT RER and heart rate.

7.2.3.(b) SUBMAXIMAL VALUES - THE EFFECT OF BETA BLOCKADE.

A GLM was used to investigate the therapy effects for the submaximal variables. No statistical analysis was carried out for minutes 16 and 17 as there was insufficient data to draw meaningful conclusions. The values displayed on the graphs (see Figures 7.7-7.15) illustrate these therapy effects for all relevant physiological variables.

VE.

At minute 8 VE was significantly LOWER on the active treatment compared with the non beta blocker tests. At minute 14 and 15 VE was significantly INCREASED compared with the non beta blocker tests (see Figure 7.7).

VO_2

At ALL timepoints VO_2 was significantly LOWER on non beta blocker tests (see Figure 7.8).

VCO_2

At minutes 8, 11 and 15 VCO_2 was significantly HIGHER on the non beta blocker tests (see Figure 7.9).

FREQUENCY OF BREATHING.

The frequency of breathing at minutes 14 and 15 with beta blockade was significantly HIGHER than on the non beta blockade tests (see Figure 7.10).

HEART RATE.

Heart rate was significantly LOWER at ALL timepoints with beta blockade compared with the non beta blocker tests (see Figure 7.11).

VE/VO_2

The VE/VO_2 ratio was significantly INCREASED from minute 10 to minute 15 compared with the non beta blocker tests (see Figure 7.12).

VE/VCO_2

The VE/VCO_2 ratio was significantly INCREASED from minute 10 to minute 15 compared with the non beta blocker tests (see Figure 7.13).

TIDAL VOLUME.

Tidal volume was significantly INCREASED at minutes 14 and 15 compared with the non beta blocker tests (see Figure 7.14).

RER.

RER was significantly INCREASED from minute 10 to minute 15 compared with the non beta blocker tests (see Figure 7.15).

7.2.4. THE RELATIVE MAGNITUDE OF ANY VISIT EFFECTS.

The visit and therapy effects for the physiological variables for minute 15 are given in Table 7.8. Minute 15 was chosen to give an in-depth examination of the visit and therapy effects as it is unrealistic to examine all timepoints in detail. There were no significant visit effects for any variable.

The therapy effect was significant for all variables i.e. there were significant INCREASES for VE, frequency of breathing, VE/VO_2, VE/VCO_2, tidal volume and RER and significant DECREASES for VO_2, VCO_2 and heart rate due to the intervention of a beta blocker.

7.2.5. SUMMARY.

MAXIMAL VALUES.

The maximal values for VE, VO_2, VCO_2, frequency of breathing, tidal volume and endurance time were very reproducible. There were no significant visit effects. There were significant differences between the beta blockade and non beta blockade tests for VE, VO_2, VCO_2, frequency of breathing, heart rate, tidal volume and endurance time. All these variables showed a significant decrease under beta blockade.

SUBMAXIMAL VALUES.

In the latter stages of the test, there were significant differences for all submaximal variables. VE, VCO_2, frequency of breathing, VE/VO_2, VE/VCO_2, tidal volume and RER were increased. Heart rate and VO_2 were significantly reduced throughout the test. There were no significant visit effects.

CHAPTER 7
SECTION THREE.

AN EVALUATION OF THE STEXT PROTOCOL

RESULTS OF THE RELATIONSHIP BETWEEN PHYSIOLOGICAL VARIABLES AND THE SUBJECTIVE MEASURES OF BREATHLESSNESS AND GENERAL FATIGUE.

7.3.1. WHY? HOW?

It was decided that the best way to indicate which perception of symptom was best related to each physiological variable was to evaluate individual subject correlations based on all observations for each subject across all timepoints.

An explanation of how the correlations were calculated is given in Section 4.5.

7.3.2. A VISUAL IMPRESSION OF THE RELATIONSHIP BETWEEN THE VAS AND VE.

A flavour of the relationship between the subjective scales and physiological variables is given by taking the VAS (breathlessness) and VE and displaying these variables graphically in the following examples. For minutes 3 to 17, Figure 7.16 shows the VE/VAS (breathlessness) relationship for subject 4. The limited movement in the scales in the early stages of the test is evident. Figure 7.17 shows the VE/VAS (breathlessness) relationship for all subjects for all tests for minutes 3-17. For almost all subjects, there is little movement in the scales for the first few timepoints.

7.3.3. CORRELATIONS.

A visual impression of the various correlations for one subjective scale and one physiological variable is given in Figure 7.18. Figure 7.18 gives the correlations for VE and VAS (breathlessness) for:

1) individual visit correlations for each subject.
2) pooled individual correlations.
3) estimated pooled correlation (overall group correlation).

The individual visit correlations for subject 7 are wide ranging and the pooled individual correlation is lowest for subject 10 and highest for subjects 4, 11 and 12.

The overall group correlations, the pooled individual correlations and the minimum and maximum individual visit correlations for VAS and Borg CR10 scales (breathlessness and general fatigue) and VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2 VE/VCO_2 and tidal volume are shown in Table 7.9. For both scales, for breathlessness and general fatigue, there were high correlations for all physiological variables apart from VE/VCO_2 and VE/VCO_2. For VE and VCO_2 the correlation was greater than 0.8 for all four scales. Apart from VE/VO_2 and VE/VCO_2 all the other correlations were above 0.7. The minimum and maximum individual visit correlations for the physiological variables and the subjective scales showed a wide range. Several maximum individual visit correlations were 0.99 but some minimum individual visit correlations were under 0.1. The range was not so great with the pooled individual visit correlations.

There were no meaningful differences among the subjective scales i.e. a similar correlation was found for each subjective scale for effectively every physiological variable. All the subjective scales showed a negative correlation with VE/VCO_2

7.3.4. SUMMARY.

There appeared to be a close relationship between all the physiological variables (apart from VE/VCO_2 and VE/VCO_2) with all four subjective scales.

Table 7.1

Reproducibility coefficients and 95% Confidence Intervals for Visual Analogue and Borg CR10 Scales for Breathlessness.

REPRODUCIBILITY.				
Time (Minute)	VAS		Borg CR10	
	Reproducibility Coefficient	95% Confidence Interval	Reproducibility Coefficient	95% Confidence Interval
3	48%	(18, 68)	23%	(1, 44)
5	63%	(33, 79)	60%	(29, 77)
7	77%	(51, 88)	77%	(51, 88)
9	83%	(61, 92)	74%	(47, 86)
11	82%	(59, 91)	76%	(49, 87)
13	83%	(61, 92)	76%	(49, 87)
15	82%	(58, 91)	69%	(40, 83)
Max	81%	(57, 90)	76%	(50, 88)

Table 7.2

Sensitivity ratio and 95% Confidence Intervals for Visual Analogue and Borg CR10 Scales for Breathlessness.

SENSITIVITY				
Time (Minute)	VAS		Borg CR10	
	Sensitivity Ratio	95% Confidence Interval	Sensitivity Ratio	95% Confidence Interval
3	0.32	(0.02, 0.62*)	-0.01	(-0.52, 0.55)
5	0.02	(-0.26, 0.31)	-0.07	(-0.51, 0.65)
7	0.12	(-0.16, 0.41)	0.45	(-1.03, 0.12)
9	0.54	(0.25, 0.83*)	0.46	(-0.11, 1.04)
11	0.88	(0.59, 1.17*)	0.80	(0.22, 1.38*)
13	1.13	(0.84, 1.41*)	0.77	(0.19 1.35*)
15	1.25	(0.95 1.54*)	1.09	(0.51 1.67*)

* Scale shows a significant beta blocker effect.

Table 7.3

Reproducibility coefficients and 95% Confidence Intervals for Visual Analogue and Borg CR10 Scales for General Fatigue.

REPRODUCIBILITY.				
Time (Minute)	VAS		Borg CR10	
	Reproducibility Coefficient	95% Confidence Interval	Reproducibility Coefficient	95% Confidence Interval
3	35%	(9, 57)	26%	(3, 48)
5	62%	(32, 79)	72%	(43, 85)
7	74%	(47, 86)	70%	(41, 84)
9	84%	(63, 92)	73%	(45, 86)
11	87%	(67, 93)	83%	(61, 91)
13	86%	(67, 93)	84%	(63, 92)
15	82%	(60, 91)	77%	(51, 88)
Max	84%	(62, 92)	86%	(66, 93)

Table 7.4

Sensitivity ratio and 95% Confidence Intervals for Visual Analogue and Borg CR10 Scales for General Fatigue.

SENSITIVITY				
Time (Minute)	VAS		Borg CR10	
	Sensitivity Ratio	95% Confidence Interval	Sensitivity Ratio	95% Confidence Interval
3	-0.05	(-0.64, 0.53)	-0.10	(-0.67, 0.47)
5	-0.05	(-0.63, 0.52)	-0.08	(-0.65, 0.49)
7	0.42	(-0.15, 1.0)	0.36	(-0.22, 0.93)
9	0.63	(0.05, 1.21*)	0.68	(0.10, 1.26*)
11	0.90	(0.32, 1.48*)	0.84	(0.26, 1.42*)
13	1.45	(0.87, 2.03*)	1.10	(0.52, 1.68*)
15	1.63	(1.04, 2.21*)	1.72	(1.13, 2.30*)

* Scale shows a significant Beta Blocker effect.

Table 7.5

Visit and Therapy Effects for Minute 15 for the Subjective Scales.

Visit	1	2	3	4	5	6	7	8	P Value for Visit Effect	Standard Error of Visit Effect	Therapy Effect (All Significant)
VAS Breathlessness	-10.13 a	4.29 ab	-0.70 b	1.71 b	6.47 b	4.32 b	1.65 b	1.1 b	0.015	2.8	12.4
VAS General Fatigue	-8.78 a	-2.03 ab	-0.003 b	-0.37 b	4.44 b	5.28 b	0.20 b	1.29 b	0.05	3.5	20.00
Borg Breathlessness	-0.92 a	-0.21 ab	0.04 b	0.12 b	0.60 b	0.33 b	0.46 b	-0.42 b	0.05	0.32	1.24
Borg General Fatigue	-0.81 a	-0.27 ab	-0.19 ab	-0.06 ab	0.28 b	0.78 b	0.12 b	0.15 b	0.05	0.34	2.06

A common symbol (eg. a) denotes visits are in common (i.e. no statistically significant difference).

Table 7.6

Mean and Standard Deviation of Maximum Values for the Physiological Variables.

Visit	1	2	3	4	* 5	* 6	* 7	* 8	P Value for Therapy Effect
VE (litres.min^{-1})	140.9 21.3	145.1 16.4	144.9 12.8	145.8 16.1	146.2 20.0	114.3 16.5	147.8 17.1	121.4 *14.8*	0.001
VO_2 (ml.kg^{-1} min^{-1})	56.1 5.9	57.1 6.2	56.6 5.6	57.4 6.0	56.5 5.8	45.8 3.7	57.6 5.1	46.3 *5.2*	0.001
VCO_2 (litres.min^{-1})	4.65 *0.70*	4.76 0.53	4.76 0.51	4.81 0.55	4.85 0.60	3.83 0.53	4.82 0.50	3.93 *0.45*	0.001
Frequency of breathing (breaths.min^{-1})	50.3 *6.6*	51.1 6.1	50.1 9.2	52.2 9.6	51.8 8.6	45.7 7.8	50.5 8.1	47.1 *7.9*	0.001
Heart Rate (beats.min^{-1})	197.3 *7.7*	197.1 10.0	197.2 8.3	195.6 6.9	193.9 11.5	127.6 15.2	194.2 11.0	132.8 *12.1*	0.001
Tidal Volume (litres)	2.84 *0.51*	2.85 0.29	2.97 0.50	2.85 0.44	2.88 0.49	2.53 0.36	2.97 0.44	2.64 *0.48*	0.001
RER	1.127 *0.067*	1.143 0.056	1.133 0.055	1.137 0.065	1.161 0.047	1.135 0.030	1.147 0.055	1.159 *0.050*	0.490
Endurance time (minutes)	16.76 *0.75*	16.71 0.87	16.75 0.78	16.80 0.87	16.73 0.76	15.10 0.48	16.81 0.72	15.31 *0.62*	0.001

* Tests 5 and 7 have been grouped as placebo tests and tests 6 and 8 as Propranolol tests.

Standard Deviation is given below each mean value.

Table 7.7

Reproducibility of Maximum Values for the Physiological Variables.

Variable	Reproducibility (Percentage and 95% C.I.)	
VE (litres.min^{-1})	77	(51, 88)
VO_2 (ml.kg.$^{-1}$min^{-1})	76	(49, 87)
VCO_2 (litres.min^{-1})	96	(90, 98)
Frequency of Breathing (breaths.min^{-1})	73	(46, 86)
Heart Rate (beats.min^{-1})	43	(15, 64)
Tidal Volume (litres)	80	(56, 90)
RER	54	(23, 73)
Endurance Time (seconds)	79	(54, 89)

Table 7.8

Visit and Therapy Effects for Minute 15 for the Physiological Variables.

Visit	1	2	3	4	5	6	7	8	P value for Visit Effect	Standard Error of Visit Effect	Therapy Effect (All Significant)
VE ($litres.min^{-1}$)	-2.70 a	0.03 a	0.42 a	-0.55 a	-0.17 a	0.53 a	-0.04 a	2.48 a	0.68	1.6	4.83
VO_2 ($litres.min^{-1}$)	-0.64 a	0.73 a	-0.41 a	-0.21 a	-0.22 a	-0.25 a	0.29 a	0.29 a	0.63	0.6	-4.64
VCO_2 ($litres.min^{-1}$)	-0.04 a	0.00 a	0.00 a	-0.05 a	0.03 a	0.02 a	0.05 a	0.01 a	0.91	0.04	-0.11
Frequency of Breathing ($beats.min^{-1}$)	-0.21 a	-0.18 a	1.25 a	0.19 a	-1.82 a	0.12 a	-0.98 a	0.90 a	0.70	1.5	4.55
Heart Rate ($beats.min^{-1}$)	2.51 a	0.18 a	3.34 a	1.34 a	-3.43 a	-2.23 a	0.10 a	-1.81 a	0.71	2.6	-50.35
VE/VO_2	0.01 a	-0.01 a	0.01 a	-0.02 a	0.01 a	0.01 a	0.01 a	-0.02 a	0.29	0.01	0.07
VE/VCO_2	-0.54 a	0.17 a	0.70 a	0.24 a	-0.34 a	0.01 a	-0.43 a	0.17 a	0.50	0.43	2.50
Tidal Volume (litres)	-0.05 a	0 a	-0.04 a	-0.07 a	0.11 a	-0.01 a	0.08 a	-0.02 a	0.47	0.06	0.15
RER	0.01 a	-0.01 a	0.01 a	-0.02 a	0.01 a	0.01 a	0.01 a	-0.02 a	0.29	0.01	0.07

A common symbol (.e.g. a) denotes visits are in common i.e. no statistically significant difference.

Table 7.9 **Correlations for the Subjective Scales and Physiological Variables.**

The Estimated Overall Pooled Correlation, the Minimum and Maximum Pooled Individual Visit Correlations and the Minimum and Maximum Individual Visit Correlations for all Subjective Scales and Physiological Variables.

	Visual Analogue Scale		CR10 Scales	
	Breathlessness	General Fatigue	Breathlessness	General Fatigue
VE	0.81 0.53 0.98 0.09 1.00	0.82 0.51 0.98 0.12 1.00	0.80 0.55 0.99 0.11 1.00	0.82 0.54 0.99 0.22 1.00
VO_2	0.78 0.49 0.97 0.08 1.00	0.80 0.45 0.99 0.11 1.00	0.79 0.54 0.97 0.12 0.99	0.80 0.52 0.97 0.22 1.00
VCO_2	0.81 0.52 0.99 0.08 1.00	0.83 0.49 0.98 0.12 0.99	0.81 0.54 0.98 0.12 1.00	0.82 0.53 0.99 0.22 1.00
Frequency of Breathing	0.74 0.52 0.96 0.08 0.99	0.74 0.50 0.96 0.09 1.00	0.75 0.55 0.95 0.11 1.00	0.76 0.54 0.96 0.22 0.99
Heart Rate	0.73 0.45 0.93 0.00 1.00	0.75 0.39 0.95 0.00 0.99	0.74 0.49 0.93 0.00 1.00	0.75 0.50 0.92 0.00 0.99
Tidal Volume	0.79 0.44 0.96 0.07 0.99	0.81 0.36 0.98 0.11 1.00	0.79 0.44 0.96 0.12 0.99	0.80 0.41 0.96 0.14 0.99
R.E.R.	0.78 0.54 0.97 0.07 1.00	0.79 0.45 0.97 0.12 0.99	0.78 0.51 0.97 0.12 0.99	0.79 0.49 0.96 0.20 0.99
VE/VO_2	0.53 0.12 0.81 -0.32 0.98	0.50 0.04 0.98 -0.26 0.98	0.52 0.11 0.82 -0.28 0.97	0.50 0.04 0.98 -0.35 0.99
VE/VCO_2	-0.35 -0.66 0.22 -0.86 0.89	-0.39 -0.76 0.26 -0.88 0.79	-0.40 -0.70 0.25 -0.87 0.89	0.49 -0.70 0.25 -0.87 0.72

An example of how the data is presented is given for VE and VAS breathlessness. The estimated overall pooled correlation is 0.81. Minimum and maximum pooled individual visit correlations are 0.53, 0.98. Minimum and maximum individual visit correlations are 0.09, 1.00

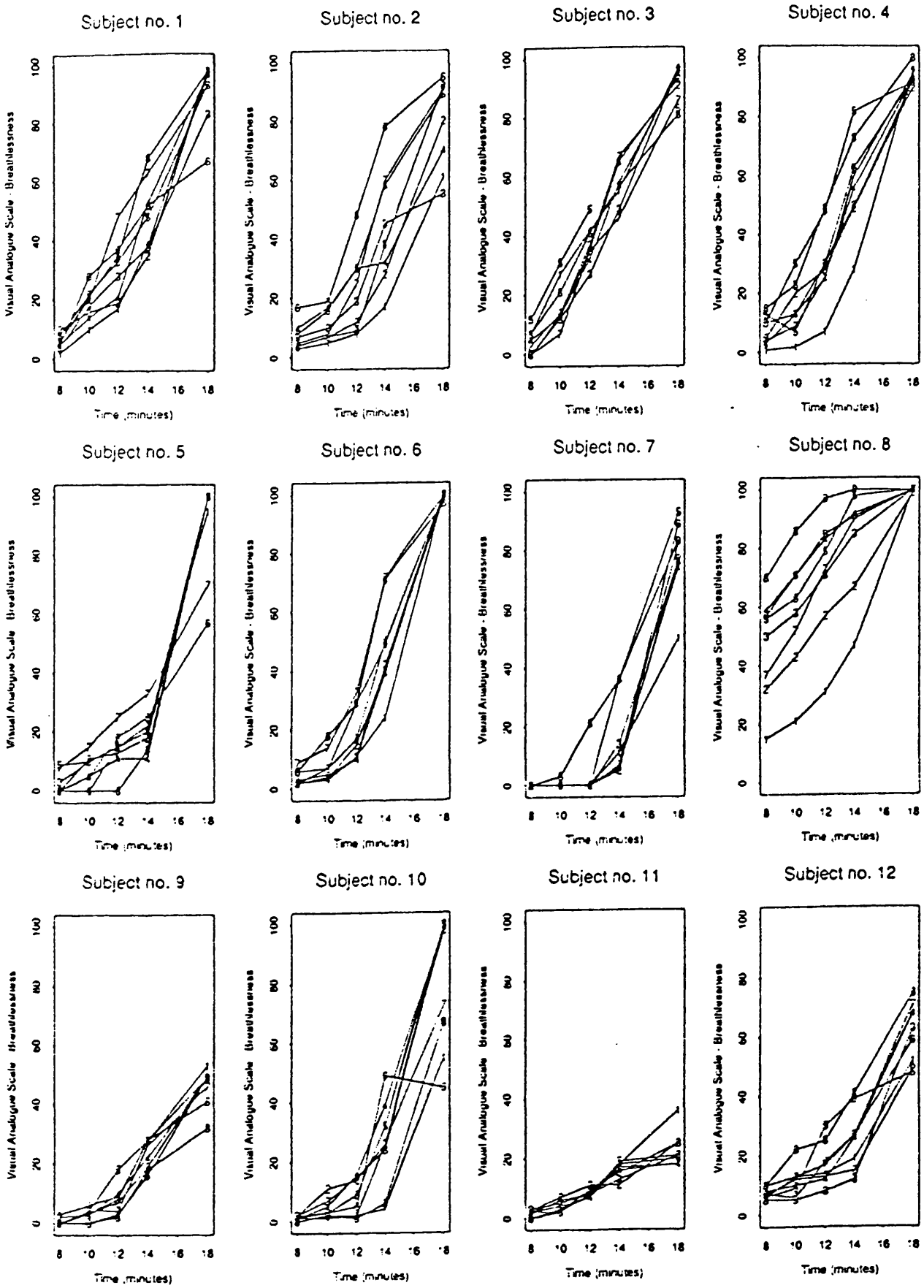


Fig 7.1

Visual analogue breathlessness scores for all subjects for all tests from 8 minutes to maximum.

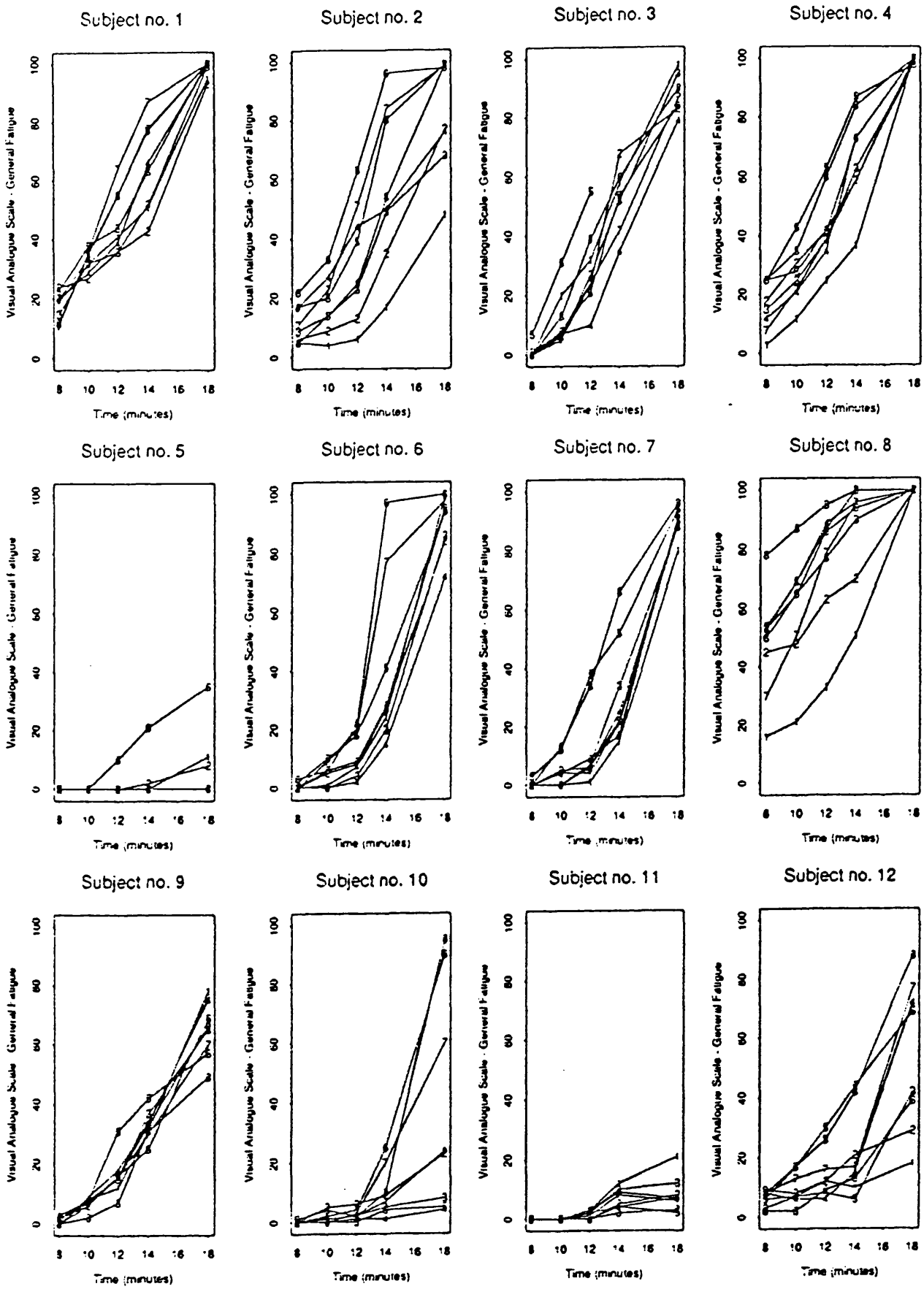


Fig 7.2

Visual analogue general fatigue for all subjects for all tests from 8 minutes to maximum.

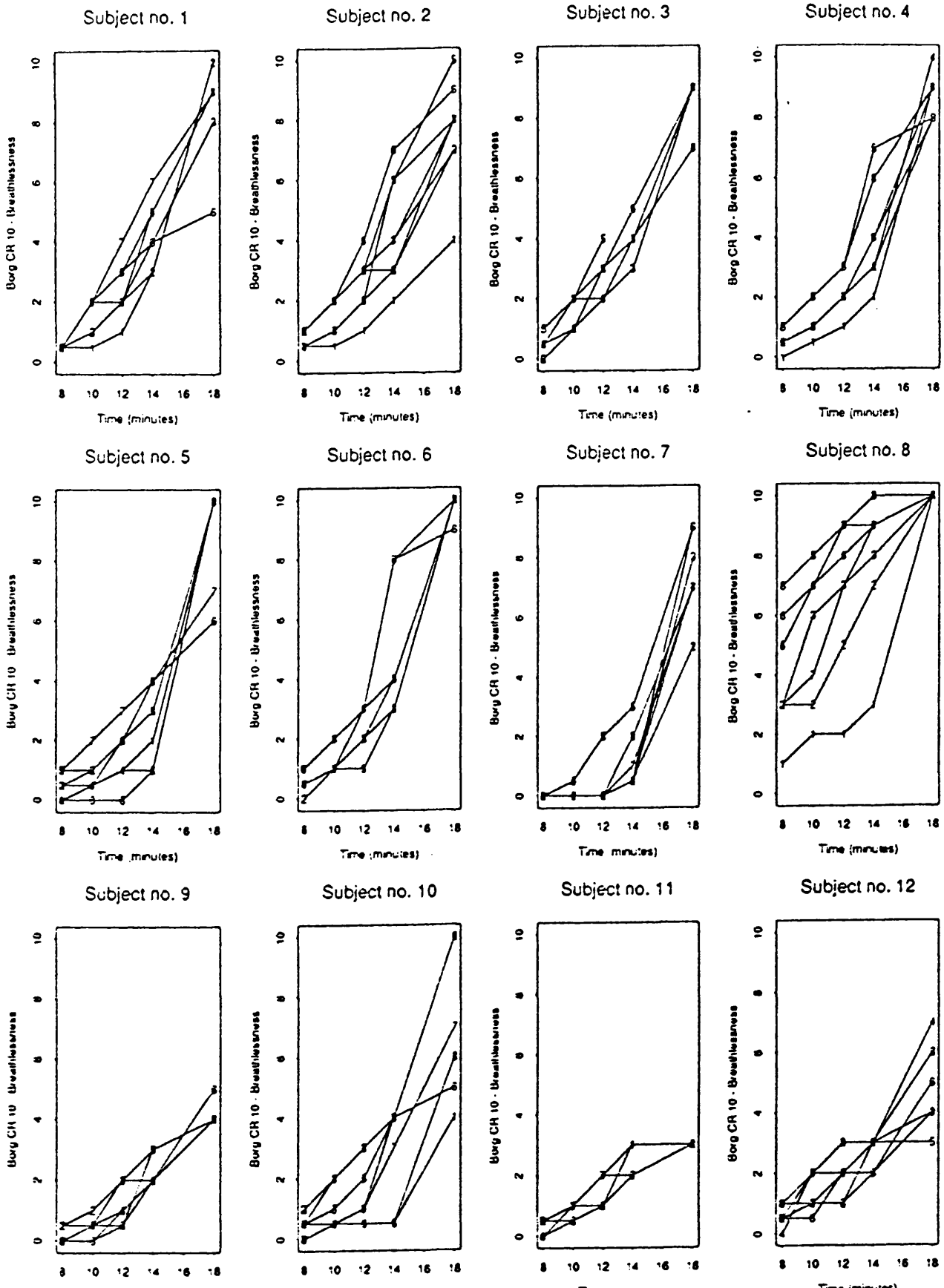


Fig 7.3

Borg CR10 breathlessness scores for all subjects for all tests from 8 minutes to maximum.

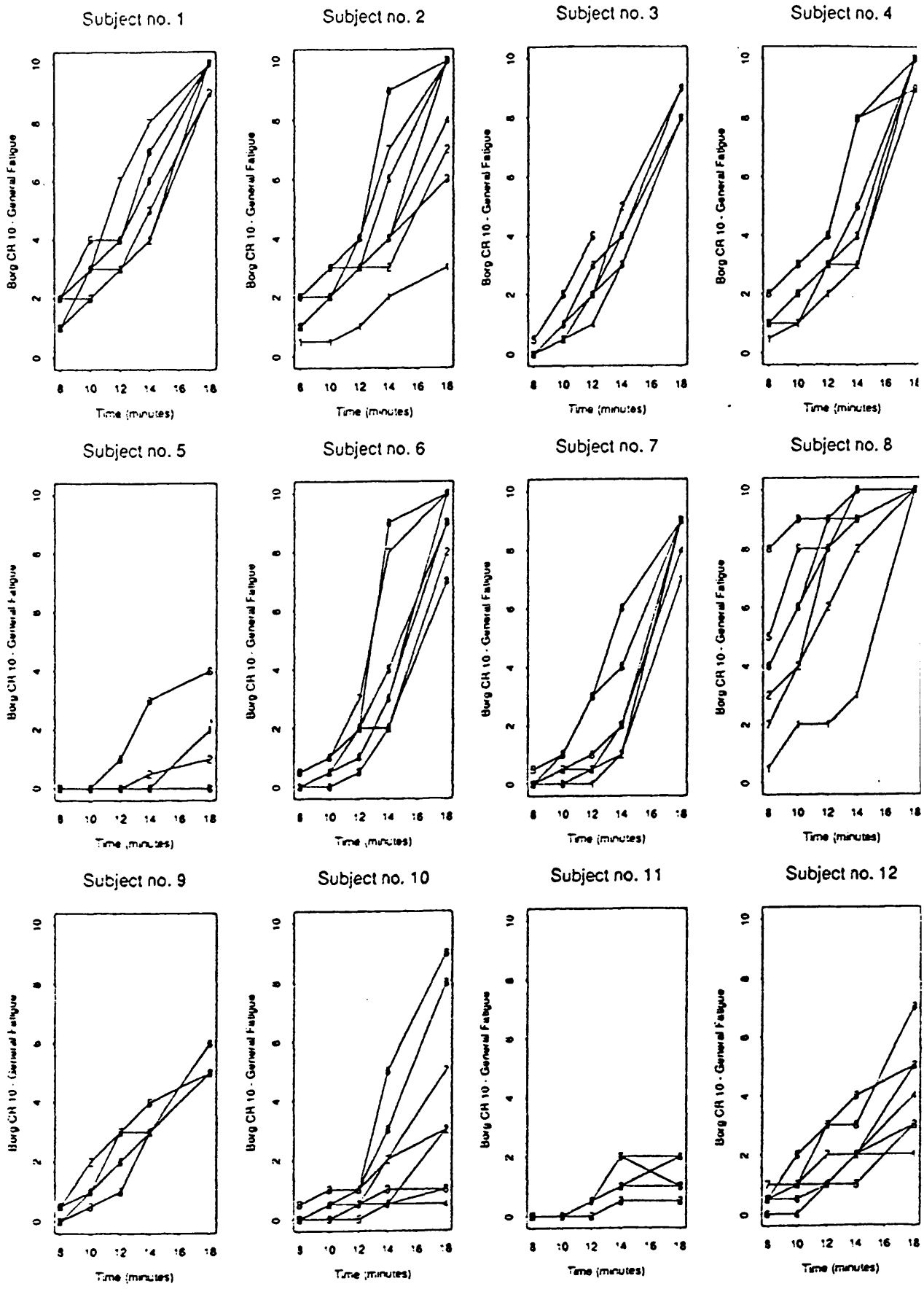


Fig 7.4

Borg CR10 general fatigue for all subjects for all tests for 8 minutes to maximum.

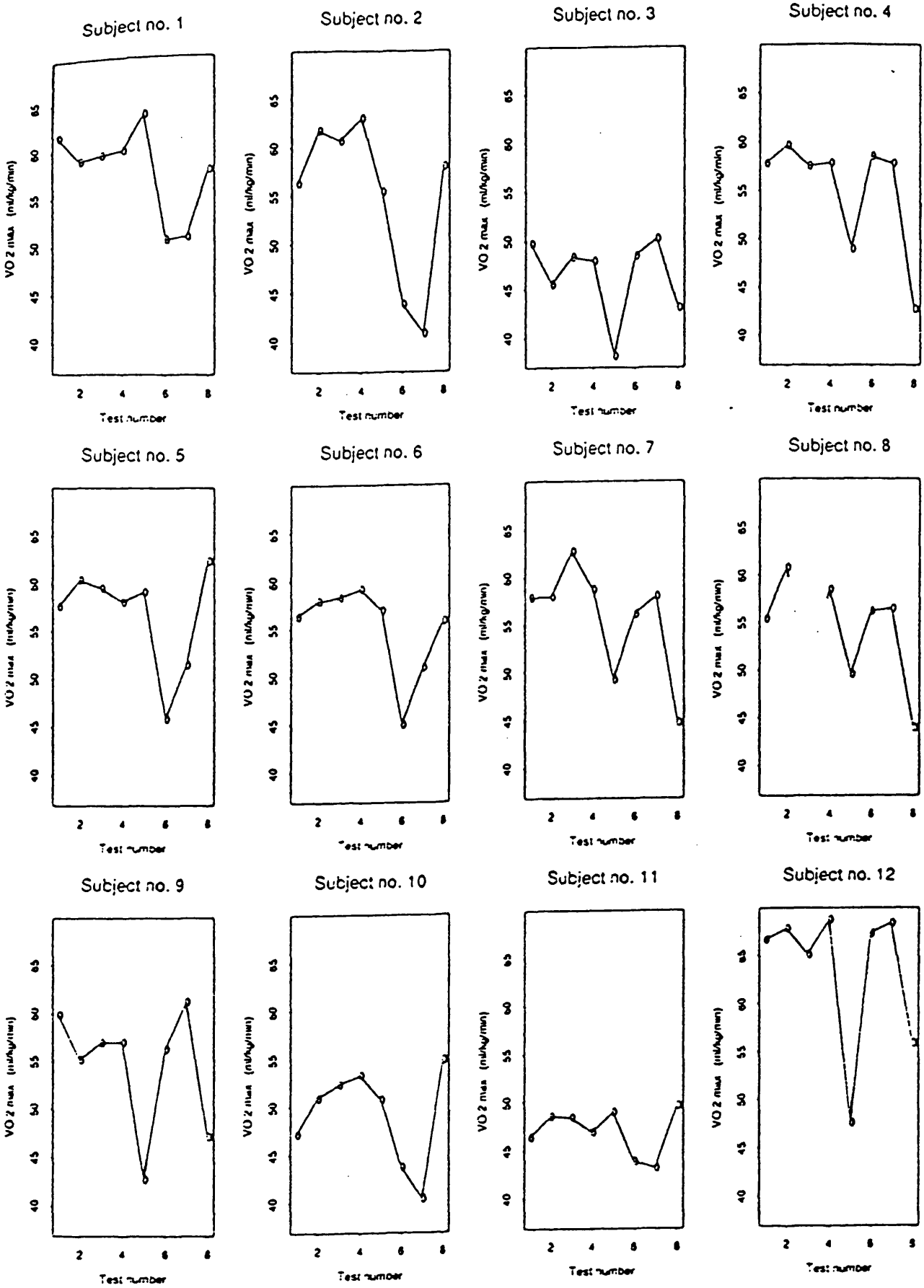


Fig 7.5

VO_2 max. for all subjects for all tests.

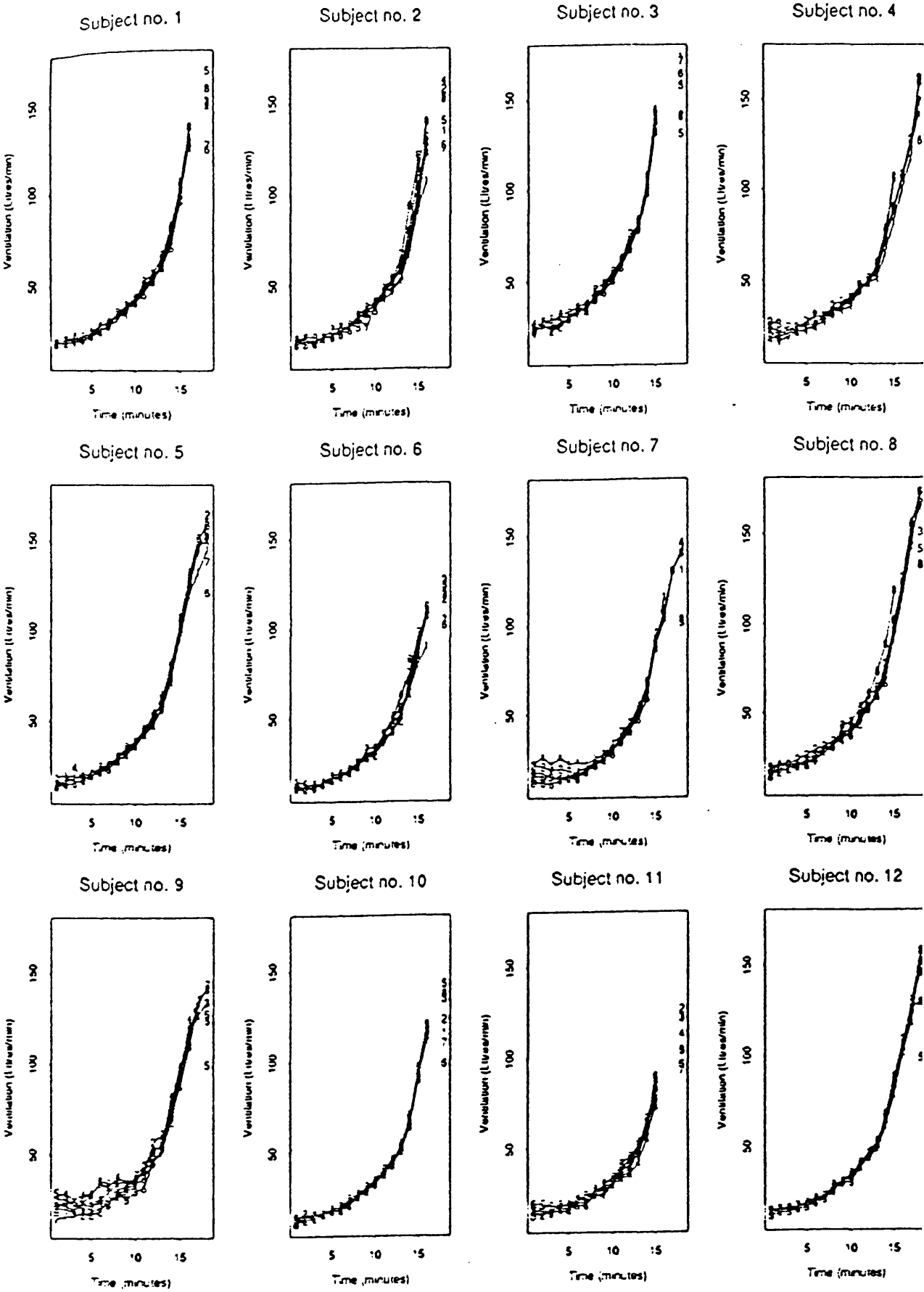


Fig 7.6

VE for all subjects for all tests.

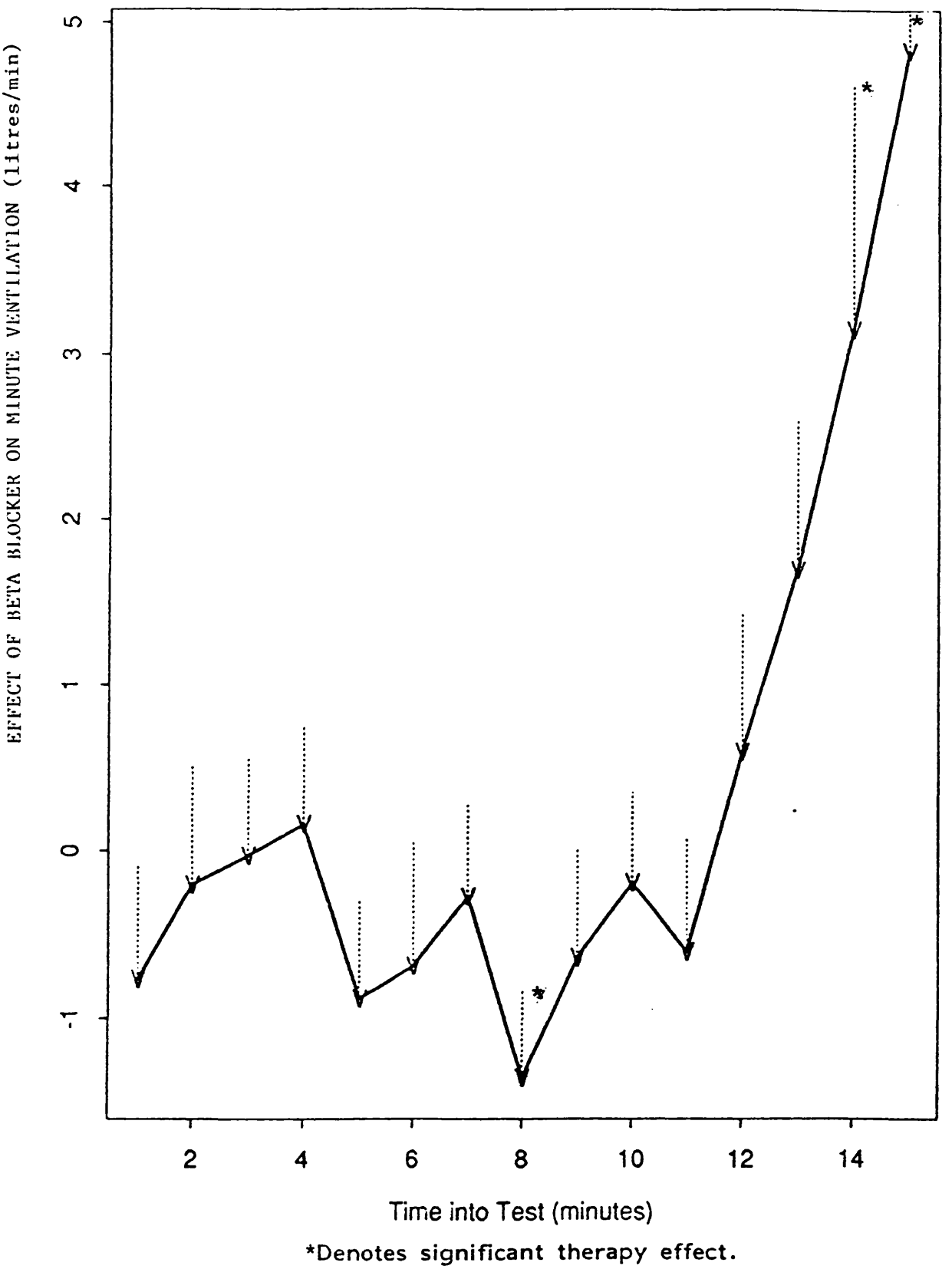


Fig 7.7

Effect of beta blocker on minute ventilation.

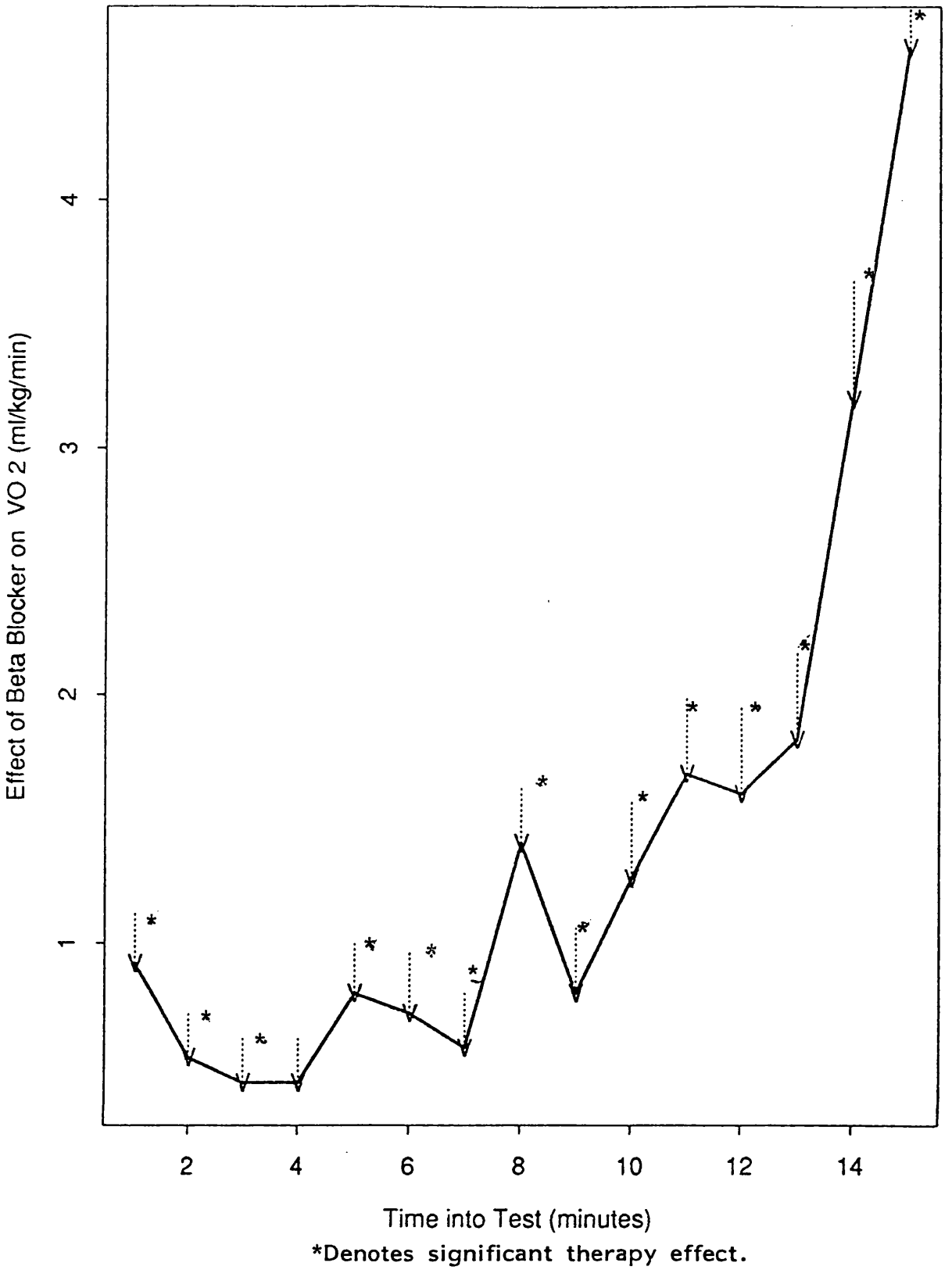


Fig 7.8

Effect of beta blocker on VO_2

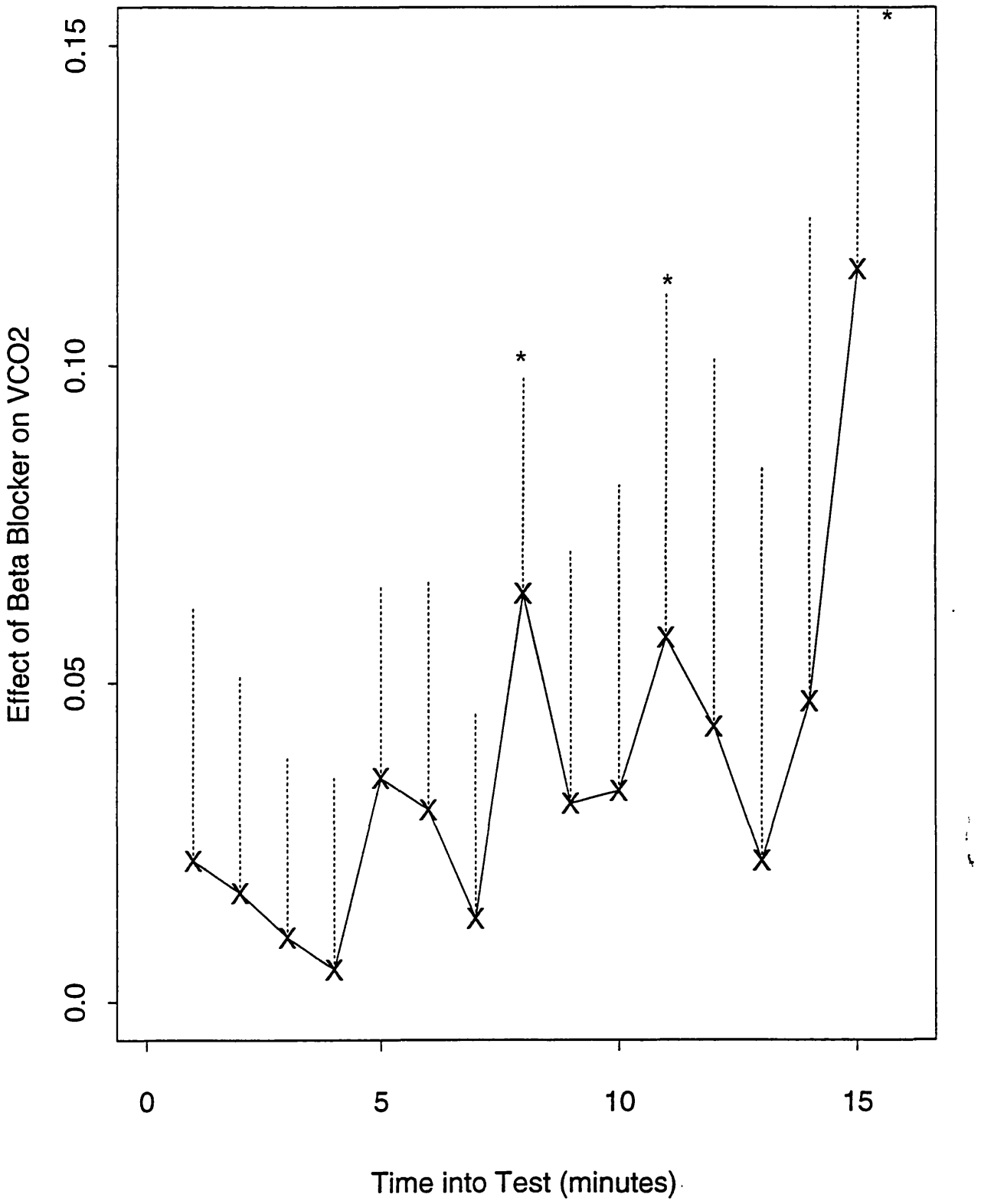


Fig 7.9

Effect of beta blocker on VCO_2.

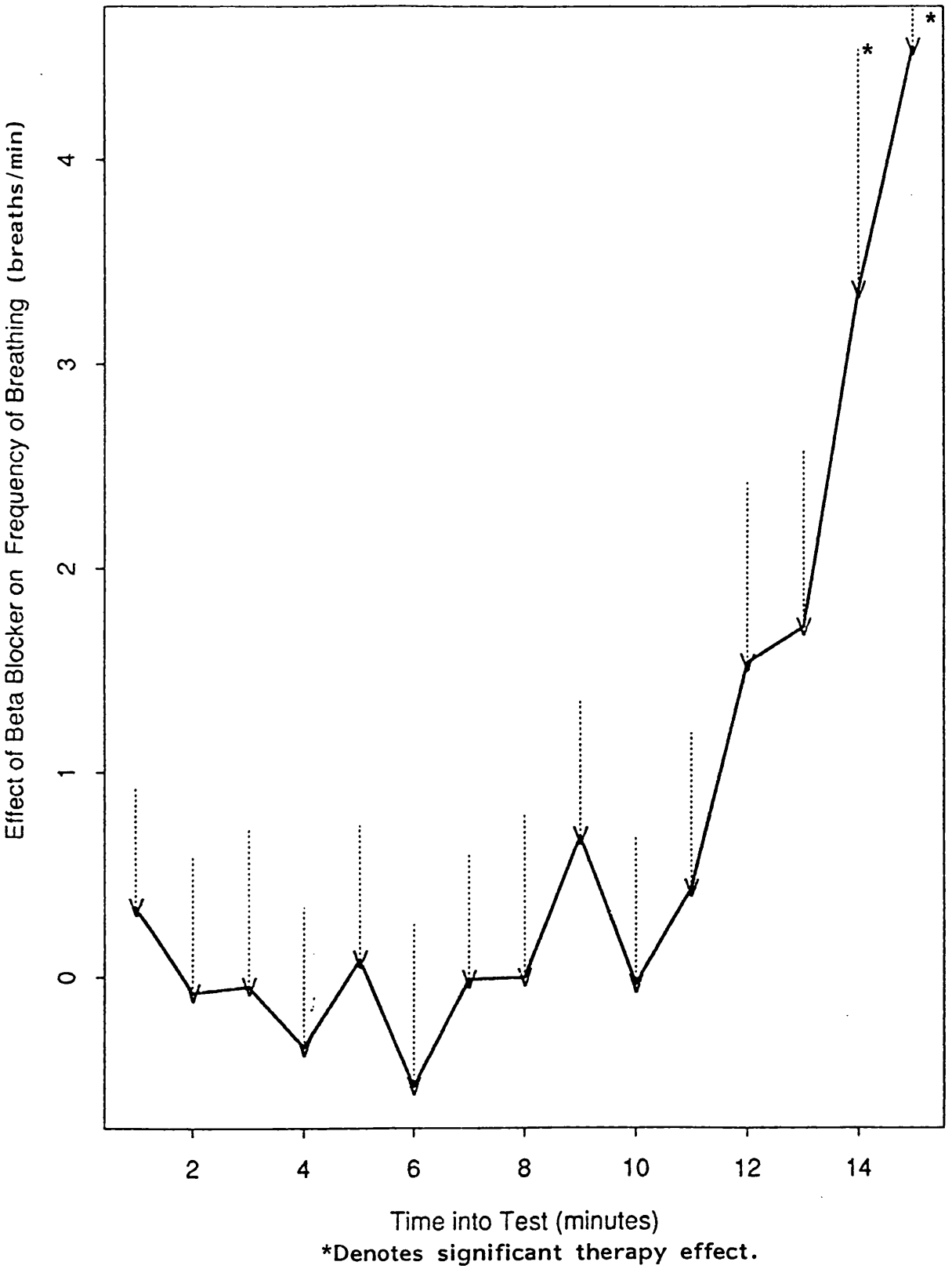


Fig 7.10

Effect of beta blocker on frequency of breathing

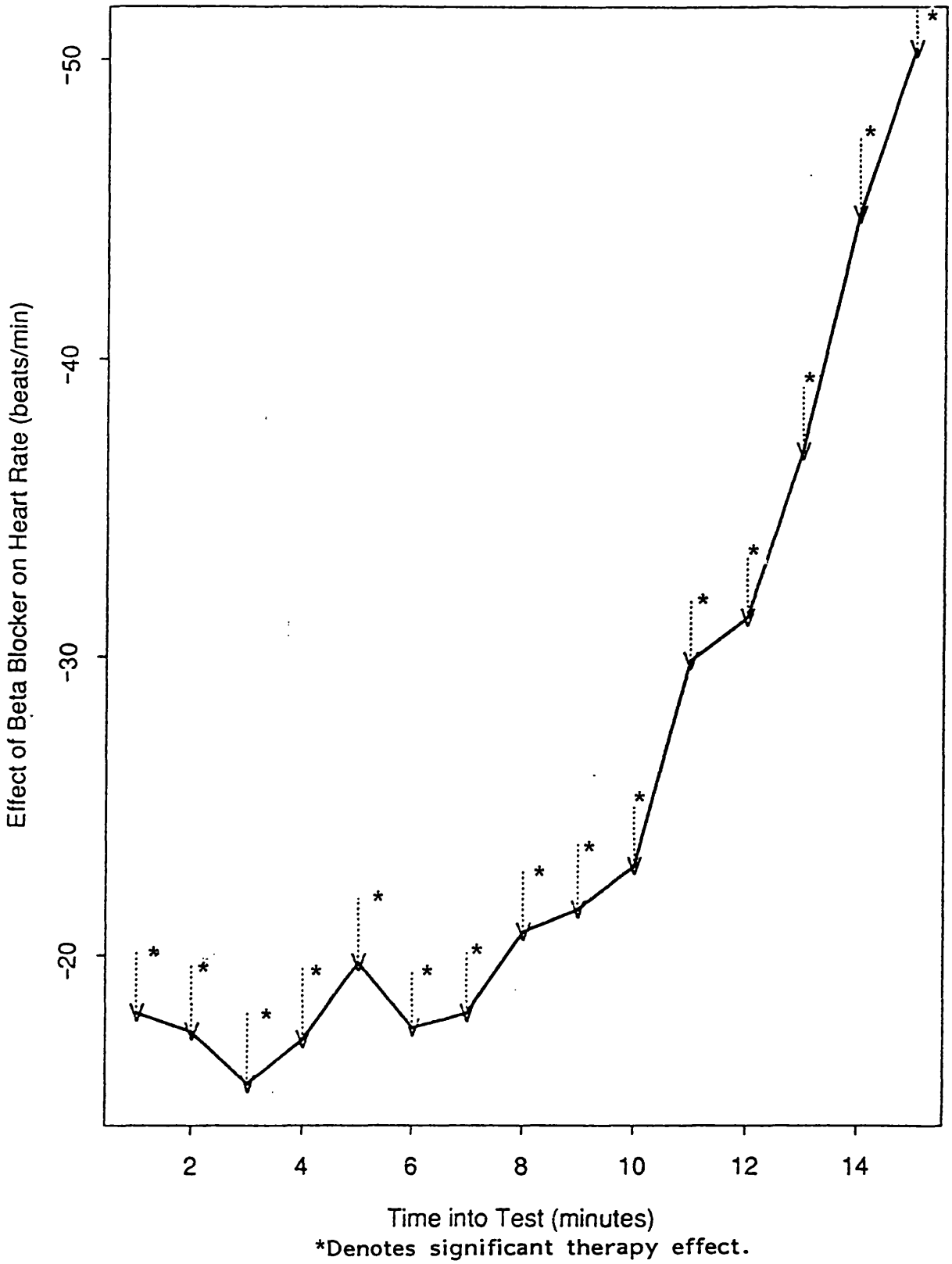


Fig 7.11

Effect of beta blocker on heart rate

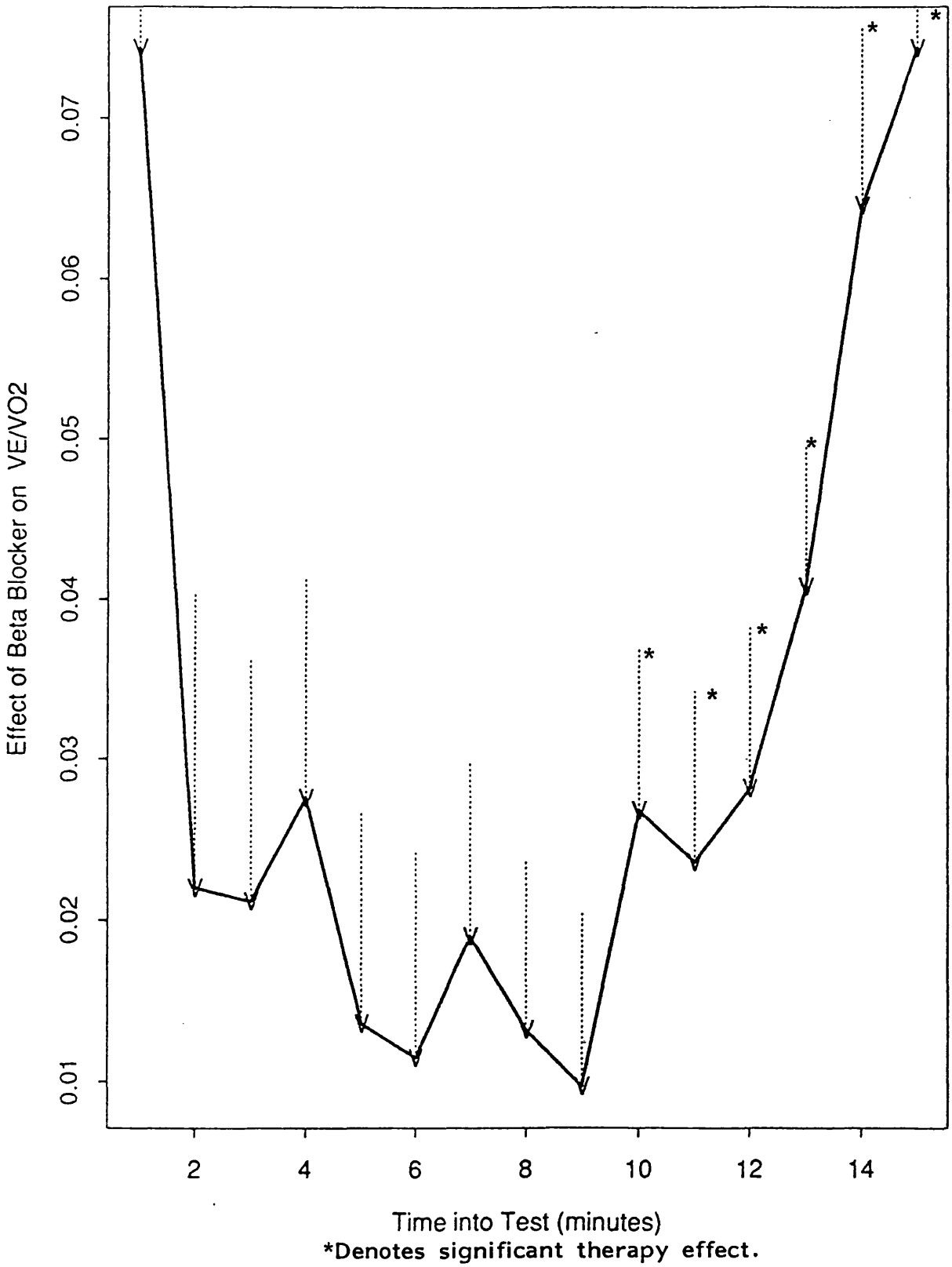


Fig 7.12

Effect of beta blocker on VE/VO_2

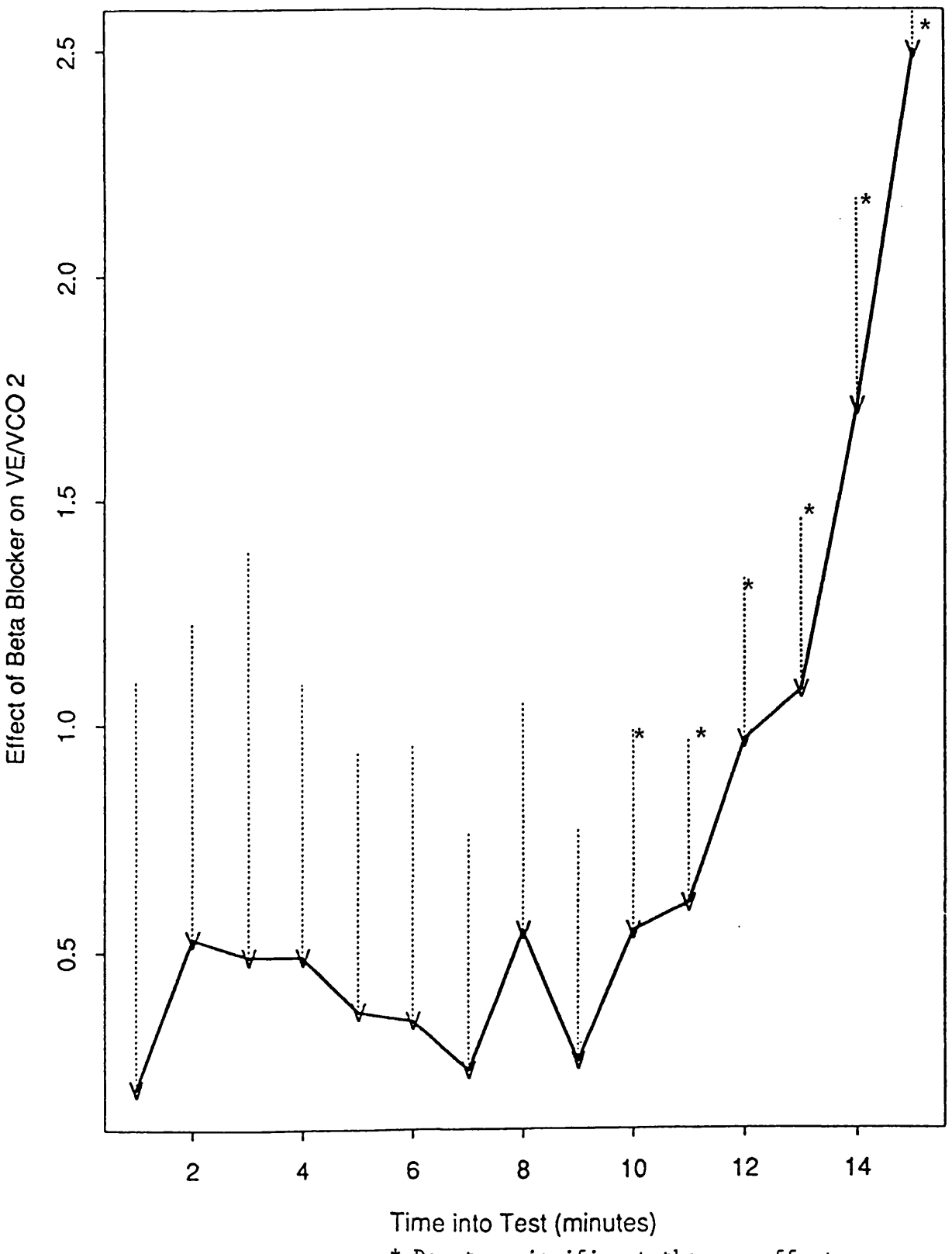


Fig 7.13

Effect of beta blocker on VE/VCO_2

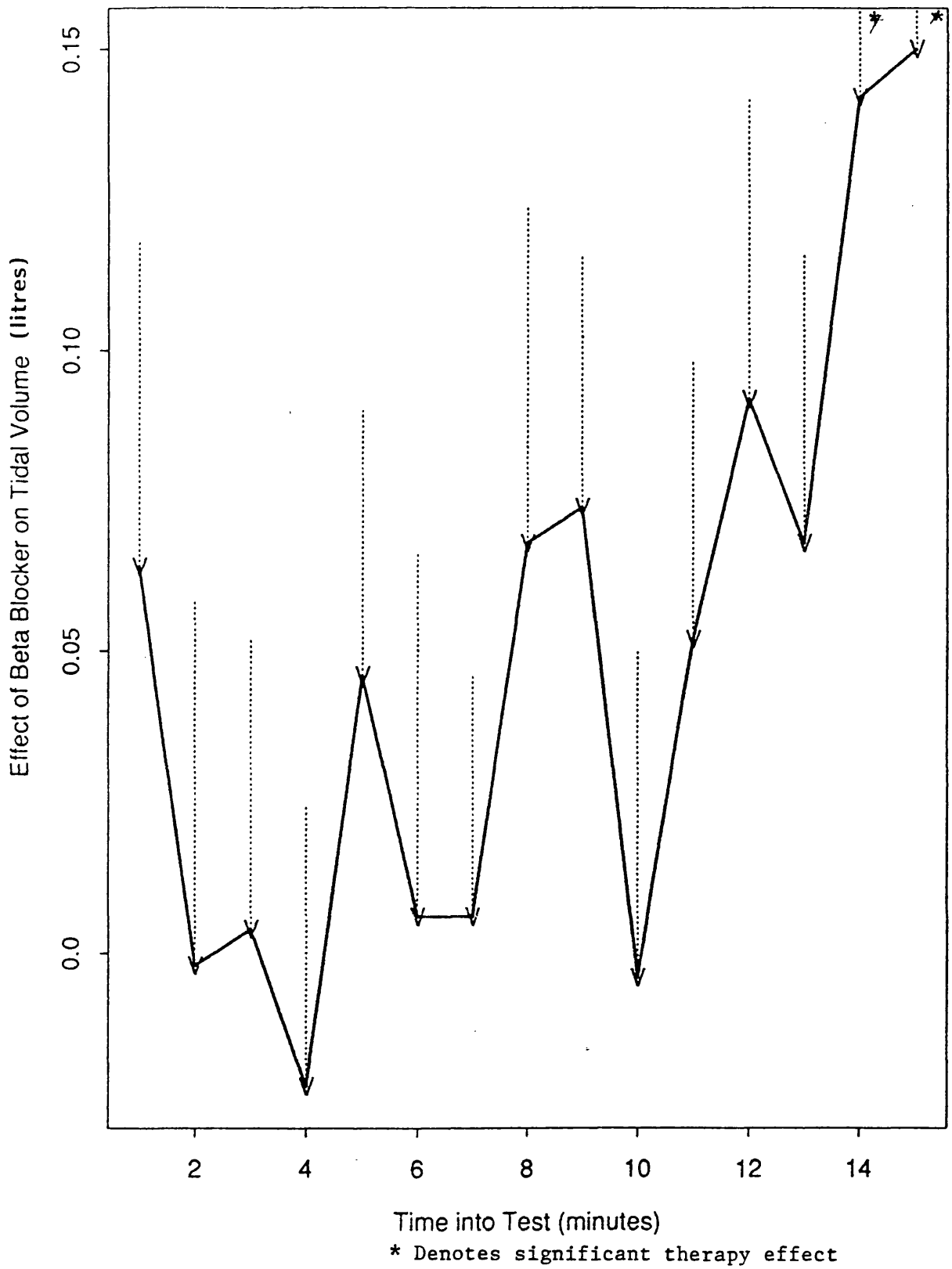


Fig 7.14

Effect of beta blocker on tidal volume.

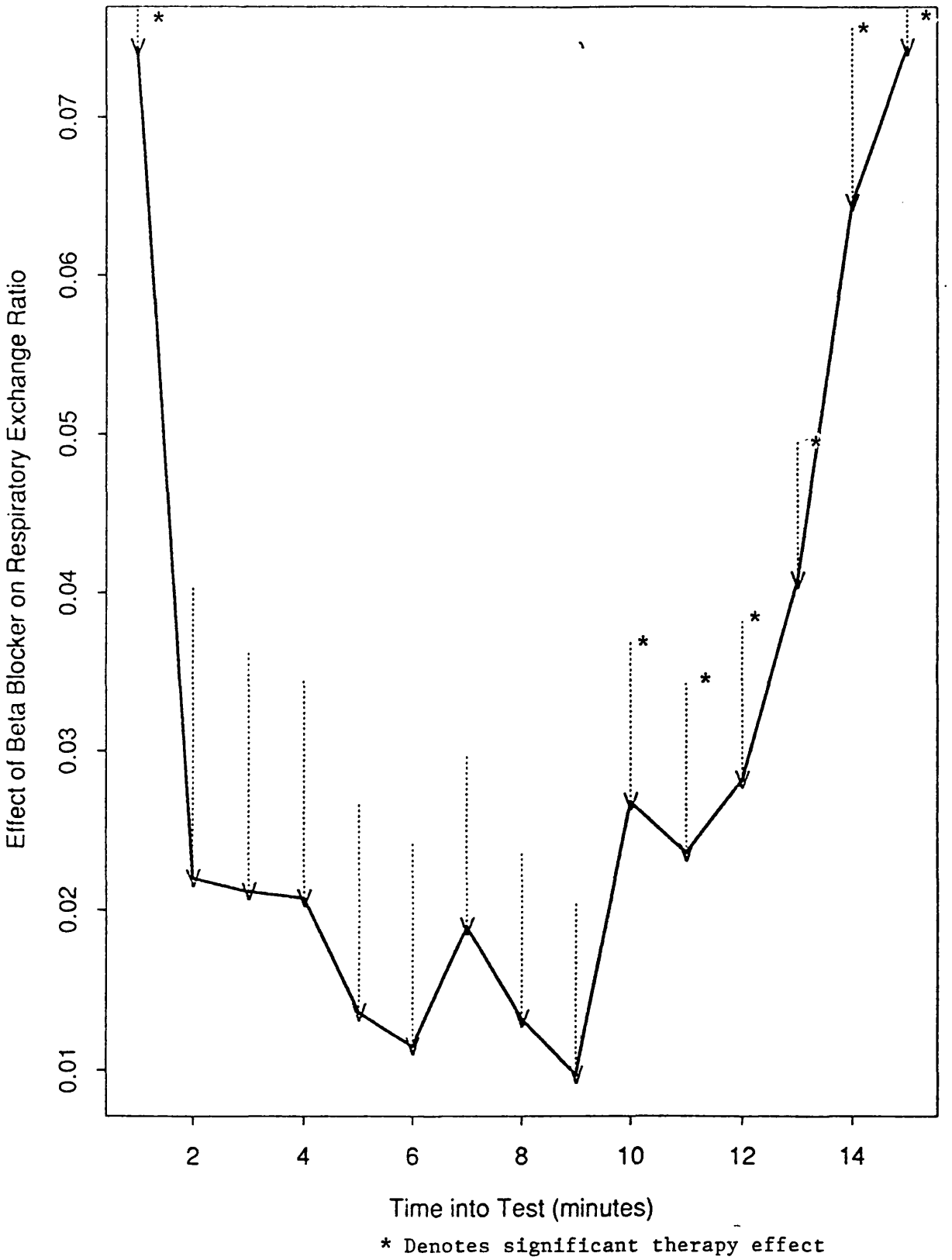


Fig 7.15

Effect of beta blocker on respiratory exchange ratio.

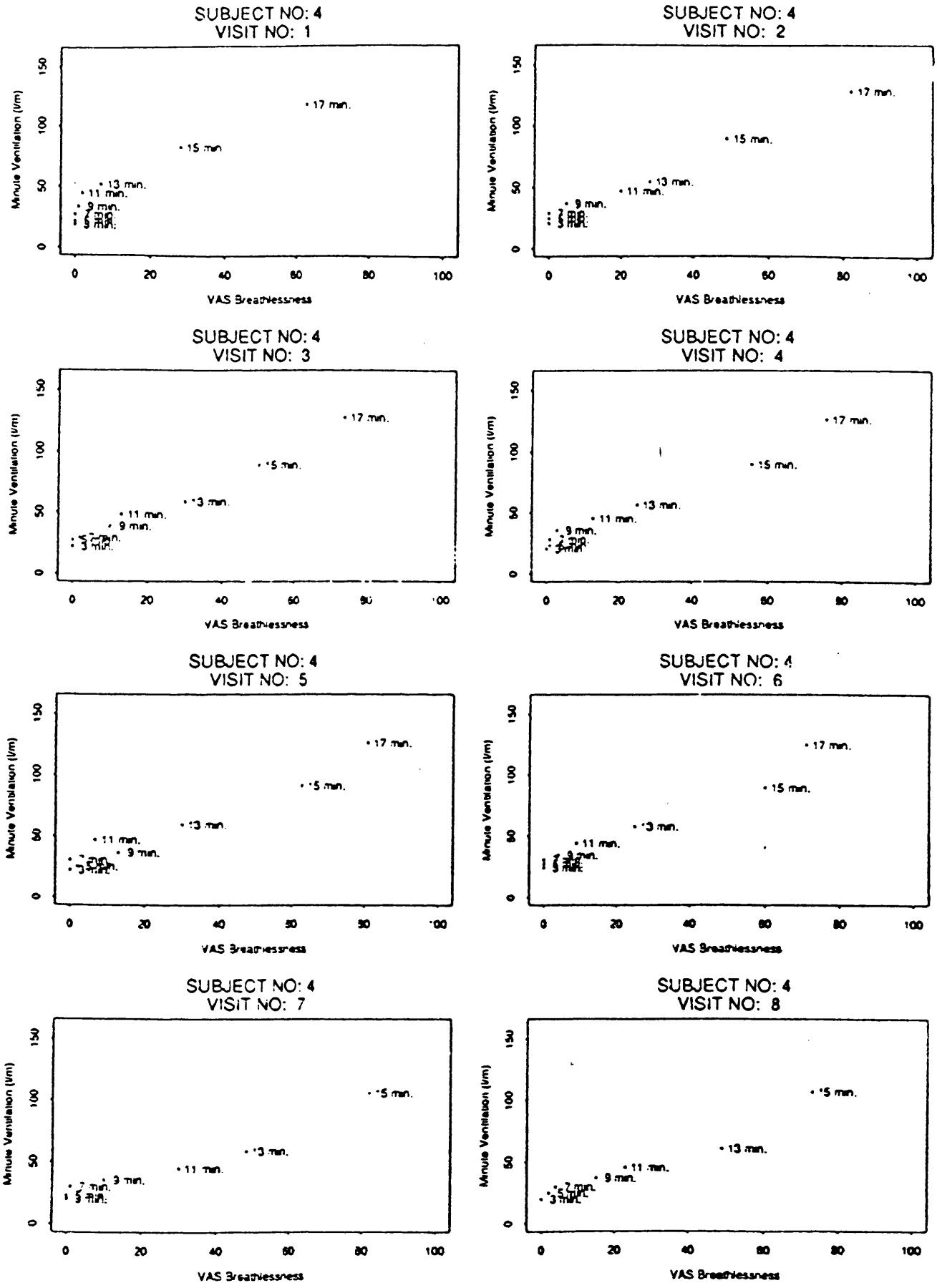


FIG 7.16

The VE/VAS breathlessness relationship for subject 4 for all tests.

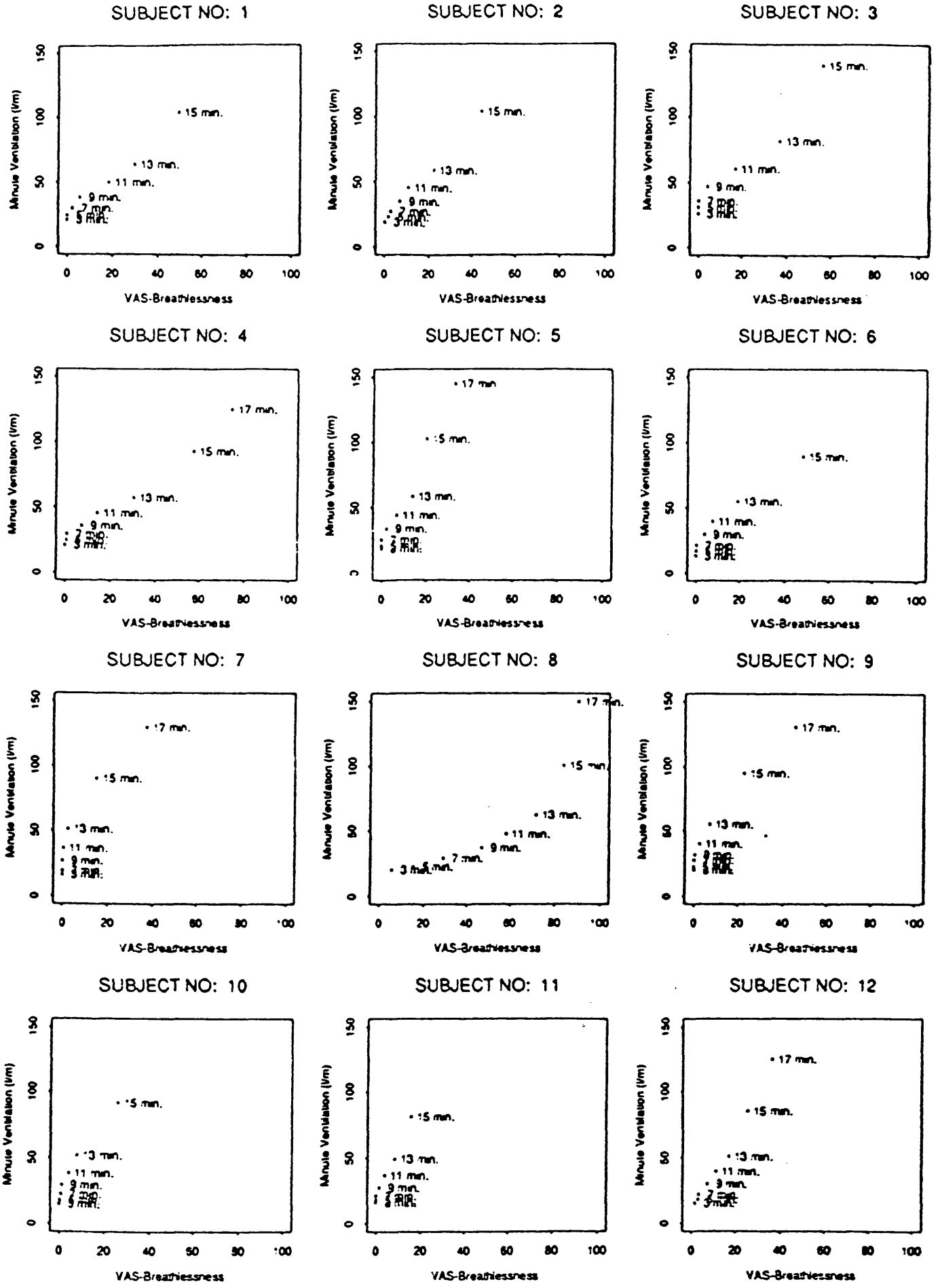


FIG 7.17
The VE/VAS breathlessness relationship for all subjects for all tests.

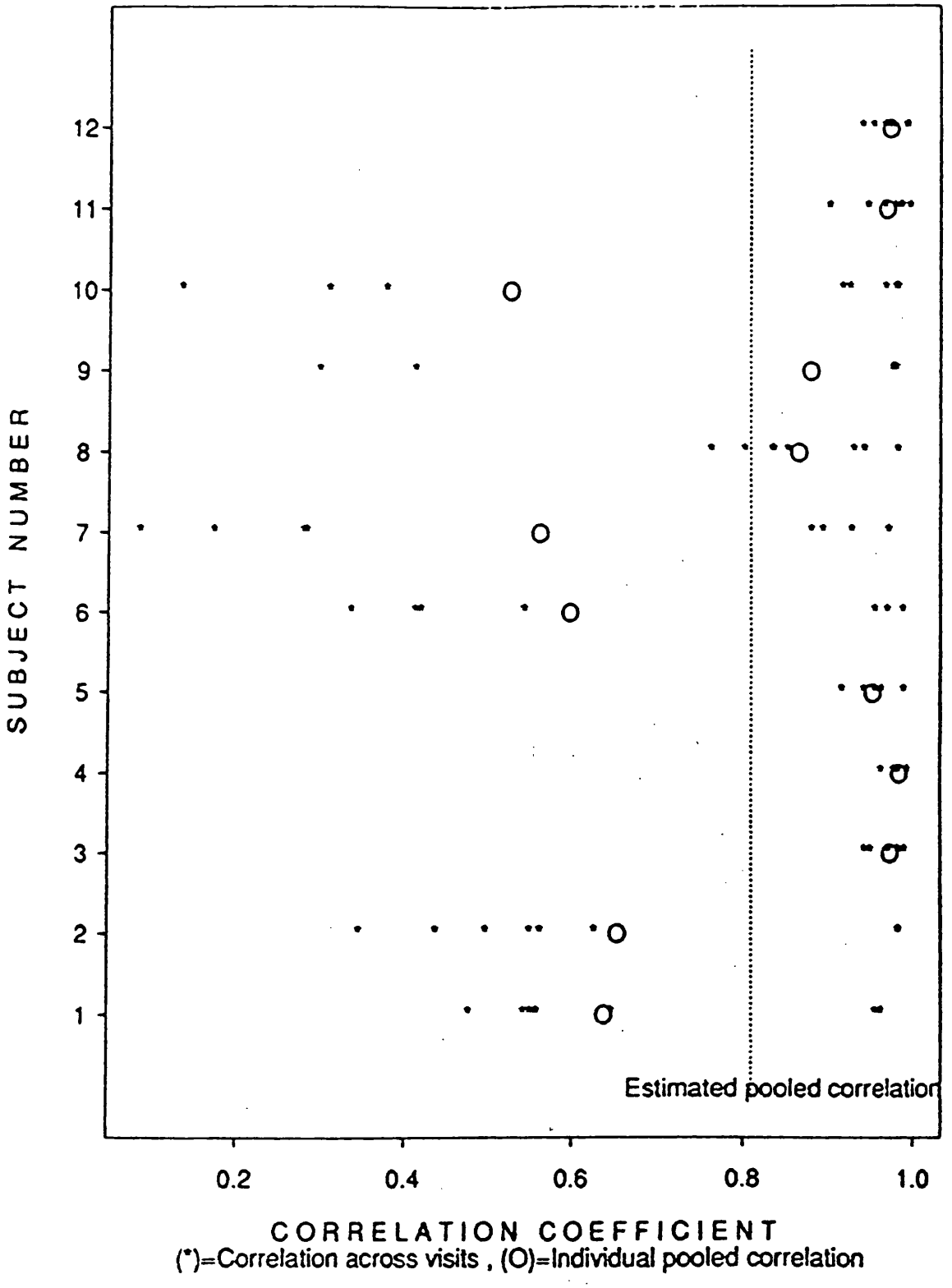


FIG 7.18

The correlations for VE and VAS breathlessness.

1) Individual visit correlation for each subject
11) Individual pooled correlation
111) Estimated pooled correlation

CHAPTER 8
SECTION ONE.

DISCUSSION.

A COMPARISON OF THE REPRODUCIBILITY AND THE SENSITIVITY TO CHANGE OF VAS, BORG CR10 AND LIKERT SCALES.

8.1. SUBJECTIVE SCALES.

8.1.1. MEASUREMENT OF BREATHLESSNESS - REPRODUCIBILITY.

In this study, the VAS was more reproducible for the measurement of breathlessness than the Borg CR10 scale. The Likert scale tended to perform better than the Borg CR10 scale but there were no significant differences between the scales. The Likert scores tended to be lower than the VAS.

Several groups have shown that the VAS allows reproducible measurement of breathlessness, in the short term, in both normal subjects and patients (O'Neil et al; 1986, Stark et al; (1982), Stark et al; (1981). Wilson and Jones have shown that the Borg CR10 scale measurements of breathlessness are also reproducible in both the short and long term (Wilson and Jones, 1989, 1991a). Due to different exercise protocols and statistical methods of evaluation, it is impossible to say from these studies whether one scale is more reproducible than the other. There have, however been no descriptions of the reproducibility of Likert scale measurements of breathlessness during exercise. In the only other direct comparison of the repeatability of the VAS and the Borg CR10 scale, Wilson and Jones, (1989) reported that the Borg CR10 scale was more reproducible over the short term (a 2 to 6 week period) than the VAS. Wilson and Jones, (1989) favoured the use of the Borg CR10 because it correlated with VE more closely than the VAS and provided a more reproducible measure. These authors, however, made repeatability measurements of the slope of the relationship between the breathlessness score and VE and not on scores at fixed time points, as was carried out in this study.

8.1.2. MEASUREMENT OF BREATHLESSNESS - SENSITIVITY.

The VAS demonstrated significantly better sensitivity at 6 and 8 minutes than the Borg CR10 scale. The Likert scale tended to be higher than the Borg CR10 scale but there was no significant difference. There was a non significant trend for the VAS to be higher than the Likert scale. There is limited published information on the sensitivity of scales to protocol, drug or disease induced changes in breathlessness. Stark et al; (1983) found the VAS to be sensitive to change in three of five patients with chronic obstructive airways disease before and after non-randomised bronchodilator or placebo treatment, given in a single session. O'Neil et al; (1986) increased the respiratory resistance to assess the sensitivity of the VAS scale before evaluating beta blockers and concluded that the VAS was sensitive to change. Muza et al; (1990) suggested that the VAS may be better at identifying changes in breathlessness than the Borg 6-20 scale as there were less restrictions with the VAS. In the present study the VAS was the most sensitive for detecting change in breathlessness following pharmacological intervention, though it should be noted that this change was in a different direction (i.e. increased symptom intensity) than in the Stark et al; (1983) study.

Some studies have induced a greater degree of breathlessness using resistive loading and found that the VAS and Borg CR10 scales to be responsive to this type of intervention. An increase in the inspiratory resistance was used to increase the perception of breathlessness at a given VE in normals (Stark et al; 1981). They found that breathlessness was more severe with the inspiratory resistance and they suggested that the plot of breathlessness (using the VAS) and VE was sensitive to change. El-Manshawi et al; (1986) used the Borg CR10 scale to quantify the intensity of breathlessness associated with exercise and respiratory resistive loading. They found that the perception of breathlessness increased at any given workload with resistive loading.

8.1.3. MEASUREMENT OF GENERAL FATIGUE - REPRODUCIBILITY.

In this study the VAS tended to be the most reproducible scale. The Borg CR10 scale tended to perform better than the Likert scale but not as well as the VAS. No other reproducibility study has been carried out on general fatigue.

8.1.4. MEASUREMENT OF GENERAL FATIGUE - SENSITIVITY.

The Borg CR10 was clearly much more sensitive to change than the other two scales for general fatigue. It is unknown why the Borg CR10 scale was the most sensitive of the three scales. Furthermore, it is unclear why the Borg CR10 scale for general fatigue is much more sensitive than the Borg CR10 scale for breathlessness.

The fact that there is such a great difference in the performance of the Borg CR10 scale between breathlessness and general fatigue indicates that the subjects were able to differentiate between breathlessness and general fatigue. Lees et al; (1987) failed to alter the perception of fatigue (Borg Category Scale) after epanolol or metoprolol during an incremental cycle test compared with placebo.

While this study asked subjects to quantify general fatigue, it may be of value to examine how other studies have used subjective scales to assess RPE as some authors have suggested that RPE scores could have implications for fatigue. Using the Borg category scale Pearson et al; (1979) reported that RPE scores were higher on propranolol than placebo and concluded that this finding may have relevance to the symptom of fatigue reported by patients on these drugs. Van Herwaarden et al; (1979) found that propranolol had no effect on RPE but their subjects worked at only moderate intensities.

Other studies have distinguished between "central" and "leg" effort. During 25 minutes at 65% VO_2 max Kaiser et al; (1985) found that "central" RPE was increased in 3 out 5 timepoints but "leg" effort was higher at all 5 timepoints with 80 mg of propranolol compared with placebo. Tesch and Kaiser, (1983) found that "leg" RPE (Borg Category) was higher than central RPE during steady state exercise at 73% Vo_2 Max with 80 mg of

propranolol compared with placebo. The authors speculated that changes within the skeletal muscles were probably causing an increased sensation of fatigue. Tesch et al; (1984) asked subjects to rate "local and central" fatigue during incremental steady state exercise using the Borg category scale. Both were significantly increased at the higher workrates after beta blockade compared with placebo but they found no difference at the low workrates. The authors concluded that the subjects reported an increased sensation of fatigue with propranolol compared to placebo during heavy steady state exercise.

The findings of Tesch that the perception of leg effort was increased more than "central" with beta blockade may indicate that "overall fatigue" may not have been affected. However, subjects in this study were asked to clearly distinguish between general fatigue and leg fatigue. Somewhat surprisingly Violante et al; (1984) reported that untrained subjects scored RPE lower at 25 and 150 watts after 40 mg of propranolol compared with placebo.

8.1.5. BREATHLESSNESS/GENERAL FATIGUE DIFFERENCES.

Reproducibility coefficients for breathlessness and general fatigue were highest for the VAS throughout the three timepoints but only statistically significant at minute 6 for breathlessness. Indeed, the reproducibility coefficients for breathlessness and general fatigue follow a similar pattern. It could be hypothesised that the subjects were unable to distinguish between the two symptoms. However, all subjects reported that they could discriminate between breathlessness and general fatigue. Furthermore, there is a marked difference in the sensitivity scores between the two symptoms. It may be expected that the VAS would be the most sensitive scale as it offers finer adjustment. In breathlessness, this is the case but perhaps somewhat surprisingly for general fatigue the Borg CR10 scale is the most sensitive of the three scales.

8.1.6. RANGE OF SCALES.

The VAS and Likert scales were used over a wider range than the Borg CR10 scale for breathlessness and for general fatigue. As in the study of Wilson and Jones, (1989) the

Borg CR10 scale was used over a narrower range for breathlessness than the VAS. The terminology used in the upper part of the Borg CR10 scale is likely to restrict the use of the upper part of the scale particularly during submaximal exercise. For example, five on the Borg CR10 is "severe". The verbal descriptors in the Borg CR10 scale may have imposed a certain threshold of sensation intensity at each level before proceeding to the next digit. The Borg CR10 has an in-built ratio bias and a resultant tendency to restrict scores to the lower half of the scale. Wilson and Jones (1989) concluded that the limited range of the Borg CR10 scale may have contributed to the higher repeatability of breathlessness using this scale in their study. However, the repeatability comparisons were compared on the slope of the relationship.

Conversely, it could be expected that the VAS was more reproducible than the Borg CR10 scale because it allows greater precision in measurement than the Borg CR10 scale. The Borg CR10 scale has constrictors. Differences between VAS and category scales have been detected in other studies. For example, the level of discomfort during a helicopter trip was assessed using a category scale and a scale without descriptors. The former scale was scored within the central region while the latter was used in a more progressive manner (Osborne and Clarke, 1976). A similar finding was reported by Scott and Huskinson, (1976) who used different scales to estimate pain. It could be hypothesised that the Borg CR10 and the Likert scales would be more reproducible as the verbal descriptors may have enabled subjects to target a particular number by increasing preferential use of certain digits whereas the VAS offers more opportunity for a wider selection.

Furthermore, it could be hypothesised that it is necessary for large changes in status before subjects are likely to move to another point on the Likert scale. If this were true, it would be anticipated that the Likert scale would be very reproducible in similar conditions. However, any movement in subjects' scores is likely to heavily "penalise" the Likert scale as a change of one is equivalent to 20% of the range of possible scores. Word descriptors

did not restrict the use of the Likert scale as a score of 4 was given for Likert (breathlessness and general fatigue) on the active treatment and R1 and placebo.

8.1.7. ANCHOR POINTS.

Subjects were asked to refer to their common experience of the symptoms, breathlessness and general fatigue. In addition, they were asked to score their perception of these symptoms at the end of the maximal test. It is unknown if these procedures had any influence on the results obtained. Stark et al; (1982) fixed the 100% mark on a breathlessness VAS scale by reference to a familiar everyday activity. Others have found acceptable reproducibility without any attempt to anchor (Guz et al; (1981). It was felt that reference to "common experience" and feelings at the end of the maximal test were of value. Subjects reported that reference to theses "markers" helped them establish reference points. Restricting the anchor points to familiar everyday activities or maximal test endpoints could have limitations. For example, one subject scored relatively low on general fatigue at the end of the maximal test as he reported that he had experienced much greater general fatigue after he had run up Ben Lomond. Subjects who have not exerted themselves for a long period of time may not have a meaningful reference point to which they can refer.

8.1.8. COMPARISON OF THE VISIT AND THERAPY EFFECTS.

The VAS (breathlessness and general fatigue) and Likert (breathlessness) showed a significant visit effect. These visit effects were small compared with the therapy effects but fairly large in comparison with the absolute scores. Care has to be taken in the use of this protocol as it has been shown that there is a visit effect for some scales. Despite the fact that the therapy effect was much greater than the visit effect, it is advisable to incorporate a "run-in" period when this protocol is used. Wilson and Jones, (1989) found that the mean score for the Borg CR10 scale (breathlessness) was reduced by 16% compared with day 1 and the VAS (breathlessness) score was 27% lower on day 2.

8.1.9. SUMMARY.

BREATHLESSNESS AND GENERAL FATIGUE.

Overall the VAS was the best scale with the Borg CR10 scale second and the Likert third. Therefore, it was decided to evaluate the VAS and Borg CR10 scale in CHF patients using a submaximum protocol.

CHAPTER 8
SECTION TWO.

A COMPARISON OF THE REPRODUCIBILITY AND SENSITIVITY TO CHANGE OF VISUAL ANALOGUE, BORG CR10 AND LIKERT SCALES

8.2. PHYSIOLOGICAL DISCUSSION.

8.2.1. AEROBIC POWER AND SUBMAXIMAL RELATIVE INTENSITY.

The mean VO_2 max of 56.5 $\pm$ 5.8 $ml.kg^{-1}.min^{-1}$reflects the high aerobic fitness level of this group of recreationally active males. The projected steady state relative intensity was 70% VO_2 max and the measured mean %VO_2 max of 70.8% is very close to this targeted value of 70% VO_2 max. The fact that there was no significant difference between the minute 6 and minute 8 values on R1, R2 and placebo for VO_2, VCO_2 and VE indicates that a steady state was achieved in these treatments.

8.2.2. EFFECT OF PROPRANOLOL.

No blood analysis was undertaken to verify that the subjects had taken the propranolol tablets. However, on the active treatment day all subjects showed a marked decrease in exercise heart rates. The magnitude of decrease during the eighth minute of exercise was 42 $beats.min^{-1}$ on propranolol compared with placebo (155 to 113 $beats.min^{-1}$ i.e. 27%). This decrease is similar to other studies which have used the same dosage of propranolol. For example, the normal subjects of Wilmore et al; (1985) showed a decrease in heart rate from 158 to 116 $beats.min^{-1}$ and those of Anderson et al; (1985) from 154 to 116 $beats.min^{-1}$ during submaximal steady state exercise. Tesch (1985) in his review indicated that heart rates at 50-70% VO_2 max are normally reduced by 18-28% after short term administration of propranolol. There was a significant decrease in heart rate at each minute during the 8 minutes of exercise. The increase in heart rate associated with the onset of exercise is blunted after beta blockade as is the normal augmentation of myocardial contractility (Epstein et al; (1965). Most studies have shown that cardiac output is decreased by about 10% during submaximal exercise, with an increased stroke volume. Joyner et al; (1986) reported that an increase in stroke volume maintained

cardiac output at >94% of unblocked values at 60% VO_2 max. The decrease in cardiac output of around 5-15% during beta blockade is counteracted by an increase in oxygen extraction from the blood (Van Baack, 1988).

Propranolol will influence peripheral circulation as it potentiates the normal rise in catecholamines during exercise (Galbo et al; (1976) and blocks beta receptors which are involved in vasodilation in forearm blood vessels (Brick et al; (1966). At the start of exercise muscle perfusion will probably be decreased as cardiac output is lower. Consequently O_2 delivery will be decreased and the contribution of anaerobic metabolism will be increased and the rate of CO_2 and lactate removal from exercising muscle will be decreased. As anaerobic metabolism metabolites increase, it is probable that they will over-ride any local beta blockade resulting in vasodilation and an increase in the removal of metabolites will result, leading to an increase in CO_2 flux to the lungs.

It is concluded that all subjects took propranolol and this resulted in a variety of physiological changes compared with placebo.

8.2.3. VO_2 $VCO_2$and VE.

The lower VO_2 values for timepoints 1-7 minutes, the lower VCO_2 values early in exercise, the higher values later in exercise and an increase in VE between 3-8 minutes are consistent with the findings of Twentyman et al; (1981) whose normal subjects worked at 70% Vo_2max one hour after taking 80 mg of propranolol.

8.2.4. VO_2 and RER.

The decrease in VO_2 in this study for most of the exercise period is consistent with some but not all of the literature. In heavy submaximal exercise (over 60% VO_2 max) VO_2 is reduced or the same (Van Baack, 1988). Other researchers have shown that oxygen kinetics are delayed in steady state exercise as a consequence of beta blockade (Hughson et al; 1978, Twentyman et al; 1981). Wilcox et al; (1984) concluded that the administration of propranolol lengthens the time constant relating to the increase in VO_2

but has no effect on the eventual steady state value. Van Herwaarden et al; (1979) found no fall in VO_2. This finding was probably due to the low relative intensity selected.

In some instances as in this study a decreased VO_2 has been accompanied by an increased RER suggesting a shift towards a greater fractional use of carbohydrate. Joyner et al; (1987) found an increase in RER at 75% VO_2 max with trained subjects but not with untrained. McLeod et al; (1985) found no difference in RER at 20% VO_2 max after 40 mg of propranolol but reported a significant increase at the 10th minute of steady state at 60% VO_2max.

The increased RER in this study is suggestive of an increase in glycolysis and decreased lipolysis. Assuming a greater reliance and usage of glycolytic precursors as fuel, a small decrease in VO_2 could be expected as carbohydrate utilisation gives approximately 10% higher energy yield per litter of O_2compared with fat.

8.2.5. VCO_2

There has been a varied response in VCO_2 after beta blockade and some "beta blocker" studies have failed to report VCO_2 values. Van Herwaarden et al; (1979) and Petersen et al; (1983) found that VCO_2 was unaffected with propranolol administration. In both these studies the subjects worked at fairly low relative intensities. Butland et al; (1982) found a decrease in VCO_2 after infusion of propranolol which they attributed either to a decrease in metabolic rate or directly by an effect on chemoreceptors. The differences for VCO_2 following beta blockade can be explained by changes in cardiac output and muscle blood flow. The decreased VCO_2 in the early stages can be explained by a lower cardiac output (Winsborough et al; 1980) and a resultant increase in mixed venous PCO_2 and CO_2 stores. Until a new equilibrium was reached this would lower VCO_2 after propranolol. At a later stage in exercise, VCO_2 would reflect CO_2 production in the tissues.

8.2.6. VE.

VE was increased from 3-8 minutes compared with placebo. The increase in VE during high intensity steady state exercise during the later stages of the exercise bout agrees with Twentyman et al; (1981) and Pearson et al; (1987). Wilcox et al; (1984) found no change in VE with propranolol but at low relative intensities while Tesch and Kaiser, (1983) reported a non significant increase in VE at 64-69% of VO_2 max. Pearson et al; (1987) showed that VE was increased compared to placebo with atenolol at "higher" intensity steady state exercise. Propranolol showed the same trend but did not reach statistical significance. Some studies have shown a decrease in VE with propranolol. Pearson et al; (1987) found that VE was depressed at "lower" steady state intensities on atenolol compared with placebo. The lack of consensus may be explained by the varying intensities and dosage of the different studies.

An increase in plasma potassium during exercise after beta blockade due to reduced reuptake in inactive tissues has been found (Van Baak, 1988). This could result in an increased ventilatory drive via the peripheral chemoreceptors (Busse et al; 1990). Changes compared with placebo might be due to an effect on respiratory control mechanisms, cardiovascular function or metabolism. Twentyman et al; (1981) concluded that the above effects on VO_2 and VCO_2 and the increase in VE at the end of the 70% steady state cannot be explained by depression of central or peripheral ventilatory control by propranolol or changes in lung mechanics. Twentyman et al; (1981) suggested that the increase in VE in the latter stages of the 70% VO_2 max steady state was the VE responding to increased levels of lactic acid. Airway resistance and lung mechanics are not usually influenced to any great extent by propranolol at rest or during exercise in normals and cannot explain the increase in VE (Warren et al; 1984).

8.2.7. FREQUENCY OF BREATHING/TIDAL VOLUME.

On the "active" treatment, the frequency of breathing was significantly increased from minute 2 onwards but there were only 2 timepoints when tidal volume was lowered by beta blockade. Joyner et al; (1987) reported a small decrease in tidal volume after non

selective blockade which was compensated by an increased frequency of breathing. Pearson et al; (1987) reported that tidal volume was increased with atenolol but not with propranolol.

8.2.8. VE/VO_2 AND VE/VCO_2

The increase in these ratios are a reflection of an increase in VE and/or a decrease in VO_2/VCO_2 at various timepoints.

8.2.9 VISIT EFFECT.

At minute 8, VE, frequency of breathing and VE/VCO_2 showed a visit effect. These visit effects were very small. There were no other significant visit effects for any of the other physiological variables. Armstrong and Costill, (1985) found significant day to day differences for VO_2 and VE on a treadmill in some but not all of a wide range of submaximal intensities. They found a systematic decrease in VE at low intensities and a decrease in VO_2 over range of intensities. These authors stressed that little work has been done in this area.

8.2.10. SUMMARY.

There were small but significant visit effects for only VE, frequency of breathing and VE/VCO_2. Therefore, it is suggested that subjects had very similar physiological responses to the exercise tests throughout the "non beta blocker" tests. The active treatment had a lowering effect on heart rate and increased several respiratory variables including VE, frequency of breathing, RER, VCO_2, VE/VO_2, VE/VCO_2 at some or all timepoints. At some timepoints, VO_2 and VCO_2 were reduced. These findings suggest that these differences could result in a change in perception of breathlessness and general fatigue.

CHAPTER 8
SECTION THREE.

8.3. THE RELATIONSHIP BETWEEN THE PERCEPTION OF SYMPTOMS AND PHYSIOLOGICAL VARIABLES.

8.3.1. BREATHLESSNESS.

All the scales showed high overall group correlations with VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, tidal volume and RER. However, it must be stressed that a high correlation does not necessarily imply a causal relationship.

Other studies have shown a very strong relationship between VE and the perception of breathlessness assessed by VAS and Borg CR10 scales (Muza et al; 1990) Wilson and Jones, 1989). However, it has been suggested that breathlessness is not merely a sensing of VE. O'Neil et al; (1986) have shown that the perception of breathlessness increased despite no change in the level of VE. In this study VE remained stable between 6 and 8 minutes in the R1, R2 and placebo "treatments" but rose by 4 litres.min^{-1} in the active treatment. Despite the stability of all respiratory variables on R1, R2 and placebo, the perception of breathlessness increased as measured by the VAS and Borg CR10 scales.

Chronos et al; (1988) investigated the subjective changes accompanying alterations in inspired oxygen concentration in normal subjects. During and after inspiration of 15% oxygen, changes in the VAS score occurred relatively more quickly than VE. The authors suggested that hypoxia per se could be a contributory factor to the genesis of breathlessness. The authors speculated that there was a neural basis for the dissociation between breathlessness and VE observed in studies in which hypoxia was induced. They hypothesised that increases in neural traffic from the stimulated carotid body may be directly perceived as breathlessness whereas the ventilatory responses take longer to develop because of the time constant of the integrating mechanisms within the medullary respiratory centres. Using normal subjects Lane et al; (1987) concluded that it was not the

level of VE per se which related to the level of breathlessness but it was the reflexly driven VE which was responsible for the perception of breathlessness. Thus, the relationship of breathlessness to VE is not fixed but depends on the methods used to induce the sensation.

Despite a good correlation between VE and the subjective scales, there was a large inter subject variation in the range of the scales used in relation to VE. The wide ranging use of the scales has also been found by previous workers (Wilson and Jones, 1989, Stark et al; 1981). Therefore, comparison between subjects is hazardous because of the individual use of scales. There are a number of possible reasons for the inter-subject variation. The subjects may use the scales in a different way. Interpretation of the instructions and varying sensitivities of the sensory inputs provoking a sensation of breathlesness are two possible explanations. The subjects may be influenced by the experimenter and could perhaps score lower than what is perceived.

The correlations between breathlessness (VAS) and frequency of breathing was 0.85 and 0.89 for the correlation between tidal volume and the Likert scale (the highest correlations for frequency of breathing and tidal volume). Chronos et al; (1988) compared ventilatory responses with the sensation of breathlessness using a VAS. They concluded that changes in the perception of breathlessness did not correspond with changes in frequency of breathing or tidal volume. Using a least squares correlation analysis and rank correlation analysis the authors were unable to demonstrate any statistically significant relationship between the individual's VAS scores and the level of any of the physiological variables measured.

8.3.2. GENERAL FATIGUE.

All 3 scales showed very high correlations between VE, VO_2, VCO_2, heart rate, and RER and general fatigue. In their review of RPE scales, Carton and Rhodes, (1985) stated that it is VE and frequency of breathing which have the greatest impact on the perception of

effort. In this study the correlations for VE and the frequency of breathing and the 3 scales was around 0.92 and 0.80 respectively. The fact that there was no significant difference in VE and frequency of breathing between 6 and 8 minutes in R1, R2 and placebo and the perception of general fatigue was higher at 8 minutes compared with 6 minutes, suggests that the perception of general fatigue is not merely a sensing of VE and frequency of breathing. Noble et al; (1973) reported that VE and frequency of breathing were the best predictors of RPE in a hot or "normal" environment. Edwards et al; (1972) indicated that VE has afferent nervous system input which can be consciously monitored unlike VO_2. In their review, Watt and Grover, (1993) concluded that RPE "involved a weighted average of dominant local signals and perceptibly less intense central signals." They suggested that central factors serve as amplifiers to local factors relative to aerobic demand. This implies that central factors dominate at high intensities.

All the subjective scales were highly correlated with heart rate. Several studies have reported that heart rate and RPE are highly correlated (Borg, 1962; Edwards et al; 1972) but Carton and Rhodes, (1985) stressed that at no point has it been implied that these variables are causally related. Furthermore, it has been shown that the relationship between heart rate and RPE can be disturbed. For example, it has been demonstrated that heart rate can be lowered using beta blockade without affecting RPE at a given relative percentage of VO_2max (Davies and Sargeant, 1979)

8.3.3. SUMMARY.

The Borg CR10 scale was used over a narrower range than the VAS. Thus it may have been expected that the VAS would have shown a better correlation with physiological variables such as VE.

All the scales had high correlations with VE, VO_2, VCO_2, frequency of breathing, heart rate, VE/VO_2, tidal volume and RER for breathlessness and general fatigue. Several physiological variables, VE, VO_2, VCO_2, frequency of breathing, and heart rate) were stable between 6 and 8 minutes. Despite this stability the scores for the subjective scales

increased. These findings suggest that there is not a direct association between the perception of symptoms and physiological variables.

CHAPTER 8
SECTION FOUR.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

8.4.1. SUBJECTIVE SCALES.

In this study the VAS tended to be more reproducible than the Borg CR10 for breathlessness and general fatigue. However, 95% confidence intervals showed no significant difference between the scales. Reproducibility coefficients were highest with the VAS scale measuring general fatigue. There have been no other studies on the reproducibility of subjective scales in CHF.

8.4.2. MEASUREMENT OF BREATHLESSNESS.

In the CHF pilot study, it was found that the higher the relative intensity, the higher the reproducibility coefficient. In the CHF main study the mean % of peak VO_2 was 89% and the mean % peak VO_2 on the third stage in the CHF pilot study was 83%. While the VAS tended to be more reproducible than the Borg CR10 in the CHF main study, there was hardly any difference between the scales in the CHF pilot study. In the comparison of the VAS, Borg CR10 and Likert scales the VAS was clearly more reproducible than the Borg CR10 scale. In the above study using normal subjects, the reproducibility coefficient for the VAS was 78% for breathlessness at the third timepoint. For this CHF study, reproducibility was highest (83%) at 5 minutes for breathlessness and fell to 66% at 10 minutes. Compared with 5 minutes, reproducibility was also much lower at 7.5 minutes (68%). Thus the reduced number of subjects at 10 minutes cannot be the only explanation for the change over time.

8.4.3. MEASUREMENT OF GENERAL FATIGUE.

In the CHF pilot study and main study, the VAS tended to be was more reproducible than the Borg CR10 scale. Similarly the VAS scale tended to be higher than the Borg CR10 in the VAS Borg CR10 and Likert comparison. In this CHF study, the reproducibility

coefficients for VAS were very constant throughout the first 10 minutes whereas the reproducibility coefficients for the Borg CR10 scale showed a large fluctuation in values.

8.4.4. BREATHLESSNESS/GENERAL FATIGUE.

In the CHF main study it is unknown why the reproducibility coefficients for general fatigue were higher than breathlessness. Reproducibility coefficients for breathlessness and general fatigue for the VAS were favourable and compare well with the results from the VAS, Borg CR10 and Likert scales comparison using normal subjects.

8.4.5. VISIT EFFECT.

Analysis showed that there was no visit effect over the four tests for the VAS and the Borg CR10 scales. In this CHF study the subjects were given 2 maximal incremental tests but only one maximal test was given in the comparison of the VAS, Borg CR10 and Likert scales. With only one maximal test, this "normals" study showed a significant visit effect in both VAS scales and for Likert (breathlessness) in the subsequent submaximal tests. There were no significant differences between the incremental test 1 and test 2 values for any subjective scale in the CHF study. Thus, experience gained in Test 1 does not appear to influence the perception of breathlessness and general fatigue in Test 2. Some subjects reported that they felt the start of the test to be somewhat daunting as they had to "jump on" the treadmill at the selected speed and gradient. At all times a relaxed friendly atmosphere was promoted and this factor may have contributed to a lessening of apprehension and a "non visit" effect. In addition, there was no visit effect on any physiological variable. The fact that there was no learning effect suggests that the use of the VAS offers a stable baseline from which assessment of changes in patient status may be assessed.

8.4.6. ANCHOR POINTS.

It is unknown if the use of the scales at the end of the two progressive maximal tests helped the subjects to relate the intensity of their symptoms to other situations. This procedure did not exclude the possibility of the subjects referring to their previous

experience of these symptoms as they were asked to, "refer to their common experience of", for the appropriate symptom. The subjects considered that the use of the scales at the end of the two progressive maximal tests was a useful reference point for the subsequent submaximal tests.

8.4.7. UNDERSTANDING OF TERMINOLOGY.

Before each constant workrate test subjects confirmed that they understood the instructions and they indicated that they could differentiate between breathlessness and general fatigue. Two subjects were excluded from the study as they could not grasp the use of the scales. For some subjects, considerable time was taken to give advice on the use of the lever and button on the treadmill and to clarify the problems relating to the use of the scales. These problems were also highlighted by Stark, (1988) when he referred to a patient group.

8.4.8. RANGE OF SCALES.

At the end of the maximal incremental tests, there was a wide range of values for the perception of breathlessness and general fatigue using both scales. Somewhat surprisingly a score of two was given for breathlessness and general fatigue on the Borg CR10 scale. Similarly, on the VAS scale it was not anticipated that subjects would rate breathlessness and general fatigue under 30 at the end of a maximal test. Sylven et al; (1991) concluded that CHD patients interrupt exercise tests at lower ratings of leg exertion and breathlessness than healthy volunteers in an incremental protocol. The authors speculated that patient apprehensiveness and/or quality of symptom could be the explanation.

During the constant workrate tests the mean scores increased throughout the test but there was a very wide range of values at each timepoint for both scales for breathlessness and general fatigue. These wide ranges illustrate the individual use of the scales. For example, taking into account the 4 tests, at 2.5 minutes, the range for the VAS (breathlessness) was 5-79 and 4-81 for the VAS (general fatigue). At 2.5 minutes the range for the Borg CR10 scale was between 0.5 and 4 for breathlessness and 0 to 5 for

general fatigue. At 7.5 minutes, and encompassing all 4 tests, the range of values for VAS breathlessness and general fatigue was 17-88 and 25-62 respectively. For the Borg CR10 scale at 7.5 minutes, the range of values for breathlessness and general fatigue was 1-8 and 1-7 respectively. These ranges highlight the fact that CHF patients perceive symptoms quite differently despite exercising at similar intensities. While the Borg CR10 scale has been shown to be used over a limited range in other studies (Wilson and Jones, 1989) and Grant et al; (1992), a number of the CHF patients in this study used the upper part of the scale. While this study and the studies of Wilson and Jones and Grant asked the subjects to exercise submaximally, the relative intensity of the CHF patients was much higher than that of the other two studies. As the CHF patients were working near maximum, it is not surprising that the verbal anchors did not impose a limitation on the CHF patients.

8.4.9. SUMMARY.

Overall the VAS tended to be more reproducible than the Borg CR10 scale for breathlessness and general fatigue. There was no visit effect for any of the scales. There was a wide range of values for the perception of breathlessness and general fatigue, using both scales for the submaximal and maximal tests.

CHAPTER 8
SECTION FIVE.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

8.5. PHYSIOLOGICAL VARIABLES.

8.5.1. PEAK VALUES.

The peak VO_2 values of 20.6 $ml.kg^{-1}.min^{-1}$ are similar to other studies which have tested CHF patients in NYHA classification 1 and 2. (Lipkin et al; 1986b) and Cohen-Solal et al; (1991) reported scores of 19.7 and 20.5 $ml.kg.^{-1}.min^{-1}$ respectively. There was no significant increase in Peak VO_2 between Test 1 and Test 2. These findings are not in agreement with Elborn et al; (1990) who concluded that at least two tests are needed to establish representative maximum baseline measures for CHF patients. Two incremental tests were given in an attempt to find a "representative" maximum. In 8 out 10 subjects the first test produced the higher score. This finding indicates that the subjects were unlikely to produce a much longer time or a higher peak VO_2 in a third incremental test. It may be that the thorough treadmill familiarisation carried out before the maximal tests in this study produced this finding.

8.5.2. RANGE OF RELATIVE INTENSITIES - CONSTANT WORKRATE TESTS.

The mean VO_2 relative intensity of 89% was the overall value calculated for all tests. The relative intensities for VO_2 ranged from 80 to 99% of Peak VO_2. Thus, most subjects were working very close to their maximum as determined by the incremental test. The relative intensities in this study are high in comparison with the values (68% and 79%) of Sullivan et al; (1988) but similar to that of Kiilavouri et al; (1993) of 85%. The endurance times in this study are also close to that of Kiilavouri et al; (1993) but much shorter than that of Sullivan et al; (1988) whose subjects worked for 24 minutes at 79% peak VO_2. The mean relative peak VO_2 of 89% and the fairly wide standard deviation is worthy of

discussion. Subject 2 had relative intensities of 99, 100, 96 and 98% of the higher Peak VO_2 score for constant workrate tests 1,2, 3 and 4 respectively. For the same tests the relative heart rates were 97, 97, 98 and 99% of maximum and the relative VE was 88, 93, 81 and 88% of peak. These values highlight the fact that subject 2 attained values in the constant workrate test which were very close to the peak scores. Other subjects worked close to their peak values obtained in the maximal incremental test or even above them. No clear pattern emerges when a comparison of the peak and constant workrate values is made. Subject 8 had heart rates in the constant workrate test at or above 100% of the peak values and VO_2 was 91%, while the VE was on average 112% of the peak values. Subject 1 had a mean relative VO_2 of 81%, 82% for VE and 94% for heart rate.

The fact that some subjects had values on the constant workrate tests at or above 100% of the peak values in the incremental test suggests that some subjects did not produce a "maximal" effort on the incremental test. This range substantiates the hypothesis that the "quality" of maximum test varied. Thus, it would be expected that the submaximal workrate (given as a % of Peak $V0_2$) would depend on the degree to which the subject approached his "true" maximum in the incremental test. Evidence supporting this hypothesis is the low maximum RER values of some subjects on the incremental test. The mean RER values of the two incremental tests were 1.02 and 0.97 (range 0.85-1.18 and 0.8-1.2). These maximal values are similar to Riley et al; (1990) who reported a mean of 0.97 in CHF patients. The mean constant workrate RER at the end of the tests was 0.97. It may be that some subjects felt the constant workrate test to be less threatening than the incremental test which had a one minute increase in workrate whereas the subject was aware that there would be no increase in workrate during the constant workrate test. Comparison of the heart rates in the two different types of tests showed that the mean values were very similar.

It is probable that some subjects did not produce a "true" maximum in the incremental tests. This speculation is supported by the literature which suggests that it is difficult to attain a "true" maximum with CHF patients (Poole-Wilson, 1989a).

These findings suggest that CHF patients can sustain a workrate very close to maximum (as described by an incremental test) for between 8-17 minutes. However, the question remains - is the maximum attained in a incremental test representative of a "true" maximum?

8.5.3. TEST TIME FOR THE SUBMAXIMAL TEST.

One of the aims of this study was to establish a method of predicting a treadmill endurance time between 8-17 minutes. In out of 40 tests this aim was achieved on 34 occasions (85%). Three tests were over 17 minutes and three tests were under 8 minutes. The three tests under 8 minutes were between 6 and 8 minutes and the three tests above 17 minutes were between 18 and 22 minutes. Thus, this method appears to have application in a clinical setting.

The method of selecting the constant workrate for each subject is not based on any scientific formula. This method was developed on a trial and error basis with a number of patients. Prior to the CHF pilot study the attempted use of a ventilatory threshold or an arbritary relative intensity gave wide-ranging results. It may well be that there is no method based on a scientific formula which will allow an appropriate timescale to be selected.

The endurance time had a 76% reproducibility coefficient. This figure excludes the first test of subject 6 who stopped after 6 minutes but in the next 3 tests walked for between 17 and 21 minutes. If this subject is included, the reproducibility coefficient plummets to 51%. The GLM showed that there was no significant learning effect over the four tests.

These stable endurance times may provide a baseline which can be of value in evaluating the impact of a drug intervention.

Selection of the work rate using 80% of the predicted energy cost has sound clinical application. Incremental tests on CHF patients are regularly carried out without gas collection. Therefore it is important to establish a method of prescribing a treadmill speed and gradient using non ventilatory parameters. Originally, selection of a work rate was made by selecting a work rate 2 stages below the final stage. It was found that this method had limitations as some subjects achieved only a few seconds into a stage while others nearly completed a stage. The use of the diagrammatic aid allows the attainment of part of a stage to be considered when work rate selection is made.

Previous studies have attempted to use sub-maximal tests in CHF to a symptom limited endpoint. A wide range of workrate selection methods and endurance times have been reported. Koch and Broustet, (1993) assessed CHF patients by asking them to exercise at two stages below the maximum achieved in a 10 watt incremental cycle test. Mean endurance times were around 10 minutes but the authors reported a a very large standard deviation of 13. Cowley et al; (1986) used stage four of the Modified Bruce protocol to determine exercise tolerance in CHF patients. They reported that mean endurance times were 6 minutes. Sullivan et al; (1988) selected a workrate 25 watts below the maximum workrate achieved in a maximum test to assess the effects of a training programme in CHF patients. Test 1 endurance times were 16 minutes and rose to 24 minutes after training. The constant workrate represented 79% peak $V0_2$ before training and 68 % peak $V0_2$ after training. Kiilavuori et al; (1993) used a submaximal endurance test at 85% of peak VO_2 to evaluate a 6 month training programme. At week 0 the mean endurance times were 15 minutes rising to nearly 30 minutes at 3 months and 6 months. Interestingly, peak VO_2 values did not show any improvement throughout the training programme.

8.5.4. EVERYDAY ACTIVITY.

Subjects were asked if the constant workrate selected related to everyday activities. All subjects were able to cope with the selected workrate but some expressed surprise at the initial "fast" speed. Several reported that the workrate selected resembled some occasions when they were "in a hurry". Others indicated that they would not walk at the specified speed and gradient in everyday life for more than a short period of time as they realised that they could not sustain this pace for very long. Thus, it appears that the selected workrate for these CHF patients has some relevance to every day life. A common complaint was a dislike of the mouthpiece. As it is possible to carry out the above procedures without gas analysis, it would be worthwhile to evaluate the subjective scales without gas analysis.

8.5.5. CONCLUSIONS.

The method of selecting the workrate for the submaximal test (to elicit an endurance time of between 8-17 minutes is appropriate for most patients.

The intensities elicited by the test reflected some aspects of everyday life. The CHF patients found the test procedures to be acceptable. The use of the above exercise protocol with the VAS scale can offer a useful means of evaluating symptoms in CHF.

8.5.6. FURTHER RESEARCH.

As many CHF clinical tests are carried out without gas collection, it is suggested that this study is replicated without gas collection.

The test protocol should be evaluated using larger numbers.

An examination of the sensitivity to change in CHF patients would be of value. A method has yet to be established to improve the status of the patients to assess the sensitivity of subjective scales and endurance time to any intervention. As many variables are involved, the selection of an "appropriate" intervention is likely to prove to be a problem.

CHAPTER 8
SECTION SIX.

SYMPTOMATIC AND PHYSIOLOGICAL RESPONSES TO SUBMAXIMAL EXERCISE IN CHRONIC HEART FAILURE.

8.6. THE RELATIONSHIP OF SYMPTOMS AND PHYSIOLOGICAL VARIABLES.

8.6.1. BREATHLESSNESS AND GENERAL FATIGUE.

Both scales showed a good relationship with heart rate where correlations were around 0.84 with the VAS (breathlessness and general fatigue) and 0.80 for the Borg CR10 (breathlessness and general fatigue). It has been shown that abrupt increases in right ventricular strain resulted in immediate and proportional increases in VE (Jones et al; 1982). Wasserman and Cassaburi, (1988) have suggested that it would be expected that CHF patients would have right ventricular pressure elevation which would provide an increased stimulus to breathe and a feeling of breathlessness. The immediate increase in VE following the artificially induced, abrupt increase in blood flow through the heart, is suggestive of a linkage between the cardiovascular and respiratory systems (Jones et al; 1982). These findings could be a possible explanation for the high correlations between heart rate and the VAS and Borg CR10 (breathlessness) scales.

For VO_2 , there was a good correlation (around 0.79) with VAS (breathlessness and general fatigue) whereas for the Borg CR10 scale the correlations were around 0.67. These findings are not in full agreement with the Grant et al; (1992) study in normals which found that VE, VO_2, VCO_2 and heart rate had correlations over 0.9 with the same subjective scales. In the "normals" study, there was a small increase in work rate 2 minutes into the exercise bout. This feature of the protocol may have had the effect of "pulling out" the relationship between the physiological variables and the subjective scales resulting in higher correlations for the Grant et al; (1992) study.

Several factors may explain the poor relationship between the respiratory variables and the subjective scales in this study with CHF patients. There are probably multifactorial causes of breathlessness and general fatigue in CHF. Thus, it may be simplistic to attempt to establish links between subjective scales and physiological variables which respond to a variety of inputs.

8.6.2. BREATHLESSNESS AND RESPIRATORY VARIABLES.

The cause of breathlessness in CHF is unknown. It has been postulated that the causes of breathlessness in CHF include; a ventilation/perfusion mismatch (Buller and Poole-Wilson, 1989); weakness in the inspiratory and expiratory muscles, reduced blood flow to the respiratory muscles (McParland et al; 1992, Hammond et al; 1990) and respiratory muscle deoxygenation (Mancini et al; 1991). McParland et al; (1992) found a good correlation between inspiratory muscle weakness and breathlessness experienced during daily activities ($r = 0.89$). They suggested that weakness in inspiratory muscles necessitates a greater inspiratory motor output to produce a given increase in dynamic inspiratory muscle pressure and VE. The magnitude of breathlessness experienced is at least partly determined by the perception of the outgoing central motor command to the muscles involved in inspiration (Cockcroft and Guz, 1987).

While CHF patients require a disproportionately large increase in VE during exercise, one recent study indicated that breathlessness is not merely a sensing of VE. Davies et al; (1993) examined the relationship between VE and VAS (breathlessness) during a constant workrate test at 70% peak VO_2 in CHF patients. They concluded that the temporal dissociation between the VAS scores and VE indicated that breathlessness in CHF is not simply an awareness of total ventilation. Thus, it may not be surprising that there was a poor relationship between the respiratory variables and the subjective scales (breathlessness). In this study subjective scale scores increased over nearly all of the timepoints but VE, frequency of breathing, VO_2 and heart rate increased over the first three timepoints. Thus, the comparison of a stable VE with a rise in the subjective scales

as in the Davies et al; (1993) study was not possible in the present study. Therefore, it is difficult to make a meaningful conclusion about any interaction between the subjective scales and physiological variables.

The conclusions of Clark et al; (1993) cast doubt on the value of the VE/VCO_2 ratio as a meaningful measure of impairment and a marker of physiological dead space. They showed that the VE/VCO_2 ratio was a function of the exercise protocol and it was not possible to compare values between studies utilising different exercise protocols. Clark et al; (1993) showed that the increase in VE/VCO_2 ratio was faster with a one minute incremental protocol compared with a three minute incremental protocol. Therefore, the VE/VCO_2 ratio of around 38 in this study may not provide a meaningful comparative figure to the range suggested by Fink et al; (1986) and may not be of value in assessing the extent of "excess" ventilation due to an increased physiological dead space.

8.6.3. BREATHLESSNESS, GENERAL FATIGUE AND PERIPHERAL ABNORMALITIES.

Recent evidence confirms that there are a range of peripheral abnormalities in CHF which may contribute to breathlessness and general fatigue. Abnormalities in peripheral circulation (Magnuson et al; 1993), skeletal muscle structure Volterrani et al (1993), skeletal muscle function (Derman et al; (1993) have been shown to contribute to a decreased work capacity and probably promote a feeling of general fatigue. Wilson et al ; (1984) demonstrated that CHF patients developed fatigue when muscle underperfusion reached a critical level. The decrease in oxidative capacity and increase in anaerobic metabolism may contribute to an increase in VE via bicarbonate buffering of lactate and stimulation of the peripheral chemoreceptors. In addition, the high levels of arterial K^+ in CHF during submaximal exercise may contribute to an increased VE and could play a role in fatigue (Barlow et al, 1994). The wide range of abnormalities found within a "homogeneous" group may result in a variety of factors involved in the promotion of breathlessness and general fatigue with little degree of commonality among the subjects.

The individual use of the scales may be another factor. Some subjects scored low on the subjective scales compared to others despite exercising at similar relative intensities.

The reason why the patients stopped exercising in the submaximal tests is unclear. The patients stated that they stopped exercising because of breathlessness, general fatigue or leg fatigue. Most subjects stopped around the maximum heart rate attained in the incremental test.

8.6.4. SUMMARY.

The highest correlations (around 0.8) were for heart rate on all four scales. It was not possible to relate symptoms to any respiratory markers in any meaningful way using a constant workrate protocol in CHF patients. Correlations were low (except for VO_2) for the respiratory variables and the subjective scales (breathlessness and general fatigue). These results indicate that there is no direct relationship between respiratory variables and the subjective scales.

It is hypothesised that the use of an incremental protocol may result in a high correlation between respiratory variables and subjective scales but whether this would be a causal relationship remains debatable. The fact that sensory input may vary depending on the severity of impairment, may also create further difficulties in establishing a meaningful relationship between the perception of symptoms and physiological variables. The individualistic way of using the subjective scales may also lead to difficulties in establishing a link between the physiological variables and the scales.

CHAPTER 8
SECTION SEVEN.

AN EVALUATION OF THE STEXT PROTOCOL.

8.7.1. SUBJECTIVE SCALES.

8.7.2. MEASUREMENT OF BREATHLESSNESS - REPRODUCIBILITY.

Reproducibility for the VAS and Borg CR10 scales was low at minute 3 (48% and 23% respectively) but by minute 7 had increased to 77% on both scales. Thereafter, reproducibility was consistently high to maximum. The reproducibility coefficients in the mid 70's for the Borg CR10 and low 80'S for the VAS compare favourably with the 78% for the VAS and 50% for the Borg CR10 scale at minute 8 in the comparison of the VAS and Borg CR10 scales during steady state exercise (Grant et al; 1992). However, in this previous study there was a trend for the VAS to be better than the Borg CR10, and at one timepoint the VAS was significantly more reproducible than the Borg CR10 scale. In the STEXT study the reproducibility coefficients were very similar for both scales and the 95% confidence intervals showed a wide overlap. It is difficult to explain why the absolute reproducibility coefficient values (after the first two timepoints) for the Borg CR10 scale were much higher in the STEXT study compared with the "steady state " values (Grant et al; 1992). The subjects in both studies were similar, and the only obvious differences are the number of tests and the markedly different exercise protocols.

8.7.3. MEASUREMENT OF BREATHLESSNESS - SENSITIVITY.

While sensitivity coefficients were significant between 9 and 15 minutes, the ratios were low compared with the VAS Borg CR10 comparison during steady state exercise (Grant et al; 1992). In the "steady state" study sensitivity was 2.7 for the VAS and 2.0 for the Borg CR10. The highest ratios in the STEXT study were 1.25 for the VAS and 1.1 for the Borg CR10. There were no significant differences between the scales for sensitivity unlike the previous comparison in normals (Grant et al; (1992) where the VAS was significantly better than the Borg CR10 scale at two out of the three timepoints.

8.7.4. MEASUREMENT OF GENERAL FATIGUE - REPRODUCIBILITY.

Both scales showed a very similar picture throughout all timepoints. The reproducibility coefficients were high for both scales from 11 minutes onwards. There were no significant differences between the scales which is the same finding reported by Grant et al; (1992) who reported that the VAS scores tended to be higher.

8.7.5. MEASUREMENT OF GENERAL FATIGUE - SENSITIVITY.

There was a significant sensitivity effect from minutes 9 to 15 on both scales. There were no significant differences between the scales. This finding contrasts with the Grant et al; (1992) study which showed that the Borg CR10 scale was significantly more sensitive than the VAS at 6 minutes but at 8 minutes there was no significant difference despite a trend in that direction. The sensitivity ratios were lower in the STEXT study (1.6 for VAS and 1.7 for Borg CR10) compared with the "steady state" study of Grant et al; (1992) which produced ratios of 2.4 and 3.0 for VAS and Borg CR10 scales respectively.

8.7.6. VAS and BORG CR10 SCALES.

Both scales for all but the first two timepoints showed good reproducibility. There were no differences between the scales for reproducibility or sensitivity. These results indicate that there was no meaningful difference between the scales using the STEXT protocol in normals. The STEXT protocol starts at a very low energy cost with small energy cost increments in the first few stages. It may be that this protocol enables subjects to estimate breathlessness and general fatigue in a reproducible manner after the first few minutes as the gradual progression in work rate enables subjects to estimate breathlessness and general fatigue throughout "a full range".

For the first three timepoints in all scales apart from the first timepoint in the VAS breathlessness scale there was no significant active treatment effect. This finding is not surprising as the subjects were exercising at very low relative intensities in the early stages.

8.7.7. RANGE OF SCALES.

As might be expected with a test which begins at an energy cost of 8.0 $ml.kg^{-1}.min^{-1}$ to a maximum of around 56.5$ml.kg^{-1}.min^{-1}$ (for most subjects) the subjective scales were used in most instances over a full range. In the submaximal test of Grant et al; (1992) it was anticipated that the upper part of the scales would not be used, especially the Borg CR10 scale which has verbal restrictors. In the STEXT study, subject 10 consistently scored low for all four scales. Despite low symptomatic scores he maintained that he had given maximum effort. Subject 8 scored very high on all scales even at low levels of exercise. These examples demonstrate how subjective scales are used in an individualistic manner and highlight the fact that it is not possible to make meaningful inter-subject comparisons.

8.7.8. VISIT EFFECT.

All four scales showed a visit effect i.e. over time the scores for all the scales increased. For all scales test 1 was significantly lower than tests 4-8. There were no significant differences among tests 2-8. This finding demonstrates that during the "run-in" period (i.e. tests 1-2) the subjects reassessed their perception of symptoms over time. The "run-in" period was effective in promoting stability in the subjective scale scores. Interestingly, the direction of the visit effect was opposite to that of the Grant et al; (1992) study. In the STEXT study the scores increased over time whereas scores decreased in the previous study. The therapy effect was much larger than the visit effect for all the scales except the VAS breathlessness which showed a very large increase in scores between test 1 and test 5.

The subjects in this study were regular exercisers and consisted almost totally of university students and staff. Thus, it must be stressed that these results may not be generalisable to other populations. However, the subjects reported that they found the instructions to be clear and could carry out the operation of recording scores easily.

8.7.9. SUMMARY.

Reproducibility was high for the VAS and Borg CR10 for breathlessness and general fatigue. Both scales were sensitive to change through a range of timepoints for breathlessness and general fatigue. It is concluded that there were no meaningful differences between the VAS and Borg CR10 scales for reproducibility and sensitivity in a group of physically active males using the STEXT protocol. The "run-in" period was effective in providing stable values for the intervention part of the study.

8.7.10. FUTURE RESEARCH.

The STEXT protocol may be of value in the evaluation of symptoms in CHD patients. The use of an incremental protocol which encompasses a wide range of work rate energy costs in a reasonably short timescale can be administered to a group of wide ranging fitness and obviates the necessity of determining an individual steady state or using a specific protocol to accommodate the capabilities for each subject.

CHAPTER 8
SECTION EIGHT.

AN EVALUATION OF THE STEXT PROTOCOL.

8.8. PHYSIOLOGICAL VARIABLES.

8.8.1. VO_2 max.

A VO_2 max mean score of 56.5 $ml.kg^{-1}.min^{-1}$ is typical of physically active young to middle aged male subjects. VO_2 max was reduced by propranolol from 56.5 $ml.kg^{-1}.min^{-1}$ to 45.8 $ml.kg^{-1}min^{-1}$ at the third timepoint (tests 5 & 6) and from 57.6 ml.kg $^{-1}$min $^{-1}$ to 46.3 $ml.kg^{-1}.min^{-1}$ at the fourth timepoint (tests 7 & 8). These findings are consistent with a number of studies which have demonstrated a range of reduced VO_2 max scores using either trained or normal subjects. These decreases of 19% and 20% respectively are greater than those studies which have used subjects with a VO_2 max of around 50-63 $ml.kg^{-1}.\ min^{-1}$. Pooled data from these studies (Tesch and Kaiser (1981), Mac Farlane et al; 1983) Hughson et al; (1984) and Joyner et al (1986) show that VO_2 max was decreased on average by 10.3%. In trained subjects with VO_2 max values of 65 $ml.kg^{-1}.min^{-1}$ Anderson et al; (1985) showed a decrease of 13% in VO $_2$ max with the same level of propranolol as this study. In his review Tesch (1985) stated that VO_2 max is typically decreased by 10 to 15% when heart rate is lowered by at least 30%. In their review Allen et al; (1984) reported that acute beta blockade on VO_2 max ranged from a decrease of 11 to 21% and that they found that the magnitude of decrease in heart rate and VO_2 max was dose related i.e. increasing doses had a greater effect but they found a marked variation in drug susceptibility among subjects. Somewhat surprisingly Wilmore et al; (1985) reported no fall in VO_2 max after beta blockade despite a decrease of 47 $beats.min^{-1}$ in maximum heart rate.

Other studies using untrained or low fitness groups have shown no change in VO_2 max after beta blockade (Violante et al; 1984, Reybrouck et al; 1977, Sklar et al; 1982) which

suggests that there has been complete central and/or peripheral compensation for the decrease in maximal heart rate. The decrease in VO_2 max after beta blockade in this study indicates that the subjects cannot fully compensate for the decreased maximal heart rate in order to maintain maximal cardiac output, maximal blood flow and consequently VO_2 max. It has been suggested that the increased loss of potassium from the muscles with beta blockade may affect membrane excitability, reduce muscle contractility and result in increased fatigue (Sjogaard et al; 1985).

The decrease in VO_2 max is linearly related to the magnitude of reduction in maximum heart rate. However, it has been suggested that non-selective beta blockade will reduce VO_2 max to a greater extent. The maximum heart rate in this study was lowered on propranolol by 34.2% and 31.6% at timepoint 3 and timepoint 4 respectively. It is hypothesised that the greater decrease in maximum heart rate found in this study is partly the explanation for the greater magnitude of decrease in VO_2 max found in this study compared with Tesch and Kaiser, 1981, Mac Farlane et al; 1983, Hughson et al; 1984) and Joyner et al; (1986). Tesch, (1985) stated that the increased A-VO_2 difference can partially compensate for a decreased cardiac output during modest beta blockade but in this study it appears that it cannot compensate for a fall in maximum heart rate of 30%.

8.8.2. VE/VCO_2 max.

VCO_2 max was reduced with propranolol compared with placebo in this study, and the study of MacFarlane et al; (1983) who found that the decrease in VCO_2 was in direct proportion to the fall in VO_2. The decreased VE max values with propranolol were probably a reflection of reduced stimuli i.e. a reduced work intensity and VCO_2. Joyner et al; (1987) suggested that the decreased VCO_2 max indicates a fall in maximum CO_2 flow to the lung so that any chemically mediated drive to breathe should be lower at maximum during beta blockade. A decrease in maximum work rate could also lower the contribution of the "central command" to exercise hypernea under beta blockade (Joyner et al; (1987). A lowered VE max could also be as a result of inhibition of the beta 2

mediated dilation of the bronchioles. However, in subjects with a healthy bronchial system, blockade of beta 2 adrenoreceptors does not impair VE during exercise probably because bronchodilation during exercise results mainly from the withdrawal of resting vagal tone (Warren et al; 1984).

8.8.3. FREQUENCY OF BREATHING.

There was a decrease in the frequency of breathing at VO_2 max under beta blockade. This finding contrasts with Joyner et al; (1987) who found no difference in the frequency of breathing. They speculated that the same level of frequency of breathing with and without beta blockade suggested a "compensatory increase".

8.8.4. RELIABILITY AND SENSITIVITY OF VO_2 max.

In the "non beta blocker" tests there were no significant differences in the six tests and the reproducibility coefficient was high. These findings indicate that the VO_2 max tests were reproducible. Davies et al; (1970) investigated the effects of repeated continuous exercise to maximum. Eight maximum tests were given at 2 day intervals. There was a significant increase in VO_2 max in tests 3 and 4 compared with the other tests. There was no change in VE max or maximum heart rate. Taylor et al; (1955) reported a correlation coefficient of 0.95 between 28 duplicate VO_2 max tests.

8.8.5. TREADMILL TIME.

Treadmill time decreased at timepoint 3 from 16.73 minutes to 15.1 minutes (9.7%) and at timepoint 4 from 16.81 minutes to 15.31 minutes (9.0%). It is not possible to compare the magnitude of change in treadmill time with other studies because different exercise protocols have been used. However, using beta blockade, exercise time has been significantly reduced in a number of studies (Tesch and Kaiser, 1983).

8.8.6. CONCLUSION.

VO_2 max was found to be highly reproducible in the "non beta blocker" tests. Beta blockade resulted in a decrease in maximum values for VO_2, VCO_2, VE, heart rate, tidal volume and a reduction in endurance time.

8.8.7. SUBMAXIMAL PHYSIOLOGICAL VARIABLES OF THE STEXT PROTOCOL.

It is the first time that the STEXT protocol has been used to evaluate the effect of beta blockers on normal subjects. Twentyman et al; (1981) caution that it may be inappropriate to compare studies when the type of exercise, work rate and measurement times differ.

8.8.9. EFFECT OF PROPRANOLOL.

8.8.10. HEART RATE.

A clear reduction in heart rate was found throughout the complete range of submaximal heart rates with propranolol compared with the other "treatments". This finding has been reported in other studies of similar design (Petersen et al; 1983, Pearson et al; 1987). The increase in heart rate normally associated with exercise is blunted by beta blockade as is the normal augmentation of myocardial activity. Most studies have shown that cardiac output is decreased by about 10% during submaximal exercise with an increase in stroke volume. The decrease in cardiac output of around 5-15% during beta blockade is counteracted by an increase in oxygen extraction from the blood (Van Baack, 1988). A wider discussion of the effects of propranolol on haemodynamics during submaximal exercise is given in Section 8.2.2.

8.8.11. VE.

The decrease in VE with beta blockade at one timepoint fairly early in exercise is in agreement with Violante et al; (1984) and Pearson et al; (1987) but some studies have reported no effect of beta blockade on VE early in exercise (Pearson et al; 1979, Leitch et al; 1980). It has been shown that beta blocking drugs have a direct effect on the chemical drive to breathing. It is suggested that propranolol can cause a small decrease in the VE response to CO_2 (Patrick et al; 1978). Propranolol has a small but consistent effect in depressing the ventilatory response to CO_2 inhalation. A central action depressing either the medullary chemoreceptors or respiratory centres are the likely explanation for the effects of propranolol on CO_2 response. It is possible that beta blockers depress some

other source of respiratory drive during exercise after beta blockade. Twentyman et al; (1981) postulated that the reduction in VE which they found in the early part of exercise was a result of delayed cardiovascular responses following beta blocker drugs. The low energy cost starting level of the STEXT protocol and small energy cost increments early in the protocol may explain why propranolol had little impact on VE in the early stages of exercise. While rates of cardiovascular adjustment could be an important influence on VE, it should be noted that VO_2 was depressed over the whole protocol with VE only decreased at minute 8.

On beta blockade Twentyman et al; (1981) and Pearson et al; (1987) reported an increase in VE at the highest levels of exercise as in this study where VE was significantly higher at minute 14 and 15 compared with the other "treatments". The increase in VE at minutes 14 and 15 could be as a result of greater anaerobiosis and metabolic acidosis and/or an increased tendency to pulmonary venous congestion with beta blocker drugs (Younes and Burke, 1985). It is to be anticipated that the greater magnitude of work rate increments in the later stages of the STEXT protocol would result in an increase in anaerobic metabolism.

8.8.12. VO_2 and RER.

VO_2 was significantly lower throughout the exercise protocol on propranolol compared with the other treatments. From minutes 10 to 15 the RER was significantly increased on propranolol compared with the other "treatments". Pearson et al; (1979) reported that 80 mg of propranolol decreased VO_2 by 3.5% over the whole range of their incremental test. Twentyman et al; (1981) reported a small but intermittent reduction in VO_2 after beta blockade during an incremental test while Petersen et al; (1983) found no significant change in VO_2 after beta blockade during incremental exercise. The above examples confirm the statement of Tesch (1985) that the studies of VO_2 during submaximal exercise with beta blockade have produced inconsistent results. Pearson et al; (1979) hypothesised that the decrease in VO_2 was a consequence of a decreased blood flow as a

result of a decreased cardiac output leading to a greater energy production from anaerobic metabolism. It may be however, that changes in cardiac output may not be directly related to proportional changes in skeletal muscle blood flow as compensatory changes in regional circulation may also have a role to play. Twentyman et al; (1981) postulated that propranolol may have a direct effect on peripheral circulation because it potentiates the normal increase in circulating catecholamines during exercise and blocks beta receptors involved in vasodilation.

The increased RER from 10-15 minutes in this study is suggestive of an increase in glycolysis and decreased lypolysis. Assuming a greater reliance and usage of glycolytic precursors as fuel a small decrease in VO_2 would be expected as carbohydrate utilisation gives approximately 10% higher energy yield per litre of O_2 compared with fat.

8.8.13. $VC0_2$

With propranolol, VCO_2 was increased at minutes 8 and 15. The increase in VCO_2 at minute 15 is probably as a consequence of greater anaerobic metabolism, buffering of lactic acid and subsequently greater CO_2 production. The increase in VCO_2 at minute 8 was unexpected and cannot be easily explained.

8.8.14. FREQUENCY OF BREATHING/TIDAL VOLUME.

Frequency of breathing and tidal volume increased significantly at minutes 14 and 15 on beta blockade compared with the other "treatments". These increases were in tandem with a greater VE. Pearson et al; (1987) and McLoed et al; (1985) reported that atenolol produced larger tidal volumes but no change in tidal volume after propranolol. It is unlikely that propranolol will influence airway resistance in healthy subjects (Warren et al; 1984). Joyner et al; (1987) showed a small decrease in tidal volume resulting in a compensatory increase in frequency of breathing after propranolol. They suggested that the contribution of airway beta receptors (particularly type 2) which promote airway dilation is decreased during beta blockade.

8.8.15. VE/VO_2

The VE/VO_2 ratio was significantly higher from minutes 10 to 15 on propranolol compared with the other "treatments". Petersen et al; (1983) also reported an increase in VE/VO_2 on beta blockade on an incremental protocol compared with placebo.

8.8.16. VE/VCO_2

The VE/VCO_2 ratio was unaffected on beta blockade up to minute 11. From minutes 12-15 there was an increase with no change at minute 16 or maximum. Petersen et al; (1983) showed that the VE/VCO_2 relationship was unaffected by propranolol. They reported that the stability of the end tidal CO_2 suggests that the fall in tidal volume did not have sufficient impact on the dead space/tidal volume ratio to cause a significant reduction in alveolar ventilation and change CO_2 tension.

8.8.17. VISIT EFFECT.

There were no significant visit effects for any of the physiological variables. These findings indicate that the "run-in" period would appear to be unnecessary to attain stable values in the physiological variables before any intervention. The therapy effect was significant for all variables.

8.8.18. SUMMARY.

VO_2 and heart rate were significantly lower at all timepoints on beta blockade compared with other treatments. On beta blockade several physiological variables (VE, frequency of breathing and tidal volume) showed increases at minutes 14 and 15. There were also increases in VCO_2 , tidal volume, RER, VE/VO_2 , and VE/VCO_2 at some timepoints.

CHAPTER 8
SECTION NINE.

AN EVALUATION OF THE STEXT PROTOCOL.

8.9. RELATIONSHIP BETWEEN THE PERCEPTION OF SYMPTOMS AND PHYSIOLOGICAL VARIABLES.

8.9.1. BREATHLESSNESS.

The overall group correlations for VE and VCO_2 were all over 0.8 for both the VAS and Borg CR10 scales. Apart from VE/VO_2 and VE/VCO_2 all other correlations were over 0.7. The range of the pooled individual correlations was wide with minimum and maximum correlation values between -0.76 to 0.99. The individual visit correlation range was -0.87 to 1.0 There were no meaningful differences between the scales and any physiological variable. Other studies have reported high correlations between subjective scales and VE using incremental protocols. Wilson and Jones, (1991a) reported median correlations between VE and Borg CR10 scale (breathlessness) of 0.85 (range 0.7 to 0.95). In 1989, the same authors found mean correlations for VE/VAS (breathlessness) of 0.68 and 0.75 for VE/Borg CR10 scales. Muza et al; (1990) reported a correlation of 0.85 between VE and VAS (breathlessness).

8.9.2. GENERL FATIGUE.

As for breathlessness, both scales for general fatigue showed high overall group correlations of over 0.8 for VE and VCO_2. The range of pooled individual correlations was wide, ranging from -0.76 to 0.99 and the individual subject visit correlations from -0.88 to 1.0.

In other studies, correlations between VE and RPE have shown a wide range (0.54-0.92) (Carton and Rhodes, 1985). Edwards et al., (1972) reported high correlations between RPE and several physiological variables in both continuous and intermittent exercise.

Correlations between RPE and VO_2, heart rate and VE were around 0.9 but the correlation between RPE and frequency of breathing was only 0.67.

The authors suggested it may be possible to predict physiological variables in field experiments on previously "calibrated" subjects.

8.9.3. BREATHLESSNESS AND GENERAL FATIGUE.

Overall group correlations for the subjective scales and the physiological variables were not so high on the STEXT protocol compared with the "steady state" study. These lower correlations may be explained by the different exercise protocols. It may have been expected that the progressive nature of the increase in energy cost would result in a high correlation between the subjective scales and the physiological variables. It was anticipated that subjects would score 0 for breathlessness and general fatigue at 7.5 $ml.kg^{-1}.min^{-1}$ (the energy cost of minute one on the STEXT protocol) with a mean aerobic power of 57 $ml.kg^{-1}.min^{-1}$In almost all subjects, there was no movement in the subjective scales over the first few stages but there was a small increase in most of the physiological variables. During the first few minutes, there was a decrease in VE/VO_2 and VE/VCO_2. Thus, the above factors would be expected to adversely influence the correlations. Correlations were calculated using the subjective scales and physiological variables from 9 minutes onwards. This procedure resulted in a small increase in almost all correlations.

It may have been expected that correlations would have been higher in the STEXT protocol compared with the "steady state" study. In the "steady state" study, there was a sharp increase in the subjective scales and physiological variables between timepoint 1 and timepoint 2. From timepoint 2 to timepoint 3 there was a significant increase in the subjective scales but there was no significant increase in almost all the physiological variables. However, the upward trend throughout the "steady state" protocol in the

subjective scales and the physiological variables may be one possible explanation for the very high correlations in the "steady state" study.

It may be unrealistic to expect a good relationship between subjective scale responses and physiological variables. Subjects have varying sensitivities to sensory inputs provoking the sensations of breathlessness and general fatigue. The manner in which the subjects interpret and use the scales is likely to vary and responses could be influenced by the experimenter.

The findings of other studies in this area have already been reported in Section 8.3.

SUMMARY.

These results showed good overall group correlations between VE, VO_2, VCO_2 frequency of breathing, heart rate, tidal volume, RER and VAS/Borg CR10 scales (breathlessness and general fatigue). There were no meaningful or systematic differences between the scales.

CONCLUSIONS.

The above studies have shown a slight tendency for the VAS to be more reproducible than the Borg CR10 scale for breathlessness and general fatigue. For sensitivity, there was no meaningful difference between these scales. The degree of reproducibility has varied among the studies. This finding may be due to the use of different subjects and number of subjects. The higher sensitivity ratios in the "steady state" study compared with the STEXT protocol may be a result of less impact of propranolol with the STEXT protocol as the subjects worked for a shorter period of time at high intensities during the STEXT protocol.

The results from the "steady state," CHF and STEXT studies indicate that subjective scales can be used in a meaningful way to assess the symptoms of breathlessness and general fatigue. All three studies have shown that subjective scales can reproducibly measure the symptoms of breathlessness and general fatigue. In two of the studies, subjective scales have been able to detect the effect of drug intervention. It must be conceded that assessment of the sensitivity of the scales was carried out in the "wrong direction" i.e. the subjects were made to feel worse. However, it has been shown that physiological changes after beta blockade have been reflected in differences in the perception of symptoms.

In the "steady state" study there was a very good correlation between some physiological variables and the subjective scales whereas in the CHF study correlations were generally low. In the STEXT study a good relationship between some physiological variables and the subjective scales was found. It has already been stressed that the relationship between the subjective scales and physiological variables may not be causal.

The impact of beta blockade on physiological variables in the "steady state" and STEXT studies was similar to that reported in other studies. Maximal physiological values have been shown to be reproducible using the STEXT protocol. These findings indicate that the STEXT protocol can be used to assess aerobic fitness reproducibly. Subjective scales have also been shown to be reproducible and sensitive to change using the STEXT protocol. These results demonstrate that the STEXT protocol can be of value in assessing physiological values and symptoms using subjective scales.

It has been shown that subjective scales can be incorporated in to a submaximal test to evaluate symptoms with CHF patients. Both the subjective scales and endurance time are reproducible. The establishment of a clinically acceptable length of endurance treadmill times and the selection of an appropriate work intensity indicates that this method has potential for the evaluation of symptoms in a situation which resembles everyday life.

FUTURE RESEARCH.

It would be of value to use the CHF submaximal test to evaluate an intervention with CHF patients. Thus, the sensitivity of the subjective scales could be assessed and the effect on endurance time measured.

It seems logical to apply the STEXT protocol format used in this study to a group of angina patients to evaluate a drug intervention. Using a population of wide ranging fitness levels, it may be possible to predict VO_2 max from endurance time attained on the STEXT protocol.

REFERENCES

Adams, L., Chronos, N., Lane, R., Guz, A. (1985a) The measurement of breathlessness induced in normal subjects: validity of two scaling techniques. Clinical Science. 69, 7-16.

Adams, L., Chronos, N., Lane, R., Guz, A. (1985b) Breathlessness during different forms of ventilatory stimulation: a study of mechanisms in normals and respiratory patients. Clinical Science. 69, 663-672.

Adams, L., Guz, A. (1991) Dyspnoea on exertion. Chapter 14, 449-494 in Exercise Pulmonary Physiology and Pathophysiology. Edited by B.J. Whipp and K. Wasserman.

Allen, C.J., Craven, M.A., Rosenbloom, D., Sutton, J.R. (1984) Beta-Blockade and Exercise in Normal Subjects and Patients with Coronary Artery Disease. The Physician and Sportsmedicine. 12. No.10. 51-63.

American College of Sports Medicine. (1986) Guidelines for Exercise Testing and Prescription. Lea and Febiger. Philadelphia.

Anderson, R.L., Wilmore, J.H., Joyner, M.J., Freund, B.J., Hartzell, A.A., Todd, C.A., Ewy, G.A. (1985) Effects of Cardioselective and Nonselective Beta-Adrenergic Blockade on the Performnce of Highly Trained Runners. American Journal Cardiology. 55. 149D-154D.

Armstrong, L.E., and Costill, D.L. (1985) Variability of respiration and metabolism responses to submaximal cycling and running. Research Quarterly for Exercise and Sport. 56.(2). 93-96.

Astrand, P.O., Rodahl, K. (1986) Textbook of work physiology. McGraw-Hill Book Company. New York.

Astrom, H. (1986) Exercise testing in patients with heart disease. Acta Pharmacology Toxicology. 59. Supplement VI. 65-70.

Baker, J.R., Wilen, M.M., Body, C.M., Dinh, H., Franciosa, J.A. (1984) Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. American Journal of Cardiology. 54. 596-599.

Barlow, C.W., Qayyum, M.S., Davey, P.P., Conway, J., Paterson, D.J., Robbins, P.A. (1994) Effect of physical training on exercise-induced hyperkalemia in chronic heart failure. Circulation. 89. 1144-1152.

Bergstrom, J., Hultman. (1967) A study of the glycogen metabolism during exercise in man. Scandinavian Journal of Clinical and Laboratory Investigation. 19: 218-228.

Bigland-Ritchie, B., Kukulka, C.G., Lippold, O.C.J., Woods, J.J. (1982). The absence of neuromuscular junction transmission failure in sustained maximal voluntary contractions. Journal of Physiology. 330. 265-278.

Borg, G. (1962) Physical performance and perceived exertion. Studia Psychologica et Paedagogica. Series altera. Investigationes XI.

Borg, G. (1978) Subjective effort in relation to physical performance and working capacity: in Pick, H.L. Jr. Editor: Psychology: From Research to Practice. New York, Plenum Publishing Corp. 333-361.

Borg, G. (1979) Perceived exertion as an indicator of somatic stress. Scandanavian Journal Rehabilitation Medicine. 2-3. 92-98.

Borg, G.A.V. (1982) Psychophysical bases of perceived exertion. Medicine and Science in Sports and Exercise. Vol.14. No.5. 377-381.

Braunwald, E.G. (1988) Heart Disease. A textbook of Cardiovascular Medicine. Third Edition. W.B. Saunders & Company. Philadelphia, London.

Brice, P. (1993) Quality of Symptom Control - The Patients' Perspective in Quality of Life in Heart Failure: Relationship of Exercise Capacity and Symptomatology. Satellite Symposium at the 2nd International Conference on Heart Failure - Mechanisms and Management. Geneva, Switzerland.

Brick, I., Glover, W.E., Hutchison, K.J., roddie, I.C. (1966) Effects of propranolol on peripheral vessels in man. American Journal of Cardiology. 18. 329-333.

Buchfuhrer, M.J., Hansen, J.E., Robinson, T.E., Sue, D.Y., Wasserman, K., Whipp, B.J. (1983) Optimising the protocol for cardiopulmonary assessment. Journal of Applied Physiology. 1558-15564.

Buller, N.P., Poole-Wilson, P.A. (1988) Extrapolated maximal oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise. British Heart Journal. 59. 212-217.

Buller, N.P., Poole-Wilson, P.A. (1990) Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. British Heart Journal. 63. 281-283.

Busse, M.W., Maassen, N., Konrad, H. (1991) Relation between plasma K^+ and ventilation during incremental exercise after glycogen depletion and repletion in man. Journal of Physiology. 60. 217-225.

Butland, R.J.A., Pang, J.A., Geddes, D.M. (1982) The selectivity of the B-adrenoceptor for ventilation in man. British Journal of Clinical Pharmacology. 14. 707-711.

Cady, E.B., Elshove, H., Jones, D.A., Moll, A. (1989). The metabolic causes of slow relaxation in fatigued human skeletal muscle. Journal of Physiology. 418. 327-337.

Campbell, E.J.M., Howell, J.B.L. (1963) The sensation of breathlessness. British Medical Bulletin. 19: 36-40.

Carton, R.L., Rhodes, C.R. (1985) A Critical Review of the Literature on Ratings Scales for Perceived Exertion. Sports Medicine. 2. 198-222.

Christensen, E.H. (1960) Muscular work and fatigue. Chapter 9 in K. Rodahl and S.M. Horvath (eds.) "Muscle as a Tissue", McGraw-Hill Book Company, New York.

Chronos, N., Adams, L., Guz, A. (1988) Effect of hyperoxia and hypoxia on exercise-induced breathlessness in normal subjects. Clinical Science. 74. 531-537.

Clark, A.L., Volterrani, M., Piepolo, M., Poole-Wilson, P.A., Coats, A.J.S. (August, 1993) The influence of stage duration during incremental treadmill exercise on metabolic gas exchange measurements. European Heart Journal. 2363.

Cockcroft, A., Adams, L. (1986) Measurement and mechanisms of breathlessness. Bulletin European Physiopathology Respiration. 22. 85-92.

Cockcroft, A., Guz, A. (1987) Breathlessness. Postgraduate Medical Journal. 63: 637-641.

Cohen-Solal, C.A. (1989) Editorial. Improving exercise tolerance in patients with chronic heart failure: should we treat the heart or the periphery? European Heart Journal. 10. 866-871.

Cohen-Solal, C.A., Chabernauld, J.M., Gourgon, I. (1990) Comparison of oxygen uptake during bicycle exercise in patients with chronic heart failure and in normal subjects. Journal of American College of Cardiology. 16. No.1. 80-85.

Cohen-Solal, C.A., Zannad, F., Kayanakis, J.G., Gueret, P., Aupetit, J.F., Kolsky, H. (1991) Multicentre study of the determination of peak oxygen uptake and ventilatory threshold during bicycle exercise in chronic heart failure. Comparison of graphical methods, interobserver variability and influence of the exercise protocol. European Heart Journal. 12. 1055-1063.

Colucci, W.S., Alexander, R.W., Williams, G.H., Rude, R.F., Holman, B.I. Konstram, M.A. (1989) Decreased lymphocyte beta-adrenergic receptor density in patients with heart failure and tolerance to the beta-adrenergic agonist pubeterol. New England Journal of Medicine. 305. 184-190.

Comroe, J.H. (1966) Some theories of the mechanisms of dyspnoea. In: Breathlessness. Edited by J.B.L. Howell and E.J.M. Campbell. Oxford, Blackwell Scientific. 1-7.

Cook, R and Pate. (1985) The effects of ADP and phosphate on the contraction of muscle fibres. Biophysical Journal. 48. 703-720.

Costill, D.L., Hargreaves, M. (1992) Carbohydrate nutrition and fatigue. Sports Medicine. 13(2), 86-92.

Cowley, A.J., Stainer, K., Rowley, J.M., Hampton, J.R. (1986) Abnormalities of the peripheral circulation and respiratory function in patients with severe heart failure. British Heart Journal. 55. 75-80.

Cowley, A.J., Fullwood, L., Stainer, K., Hampton, J.R. (1991) Exercise tolerance in patients with heart failure - how should it be measured? European Heart Journal. 12. 50-54.

Dargie, H.J., Grant, S., McLenachan, C. (1991) Angina, ischaemia and effort tolerance with vaso-dilating betablockers. Supplement to American Heart Journal. 121, 3(2), 1117-1120.

Davies, C.T.M., Tuxworth, W., Young, J.M. (1970) Physiological effects of repeated exercise. Clinical Science. 39: 247-258.

Davies, C.T.M., Sargeant, A.J. (1979) The effects of atropine and practolol on the perception of exertion during treadmill exercise. Ergonomics. No.10. 1141-1146.

Davies, S.W., Jordan, S.L., Lipkin, D.P. (1993) Does increased dead space ventilation during exercise explain dyspnoea in chronic left heart failure? The Journal of Heart Failure. 1, 890 (Abstract)

Deedwania, P., Braun, S., Massie, B. (1993) Interrelation of right and left ventricular ejection fraction and exercise capacity in congestive heart failure. The Journal of Heart Failure. 1, 342. (Abstract)

Derman, E.W., Selley, K.L., Emms, M., Sinclair-Smith, C., Brink, J. Noakes, T.D. (August, 1993) Exercise performance and skeletal muscle pathology improves after cardiac transplantation and exercise training. European Heart Journal. 2358. (Abstract)

Drexler, H., Riede, U., Schafer, H.E. (1987) Reduced oxidative capacity of skeletal muscle in patients with severe heart failure. Circulation. 76. Supplement IV. IV-178. (Abstract).

Drexler, H. (1992) Exercise training in chronic heart failure. Deutsche Zeitschrift Fur Sportmedizin. 43: 12, 587-594.

Edwards, R.H.T., Melcher, A., Hesser, C.M., Wigerty, O., Ekelund, L.G. (1972) Physiological correlates of perceived exertion in continuous and intermittent exercise with the same average power output. European Journal of Clinical Investigation. 2: 108-114.

Elborn, J.S., Stanford, C.F., Nicholls, D.P. (1990) Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test. European Heart Journal. 11. 75-81.

El-Manshawi, A., Killian, K.J., Summers, E., Jones, N.L. (1986) Breathlessness during exercise with and without resistive loading. Journal of Applied Physiology. 61(3). 896-905.

Enoka, R.M. (1988) Neuromechanical basis of kinesiology. Human Kinetic Books. Champaign, Illinois.

Epstein, S.E., Robinson, B.F., Kahler, R.L., Braunwald, E. (1965) Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. Journal of Clinical Investigation. 44. 1475-1753.

Eriksson, H., Svardsudd, K., Larsson, B., Welin, L., Ohlson, L.O., Tibblin, G., Wilhelmsen, L. (1988) Quality of life in early heart failure. Scandinavian Journal of Primary Health Care. 6. 161-167.

Fink, L.I., Wilson, J.R., Ferraro, N. (1986) Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. American Journal Cardiology. 57. 249-253.

Firth, B.G. (1988) The multifacetted role of angiotensin converting enzyme inhibitors in congestive heart failure. American Journal Medical Science. 296. 275-288.

Francis (1987) Haemodynamic and neurohumoral responses to dynamic exercise: normal subjects versus patients with heart disease. Circulation. 76. VI-II-VI-17.

Franciosa, J.A., Ziesche, S., Wilen, M. (1979) Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and haemodynamic characterisation. The American Journal of Medicine. 67. 460-466.

Franciosa, J.A., Park, M., Levine, B. (1981) Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. The American Journal of Cardiology. 47 33-39.

Franciosa, J.A., Leddy, C.L., Wilen, M., Schwartz, D.E. (1984) Relation between haemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. American Journal Cardiology. 53. 127-134.

Franciosa, J.A. (1984) Exercise testing in chronic congestive heart failure. American Journal of Cardiology. 53. 1447-1450.

Galbo, H., Holst, J.J., Christensen, N.J., Hilsted, J. (1976) Glucagon and plasma catecholamines during beta-receptor blockade in exercising man. Journal of Applied Physiology. 40. 855-863.

Gibbs, J.S.R., Keegan, J., Wright, C., Fox, K.M., Poole-Wilson, P.A. (1990) Pulmonary artery pressure changes during exercise and daily activities in chronic heart failure. Journal of American College of Cardiology. 15. No.1. 52-61.

Gillum, R.F. Heart Failure in the United States 1970-1985. (1987) American Heart Journal. 113. 1043-1045.

Goldman, L., Hashimito, B., Cook, E.F., Loscalo, A. (1981) Comparative Reproducibilities and Validation of Systems for the Assessment of Cardiovascular Functional Class. Circulation. 64. 1227-1234.

Goldman, L., Cook, E.F., Mitchell, N., Flatley, M., Sherman, H., Cohn, P.F. (1982) Pitfalls in the serial assessment of cardiac functional status. How a reduction in "ordinary" activity may reduce the apparant degree of cardiac compromise and give a misleading impression of improvement. Journal of Chronic Disease. 35. 763-771.

Goldsmith, S.R., Francis, G., Cohn, J.N. (1989) Attenuation of the pressor response to intravenous furosemide by angiotensin converting enzyme inhibition in congestive heart failure. American Journal Cardiology. 64. 1382-1385.

Grant, S., Henderson, E., Abdullah, I., Christie, J., Aitchison, T., Donelly, M., McMurray, J., Dargie, H.J. (1992) Is there a reproducible and sensitive method of measuring symptoms during exercise in humans? European Heart Journal. 13. August, 1992. 118. (Abstract).

Gullestad, L.O., Dolva, O.A., Kjekshus, J. (1989) Interaction of naloxone and timolol on maximal exercise capacity and the subjective perception of fatigue. International Journal Sports Medicine. 10. 259-263.

Guz, A., Adams, L., Minty, K., Murphy, K. (1981) Breathlessness and ventilatory drives of exercise, hypercapnoea and hypoxia. Clinical Science. 60. 17P. (Abstract).

Guyatt, G.H., Thompson, P.J., Berman, L.B., Sullivan, M.J., Townsend, M., Jones, N.L., Pugsley, S.O. (1985) How should we measure function in patients with chronic heart and lung disease? Journal of Chronic Disease. 38. 517-524.

Guyatt, G.H., Townsend, M., Berman, L.B., Keller, J.L. (1987) A comparison of Likert and Visual Analogue scales for measuring change in function. Journal of Chronic Disease. 40. 1129-1133.

Hagberg, J.M., King, I.D., Rogers, M.A. (1989) Exercise hyperventilation and recovery VO_2 responses of McArdle's disease patients. Federation Proceedings. 3. A849.

Hammond, M.D., Bauer, K.A., Sharp, J.T., Roche, R.D. (1990) Respiratory muscle strength in congestive heart failure. Chest. 98: 1091-1094.

Hammond, H.K. (1993) Mechanisms for Myocardial B-Adrenergic Receptor Desensitization in Heart Failure. Circulation. Vol. 87. No.2. 652-654.

Harris, P. (1987) Congestive cardiac failure: central role of arterial blood pressure. British Heart Journal. 58. 190-203.

Hayward, G.W., Knott, J.M.S. (1955) The effect of exercise on lung distensibility of respiratory work in mitral stenosis. British Heart Journal. 17. 303-311.

Higgens, C.B., Vatner, S.F., Eckberg, D.L., Braunwald, E. (1972) Altrations in the baroreceptor reflex in conscious dogs with heart failure. Journal of Clinical Investigation. 51: 715-724.

Hughson, R.L., Russell, C.A. Marshall, M.R. (1984) Effect of Metoprolol and cycle and treadmill maximal exercise performance. Journal of Cardiac Rehabilitation. 4: 27-30.

Jessup, M. (1986) The assessment of the quality of life and exercise response in patients with chronic heart failure in Congestive Heart Failure. Proceedings of the Symposium on New Drugs and Devices. October. 30-31. 1986. Philadelphia, Pennsylvania. Edited by J. Morganroth and E.N. Moore.

Jones, P.W., Husycyuk, A., Wasserman, K. (1982) Cardiac output as a controller of ventilation through changes in right ventricular load. Journal of Applied Physiology. 53: 218-224.

Jones, P.W., Al, H.A., Wakefield, J.M. Johnson, N.M., Jelliffe, A.M. (1984) Differences in the effect of mediastinal radiotherapy on lung function and ventilatory response to exercise. Clinical Science. 67, 389-396.

Jones, D.A., Round, J.M. (1990) Skeletal Muscle in Health and Disease. Manchester University Press.

Joyner, M.J., Freund, B.J., Jilka, S.M., Hetrick, G.A., Martinez, E., Ewy, G.A., Wilmore, J.H. (1986) Effects of B-blockade on exercise capacity of trained and untrained men: a hemodynamic comparison. Journal of Applied Physiology. 60: 1429-1434.

Joyner, M.J., Jilka, S.M., Taylor, J.A., Kalis, J.K., Nittolo, J., Hicks, R.W., Lohman, T.G., Wilmore, J.H. (1987) B-Blockade reduces tidal volume during heavy exercise in trained and untrained men. Journal of Applied Physiology. 62(5) 1819-1825.

Kaiser, P., Tesch, P.A., Thorsson, A., Karlsson, J., Kaijser, L. (1985) Skeletal muscle glycolysis during submaximal exercise following acute B-adrenergic blockade in man. Acta Physiol. Scand. 123. 285-291.

Kaiser, L., Spickard, R.C., Oliver, N.B. (1988) Heart failure depresses endothelial cell dependent relaxation to acetylcholine in the canine femoral artery (Abstract). F.A.S.E.B. 2. A942.

Katz, A. (1987) A physiologic approach to the treatment of heart failure. Hospital Practice. Vol.22. No.2. 117-148.

Karlsson, J., Jacobs, I. (1982). Onset of blood lactic accumulation during muscular exercise as a threshold concept. Theoretical considerations. International Journal of Sports Medicine. 3. 190-201.

Kiilavouri, K.K., Ikonen, H., Harkonen, M., Sovijarvi, A., Leinonen, H. (1993) Effect of physical training on exercise capacity and muscle metabolism in chronic heart failure. Journal of Heart Failure. I. (Abstract). 888.

Killian, K.J. and Jones, W.L. (1984) The use of exercise testing and other methods in the investigation of dyspnoea. Clinical Chest Medicine. 5, 99-108.

Killian, K.J. (1988) Assessment of dyspnoea. European Respiratory Journal. 1. 195-197.

Kiowski, W. (1989) Compensatory and adaptive mechanisms in congestive heart failure. Journal of Cardiovascular Pharmacology. 14. (Suppl 1): S3-S8.

Kirschner, B., Guyatt, G. (1985) A Methodological Framework for Assessing Health Indices. Journal of Chronic Disease. 38, 1. 27-36.

Koch, J. Brouslet. (1993) The benefit of graded physical exercise in chronic heart failure. Proceedings of the Vth World Congress on Cardiac Rehabilitation. Edited by J.P. Broustet. Intercept Ltd., P.O. Box 716, Andover, Hampshire, SP10 176.

Lamb, D.R. (1984) Physiology of exercise, responses and adaptions. McMillan Publishing Company. New York.

Lane, R., Cockcroft, A., Guz, A. (1987) Voluntary isocapnic hyperventilation and breathlessness during exercise in normal subjects. Clinical Science. 73. 519-523.

Lannergren, J., Westerblad, H., Allen, D.G. (1992) Mechanisms of fatigue as studied in single muscle fibres in Neuromuscular Fatigue. edited by A.J. Sergeant and D. Kernell. Proceedings of Royal Netherlands Academic of Arts and Sciences.

Lees, K.R., Curzio, J., Farish, E., Borland, W.W., Rubin, P.C. (1987) The influence of Beta-Adrenoceptor antagonists with and without partial agonist activity on exercise tolerance and muscle lactate production. European Journal of Clinical Pharmacology. 33. 415-417.

Leier, C.V., Huss, P., Magorien, D., Unverferth, D.V. (1983) Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. Circulation. 67. 817-822.

Leitch, A.G., Hopkin, J.M., Ellis, D.A., Clarkson, D., Merchant, S., McHardy, G.J.R. (1980) British Journal of Clinical Pharmacology. 9. 493-498.

Lipkin, D.P., Poole-Wilson, P.A. (1985) Measurement of cardiac output during exercise by the thermodilution and Direct Fick Techniques in patients with chronic congestive heart failure. American Journal of Cardiology. 56: 321-324.

Lipkin, D.P., Canepa-Anson, R., Stephens, M.R., Poole-Wilson, P.A. (1986A) Factors determining symptoms in heart failure: comparison of fast and slow exercise tests. British Heart Journal. 55. 439-445.

Lipkin, D.P., Scriven, A.J., Crake, T., Poole-Wilson, P.A. (1986B) Six minute walking test for assessing exercise capacity in chronic heart failure. British Medical Journal. 292. 653-655.

MacFarlane, B.J., Hughson, R.L., Green, H.J., Walters, D.J., Ranney, D.A. (1983) Effects of oral propranolol and exercise protocol on indices of aerobic function in normal man. Canadian Journal of Physiological Pharmacology. 61. 1010-1016.

McKee, P.A., Castelli, W.P., McNamara, P.M., Kannel, W.B. (1971) The natural history of congestive heart failure. New England Journal Medicine. 285. 781-787.

McLeod, A., Knopes, K.D., Shand, D.G., Williams, R.S. (1985) B-selective and non-selectivie B-adrenoceptor blockade, anaerobic threshold and respiratory gas exchange during exercise. British Journal of Clinical Pharmacology.. 19. 13-20.

McMurray, J., Morrison, C.E., Dargie, H.J. (1993) Trends in hospitalisation for chronic heart failure in the United Kingdom. The Journal of Heart Failure. 1. 357. (Abstract).

McParland, C., Krishman, B., Wang, Y., Gallacher, C.G. (1992) Inspiratory muscle weakness and dyspnoea in chronic heart failure. American Review of Respiratory Disease. 146. 467-472.

Magnusson, G., Kaijser, L., Isberg, B., Sylven, C., Saltin, B. (August, 1993) Maximal perfusion of skeletal muscle in patients with chronic heart failure. European Heart Journal. 1850.

Mahler, D.A., Weinberg, D.H., Wells, C.K., Feinstein, A.R. (1984) The Measurement of Dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 6. 751-758.

Mahler, D.A., Rosiello, R.A., Harver, A., Lentine, T., McGovern, J.F., Daubenspeck, J.A. (1987) Comparison of clinical dyspnoea ratings and psychophysical measurements of respiratory sensation in obstructive airway disease. American Review of Respiratory Disease. 135: 1229-1233.

Mancini, D.M., Ferraro, N., Nazzaro, D., Wilson, J.R. (1991) Respiratory Muscle Deoxygenation during exercise in patients with heart failure demonstrated with near-infrared spectroscopy. Journal of American College of Cardiology. 18. No.2. 492-298.

Maresh, C.M., Noble, B.J. (1984) Utilization of perceived exertion ratings during exercise testing and training. Cardiac Rehabilitation: Exercise Testing and Prescription. 155-173.

Marin-Neto, J.A. (1991) Abnormal baroreflex control of heart rate in decompensated congestive heart failure and reversal after compensation. American Journal Cardiology. 67. 604-610.

Mason, D.T. (1991) Angina, ischemia, and effort tolerance with vasodilating B-blockers. American Heart Journal. 121. No.3. Part 2. 1017-1020.

Massie, B.M. Kramer, B.L. (1984) Lack of relationship between short-term haemodynamic effects of captopril and subsequent clinical responses. Circulation. 69. 1135-1141.

Massie, B., Conway, M., Yonge, R. (1987) Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. Circulation. 76. 1009-1019.

Medical Research Council (1966) Questionaire on respiratory symptoms. London, Medical Research Council. Cardiovascular Disease. 24: 437-459.

Metra, M., Raddino, R., Cas, L.D., Visioli, O. (1990) Assessment of peak oxygen consumption, lactate and ventilatory thresholds and correlation with resting and exercise haemodynamic data in chronic congestive heart failure. American Journal Cardiology. 65. 1127-1133.

Miller, V.M., Aarhus, L.L., Vanhouette, P.M. (1986) Modulation of endothelium dependent responses by chronic alterations in blood flow. American Journal of Physiology. 251. H520-527.

Morgan, W.P., Hirota, K., Weitz, G.A., Balke, B. (1976) Hypnotic perturbation of perceived exertion: Ventilatory consequences. American Journal of Clinical Hypnosis. 189: 187-190.

Mutch, B.J., Bannister, E.W. (1983) Ammonia metabolism in exercise and fatigue: a review. Medicine and Science in Sports and Exercise. 15. 41-50.

Muza, S.R., Silverman, M.T., Gilmore, G.C., Hellerstein, H.K., Kelsen, S.G. (1990) Comparison of sclaes used to quantitate the sense of effort to breathe in patients with chronic obstructive pulmonary disease. American Review of Respiratory Disease. 141. 909-913.

Myers, J., Froelicher, V.E. (1991) Hemodynamic Determinants of exercise capacity in chronic heart failure. Annals of Internal Medicine. 115. No.5. 377-387.

Nemanick, J.W., Kremser, C.B., Rajfer, S.I., (1986) Evaluation of the falling heart by dynamic exercise testing. Cardiopulmonary Exercise Testing. 123-138.

Newsholme, E.A., Bloomstrand, E., Ekblom, E. (1992) Physical and mental fatigue: metabolic mechanisms and importance of plasma amino acids. British Medical Bulletin. 48. 3. 477-495.

Noble, B.J., Metz, K.F., Pandolf, K.B., Cafarelli, E. (1973) Perceptual response to exercise: A multiple regression study. Medicine and Science in Sports. 5: 104-109.

Northridge, D.B., Grant, S., Ford, I., Christie, J., MacLenachan, J., Connelly, D., McMurray, J., Roy, S., Henderson, E., Dargie, H.J. (1990) Novel exercise protocol suitable for a tradmill or a bicycle ergometer. British Heart Journal. 64: 313-316.

Oborne, D.J., Clarke, M.J. (1975) Questionnaire surveys on passenger comfort. Applied Ergonomics. 6. 97-103.

O'Neill, P.A., Morton, P.B., Sharman, P., Marlow, H.F., Stark, R.D. (1984) The effects of ICI 1883, 587 and atenolol on the responses to exercise and on breathlessness in healthy subjects. British Journal of Clinical Pharmacology. 17. 37-41.

O'Neill, P.A. Stark, R.D., Allen, S.C., Stretton, T.B. (1986) The relationship between breathlessness and ventilation during steady-state exercise. Bulletin European Physiopathology Respiration. 22. 247-250.

Osborne, D.J., Clarke, M.J. (1975) Questionnaire surveys on passenger comfort. Applied Ergonomics. 6. 97-103.

Paintal, A.S. (1969) Mechanism of stimulation of type J pulmonary receptors. Journal of Physiology. 203. 511-532.

Parameshwar, Dambrink, J.H.E., Sparrow, J., Wright, C., Park, A., Poole-Wilson, P.A. (1989) A new exercise test for the assessment of heart failure: use of a self-powered treadmill. British Heart Journal. 61. 421-425.

Paterson, D.J., Friedland, J.S., Bascom, D.A., Clement, I.D., Cunningham, D.A., Painter, R., Robbins, P.A. (1990) Changes in arterial K_+ and ventilation during exercise in normal subjects and subjects with McArdle's syndrome. Journal of Physiology. 429. 339-348.

Patrick, J.M., Tutty, J., Pearson, S.B. (1978) Propranolol and ventilatory response to hypoxia and hypercapvia in normal man. Clinical Science Molecular Medicine. 55. 491-497.

Pearson, S.B., Banks, D.C., Patrick, J.M. (1979) The effect of B-adrenoceptor blockade on factors affecting exercise tolerance in normal man. Journal Clinical Pharmacology. 8. 143-148.

Pearson, S.B., Morrison, J.F.J., Simpson, F.G. (1987) The effects of B-adrenoceptor blockade on breathing during progressive exercise in normal man. British Journal Clinical Pharmacology. 24. 173-178.

Petersen, E.S., Whipp, B.J., Davis, J.A., Huntsman, D.J., Brown, H.V., Wasserman, K. (1983) Effects of B-adrenergic blockade on ventilation and gas exchange during exercise in humans. American Physiological Society. 1306-1313.

Pina, I.L., Karalis, D.G. (1990) Comparison of four exercise protocols using anaerobic threshold measurement of functional capacity in congestive heart failure. The Americal Journal of Cardiology. 1269-1272.

Pollock, M.L., Wilmore, J.H., Fox, S.M. (1984) Exercise and health and disease. W.B. Saunders Company, Philadelphia.

Poole-Wilson, P.A., Buller, N.P. (1988) Causes of Symptoms in Chronic Congestive Heart Failure and Implications for Treatment. American College of Cardiology. 62. 31A-34A.

Poole-Wilson, P.A. (1988) Current therapeutic principles in the acute management of severe congestive heart failure. American College of Cardiology. 62. 4C-8C.

Poole-Wilson, P.A. (1989a) Exercise as a means of assessing heart failure and its response to treatment. Cardiology. 76. 347-356.

Poole-Wilson, P.A. (1989b) Heart failure. Medicine International. Cardiovascular Disorders. 67. July, 1989. 2791-2795.

Rector, T., Cohn, J. (1993) Experience with the Minnesota Living with Heart Failure Questionnaire. Quality of Life in Heart Failure Relationship of Exercise Capacity and Symptomatology. Satellite Symposium at the 2nd International Conference on Heart Failure - Mechanisms and Management. Geneva. Switzerland.

Reddy, H.K., Weber, K.T., Janicki, J.S., McElroy, P.A. (1988) Hemodynamic, ventilatory and metabolic effects of light isometric exercise in patients with chronic heart failure. Journal of American College of Cardiology. 12. No.2. 353-358.

Rejeski, W.J. (1981) The perception of exertion: A social psychophysiological integration. Journal of Sport Psychology. 4. 305-320.

Reybrouck, T., Amery, A., Billiet, L. (1977) Hemodynamic response to graded exercise after chronic beta-adrenergic blockade. Journal of Applied Physiology. 42. 133-138.

Richards, A.M. (1989) Left ventricular function and ischemic heart disease: neuroendocrine aspects. Cardiovascular Reviews and Reports. Vol.10. No.5. Supplement. May 7-13.

Riegger, G.A.J. (1991) Effects of quinapril on exercise tolerance in patients with mild to moderate heart failure. European Heart Journal. 12. 705-711.

Riley, M., Elbom, J.S. Stanford, C.F., Nicholls, D.P. (1990). Maximal VO_2 in chronic cardiac failure. Symposium on exercise testing on congestive heart failure. Brussels. Abstract 8.

Rubin, S.A., Harvey, M.D., Brown, V., Swan, H.J.C. (1982) Arterial Oxygenation and arterial oxygen transport chronic myocardial failure at rest, during exercise and after hydralazine treatment. Circulation. 66. 1. 143-148.

Rubin, S.A., Brown, H.V. (1984) Ventilation and gas exchange during exercise in severe chronic heart failure. American Review of Respiratory Disease. 129. Suplement S63-S84.

Sahlin, K. (1992) Metabolic Factors in fatigue. Sports Medicine. 13 (2). 99-107.

Schlepper, M., Thormann, J., Kremer, P., Mitrovic, V., Kramer, W. (1989) Present use of positive inotropic drugs in heart failure. Journal of Cardiovascular Pharmacology. 14. (Suppl 1): S9-S19.

Scott, J., and Huskinsson, E.C. (1977) Graphic representations of pain. Pain. 2. 175-184.

Simon, P.M., Schwartzstein, R.M., Weiss, J.W., Lahive, K., Fencl, V., Teghtsoonian, M., Weinberger, S.E. (1989) Distinguishable sensations of breathlessness induced in normal volunteers. American Review of Respiratory Disease. 140. 1021-1027.

Sinoway, L.I., Minotti, J.R., Davis, D. (1988) Delayed reversal of impaired vasodilation in congestive heart failure after heart transplantation. American Journal of Cardiology. 61. 1076-1079.

Sjogaard, G., Kiens, b., Jorgensen, K., Saltin, B. (1986) Intramurscular pressure, EMG and blood flow during low-level prolonged static contraction in man. Acta Physiologica Scandinavica. 128: 475-484.

Skinner, J.S., Hutsler, R., Bergsteinova, V., Buskirk, E.R. (1973a) The validity and reliability of a rating scale of perceived exertion. Medicine and Science in Sports. 5: 94-96.

Skinner, J.S., Hutsler, R., Bergsteinova, V., Buskirk, E.R. (1973b) Perception of effort during different types of exercise under different environmental conditions. Medicine Science in Sports. 5: 110-115.

Sklar, J., Johnston, G.D., Overlie, P., Gerber, J.G., Brammell, H.L., Gal, J., Nies, A.S. (1982) The effects of a cardioselective (Metroprolol) and a nonselective (Propranolol) beta-adrenergic blocker on the response to dynamic exercise in normal men. Circulation. 65. No.5. 894-899.

Smith, W.M. (1985) Epidemiology of congestive heart failure. American Journal of Cardiology. 55. 3A-8A.

The SOLVD Investigators. (1990) Studies of left ventricular dysfunction (SOLVD) - rationale, design and methods: two trials that evaluate the effects of enalapril in patients with reduced ejection fraction. American Journal Cardiology. 66. 315-322.

Spurway, N., Baxendale, R., Radford, P.F. (1987) Changing ratio of EMG to force in endurance-exercise fatigue. Journal of Sports Sciences. 5. 73-74.

Spurway, N. (1992) Aerobic exercise, anaerobic exercise and the lactate threshold. British Medical Bulletin. 48, 3. 569-591.

Stark, R.D., Guz, A. (Date unknown) Dyspnoea. 1-19. Pharmaceuticals Division of I.C.I.

Stark, R.D., Gambles, S.A., Lewis, J.A. (1981) Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide. Clinical Science. 61. 429-439.

Stark, R.D., Gambles, S.A., Chatterjee, S.S. (1982) An exercise test to assess clinical dyspnoea: estimation of reproducibility and sensitivity. British Journal Disease of Chest. 76. 269-278.

Stark, R.D., Morton, P.B., Sharman, P., Percival, P.G., Lewis, J.A. (1983) Effects of codeine on the respiratory responses to exercise in healthy subjects. British Journal of Clinical Pharmacology. 15. 355-359.

Stark, R.D. (1988) Dyspnoea: Assessment and pharmacological manipulation. European Respiratory Journal. 1. 280-287.

Sullivan, M.J., Higginbotham, B., Cobb, F.R. (1988) Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation. 77. No.3. 552-559.

Sullivan, M.J., Knight, J.D., Higgenbotham, M.B., Cobb, J.R. (1989) Relation between central and peripheral haemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation. 80. 769-781.

Sullivan, M.J., Green, H.J., Cobb, F.R. (1990) Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation. 81. 518-527.

Sutton, G.C. (1990) Epidemiologic aspects of heart failure. American Heart Journal. 120. (6 part 2). 1539-1540.

Sylven, C., Borg, G., Holmgren, A., Astrom, H. (1991) Psychophysical power functions of exercise limiting symptoms in coronary heart disease. Medicine and Science in Sports and Exercise. Vol.23. 1050-1053.

Szlachic, J., Massie, B.M., Kramer, B.L., Topic, N., Tuban, R.N. (1985) Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. American Journal of Cardiology. 55: 1037-1042.

Taylor, H.L., Bieskirk, E.R., Henschel, A. (1955) Maximum oxygen uptake as an objective measure of cardiorespiratory performance. Journal of Applied Physiology. 8: 73-80.

Teerlink, J.R., Goldhaber, S.Z., Pfeffer, M.A. (1991) An overview of contemporary etiologies of congestive heart failure. American Heart Journal. 121. 1852-1853.

Tesch, P.A., Kaiser, P. (1981) Effect of B-adrenergic blockade on maximal oxygen uptake in trained males. Acta Physiol. Scand. 112. 351-352.

Tesch, P.A. and Kaiser, P. (1983) Effects of B-adrenergic blockade on O_2 uptake during submaximal and maximal exercise. Journal of Applied Physiology. 54 (4). 901-905.

Tesch, P.A. (1985) Exercise performance and B-blockade. Sports Medicine. 2. 389-412.

Tesch, P.A., Kaiser, P., Komi, P.V. (1984) Effects of B-adrenergic blockade on EMG signal characteristics during progressive exercise. Acta Physiol. Scand. 189-191.

Twentyman, O.P., Disley, A., Gribbin, H.R., Alberti, K.G.M.M., Tattersfield, A.E. (1981) Effect of B-adrenergic blockade on respiratory and metabolic responses to exercise. Journal of Applied Physiology. 51(4) 788-793.

van Baak, M.A. (1988) B-Adrenoceptor blockade and exercise. An Update. Sports Medicine. 4. 209-225.

van Baak, M.A., Jooijm, J.M.V., Wijnen, A.G., Tan, F.S. (1991) Submaximal endurance exercise performance during enalapril treatment in patients with essential hypertension. Clinical Pharmacollogical Therapy. 221-227.

Van den Broek, S.A.J., van Veldhuisen, D.J., deGraeff, P.A., Landsman, M.L.J., Hillege, H., Lie, K.I. (1992) Comparison between New York heart association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Americal Journal Cardiology. 70. 359-363.

Van Gilst, W.H., DeGraeff, P.A. (1990). Pathophysiology of heart failure in Heart Failure in Perspective - focus on ibopamine. International Congress and Symposium Series. Royal Society of Medicine Services Limited, London. New York. 11-18.

Van Herwaarden, C.L.A., Binkhorst, R.A., Fennis, J.F.M., and Van't Laar, A. (1979) Effects of propranolol and metroprolol and haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients. British Heart Journal. 41. 99-105.

Van Zweiten. (1990) Pharmacological background to the drug treatment of congestive heart failure in Heart failure in perspective - focus on ibopamine.

International Congress and Symposium Series. Royal Society of Medicine Services Limited. London. New York. 29-42.

Violante, B., Buccheri, G., Brusasco, V. (1984) Effects of B-Adrenoceptor blockade on exercise performance and respiratory response in healthy, physically untrained humans. British Journal of Clinical Pharmacology. 811-814.

Volterrani, M., Clark, A.L., Ludman, P.F., Swan, J., Coats, A.J.S. (August, 1993) Muscle wasting is a determinant of maximal oxygen consumption in patients with chronic heart failure. European Heart Journal. 338. (Abstract)

Ward, S.A. and Whipp, B.J. (1989) Effects of peripheral and central chemoreflex activation on the isopneic rating of breathing in exercise in humans. Journal of Physiology. 411: 27-43.

Warren, J.B., Jennings, S.J., Clark, T.J.H. (1984) Effect of adrenergic and vagal block on the normal human airway response to exercise. Clinical Science. 66. 79-85.

Wasserman, K.B., Whipp, B.J., Costagno, J. (1974) Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output. Journal of Applied Physiology. 36: 457-464.

Wasserman, K. (1978) Breathing during exercise. The New England Journal of Medicine. 780-785.

Wasserman, K., Casaburi, R. (1988) Dyspnoea: Physiological and pathophysiological mechanisms. Annals Review of Medicine. 39: 503-515.

Wasserman, K. (1990) Measures of functional capacity in patients with heart failure. Supplement to Circulation. 81. No.1.

Watt, B., Grover, R. (1993) Perceived Exertion. Antecedents and Applications. Sports Medicine. 15(4). 225-241.

Weber, K.T., Kinasewitz, G.T., Janicki, J.S., Fishman, A.P. (1982) Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 65. No.6. 1213-1223.

Weber, K.T., Janicki, J.S., Likoff, M. (1984) Exercise testing in the evaluation of cardiopulmonary disease. A cardiologist's point of view. Clinics in Chest Medicine. Vol.5. No.1. 173-180.

Weber, K.T., Janicki, J.S. (1985) Lactate production during maximal and submaximal exercise in patients with chronic heart failure. Journal of American College of Cardiology. Vol.6. No.4. 717-724.

Weber, K.T., Janicki, J.S., Maskin, C.S. (1986) Effects of new inotropic agents on exercise performance. Circulation. 73. Supplement III. III-196.

Westerblad, H., Allen, D.G. (1993) The contribution of Ca^{2+} to the slowing of relaxation in fatigued single fibres from mouse skeletal muscle. Journal of Physiology. 468. 729-740.

Westerblad, H., Allen, D.G. (1991) Changes of myoplasmic calcium concentration during fatigue in single mouse fibres. Journal of General Physiology. 98. 615-635.

Wiener, D.H., Fink, P.I., Maris, J., Jones, R.A., Chance, B., Wilson, J.R. (1986) Abnormal skeletal muscle bioenergetic during exercise in patients with heart failure: role of reduced muscle blood flow. Circulation. 73. 1127-1136.

Wilcox, R.G., Bennett, T., MacDonald, I.A., Herbert, M., Skene, A.M. (1984) The effects of acute or chronic ingestion of propranolol or metoprolol on the physiological responses to prolonged, submaximal exercise in hypertensive men. British Journal of Clinical Pharmacology. 17. 273-281.

Wilmore, J.H., Freund, B.J., Joyner, M.J., Hetrick, G.A., Hartzell, A.A., Strother, R.T., Ewy, G.A., Faris, W.E. (1985) Acute response to submaximal and maximal exercise consequent to beta-adrenergic blockade: Implications for the prescription of exercise. American Journal of Cardiology. 55. 135D-141D.

Wilson, J.R., Martin, J.L., Schwartz, D., Ferraro, N. (1984) Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. Circulation. 69. No.6. 1079-1087.

Wilson, J.R., Fink, L., Maris, J. (1985) Evaluation of energy metabolism in skeletal muscle of patients with heart failure with gated phosphorus nuclear magnetic resonance. Circulation. 71. 57-62.

Wilson, J.R., Wiener, D.H., Fink, L.I., Ferraro, N. (1986) Vasodilatory behaviour of skeletal muscle arterioles in patients with nonedematous chronic heart failure. Circulation. 74. No.4. 775-779.

Wilson, J.R., Mancini, D.M., Ferraro, N., Egler, J. (1988) Effect of dichloroacetate on the exercise performance of patients with heart failure. Journal of American College of Cardiology. 12. No.4. 1464-1469

Wilson, J.R., Mancini, M., Dunkman, W.B. (1993) Exertional Fatigue Due to Skeletal Muscle Dysfunction in Patients with Heart Failure. Circulation. 87. No.2. 470-475.

Wilson, R.C., Jones, P.W. (1989) A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clinical Science. 76. 277-282.

Wilson, R.C., Jones, P.W. (1991a) Long-term reproducibility of Borg scale estimates of breathlessness during exercise. Clinical Science. 80. 309-312.

Wilson, R.C., Jones, P.W. (1991b) Differentiation between the intensity of breathlessness and the distress it evokes in normal subjects during exercise. Clinical Science. 80. 65-70.

Winsborough, M., Miller, J.N., Burgess, D.W., Lasylo, G. (1980) Estimation of cardiac output from the rate of change of alveolar carbon dioxide pressure during rebreathing. Clinical Science. 58. 263-270.

Younes, M., Burke, J. (1985) Breathing pattern during and after exercise of different intensities. Journal of Applied Physiology. 59. 898-908.

Zelis, R., Flaim, S.F. (1982) Alterations in vasomotor tone in congestive heart failure. Progress in Cardiovascular Disease. 71. 57-62.

Zelis, R., Sinoway, L.I., Musch, T.I. (1988) Why do patients with congestive heart failure stop exercising? Journal of American College of Cardiology. 359-361.

Zelis, R., Musch, T.I., Sinoway, L.I. (1990) The Maximal Stress Test: Does it have any value in Heart Failure? Journal of American College of Cardiology. Vol.15. No.1. 62-63.

APPENDIX A.

CHF PILOT STUDY.

A COMPARISON OF THE REPRODUCIBILITY OF VISUAL ANALOGUE AND BORG CR 10 SCALES IN CHRONIC HEART FAILURE.

A.1.1. OBJECTIVES OF PILOT STUDY.

A pilot study was undertaken to:

1) determine the reproducibility of VAS and Borg CR10 scales in CHF patients.
2) determine a method of establishing appropriate submaximal intensities during the exercise test.
3) determine the suitability of test instructions and the subject's responses to the test.
4) evaluate the practicality of the test procedures.

A.2.1. METHODS.

A.2.2. SUBJECTS.

Six subjects participated in the study. Subjects were male between the ages of 53-75 years. All subjects had chronic heart failure (NYHA 1 and 2) and all were taking some form of diuretic. Subjects gave informed consent to this study which had been approved by the West Ethical Committee.

A.2.3. RESEARCH DESIGN.

A.2.4. PRELIMINARY EXERCISE PROTOCOLS.

Subjects reported to the laboratory at the same time of day and with the same timing of medication on each occasion. Subjects underwent two maximal incremental treadmill tests (see Appendix C) at least four days apart. Before the maximal test the subjects were familiarised with the treadmill and the use of the subjective scales (see below). At the end of the test the subjects were asked to quantify their perception of breathlessness and general fatigue.

A.2.5. SUBMAXIMAL TESTS.

On the third visit, subjects were given a submaximal test which incorporated workrate stages of 60% upwards of the previously determined peak VO_2 (higher score of the two tests). Estimation of the relative workrates was made using the American College of Sports Medicine energy cost tables (ACSM, 1986). Each stage lasted 6 minutes. No scales were given during this test but the subjects exercised through a range of relative intensities and this procedure provided the following information:

The progressive stages gave some indication of what the patient was capable of and enabled workrates to be selected so that the patient could hopefully complete three stages in the subsequent tests.

At week one, week two, week four and week six after the second maximal test the subjects performed a submaximal exercise test. This test incorporated a range of relative intensities (workrate selection was based on the subject's performance of the preliminary submaximal test) and each stage lasted six minutes. Subjects were asked to continue for as long as possible. Most subjects performed three stages on each occasion. Patients responded to the subjective scales at 2 minutes 30 seconds and 5 minutes 15 seconds for each stage.

A.2.6. EQUIPMENT - TREADMILL, ECG AND GAS ANALYSIS.

Expired air was collected using a Hans Rudolph 2700 valve with a mouthpiece which was attached by tubing to the metabolic cart. All subjects wore a noseclip. Respiratory variables were determined during exercise by an automated gas analysis system (Beckman metabolic measurement cart; classic exercise model system 2). Before each test the oxygen and carbon dioxide sensors were calibrated with a standard gas mixture containing 16% oxygen 4% carbon dioxide and 80% nitrogen. Volume was checked using standard procedures. Heart rate was taken from the electrocardiogram during the last 10 seconds of each minute. A marquette MAC2 and ECG console were used for the treadmill test.

A.2.7. EQUIPMENT - SUBJECTIVE SCALES.

Each scale was administered by a computer (BBC Master) and displayed on a colour television screen in front of the subject while he exercised on the treadmill. The subject recorded his response by means of finger controls (see below) and the information was stored in the computer. An audible prompt was given each time a new scale appeared on the screen. On each occasion the subjects had to move the lever before the cursor appeared on the screen, i.e. before any score was displayed (thus the previous score was not visible when the new scale was presented). The subjects were introduced to the subjective scales between the treadmill familiarisation and the first maximal test. Firstly, the subjects were shown how to operate the scales and they were allowed to practise until they could carry out the procedures with no difficulty. Thereafter, instructions were read to the subjects. The following instructions were also read to the subjects before each submaximal test. Details of the equipment used are given in Appendix B.

A.2.8. SUBJECTIVE SCALES - INSTRUCTIONS TO SUBJECTS.

A.2.8.(a) BREATHLESSNESS.

Breathlessness was described as "breathless, out of breath, air hunger, unable to breathe enough".

Subjects were told,

"Based on these descriptions, quantify your sensation of breathlessness by referring to your common experience of an uncomfortable awareness of breathing". Avoid simply observing that your level of breathing has increased - think of "an uncomfortable need to breathe". "Disregard other sensations like leg fatigue or general fatigue".

A.2.8.(b) GENERAL FATIGUE.

General fatigue was described as "overall tiredness", overall fatigue". "Based on these descriptions and by referring to your common experience of general fatigue you are asked to quantify your sensation of general fatigue. Disregard other sensations like leg fatigue and breathlessness."

The subjects again practised with the scales and were asked to think about the range of the scales and their past experience in relation to breathlessness and general fatigue.

The subjects were asked if they understood the instructions. It was suggested to the subjects that zero on the scales may relate to their feelings at rest and at the upper end of the scales, subjects were asked to think of previous experiences which may relate to the upper ranges of the scales. It was also suggested to them that their perception of sensations at the end of the maximum tests may help them with their judgement of the range of the scales. Any questions from the subjects were answered. Subjects were randomly assigned to a VAS/Borg CR10 or a Borg CR10/VAS sequence of presentation.

During the test the subjects were asked to respond to the scales when they appeared on the TV monitor.

A.2.8.(c) DESCRIPTION OF SCALES.

The scales had a heading of either breathlessness or general fatigue. The following scales were used:

A.2.8.(d) VISUAL ANALOGUE SCALE.

The visual analogue scale (see appendix F) consisted of a horizontal line. At the left hand side of the scale the word "none" was labelled and at the far right the word "very severe" was placed. Subjects indicated their level of breathlessness or general fatigue by moving the lever on the treadmill which adjusted the line on the TV monitor. Once the subject had chosen the desired score, he pressed the button to record this in the computer. At this point another scale appeared.

A.2.8.(e) BORG CR10 SCALE.

The Borg CR10 scale (see Appendix F) consisted of a vertical scale labelled 0-10 with verbal descriptors at various numbers on the scale. Operation of the lever and button (see above) on the treadmill allowed the subjects to select the appropriate number.

A.2.9. PROCEDURES.

The subject's feet were placed on the side of the treadmill. At a given signal the subject walked on the treadmill and held on to the support bars for a few seconds until the subject had gained balance. Thereafter, the subject walked without support. At two and half minutes and 5 minutes 30 seconds for each stage, the subjects responded to the subjective scales which appeared on the TV monitor. The subjects were asked to walk as long as possible. During all tests gas collection and analysis were continuous and respiratory values for every 30 seconds were given on a print-out. Heart rate was monitored continuously and recorded for 10 seconds at the end of each minute.

A.3. STATISTICAL METHODS.

A generalised linear model (GLM) was applied to the data to include the possible effects of visit, subject, time and natural (or error) variability. Reproducibility was quantified as the proportion of total variance (i.e. between plus within subject variance) explained by the between subject variance.

A.4. RESULTS OF PILOT STUDY.

Table A1 summarises the results of the pilot study. Reproducibility coefficients are given for each scale for each workrate. Generally, the higher the relative intensity, the better the reproducibility. There were no significant differences between the scales. The VAS tended to be more reproducible than the Borg CR10 scale.

Table A1.
Reproducibility coefficients for the Visual Analogue (VAS) and Borg CR10 Scales (Breathlessness and General Fatigue) at three relative intensities.

	Breathlessness		General Fatigue	
Relative Intensity (% Peak VO_2)	VAS	Borg CR10	VAS	Borg CR10
65%	78%	43%	55%	39%
74%	63%	65%	67%	60%
83%	82%	72%	81%	71%

There were no significant differences between the scales for breathlessness or general fatigue at any timepoint.

A.5. CONCLUSIONS OF PILOT STUDY.

1. In general, the higher the relative intensity of the test, the more reproducible the scores were for breathlessness and general fatigue.

2. Generally, the VAS tended to be more reproducible than the Borg CR10 scale for breathlessness and general fatigue.

3. The necessity of carrying out a submaximal test to establish what the patient was capable of at submaximal intensities was considered to be time consuming and unsuitable for clinical practice.

4. The test instructions were easily understood by the subjects.

5. The results indicated that a similar form of test may prove to have value in assessing symptoms.

6. It was decided to investigate the possibility of finding a simpler and faster method of determining an "appropriate" work intensity to evaluate patient symptoms.

7. An attempt would be made to establish a work intensity which resulted in a subject determined cessation of exercise between 8 and 17 minutes.

APPENDIX B.

DETAILS OF EQUIPMENT USED IN THE STUDY.

B.1.1.
Marquette treadmill.
The marquette treadmill was made in the USA by:
Marquette Electronics Inc.
Milwaukee,
Wisconsin.
U.S.A.

B.1.2.
Marquette console and ECG system.
These items were made in in the USA by:
Marquette Electronics Inc.
Milwaukee,
Wisconsin.
U.S.A.

All Marquette equipment was supplied by:
Dolby House,
Anderson Street,
Dunblane FK 15 9A.

B.1.3.
Horizon Sensor Medics metabolic cart
The Horizon Sensor Medics was made in in the USA by:
Sensor Medics,
MMC Horizon System,
Annaheim,
Caifornia.

The metabolic cart was supplied by:
Cardiokinetics Ltd.,
2 Kansas Avenue,
Salford M5 2 GL.

B.1.4.
BBC Master computer.
The BBC Master computer was made in in the UK by:
British Brodcasting Corporation.

The BBC master was supplied by:
The Computer Depot,
205 Buchanan Street,
Glasgow G12 JZ

B.1.5.
Subjective scales programme.
The subjective scales programme was made by: Mr Jim Christie,
Medical Physics,
Western Infirmary,
Glasgow.

APPENDIX C.

CHF INCREMENTAL PROTOCOL.

INCREMENTAL TEST.

STAGE (Mins)	SPEED (mph)	GRADIENT (%)
1	1.4	0
2	1.5	0
3	1.7	0
4	1.7	1.0
5	1.7	2.0
6	2.0	2.0
7	2.0	3.0
8	2.0	4.5
9	2.0	5.5
10	2.0	7.0
11	2.0	8.5
12	2.3	8.5
13	2.3	10.0
14	2.6	10.0
15	2.7	11.0
16	3.0	11.0
17	3.4	11.0
18	3.75	11.0
19	3.4	13.0

APPENDIX D.

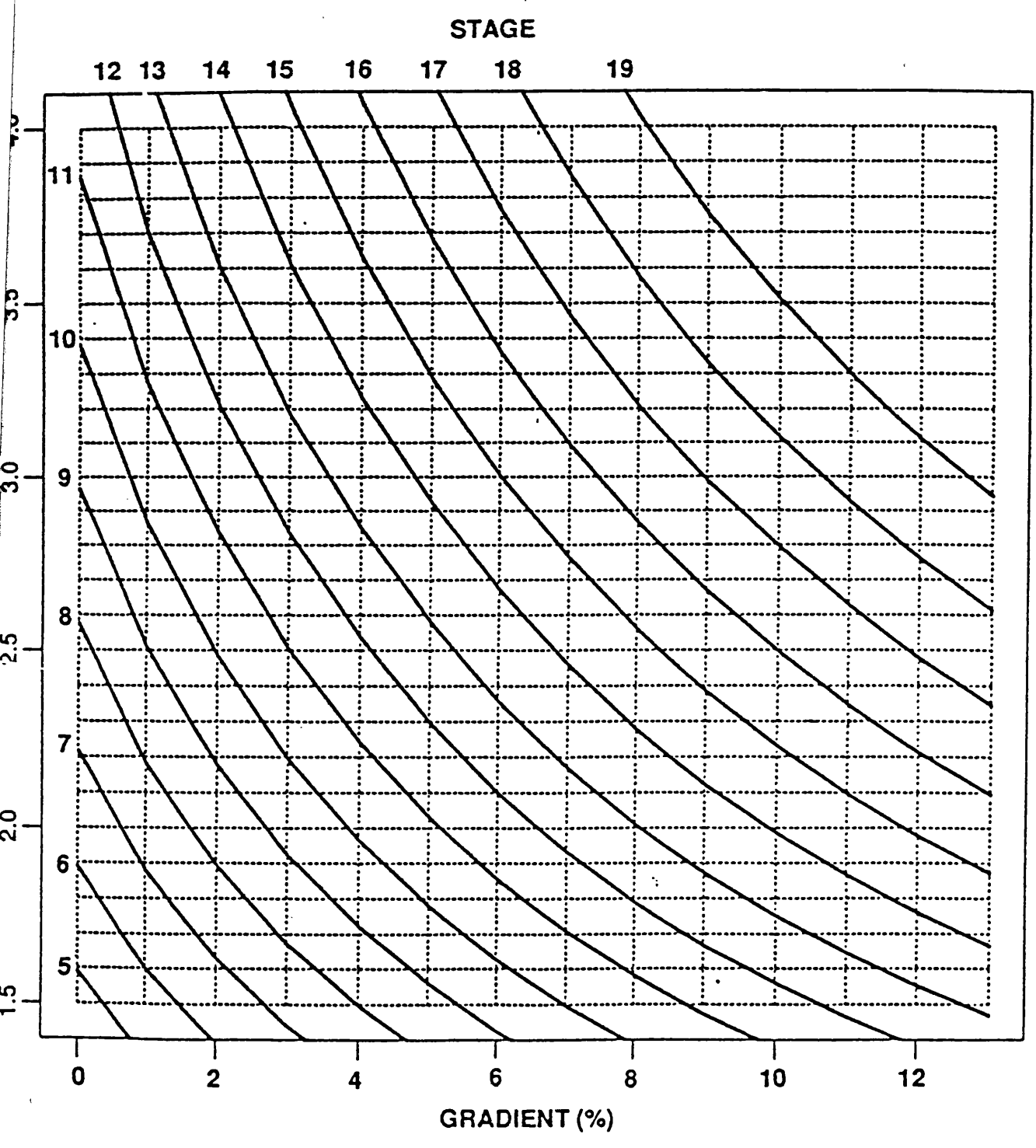
DIAGRAMMATIC AID FOR WORKRATE SELECTION.

The diagrammatic aid (see Figure AD1) was used to determine the workrate for the submaximal tests. For example, a subject who had an endurance time of 13 minutes on the incremental test could have a submaximal workrate of 2.3 mph 6.5% gradient or 2.5 mph 5.5% gradient. The speed selected was normally around that at which the subject walked at the end of the test. If the subject expressed a desire for a lower speed than that selected by the experimenter, an increased gradient with a reduced speed was selected.

The workrate selected was 80% of the predicted energy cost of the workrate attained at the end of the incremental test (American College of Sports Medicine, 1986).

e AD 1

Diagrammatic Aid for Submaximal Workload Estimation



APPENDIX E.

STEXT PROTOCOL

STAGE (Mins)	SPEED (mph).	GRADIENT (%)
1.	1.5	0
2.	2.0	0
3.	2.0	1.5
4.	2.0	3
5.	2.5	3
6.	2.5	5
7.	2.5	7
8.	3.0	7
9.	3.0	9
10.	3.0	11
11.	3.5	11
12.	3.5	13
13.	3.5	16
14.	4.2	16
15.	5.0	16
16.	5.6	16
17.	6.3	16
18.	7.1	16

APPENDIX F

SUBJECTIVE SCALES.

Examples of the Subjective Scales, Visual Analogue Scale, Breathlessness Borg CR10 Scale, General Fatigue Likert Scale Breathlessness.

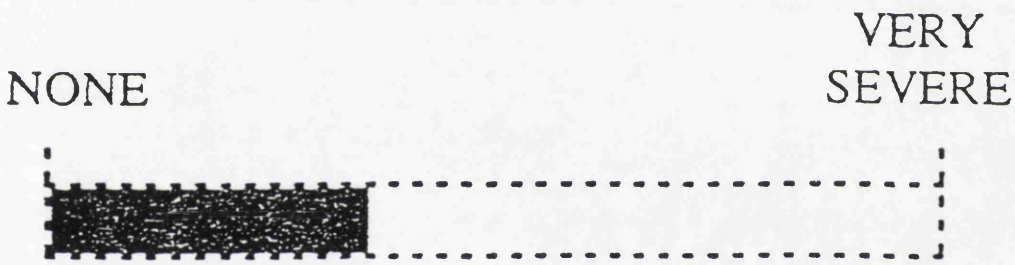
LIKERT SCALE

BREATHLESSNESS

- ☐ Not at all breathless
- ☐ Slightly breathless
- ☐ Moderately breathless
- ■ Really quite breathless
- ☐ Very breathless indeed

Visual Analogue Scale

Breathlessness



Borg CR10 scale.

General Fatigue

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

APPENDIX G.

UNITS OF MEASUREMENT.

List of Units.

Minute Ventilation	-	litres.min^{-1}
Oxygen Consumption	-	litres.min^{-1}
Volume of Carbon Dioxide Produced	-	litres.min^{-1}
Frequency of Breathing	-	breaths.min^{-1}
Heart Rate	-	beats.min^{-1}
Tidal Volume	-	litres