PHYSIOLOGICAL RESPONSES OF ASTHMATICS TO ENDURANCE RUNNING

by

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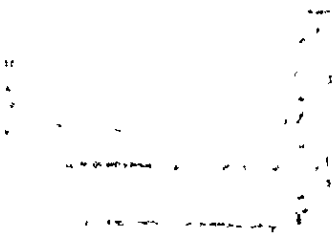

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ABSTRACT

The aim of the study was to examine the physiological effect of endurance running on the asthmatic adult, an area in which there has been little research. The specific aims were to: Firstly, examine the cardio-respiratory and metabolic responses to short term maximal and submaximal exercise of untrained asthmatics and non-asthmatics, and endurance running trained asthmatics. Secondly, compare the physiological responses to prolonged endurance running of asthmatic and non-asthmatic athletes. Thirdly, evaluate the effect of endurance running training on the previously untrained asthmatic.

The mean VO_2 max of 17 untrained asthmatics was lower than that of 17 non-asthmatics, which in turn was lower than that obtained for 16 trained asthmatics (47.0 vs 51.5 vs 61.6 $ml.kg.^{-1}min^{-1}$). Both asthmatic groups showed significant correlations between the percent predicted FEV_1, VO_2 max and V_E max, indicating that severe airflow obstruction may impair the maximal response to exercise. In submaximal exercise the blood lactate concentration was significantly higher at the same absolute running speed for the untrained asthmatics compared to the non-asthmatics , but there was no difference at the same $\%VO_2$ max. The trained asthmatic group had significantly lower blood lactate even at the same $\%VO_2$ max compared to the untrained asthmatics, suggesting a normal adaptive response to physical training.

Outdoor half-marathon times were available for 11 asthmatic athletes. They were able to utilise an estimated 81.9% VO_2 max during the half-marathon, which is similar to non-asthmatic athletes. Therefore asthma does not impair the ability to develop a high degree of endurance fitness with appropriate training. The correlation of race pace with VO_2 max ($r=0.881$) and with the running velocity at 2mM blood lactate ($r=0.971$) are consistent with those reported for non-asthmatics. The $\%VO_2$ max utilised during the half-marathon was most strongly correlated with the $\%VO_2$ max at 2mM blood lactate ($r=0.819$), so that the $\%VO_2$ max utilsed is largely dependent on the capacity of the muscles to cover the energy needs aerobically.

The similar cardio-respiratory and metabolic responses to a treadmill half-marathon race and to a 2 hour run at 70% VO_2 max for asthmatic and non-asthmatic athletes, would suggest no reason why the asthmatic is disadvantaged in endurance running if adequately protected from exercise-induced asthma (EIA). However, pre-exercise medication failed to inhibit EIA for 2 of the 6 asthmatics during and after the half-marathon, and for 2 of the 4 asthmatics after the 2 hour run. Despite a reduction in the running speed and the use of a bronchodilator inhaler in the half-marathon, it was not possible to reverse the EIA whilst running. Conventional pre-exercise medication may therefore not be adequate to control EIA in prolonged exercise. In endurance running the asthmatic may be at a competitive disadvantage and may be at risk if EIA develops.

A 5 week period of endurance running training on a treadmill for 9 untrained asthmatics resulted in increases in VO_2 max, lower blood lactate at submaximal running speeds and a decreased time and higher $\%VO_2$ max utilised for a 2 mile run. These changes were similar to those of 6 non-asthmatics performing the same training, suggesting that asthma does not impair the ability to benefit from endurance running training. The severity of EIA was however not significantly changed after training. Endurance running is a good activity to improve the aerobic fitness of asthmatics.

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CHAPTER 1

INTRODUCTION

Asthma affects approximately 5% of the population, and can be defined as, "a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways" Scadding (1983). The airways of asthmatics are abnormally sensitive to a variety of stimuli. This increased responsiveness, known as bronchial 'hyper-reactivity', is regarded as the central abnormality in the asthmatic (Pride 1983).

Since the first century AD, exercise has been identified as one of the major trigger factors to the hyper-reactive airways of the asthmatic. "If from running, gymnastic exercise or other work, the breathing becomes difficult; it is called asthma" (Aretaeus 1st Century A.D., cited in Godfrey 1974). Indeed, a high percentage of asthmatics experience asthma if they exercise hard enough under the appropriate conditions (Godfrey 1983), and therefore the asthma induced by exercise is a potential problem in the lives of a majority of asthmatics. For asthmatics in whom wheezy breathlessness after exertion is the main symptom, the term exercise-induced asthma (EIA) is used. Exercise-induced asthma is physiologically identical to asthma initiated spontaneously or following other provocations and has been defined as, "acute, reversible usually self terminating airway obstruction, which develops after strenuous exercise" (Cropp 1975).

Until relatively recently the reason why exercise acts as a precipitating factor to the asthma was largely unknown. Investigators claimed that abnormal physiological responses to exercise observed for asthmatics, such as lactic acidosis (Seaton, Davies, Gaziano and Hughes 1969), were responsible for EIA. However, hyperventilation provokes asthma to the same extent as exercise (Bundgaard, Ingemann-Hansen, Schmidt and Halkjear-Kristensen 1981) suggesting that it is the increase in ventilation rate which acts as the precipitating factor to the asthma, and not humoural factors of exercise. A closer examination revealed that either the heat loss (Deal, McFadden, Ingram, Strauss and Jaeger 1979) or the water loss (Anderson 1983) from the respiratory mucosa as the ventilation rate is increased, acts as the initial stimuli in developing airway obstruction.

Apart from the specific effect of exercise on the asthma, asthmatics may also have a degree of airflow obstruction at rest which may impair the physiological response to exercise. In untrained individuals without disease, ventilation is not usually a limiting factor for the maximum oxygen uptake (VO_2 max). However, under impaired ventilatory conditions, for example with airflow obstruction as in asthma, the maximum ventilation may pose a limitation on the maximum oxygen uptake (Dempsey 1986). Thus, with increasingly severe asthma the maximum oxygen uptake may be restricted at the ventilatory level. Indeed, Fitch (1975b) has recognised that a proportion of severe asthmatics compete in sport at a disadvantage, both respiratory and physically. In addition, the fear of developing EIA may lead to inactivity, which could impair or retard the development of the circulatory system of the asthmatic. Thus it has also been suggested that any differences in VO_2 max between asthmatics and non-asthmatics, are more likely to be due to inactivity rather than asthma per se, unless EIA is provoked during the test (McFadden 1984a).

Studies comparing the VO_2 max values of asthmatic and non-asthmatic children have yielded conflicting results. One study showed that the VO_2 max of asthmatics was lower than non-asthmatics (Cropp and Tanakawa 1977) whereas another study showed that there were no difference between the two groups (Bevegard, Eriksson, Graff-Lonnevig, Kraepelien and Saltin 1976). Similarly, equivocal results on the VO_2 max of asthmatic adults have been reported with asthmatic males showing normal VO_2 max values (Ingemann-Hansen, Bundgaard, Halkjaer-Kristensen, Siggard-Anderson and Weeke 1980), and asthmatic females showing low VO_2 max values (Afzelius-Frisk, Grimby and Lindholme 1977). In addition, it has been suggested that the cardio-respiratory response to submaximal exercise may be impaired in the asthmatic. The ventilation rate (Cropp and Tanakawa 1977), oxygen uptake (Wasserman and Whipp 1975) and lactic acid (Seaton et al 1969) have all been documented as being excessive for a given work load, compared with non-asthmatics. There is, however, a surprisingly small amount of literature comparing the response of asthmatics and non-asthmatics to exercise (McFadden 1984), and thus further work in this area would be beneficial.

It has been recognised since the late 17th century that different activities may vary in their ability to provoke EIA. "The most

agreeble exercise is riding; the greatest are sawing, bowling, ringing of a dumb bell, singing, dancing; Walking is more vehement than riding, but not so great as the other: Those exercises that move the arms, exercise the lungs most" (Floyer 1698, cited by Anderson, Silverman, Konig and Godfrey 1975).

Compared at the same metabolic stress, the ability of activities to provoke EIA was greatest for free range running, then treadmill running, then cycling, and least for swimming (Fitch and Godfrey 1976; Anderson, Silverman and Walker 1972; Fitch and Morton 1971). In addition to the mode of exercise, the continuous nature (Morton, Hahn and Fitch 1982), the relative exercise intensity (Wilson and Evans 1981) and duration (Jones 1962) of endurance running may also contribute to the heightened ability of this activity to provoke EIA. Therefore, endurance running has been identified as the sport most likely to provoke EIA, with swimming becoming the recommended activity for the asthmatic.

McFadden (1980) has suggested, however, that factors other than the type or duration of the exercise may be much more important in dictating the severity of EIA. Such factors include the underlying state of the airway inflammation, the absolute ventilation and climatological factors. For example, endurance running involves prolonged hyperventilation often in cold conditions, in contrast to swimming which is usually performed in the warm and humid conditions of the swimming pool. Thus, running will lead to a higher respiratory heat loss or water loss compared to swimming, which could act as a greater stimulus to provoke EIA. However, if asthmatic medication is taken before exercise the difference in the bronchospastic response to swimming and dry land exercise is abolished (Schnall, Ford, Gillam and Landau 1982). In addition, subsequent studies have shown that endurance running is no worse than any other land based activity in its ability to provoke EIA, if the activities are compared under conditions of the same respiratory heat loss (Bundgaard, Ingemann-Hansen, Schmidt and Halkjear-Kristensen 1982c). Thus the suitability of endurance running as a sport for the asthmatic merits careful reappraisal.

Whether bronchial asthma affects the ability to train for and participate in distance running at a high level, is questionable. A number of top level swimmers are asthmatic; five Olympic Gold medals

were won by asthmatic swimmers between 1956 to 1972, reinforcing the belief that swimming is the optimum sport and recreational activity for the asthmatic (Fitch 1975b). In addition, of the 39 top class Italian athletes affected by bronchial (Todaro, Berluttin, Caldarone and Dalmonte 1984), only five were categorised as participating in purely "aerobic" sports, and of these five none participated in endurance running. However, Fitch (1975b) has also claimed that asthmatics participate to a high level in every sport in Australia, including cross-country running.

The ability of the asthmatic to participate in endurance running may be impaired not only by EIA, but also by the resting airflow obstruction. A study by Mahler, Moritz and Loke (1981b) suggested that runners with airflow obstruction (but not asthma) were able to develop only a "moderate" level of cardio-vascular fitness with appropriate training. Whether asthma per se impairs the ability to develop and utilise a high VO_2 max with training has not been investigated.

Although the responses of the asthmatic to short term aerobic exercise has been well documented, the safety and physiological effects of prolonged running has not been reported. This is surprising, since there are numerous asthmatics participating in endurance running, for example 200 asthmatics participated in the 1982 London Marathon.

The effect of prolonged running on the asthmatic is uncertain. Although Silverman and Anderson (1972) stated that the severity of EIA may decline with more prolonged exercise, they only examined 16 minutes of activity. Indeed, this possibility of an improvement with continuing exercise would be consistent with the clinical observation that asthmatics may "run-through" their asthma (Godfrey 1973). However, the effects of prolonged exercise on the asthmatic, possibly beyond the optimum effect of pre-exercise medication, such as running a marathon, are unknown.

The physiological responses to endurance running are well documented for non-asthmatic athletes. However, the physiological responses to endurance running for trained asthmatics has not been examined. Whether the asthmatic shows any adaptations to his asthma, allowing him to participate successfully in endurance running, is not known.

Studies of the effect of physical training on the asthmatic have been shown to improve the cardio-respiratory fitness, improve self confidence and possibly reduce the severity of EIA. However, such studies have mainly been concerned with 'general conditioning programmes' often employing intermittent type exercise (Itkin and Nacman 1966; Hirt 1964; Afzelius-Frisk et al 1977). Intermittent exercise is, however, more likely to lead to gains in muscular coordination and strength rather than improved cardio-vascular efficiency when compared to continuous exercise. For non-asthmatic adults, endurance running training has been shown to lead to good improvements in the aerobic fitness. The safety and physiological effects of training programmes employing exercise of a continuous nature for asthmatic children receiving adequate therapy has been demonstrated for swimming (Fitch and Godfrey 1976) and distance running (Nickerson, Bautista, Namey, Richards and Keens (1983). However, no such studies have been undertaken with asthmatic adults.

The question of whether an improvement in physical fitness leads to a change in the severity of EIA has received much attention. A number of studies have shown no change in the severity of EIA after physical training, in spite of an improvement in physical fitness (Leisti, Finnila and Kiura 1979; Bundgaard, Ingemann-Hansen, Schmidt and Halkjaer-Kristensen 1982; Fitch, Morton and Blanksby 1976; Nickerson et al 1983). There are, however, two major limitations in the interpretation of these studies. Firstly, some investigations failed to standardise the exercise intensity for the test for EIA, performed pre- and post-training. Secondly, the exercise mode to test for EIA was not always the same as that used for the training, and thus these studies failed to adhere to the principle of the specifity of training. It is therefore difficult, from these studies, to assess the effect of an improved cardio-respiratory fitness on EIA. When studies were performed at the same absolute work load before and after training, an improved fitness has been associated with a reduction in EIA of asthmatic children (Oseid and Haaland 1978; Henriksen and Toftegaard-Nielsen 1983; Svenonius, Kautto and Arborelius 1983). Although Arborelius and Svenonius (1984) suggested that a reduction of the hyperreactivity of the airways may occur with training, the majority of investigations have suggested that the reduction in EIA can be attributed to the lower ventilatory demands at the same

absolute work load as a result of the improved fitness. However, no such studies have been performed on the asthmatic adult.

The purpose of the studies reported in this thesis was to examine the physiological effect of endurance running on the asthmatic. The specific aims were:

Firstly, to evaluate the effects of inactivity and asthma on the cardio-respiratory responses to maximal and submaximal exercise of asthmatics. The physiological responses to maximal and submaximal exercise for groups of untrained asthmatic adults, were compared to both a similar group of non-asthmatics and to a group of endurance trained asthmatic runners. The performance times from endurance running events of the asthmatic athletes were analysed in relation to their physiological responses obtained from treadmill running. The relationships between the degree of airway obstruction and the physiological responses in maximum exercise, were analysed for both the trained and untrained asthmatic groups.

Secondly, to examine the physiological responses of prolonged endurance running in asthmatic and non-asthmatic athletes. In order to do this, the two groups were compared both during a two hour treadmill run at a constant speed selected to elicit 70% VO_2 max and to a treadmill half-marathon time trial.

Thirdly, to examine and compare the physiologic effect and safety of endurance running training on groups of previously untrained asthmatic and non-asthmatic adults. Further, to evaluate the effect of an improved fitness on the severity of EIA.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Overview of the Review of Literature.

This review of the relevant literature is presented in three major sections to cover the following areas of interest:

Section A will describe and consider the phenomenon of exercise-induced asthma (EIA). This section will also include an examination of the types of exercise likely to provoke EIA, the physiological changes associated with and the possible mechanisms to account for EIA, along with the drugs used in the prevention of EIA.

Section B will examine whether asthma affects the physiological responses in maximal and submaximal exercise. In addition, the studies examining the effect of physical training on the "fitness" and the severity of the EIA in the asthmatic will be reviewed.

Section C will examine the results of studies on asthmatics participating in competitive sport, with specific reference to endurance running. The physiological factors determining success in long distance running and the physiological responses to prolonged running, in studies of non-asthmatic athletes, will be discussed.

SECTION A - The Phenomenon of Exercise-Induced Asthma

Before attempting to describe the phenomenon of exercise-induced asthma, it is appropriate to try to briefly discuss asthma, by offering a number of the commonly used definitions of this disease.

2.2 The Definition of Asthma.

The definition of any disease evolves from clinical description, through specified abnormalities of structure and function, to causation or aetiology (Scadding 1983). At present, due to the the heterogeneity of the pathology of asthma and the inability to identify causal factors in some asthmatics, definitions of asthma involving either aetiology or causal factors are not possible (Scadding 1983). Therfore, current definitions of asthma are based on clinical description and functional abnormalities.

Clinically, variable breathlessness with expiratory wheeze are the recognised features common to all asthmatics, and thus definitions have emerged, incorporating such observations, for example:

"Episodic breathlessness with wheeze, a condition characterised by generalised airways obstruction, which is variable and reversible either spontaneously or with treatment" (Gaskell 1979).

However, such clinical descriptive definitions are usually superceded if a more objective and quantifiable basis becomes available. The clinical observations of breathlessness and wheeze can be quantified in terms of a measure of resistance to air-flow in the airways of the lung. Indeed, there is good evidence that all asthmatics show a wide variation in their expiratory air-flow resistance, and thus asthma has recently been defined in terms of a disorder of function, as follows:

"a disease characterised by wide variation over short periods of time in resistance to flow in intrapulmonary airways" (Scadding 1983).

The increase in airway resistance leading to the reduction in airflow that characterises asthma, consists of two components:
(a) bronchospasm due to contraction of respiratory smooth muscle, and

(b) physical obstruction, resulting from inflammatory changes such as

(i) oedema of bronchiolar mucosa and

(ii) the accumulation in and plugging of the bronchi, with mucous.

Asthma has been broadly divided into two categories:

(a) Extrinsic asthma, in which the resistance to flow may be related to exposure to environmental factors, such as

(i) hyperreactivity of the airways to physical and chemical stimuli, or

(ii) specific antigen-antibody reactions.

(b) Intrinsic asthma, in which no apparent external cause for the resistance to flow can be found, as is usually the case with the late onset of asthma where no past history of asthma or allergy can be found.

Asthmatics, whether or not they show evidence of specific hypersensitivity reactions, are abnormally sensitive to non specific bronchoconstrictor agents, such as the chemical mediators histamine and methacholine. An abnormal responsiveness is called bronchial hyperreactivity, which is thought to be the central abnormality in the asthmatic. Numerous specific "trigger factors" of asthma can be identified, including exercise, to which the attention of the review of literature will now turn.

2.3 Exercise as a Trigger to Asthma.

It has been recognised since the 1st century AD, from the writings of Aretaeus, that exercise acts as a trigger to asthma. However, it was not until the 1960's that the effect of exercise on the pulmonary response of the asthmatic was eventually clarified.

Early work by Herxheimer in the 1940's objectively examined the effect of exercise on asthma, showing a fall in the vital capacity 'after' short term running and cycling (cited in Silverman and Anderson 1972). However, conflicting observations were made in the 1950's suggesting exercise caused a decrease in the resistance and improvement in lung function of asthmatics in some studies, while in other investigations it caused the reverse effect. This anomaly has been explained by whether the observations of lung function are made during or after exercise and by variations in the duration and level of exercise. For example, Jones (1962) observed that brief high

intensity running reduced the resistance to flow whereas a prolonged run of 8 to 12 minutes increased the resistance to flow.

Once an appreciation of the type of work required to elicit a response was recognised, the testing of asthmatics before and after exercise flourished. The mode of exercise employed ranged from stair climbing (McNeill, Nairn, Millar and Ingram 1966) to conventional exercise such as swimming, running and cycling (Fitch and Morton 1971). These early studies revealed a very consistent pattern in the response of the lung function of the asthmatic to exercise: When exercise is about 6 to 8 minutes in duration and of a 'moderate' intensity, bronchodilation occurs during and immediately after exercise (thought to be due to the catecholamine release in response to physical exertion). Then an increase in airways resistance occurs, with lung function reaching its lowest level 3-5 and 5-7 minutes post-exercise in children and adults, respectively (Godfrey 1983).

There has been some controversy as to the duration of the functional abnormalities of the asthma associated with exercise, with suggestions that the lung function may return to pre-exercise values within 15 minutes if the asthma is mild (Cropp 1975), or persist for as long as one hour (Jones 1962). For asthmatics in whom wheezy breathlessness, as a result of exertion, is the main symptom, the term exercise-induced asthma (EIA) is used, which has been defined as:

"acute, reversible usually self terminating airway obstruction, which develops after strenuous exercise in patients with asthma or hay fever" (Cropp 1975).

It is likely that exercise will act as a trigger factor to the asthma of a majority of asthmatics, as shown by studies on the incidence of asthma.

2.4 Incidence of Exercise-Induced Asthma.

The incidence of EIA among asthmatics has been the subject of many investigations. Studies have shown considerable variation in the incidence of EIA amongst asthmatics, from 13% (Itkin and Nacman 1966) to 90% (Jones 1966). Cropp (1975) has stated that such a large variation in the incidence of EIA, may be due to many reasons amongst which are patient selection, the type of exercise test, the criteria

used to define EIA, and the time interval between asthmatic medication and the exercise test. Indeed, as Anderson et al (1975) suggests, the most likely reason accounting for this range in the reported frequency of EIA, is the arbitrary definition of whether the patient develops EIA. When more stringent criteria have been applied to define EIA, 84% (Kattan, Keens, Mellis and Levison 1978) and 89% (Godfrey et al 1973) of asthmatic chidren had a fall of FEV_1 of 15% and 10% respectively. However, the incidence of EIA among asthmatic adults, is less well documented.

It has been suggested that the incidence of EIA may be related to the resting bronchomotor tone. A study by Anderson and Schoeffel (1983) investigated 313 asthmatic children, who, for the purpose of the investigation were divided into two groups which were, (a) 187 children with 'normal' lung function as defined by a PEFR 80% of predicted normal, and (b) 126 children with PEFR below 80% of predicted normal. A higher incidence of EIA was found amongst those with airway obstruction (86%) compared to the group with normal lung function (71%). However, there was no significant difference between the severity of EIA between the two groups. This is supported by Anderson (1983) who suggested that the severity of EIA is not correlated with the degree of airway obstruction so that bronchoconstriction is independent of the size of the airways prior to challenge. However, in contrast studies by Benson (1975) and Tattersfield (1981) showed that the airway response to a variety of stimuli are greater when the airways have an abnormal tone prior to challenge and less when bronchodilatation is present.

However, the incidence and the reproducibility of EIA is greatly influenced by the nature of the exercise and the conditions under which the exercise is performed, as will be considered in the next section of the review. It has been postulated that all asthmatics will develop EIA if they exercise hard enough under appropriate conditions (Godfrey 1983). Thus the clinical observation that EIA poses less of a problem to asthmatic adults, may be due to their more sedentary lifestyle, compared to asthmatic children.

2.5 Exercise-Induced Asthma and the Mode of Activity.

The degree of bronchoconstriction experienced after physical activity in an asthmatic may depend on the type, duration, intensity and pattern of exercise. Fitch (1975a) has stated that there are three principal reasons why a comparison of the available exercise systems on the provocation of EIA is useful:

(a) To assist in the development of the theory of the mechanism of EIA.

(b) To determine the optimum exercise challenge test for the diagnosis of EIA and the evaluation of pre-exercise drug therapy.

(c) To provide a scientific basis for the exercise prescription for the asthmatic.

2.5.1 The Type of Exercise and EIA.

It is well documented that different types of exercise vary in the degree of EIA they provoke (Anderson et al 1975). This specificity of exercise in the provocation of EIA was recognised as early as the seventeenth century, from the writings of Floyer, an English physician who had asthma.

Since 1970, a series of studies have been performed to examine and compare the ability of various activities to induce asthma. In an attempt to justify the prescription of swimming for the asthmatic, Fitch and Morton (1971) examined the degree of EIA provoked by 8 minutes of submaximal exercise in 3 types of activity, namely indoor swimming, cycle ergometry and treadmill running. Each activity was performed at the same exercise intensity namely at 80% to 85% of maximum heart-rate in 40 asthmatics, aged 10 to 51 years. A 15% fall in the FEV_1 occurred in 73% of the running tests; 65% of the cycling tests; and 35% of the swimming tests. In addition, in those subjects who did show a fall of greater than 15% after swimming, the magnitude of the response was significantly smaller compared to the EIA produced by these same subjects after cycling or running. This reduced ability of swimming compared to land activities to provoke EIA has been confirmed by other investigators comparing running and swimming (Silverman and Anderson 1972; Anderson et al 1975).

Furthermore, studies comparing land based activities under

conditions of the same metabolic stress, revealed that cycling was less asthmagenic than treadmill running (Fitch and Morton 1971; Anderson, Connolly and Godfrey 1971; Eggleston 1979), which in turn provided less of a stimulus for the asthma than free range running (Anderson et al 1971; Eggleston 1979; Shapiro, Pierson, Furukawa and Bierman 1979). In addition, a study by Fitch and Godfrey (1976) suggested that the severity of the asthma was the greatest for free range running compared to treadmill running and swimming (47%, 35% and 25% fall in FEV_1, respectively). On the contrary Miller, Davies, Cole and Seaton (1975), using oxygen uptake as the means to equate the metabolic stress of each activity, found no difference in the fall of the FEV_1 to treadmill running and cycling.

Therefore, it was concluded that swimming should be recommended as the type of exercise for the asthmatic in preference to running and cycling. This difference between running and swimming to provoke asthma was so clear cut that it encouraged more investigations into the reason behind this phenomenon. In addition, running was recommended as the optimum challenge to provoke EIA.

2.5.2 The Pattern of Exercise and EIA.

Several investigators have claimed that continuous exercise is much more likely to provoke EIA than intermittent exercise (Jones, Wharton and Buston 1963; Itkin and Nacman 1966; Strick 1969; Fitch and Godfrey 1976). Hence activities based on brief work periods separated by intervals of rest have been employed in the rehabilitation and physical training of asthmatics. However these studies gave little objective evidence to support the clinical impression that intermittent exercise should be administered in preference to continuous activity.

Jones et al (1963) observed that 1 to 2 minutes of running did not elicit the airway obstruction typical of more prolonged exercise. From this he concluded that forms of intermittent exercise and especially ball games are more suitable forms of exercise than continuous exercise like endurance running. However, as Morton et al (1982) has commented, this study by Jones et al (1963) is incorrect on two points: Firstly, it assumes that the overall effect of many brief periods of exercise equates to the response of one period studied in isolation, and secondly, the validity of extrapolating from exercise

of one to two minutes in duration to ball games comprising intervals usually less than 30 seconds, is questionable. As a result of these two criticisms, Morton et al (1982) compared the effect of continuous running with four different regimes of intermittent running on the incidence and severity of EIA in 27 asthmatics. The absolute work was kept constant for each of the protocols, though the pattern of the intermittent exercises varied widely in terms of running speed and the recovery intervals, to account for a variety of energy processes. Continuous running elicited a more severe bronchospasm than any of the four intermittent patterns of exercise, which in turn did not differ in their ability to provoke EIA.

Hence, Morton et al (1982) confirmed the earlier recommendations of Jones (1963), and provided scientific reasoning for the prescription of intermittent exercise for the asthmatic. The mechanism behind the reduced bronchoconstriction with intermittent exercise is not clear, although it is thought that higher circulating catecholamines as a result of intermittent work may cause inhibition of the contraction of smooth muscle (Schnall and Landau 1980).

2.5.3 Duration of Exercise and EIA.

The effect of exercise on lung function in asthmatics largely depends on its duration. Early work by Jones et al (1962) compared the effects of brief and more prolonged exercise, showing that brief exercise of 2 minutes in duration caused an increase in FEV_1, whilst prolonged exercise of 8 to 12 minutes caused a marked fall of FEV_1.

Furthermore, Silverman and Anderson (1972) examined the effect of 1 to 16 minutes of exercise on ten asthmatic children with the speed and gradient of the treadmill held constant. Exercise lasting one minute showed that bronchoconstriction is minimal though not necessarily absent, contrary to the work of Jones et al (1962). Post-exercise bronchoconstriction reached a maximum when the duration of the exercise was 6 to 8 minutes. When the duration of the exercise was extended to 16 minutes, five of the seven who completed the test, developed post-exercise bronchoconstriction. On the contrary, the remaining two subjects who had developed marked EIA after 8 minutes of running, developed little EIA after this longer duration of activity. The observation that EIA is diminished with longer exercise, reflects the clinical observation and subjective view that some asthmatics are

able to 'run through' their asthma.

An explanation for this reduced ability of exercise of a longer duration to provoke EIA, has been offered by Anderson et al (1975): During short term exercise the release of bronchoconstrictor mediators is opposed by an increased sympathetic drive, but when exercise ends sympathetic drive fails and bronchoconstriction occurs. However, during more prolonged exercise the constrictor mediators are metabolised before the end of exercise, and hence bronchoconstriction does not occur or is less severe (Anderson et al 1975).

2.5.4 Intensity of Exercise and EIA.

To examine the effect of exercise intensity on EIA, Silverman and Anderson (1972) observed the severity of EIA of asthmatic children after running at a range of gradients (0% to 20%) on the treadmill. With the speed of the treadmill and duration of the test constant, the severity of EIA was positively correlated to the treadmill gradient up to 10 to 15 percent. However, elevating the treadmill beyond this gradient produced little or no further EIA.

Indeed, various investigators have claimed that a threshold for the intensity of exercise must be exceeded before EIA will develop (Jones et al 1962; Katz et al 1971; Silverman and Anderson 1972). However, there is no agreement on the exercise intensity at which the threshold is attained, stating this occurs at heart rates of 150 to 160 $b.min^{-1}$ (Cropp 1975) or 170 to 180 $b.min^{-1}$ (Anderson et al 1975) for asthmatic children.

Other workers have suggested that a universal 'threshold' for the development of EIA is inappropriate. James, Faciane and Sly (1976) stated that heart rate does not correlate with the extent of EIA in asthmatic children, with significant bronchoconstriction occuring in some subjects when the heart rate has not reached 160 $b.min^{-1}$. Indeed the severity of each individuals asthma will determine the 'threshold' for EIA to develop. More recently Wilson and Evans (1981) illustrated that the maximum bronchoconstriction will occur at work loads eliciting 80% VO_2 max, with no further increase in EIA at work loads beyond this.

Thus, the type, duration, intensity and pattern of exercise may influence whether EIA will be provoked. Therefore, it is now

appropriate to describe the recommended procedure for an exercise challenge, as a means of diagnosing the existence of EIA.

2.6 Recommendations for the Testing for Exercise-Induced Asthma.

As previously mentioned, the disparity in the results of the incidence of EIA among asthmatic groups between various investigators, is partly due to the nature of the test for EIA. It has been previously outlined that the bronchospastic response is influenced by the duration, intensity, pattern and exercise mode employed. In addition, the length of time between taking medication and the test for EIA has varied widely between studies, which will affect the asthmatic response. Thus a study group, led by Eggleston and Rosenthal (1979), was set up to clarify and emphasise the procedures for evaluating the airway response to exercise in the clinical and laboratory settings. The recommendations outlined below are those of this study group, unless otherwise stated:

2.6.1 Medication and Pre-Exercise Lung Function.

Medications influencing the pulmonary response to exercise should be withheld prior to exercise, for the following periods:

Betaadrenergic drugs	8 hours
Cromolyn Sodium	24 hours
Anticholinergics	8 hours
Corticosteroids	Need not be excluded.

Pulmonary function should be within 80% of an individuals usual values, and FEV_1 be at least 65% of predicted normal.

2.6.2 Equipment and Protocol to Test for EIA.

A motor driven treadmill has been recommended as most appropriate for the evaluation of EIA, with the physiological response monitored by heart rate or ventilation, and pulmonary response measured by a device both simple enough for frequent testing, and sensitive enough to detect small changes in airway obstruction (either PEFR or spirometry).

The working committee recommended a stepped stress protocol with 5

to 8 minutes in 'steady state' conditions, with the level of stress determined by objective criteria such as heart rate or oxygen uptake. Eggleston and Guerrant (1976) have reported a reduced variability in EIA using a work load eliciting 90% of the predicted maximum heart rate. More recently, Wilson and Evans (1981), recognising that 90% of predicted maximum heart rate will be widely differing relative work loads for each individual in terms of $\%VO_2$ max, evaluated the response to work loads eliciting 40, 60, 80 and 100 $\%VO_2$ max. A direct relationship between work intensity and the degree of EIA up to 80% VO_2 max, beyond which there was no further increase in EIA. Thus a work load eliciting 80% VO_2 max was recommended to assess EIA.

2.6.3 The Index used to Assess EIA.

In order to quantify EIA, three indices have been used, examining the PEFR and FEV_1 recordings made before and after an exercise challenge:

(a) % Fall Index.

The diagnosis and severity of EIA is usually made using the percent fall index. This is the post-exercise fall in PEFR or FEV_1, expressed as a percentage of the pre-exercise value.

(b) Exercise Lability Index (ELI) (Bundgaard 1981).

A similar calculation of the % rise of the PEFR or FEV_1 from baseline, allows the degree of bronchodilation as a result of exercise, to be calculated. The ELI is then calculated by adding the % rise, to the largest % fall of the PEFR or FEV_1, giving an overall bronchial lability in response to exercise.

(c) Jones Lability Index (JLI).

A different index was proposed by Jones (1966) involving the summation of the exercise-induced fall in lung function and an index of bronchodilation obtained by brief exercise following a bronchodilator (isoprenaline), all expressed in relation to predicted normal lung function.

Anderson (1983) has expressed that the JLI and ELI should not be used in the assessment of the severity of EIA, because the initial bronchodilation is not specific to asthma, and is present in other respiratory diseases such as cystic fibrosis. The percent fall index has been widely used in the assessment of EIA, although some criticism has been raised when comparing responses between patients with varying

degrees of airway obstruction at rest (Benson 1975).

2.6.4 Pulmonary Function Tests to Detect EIA.

The identification of an asthmatic response is determined by the method used to measure the change in airway function (Anderson 1983). Asthma is generally thought of as a disease of the small airways (Macklem 1971), but with more severe obstruction, the large airways become obstructed. It has been suggested that different pulmonary function tests reflect obstruction of different parts of the tracheobronchial tree (Bouhuys et al 1970). Therefore, it is necessary to select pulmonary function tests to detect changes in the small and large airways, and tests which are least affected by effort.

The availability and simplicity of instruments to measure PEFR and FEV_1 led to their use in documenting the incidence and severity of EIA (Anderson 1983). More recently, the changes in large airways have been investigated by the use of whole body plethysmography measuring lung volumes and derivatives of airway resistance, with changes in small airways evaluated using maximum expiratory flow volume manoeuvres (Godfrey 1983). Considerable debate has been entered into as to the relative merits of the various lung function tests to assess for EIA.

A comparison of the sensitivity of various techniques used to assess the changes of the airways in 24 asthmatic boys by Buckley and Souhrada (1975) concluded that traditional methods of PEFR and FEV_1 were not as sensitive as other measurements such as specific airway conductance (SGaw), maximum mid-expiratory flow (MMEF) and closing volume (CV). They suggested that PEFR is not a specific test of lung function, representing both large and small airway obstruction, and thus not nearly as sensitive as other pulmonary function tests. In addition, it was suggested that FEV_1 was rather too effort dependent and not very specific, reflecting not only small and large airway obstruction but also changes of airway collapsibility and elastic recoil. They further commented that when the peak flow meter was introduced by Wright and McKerrow in 1959, its purpose was to provide only a quick screening test, a role which it has adequately fulfilled. However, due to its convenience the peak flow meter has been used when more sensitive pulmonary function tests would be more suitable, and hence has delayed the critical evaluation of exercise on asthma.

In defence of the traditional methods of measuring airway changes,

Anderson and Schoeffel (1983) stated that the measurements of PEFR and FEV_1 were much more reproducible than measurements such as SGaw, flow rate at 50% of vital capacity (V50) and the forced expiratory flow in the middle half of the vital capacity (FEF 25-75). In addition, PEFR and FEV_1 are not dependent on prolonged and complete expiration so measurements may be made at frequent intervals both during and after exercise. Indeed, the changes in PEFR and FEV_1 correlated well with the changes in FEF 25-75 and V50 (Anderson and Schoeffel 1983), so a complete expiration is not required if spirometry is to be used. In addition, it has been demonstrated that simple indices of PEFR and FEV_1 are adequate even when lung volumes are changed.

The lack of sensitivity of PEFR and FEV_1 to detect changes in pulmonary function, compared to measurements such as SGaw, V50 and FEF 25-75, must be placed in perspective. The response of the asthmatic to the pulmonary function tests, must be compared to the response of the non-asthmatic. Indeed the concept of sensitivity tends to ignore the fact that non-asthmatics have greater changes in parameters such as SGaw: For example, for the percentage reduction in SGaw to be considered abnormal, a fall of 50% or more is required. This is in contrast to FEV_1 or PEFR, where a 10% fall is required to diagnose an abnormal response (Anderson 1983). In addition, the changes of FEV_1 and PEFR are well documented for non-asthmatics. Until the responses of non-asthmatics to other pulmonary function tests are well documented, FEV_1 and PEFR remain useful tools in assessing EIA. As Godfrey (1983) has commented, it has never been convincingly shown that more specific tests of lung function are superior to simpler tests for documenting EIA, and thus remain useful in assessing EIA.

2.6.5 Definition of an Abnormal Response.

Many studies have used purely arbitrary criteria to decide whether EIA developed or not, varying from wheeze to a fall in PEFR of at least 25% (Cropp 1975). Thus, in order to measure the incidence of EIA it is necessary to examine the extent to which asthmatics differ from non-asthmatics, and set the criteria to diagnose EIA in relation to such observations. Thus, several studies have examined the bronchial lability and more specifically the post-exercise decrement in lung function of non-asthmatics.

Based on the studies of Silverman and Anderson (1972), Anderson et

al (1975) and Burr (1974), Godfrey (1983) reported that the average rise in PEFR during exercise was 3% to 4% in both non-asthmatic children and adults, with a maximum post-exercise fall in FEV_1 from pre-exercise of 9% to 10%. Furthermore, Burr et al (1974) in a study of 812 non-asthmatic 12 year old children found that 92% and 98% of them had a post-exercise falls in PEFR of less than 10% and 15% respectively. Thus, a post-exercise reduction in the PEFR or FEV_1 must be greater than 10%, if asthma is to be confirmed (Anderson 1983).

2.6.6 Reproducibility.

The reproducibility of an asthmatic response, is usually expressed as the variability of the EIA provoked as a result of repeated exercise tests in the same subjects, and this expressed as a coefficient of variation.

The EIA after cycling has been reported to be more variable than with other forms of exercise: Coefficients of variation ranging from 30% (Katz et al 1971) to 410% (Poppius, Muittar, Kreus, Korhonen and Viljanen 1970) have been reported for repeated cycle exercise tests. Thus cycle ergometry has been found to be unsatisfactory for testing EIA. However, Jones (1966) reported only a 20% coefficient of variation among treadmill tests for the assessment of EIA. Similarly, Silverman and Anderson (1972) reported an average coefficient of variation of repeated running exercise tests within one week was 21%, although this was increased if the interval between tests was longer. Therefore, running is a more reproducible test for EIA than cycling.

With the establishment of an agreed reproducible procedure for diagnosing EIA, attention turned to an exploration of the physiological consequences of EIA and to the possible mechanisms proposed to explain the pathogenesis of EIA.

2.7 The Physiological Changes with Asthma and EIA.

Exercise-induced attacks may vary from other asthma attacks by being sudden in onset, short in duration, usually self terminating and always reversible by bronchodilators. However, asthma as a result of exertion is physiologically identical to asthma initiated spontaneously or following other provocations. The physiological changes in EIA, are outlined below:

2.7.1 Lung Function.

The characteristic pattern of the response of the lung function, measured by PEFR and FEV_1, of the asthmatic to exercise has been mentioned earlier in the review. In summary, a reduction in airflow resistance with an improvement in expiratory flow rates occurs immediately after exercise, and then a widespread narrowing of the airways results in an increased airflow resistance with a corresponding reduction in expiratory flow rates, 5 to 10 minutes post-exercise. In addition, other pulmonary changes in asthma as described by Pride (1983), will equally apply to the asthma provoked with exercise. For example, the enhanced airway narrowing will lead to increases in the residual volume and the functional residual capacity, and a reduction in vital capacity, whereas a good gas transfer is usually maintained. As asthma becomes more severe the maximum flow will be reduced at all lung volumes and residual volume rises further.

2.7.2 Inequalities of Ventilation and Blood Flow.

During an asthmatic attack or even when the lung function is within the normal range, the distribution of ventilation may be uneven (Pride 1983). An uneveness of ventilation will lead to an imbalance in the ventilation and blood flow (perfusion), and thus to arterial hypoxaemia unless the pulmonary blood flow shows corresponding changes. Although it has been demonstrated that the perfusion abnormality does occur in poorly ventilated areas, this redistribution of the blood flow is not sufficient to compensate for the uneveness in ventilation. This will result in inefficient gas exchange, leading to

wide alveolar-arterial PO_2 differences and increased dead-space to tidal volume ratios (Anderson et al 1972; Young et al 1982). Usually the decrease in the $\overline{PaO_2}$ with EIA is modest, and tends to be less severe than observed with spontaneous attacks of asthma. Rarely will CO_2 retention also occur with EIA (Cropp and Tanakawa 1977; Anderson et al 1972).

Although the physiological changes occuring with EIA are well defined and understood, the mechanism by which exercise provokes the asthma is not so clear and will be examined in the following section.

2.8 The Factors Responsible for Provoking EIA.

Exercise and allergens are two of the major triggers to asthma. Allergens are well understood, in their ability to provoke asthma, because the stimulus to produce asthma can be well defined and controlled, and therefore the relationship between the stimulus and response can be quantified. On the other hand, although EIA affects a large percentage of asthmatics, and hence is a potent influence on the lives of many asthmatics, advances into the quantitative relationship between the stimulus and response in EIA have only been made in the last few years.

In order to find the property of exercise that is responsible for inducing asthma, investigations have concentrated in three main areas:
(1) An identification of abnormal humoural responses to exercise of the asthmatic, which may be responsible for provoking EIA.
(2) A critical evaluation of the ventilation rate as a stimulus to EIA, and
(3) A closer evaluation of the properties of the inspired air, such as temperature and humidity, as a stimulus to ventilation.

2.8.1 Abnormal Humoural Factors of Exercise as Stimuli to EIA.

Observations that asthmatics have an increased accumulation of blood lactate compared to non-asthmatics, led Seaton et al (1969) to suggest that the associated metabolic acidosis acts as a trigger at the cellular level to initiate bronchoconstriction. However, studies comparing exercise and isocapnic hyperventilation found no difference in the increase in airways resistance for each condition, despite no change in blood lactate for the hyperventilation challenge (Bundgaard

et al 1981a). Thus blood lactate was dismissed as a direct stimulus for EIA.

The most popular theory in the 1970's for the mechanism of EIA was based on the observation that sodium cromoglycate, an inhibitor of mediators from the mast cell, given 'before' exercise prevents EIA (Silverman and Andrea 1972). Thus Godfrey (1977) put forward a simple model to explain EIA suggesting that exercise has two opposing effects: Firstly, the catecholamine release during exercise, favouring bronchodilation; and secondly, the release of stored mediators from the mast cell favouring bronchoconstriction. During exercise, these forces are more or less balanced, with a slight bias in favour of bronchodilation. At the end of exercise, the autonomic discharge rapidly ends and the unopposed mediators cause bronchospasm.

This theory was able to explain many of the phenomenon of EIA: The observation that mediators required time for resynthesis, explained the refractory period to further EIA (Edmunds et al 1978). In addition, the protective effect of the catecholamines or the removal of mediators explains why Schnall and Landau (1980) observed that brief high intensity (30 seconds) exercise preceeding a 6 minute run caused a reduction in the EIA. In addition, Godfrey (1977) believed that the mediators of bronchoconstriction are themselves metabolised thus accounting for the reduced EIA when exercise is prolonged. This theory of the mechanism of EIA was further supported by the observations that asthmatics may have an impaired adrenaline response to exercise (Barnes, Brown, Silverman and Dollery 1981; Warren, Keynes, Brown, Jenner and McNichol 1982), suggesting that the lack of a protective effect of adrenaline against the rise of mediators in exercise contributes to EIA. However, it has been shown that matched hyperventilation causes EIA to the same extent as exercise, without any changes in circulating catecholamines (Barnes et al 1981).

Thus in recent years the whole subject of the nature of the mechanism of EIA has been reappraised. The increase in ventilation with exercise has been confirmed as the primary trigger to EIA on the hyperreactive airways of the asthmatic, and much recent research has examined why an increase in ventilation acts as a stimulus to EIA:

2.8.2 Ventilation as a Stimulus for EIA.

As long ago as 1946, Herxheimer stated that the increase in minute

ventilation with exercise caused EIA, and called this "hyperventilation asthma". To examine this various investigators have shown that isocapnic hyperventilation produced the same degree of asthma as exercise (Zeballos et al 1978; Tweedale, Godden and Grant 1981; Bundgaard et al 1981a). It appears that, as a stimulus to EIA, exercise is only a means by which the minute ventilation is increased.

Therefore, there is considerable agreement that the increase in minute ventilation with exercise has a primary role in EIA (Deal et al 1979). However, the differences in EIA provoked by running and swimming could not be explained by differences in minute ventilation (Silverman and Anderson 1972). Clearly, the trigger for EIA is not simply a mechanical stimulation by ventilation of the tracheobronchial tree, as suggested by earlier investigators. In recent years, several investigators have undertaken research to examine whether the higher temperature and humidity of the air in the swimming pool could explain the lower asthmagenicity of swimming, with very far reaching consequences for the understanding of the mechanism of EIA.

2.8.3 Temperature and Humidity of the Inspired Air as Stimuli to EIA.

To determine the effect of air temperature on the asthmatic response, Strauss et al (1977) observed asthmatics exercising on a cycle ergometer breathing air either at room or sub-freezing temperatures. The FEV_1 fell 21% when breathing air at room temperature, whereas this response was almost doubled (41%) when breathing air at sub-freezing temperatures. Hence, cooling the inspired air will exacerbate the asthmatic response. This study gives objective verification to the frequent clinical observation that EIA is worse in cold conditions.

Likewise, several investigators have shown that increasing the humidity of the inspired air reduces EIA. For example, Weinstein et al (1976) observed a 29.5% fall in the FEV_1 after exercising asthmatic children in a dry environment, compared to a 13.5% fall in the FEV_1 when inhaling nebulised saline through a mask. Similar observations were obtained on asthmatic children when the effects of breathing ambient air and saturated air at ambient temperatures, were compared (Bar-Or et al 1977; Chen and Horton 1977).

Examining the combined effects of varying the temperature and humidity of the inspired air, Strauss et al (1978) observed the effect

of breathing inspired air in four different conditions: (1) Ambient room temperature and humidity, (2) Body temperature and ambient humidity, (3) Ambient temperature and 100% humidity, and (4) Body temperature and 100% humidity. It was observed that heating the inspired air to body temperature did not reduce the asthmatic response seen in conditions of ambient humidity and temperature. However, by increasing the humidity at ambient temperatures this reduced the fall in the FEV_1. Furthermore, the inhalation of fully saturated air at body temperature completely prevented any development of EIA.

In an attempt to explain the association between EIA and the humidity and temperature of the inspired air, it is helpful to outline the sequence of events during a ventilatory cycle. Inspired air is warmed to 37°C and the water saturation increased to 100% humidity by the time the air reaches the alveoli. This 'conditioning' of the inspired air up to 37°C and 100% humidity is normally completed before it reaches the intrapulmonary airways by the nose, pharynx and trachea (Hartley 1979). However, during exercise the ventilation required cannot be taken in by the nose, and thus breathing through the mouth leads to the full 'conditioning' of the inspired air further down the respiratory tract (Chen and Horton 1977). Thus, contrary to conventionally held beliefs, during exercise the upper airway is incapable of fully conditioning the inspired air (Godfrey 1983). During the process of conditioning the inspired air, heat and water are transferred from the respiratory mucosa. During expiration, the process reverses along thermal gradients, with only some of the vapourised water condensing back onto the airways and only a third to a half of the heat transferred recovered. Thus, the net effect of these changes results in both losses of heat and water from the respiratory tract. The higher the minute ventilation and the lower the temperature and humidity of the inspired air, the greater both the heat and water loss from the airways. Thus, Chen and Horton (1977) suggested that either heat loss or the water loss may be the stimulus to EIA.

Thus, the effect of the temperature and humidity of the inspired air on EIA, led to the development of two theories about the initial stimulus of this phenomenon. Firstly, cooling of the respiratory mucosa, and secondly, airway drying. The development of these two theories are discussed below:

2.8.4 Airway Cooling as a Trigger to EIA.

On the basis of the observations from Strauss et al (1977) that exercising in cold air will cause a greater fall in FEV_1 than in ambient conditions, a group of workers from Boston focused their attention on the heat loss and the subsequent airway cooling, rather than the water loss per se, as the relevant stimuli to EIA. A highly significant and positive correlation between the heat loss from the airways and the magnitude of the obstruction after exercise, was revealed (Deal et al 1979). To further test this hypothesis, McFadden and Ingram (1979) postulated that if a cause and effect relationship exists between respiratory heat exchange and post-exercise obstruction, then equivalent thermal stresses without exercise should cause the same obstruction. To examine this, asthmatic subjects underwent isocapnic hyperventilation at rates equivalent to moderate and mild exercise workloads, while the inhaled air was conditioned to different temperatures and humidities. The results confirmed the similarity between the asthma caused by hyperventilation and exercise, confirming that the initial event in EIA was cooling of the airways due to hyperventilation.

In addition, direct measurements of the temperature in the airways revealed that airway temperature fell with exercise, further supporting heat loss as the stimulus for EIA (Deal et al 1979; McFadden et al 1982). Furthermore, the respiratory heat loss was similar in non-asthmatics and asthmatics. Therefore, they suggested that persons with asthma either do not effectively condition the inspired air or may be the hyperreactive airways of the asthmatic make them unusually sensitive to the airway cooling associated with the conditioning of the inspired air. However, when cold air is inspired at rest only minor changes occur in the lung function (Simonsson et al 1967; Ramsey 1977). Therefore, the processes associated with cooling of the airways and minute ventilation are related. Such a relationship has been quantified in an equation by McFadden and Ingram (1979), describing the quantitative association between the total heat lost from the airways during exercise and the mechanical response, which has been labelled the "heat flux hypothesis".

As a result of these experiments, the suggestion that the fall in the temperature of the intrathoracic airways was the stimulus to EIA, gained wide acceptance. Indeed this theory went a long way to explain

many of the anomalies in EIA. A study by Bundgaard, Schmidt, Ingemann-Hansen, Halkjaer-Kristensen and Bloch (1982) comparing swimming and cycle exercise under controlled conditions of temperature and relative humidity of inspired air, showed no difference between the asthmagenic properties of these two activities. Hence, they concluded that the difference between cycling and swimming observed by earlier investigators was due to differences in the RHL under which the two activities were performed. Hence, due to the higher humidity and temperature of the inspired air in the swimming pool, swimming seems to be a favourable type of exercise for the asthmatic. However, on the contrary a further study showed that at a standardised RHL the difference between running and swimming was highly significant, with the fall in FEV1 39 $\pm$ 5% after running compared to 28 $\pm$ 4% after swimming (Bar-Yishay, Gur, Inbar, Neuman, Dlin and Godfrey 1982).

Examining the questionable difference between various land based activities on the ability to provoke EIA, Bundgaardet al (1982c) compared treadmill walking, treadmill running, bicycle ergometry and free running in 11 adults with EIA, under the same conditions of air temperature (23°C), humidity (40%) and ventilation. The decreases in PEFR after exercise were not significantly different for the four types of exercise. Thus, under the same conditions of metabolic stress and heat loss, land based activities were shown not to vary in their ability to provoke EIA.

Thus it has been suggested by McFadden (1980) that the severity of EIA depends on the underlying state of the airway inflammation; the absolute level of ventilation; and the climatological factors such as air temperature and humidity. It does not depend on the specific exercise type (with the exception of swimming), as formerly thought.

Thus, the "heat flux hypothesis" offered an explanation why exercise acts as a trigger to the asthma based on the cooling of the airways during conditioning of the inspired air. This incorporated many of the factors previously offered by investigators as the trigger to EIA, and the theory of airway cooling was widely accepted by many workers. However, more recently, the possibility that the respiratory water loss leading to airway drying rather than airway cooling, may be the relevant stimulus in EIA:

2.8.5 Respiratory Water Loss as a Stimulus to EIA.

A re-analysis of the role of respiratory heat loss in the pathogenesis of EIA was necessary in the light of contradicting observations. For example, EIA has been demonstrated both under conditions of negligible respiratory heat loss from the work of Deal et al (1979), and in conditions in which only small changes in retrotracheal temperatures have been demonstrated (Hahn et al 1984; Sheppard et al 1984). In addition, patients with asthma were shown to have a fall in the FEV_1 after inhaling small doses of aerosols of hypertonic solutions (Anderson et al 1981). Thus, the respiratory water loss for the conditioning of the inspired air, leading to a drying of the airways and thus to hyperosmolarity of the epithelial fluid of the large airways, has been postulated as the stimulus to EIA (Anderson et al 1982; Anderson 1984).

In order to examine the hypothesis that airway drying is the stimulus to EIA, Hahn et al (1984) performed a study on 10 asthmatics who exercised breathing air at varied temperatures, but identical water contents. Although the range of temperatures of the inspired air varied by 26°C and thus the respiratory heat loss would be equally varied, the airway responsiveness was not different. A further study by Sheppard et al (1984) examined 12 asthmatics hyperventilating in dry air at three different temperatures (-5°C, 22°C, and 37°C). In the three conditions, the minute ventilation required to provoke a 100% increase in airways resistance was not significantly different, although the RHL varied widely. These studies suggest that the airway response will be similar if the relative water loss (RWL) remains the same, though the RHL may vary widely. Thus RWL is a more potent stimulus for EIA than respiratory heat loss.

Investigations involving the inhalation of hypotonic and hypertonic aerosols have confirmed that asthmatics are indeed very sensitive to changes in the osmotic environment of the respiratory tract. A direct relationship between the extent of the osmotic stimulus to the airways and the potency in producing airflow obstruction has been demonstrated (Anderson et al 1983). In addition, the inhalation of an iso-osmolar dextrose solution did not provoke airway obstruction whereas the inhalation of a hyperosmolar dextrose solutions provoked the asthma, thus confirming hyperosmolarity as the stimulus (Eschenbacher et al 1984). However, much of the work associated with the development of

this hypothesis has been indirect, and thus further studies are required to confirm the changes in the osmolarity of the epithelial fluid lining of the airway mucosa during EIA (Lee and Anderson 1985).

It has been suggested that both airway cooling and the hypertonic effects of the respiratory water loss may operate together as a stimulus to EIA. It is recognised that patients with asthma may differ in their sensitivity to airway cooling or changes in osmolarity since the enhancement of EIA by cold, dry air is not universal, and not all patients develop EIA when breathing hot, dry air (Lee and Anderson 1985).

2.9 Mechanisms by which Bronchoconstriction Occurs.

Although there is some agreement of opinion on the initial factor, there is less consensus regarding the sequence explaining how airway cooling or an osmotic stimulus leads to, and sustains bronchoconstriction. It is postulated that substances may be released from the mediator cells in the bronchial mucosa in response to these stimuli, which are capable of inducing the contraction of bronchial smooth muscle. Indeed it has been demonstrated that a hyperosmolar or cold stimuli can lead to mast cell activation and mediator release (Eggleston et al 1984; Wasserman et al 1977; and Shaw et al 1985).

Originally, because they were unable to detect the liberation of the mediator, leucocyte chemotactic factor, after hyperventilation-induced asthma (Deal, Wasserman, Soter, Ingram and McFadden 1980), they concluded that EIA did not involve the intervention of mediators and the respiratory heat or water loss led to a neural reflex in provoking bronchoconstriction. However, a number of observations make the involvement of mediators in the development of EIA, likely: As Godfrey (1983) has questioned, the changes in lung function lag far behind the fall in mediastinal temperature, and the FEV_1 remains depressed after the temperature returned to baseline. This is not the pattern that would be suggested for a neural reflex, and suggests the involvement of a chemical mediator. In addition, the pharmacological agent, sodium cromoglycate, which is thought to prevent mediator release, has been shown to inhibit EIA (Anderson, Seale, Ferris, Schoeffel and Lindsay 1979). Furthermore, Lee, Nagy, Nagakura, Walport and Kay (1982)

demonstrated the release of the mediator, neutrophil chemotactic factor, in EIA and its suppression by sodium cromoglycate as a result of exercise in asthmatics. These findings would indicate that mediator involvement is highly likely in the pathogenesis of airway obstruction after exercise.

However, the observation that a neutrophil chemotactic factor is detectable in the blood of only approximately 75% of asthmatic individuals experiencing EIA (Lee et al 1982), would suggest that may be for some asthmatics mediator involvement is not important for EIA. Thus future studies may reveal that for some asthmatics mediators are important, wheras a neural reflex may be more important for other asthmatics in the pathogenesis of EIA.

Airway cooling and respiratory water loss may both be important for the initial stimulus for EIA, and mediator release may or may not be important for the development of the bronchoconstriction. As suggested by Lee and Anderson (1985) an identification of sub-populations of asthmatics in whom a specific stimulus, with or without the participation of mediator release, contributes to EIA would be useful. As mentioned in this discussion, pharmacological agents may prevent the phenomenon of EIA, and thus EIA need not pose a problem to the asthmatic. The drugs used in the prevention of EIA and their proposed method of action, are discussed in the following section.

2.10 Drugs for the Prevention of EIA

The smooth muscle of the airways contracts in response to an increased local concentration of cyclic guanosine monophosphate (cGMP) and relaxes in response to an increase of cyclic adenosine monophosphate (cAMP) Thus variation in the cAMP or cGMP levels affects the tone of the bronchial smooth muscle, and the action of drugs for asthma ultimately affect the cAMP levels, either directly or indirectly.

The incidence of bronchial spasm is very variable and thus any evaluation of pharmacologic agents should involve a double blind protocol. This will avoid the placebo effect, since placebos have been shown to reduce the EIA significantly in 40% of children in a

study by Godfrey and Silverman (1973). Drugs for the prophylaxis of EIA act through a variety of pathways in either or both of two ways:
(a) by inducing bronchodilatation to compensate for EIA, and by
(b) blocking the various mediators responsible for bronchospasm.
The effectiveness of the drugs currently used in asthma for the prevention of EIA, are discussed below.

2.10.1 Anticholinergic Drugs.

Anticholinergic drugs, such as Atropine, block the action of acetylcholine on the bronchial muscle receptors. Acetylcholine is involved in the conversion of guanosine triphosphate to cGMP, thus by blocking its pathway, cAMP is allowed to dominate thus favouring bronchodilatation of the bronchial smooth muscle. Disturbed vision is a known side effect of Atropine and thus is unsuitable for use by sportsmen for the prevention of EIA (Shephard 1981).

2.10.2 Theophylline.

Theophylline probably promotes bronchodilation by reducing the intracellular concentration of calcium and by blocking the phosphodiesterase involved in the metabolism of cAMP. However, it seems that theophylline has little value in the treatment of EIA (Anderson et al 1979) although this may be because the dose used in many studies has been too low. It has been reported that blockade of EIA occurs when the plasma theophylline levels are in the therapeutic range of 10-20 ug/ml (Pollock, Krechel, Cooper and Weinberger 1977).

2.10.3 Steroids.

Steroids are effective for the management of asthma, but they offer no protection in the prophylaxis of EIA when taken before exericse (Van Neikerk 1977).

2.10.4 Sodium Cromoglycate.

Although the exact mechanism by which sodium cromoglycate has its influence is unknown, it is thought to act by inhibiting both the release of mediators of asthma from the mast cell such as histamine

and prostaglandin SRS-A, and by inhibiting phosphodiesterase, the enzyme responsible for the breakdown of cAMP. Many early investigations found cromoglycate to be the best treatment in the prophylaxis of EIA (Shephard 1981), although various studies documented an incomplete inhibition (Poppius, Muittar, Kreus, Korhonen and Viljanen 1970; Pollock et al 1977; Godfrey and Konig 1975). Anderson et al (1979) have suggested that a possible reason for this apparent discrepancy in the benefit of sodium cromoglycate in EIA, may be accounted for by the fact that patients can be divided into distinct categories of responders and non-responders. Thus it is suggested that future studies investigating sodium cromoglycate should clearly distinguish between these two groups.

2.10.5 Beta-2 receptor acting drugs.

Drugs acting on beta-2 receptors of the lung are used most frequently in the prevention of EIA, and are very effective. They promote bronchodilatation by the increased formation of cAMP, and work in the following way to prevent EIA (Sly 1984):

(a) The bronchodilation induced before exercise will compensate for the asthma induced by exercise.

(b) Enhancement of the bronchodilation in exercise, leading to a decrease or overriding the bronchoconstriction following exercise.

(c) Prevention of EIA by inhibiting mediator release or by acting directly on smooth muscle to prevent bronchoconstriction.

The most popular specific beta-2 drugs in current usage are terbutaline and salbutamol, which in the prevention of EIA are taken before exercise by aerosol. Sly (1984) examined the duration of inhibition of EIA of various beta-adrenergic drugs. Salbutamol inhibits EIA for the longest period of time (4-6 hours), and thus was suggested as the drug of choice for the inhibition of EIA. They also suggested that when beta-adrenergic drugs do not afford protection, the addition of theophylline, sodium cromoglycate or inhaled corticosteroid may enhance protection.

The majority of studies on drugs to prevent EIA have not compared the different agents on the same subjects, and therefore a comparison of the merits of various drugs is difficult. However, when such comparisons have been made, beta-2 agonists offer the greatest protection to EIA. A well controlled study by Godfrey and Konig

(1976) showed the proportion of children having a significant suppression of EIA compared to placebo (defined as greater than a 50% block in the response) was the greatest for salbutamol (100%), compared to sodium cromoglycate (80%), choline theophyllinate (80%) and atropine methonitrate (60%).

Therefore, a variety of drugs taken singly have been shown to offer asthmatics a degree of or total protection from EIA. In addition, it has been suggested that combination therapy may be useful for the prevention of EIA, indicating that for some individuals a single drug failed to offer protection from EIA, whereas combination drug therapy yielded a significant therapeutic advantage (Cummings and Strunk 1984; Bierman, Pierson and Shapiro 1975). Therefore, in patients with asthma taking adequate medication, EIA need not be a large problem.

SECTION B - The Physiological Responses to Exercise and to Physical Training of Asthmatics.

This section examines whether asthma impairs or changes the physiological responses to maximal and submaximal exercise. In addition, the physiological effect of planned programmes of physical training on the asthmatic will be discussed.

2.11 The Physiological Responses of Asthmatics to Maximal Exercise.

The interaction of the respiratory and cardiovascular systems is essential for maximum exercise performance and thus the functional impairment of either system will adversely affect exercise tolerance (Wehr 1976). Whether asthma results in a functional impairment in the respiratory system for gas exchange, will depend on two factors. Firstly, the severity of the resting airflow obstruction; and secondly, whether asthma is provoked during the exercise. In addition, many asthmatics have become inactive as a consequence of the fear of developing EIA. Thus the resulting inactivity may retard the development of the circulatory system, as it would in non-asthmatic individuals. Thus these factors may potentially influence the asthmatic's maximal response to exercise. It is helpful to examine the various physiological responses of asthmatics to maximum exercise in order to evaluate the effect of the asthma.

2.11.1 Maximum Ventilation.

In the majority of patients with chronic respiratory disorders, the exercise ventilatory capacity is highly correlated with the FEV_1 (Spiro 1975). Therefore, the maximum ventilatory capacity in asthma will be influenced by the severity of the airflow obstruction. In addition, evidence suggests that the ventilatory limits may also be reached during exercise in patients with airflow obstruction.

In non-asthmatic subjects the maximum ventilation attainable during exercise is approximately 70% of the maximum voluntary ventilation (MVV) (Jones and Campbell 1982). However, in patients with airway obstruction, the maximum exercise ventilation may equal or indeed

exceed the MVV (Clark, Freedman and Campbell 1969; Jones et al 1971). This observation suggests that the ventilatory limits during exercise are reached in patients with airflow obstruction.

Observations of the maximum ventilation attained during maximal exercise in asthmatics have yielded conflicting observations: In children with chronic asthma, Cropp and Tanakawa (1977) observed a lower maximum ventilation when compared to a similar non-asthmatic group. However, the severity of the asthma, does not seem to affect maximum ventilation for asthmatic children. A study by Bevegard et al (1976) which divided the group of asthmatic children into "severe" and "mild to moderate" groups according to the number of asthmatic attacks, showed that despite lower FEV_1 values for the "severe" asthmatic group the maximum ventilation was slightly higher (64.8 $l.min^{-1}$) than that observed for the mild to moderate group of asthmatics (58.7 $l.min^{-1}$). With adults, Ingemann-Hansen (1980) observed a maximum ventilation rate of 126.1 $l.min^{-1}$ (BTPS) for five medicated asthmatic males during treadmill running, which they claimed was a response not different to that observed with healthy males of similar ages.

Cropp and Tanakawa (1977) have claimed that any abnormalities in the ventilatory response will be related to pre-exercise pulmonary abnormalities. However, they do state that there must be a considerable deterioration in lung function before the asthmatic cannot increase the ventilation adequately in response to exercise. They have suggested that this limitation exists when FEV_1 is less than 60% and vital capacity less than 80% of predicted normal values.

Whether a possible impaired ventilatory system of the asthmatic will affect the ability of the asthmatic to perform aerobic work, has been examined by comparing the maximum oxygen uptake of asthmatic and non-asthmatic individuals.

2.11.2 Maximum Oxygen Uptake.

The maximum oxygen uptake attainable during exercise by an untrained subject is normally not limited by the maximum ventilation rate (Dempsey 1986). This is because $\dot{V}O_2$ max in untrained subjects is determined by "weaker links" in the chain of oxygen transport and oxygen utilisation, such as cardiac output and the oxidative capacity of the skeletal muscle, and not by the capacity for gas exchange

across the lung. However, airflow obstruction may limit the maximum ventilation attainable during exercise and thus prevent a level of ventilation sufficient to meet the metabolic demands required to perform the work. Thus in patients with significant airflow obstruction, the maximum ventilation attainable during exercise may become the rate limiting step in determining VO_2 max.

Cropp and Tanakawa (1977) examined the peak oxygen uptake of 21 asthmatic children and 13 comparable non-asthmatics exercising on a cycle ergometer, and observed lower aerobic work capacities in chronically asthmatic children than in the non-asthmatics. On the other hand, Bevegard et al (1976) observed the maximum oxygen uptake without pre-exercise medication for two groups of asthmatic children with different severities of EIA. On the basis of the number of asthmatic attacks, the children were divided up into a group with mild to moderate asthma and a group with severe asthma. It was found that the VO_2 max values obtained were not related to the clinical severity, and were within normal limits for the Swedish population, despite 50% of the boys developing EIA.

The work with asthmatic adults, however, has not directly compared the VO_2 max of the asthmatic with the non-asthmatic: In a study of five adult asthmatic males, with a mean age of 34 years, Ingemann-Hansen et al (1981) compared the treadmill and cycle ergometer VO_2 max values, both with the pre-exercise inhalation of salbutamol and a placebo. There was no significant difference in the VO_2 max values obtained with the inhalation of salbutamol or the placebo. The coefficient of variation reported for the determination of VO_2 max was 4.7%, which is similar to that reported for non-asthmatic subjects. The VO_2 max values observed with the pre-exercise inhalation of salbutamol were 3.13 $l.min^{-1}$ (41.3 $ml.kg.^{-1}min^{-1}$) during cycle ergometry, and 3.42 $l.min^{-1}$ (44.7 $ml.kg.^{-1}min^{-1}$) during treadmill running. This 8.2% and significantly higher VO_2 max during treadmill running, compared to cycle ergometry, is consistent with that observed for non-asthmatics. Although no control group of non-asthmatics was employed, they claimed that the values for VO_2 max were of the same magnitude as healthy young males. However, for asthmatic women Afzelius-Frisk et al (1977) reported lower VO_2 max values than those for a non-asthmatic population.

Examining the influence of sex on the VO_2 max, Bundgaard et al (1982b) employing bicycle ergometry observed VO_2 max values of 30.4

and 25.4 ml.kg.$^{-1}$min^{-1} for groups of male and female adult asthmatics. This represents a 20% difference of VO_2 max between male and female asthmatics, a value which corresponds closely to the expected difference between male and female non-asthmatics.

Therefore, there seems little agreement among investigators on the effect of asthma on VO_2 max. McFadden (1984) has stated where differences exist between the VO_2 max of asthmatics and non-asthmatics, this is more likely due to inactivity rather than asthma per se, unless EIA is provoked during the test. However, if pre-exercise abnormalities in lung function are gross then this will adversely affect the maximum ventilation, which will then be the rate limiting step determining the level of VO_2 max achieved.

2.11.3 Maximum Heart Rate.

It was suggested by Cropp (1975) that patients with severe airway obstruction find it difficult to breathe enough during exercise, hence these patients will be unable to reach a maximum heart rate appropriate for their age. This was confirmed by Cropp and Tanakawa (1977) who observed that the maximum heart rate achieved during maximal cycle ergometer exercise was significantly lower in asthmatic children (184 b.min^{-1}) compared to non-asthmatic children (197 b.min^{-1}). They claimed that this was due in part to an early onset of leg fatigue, and the increased work of breathing for the asthmatic group. Although the patients did not complain of respiratory distress at the end of exercise, it was suggested that it may have been dyspnea which caused the cessation of exercise, and hence the lower maximum heart rate. On the contrary, studies by Bevegard et al (1976) and Ingemann-Hansen (1980) on asthmatic children and adults, respectively, claimed that the maximum heart rates were within normal limits.

2.11.4 Respiratory Exchange Ratio in Maximal Exercise (R).

When pre-exercise pulmonary function is very poor, some asthmatics are reported to be unable to increase the ventilation sufficiently to eliminate the increased carbon dioxide generated by active muscles (Cropp 1977). Therefore a lower R value may be expected at maximum work loads for asthmatic individuals who have a considerable degree of pre-exercise airflow obstruction. Hence, the use of the R value over

1.15 (Issekutz et al 1962) to indicate whether VO_2 max has been reached may not be a reliable criterion for the asthmatic subject during maximal exercise.

2.12 The Physiological Responses of Asthmatics to Submaximal Exercise.

It has been suggested that with increasing pre-exercise obstruction, minute ventilation and the oxygen uptake may be greater than what would be expected for a given submaximal work load. In addition, it has been suggested that the response of blood lactate and plasma catecholamines in exercising asthmatics may be abnormal.

2.12.1 Submaximal Ventilation.

It has been stated that the ventilation required for a given submaximal task is greater for asthmatic individuals than for non-asthmatic individuals. Cropp and Tanakawa (1977) observed that at rest and throughout exercise, the ventilation was above the mean value for non-asthmatic subjects. For example at oxygen uptakes of 5, 15 and 40 $ml.kg.^{-1}min^{-1}$ the ventilation rate of the asthmatic group was 6%, 16% and 18% greater than the non-asthmatics, respectively. This higher than normal ventilation rate in asthmatics at comparable oxygen uptakes was achieved by larger tidal volumes and not by an increased respiratory rate. Thus, both the possible differences in the ventilation rate at submaximal work loads and the pattern of ventilation between asthmatics and non-asthmatics merits further attention.

Whether the response of the ventilation with increasing work loads is similar for asthmatic and non-asthmatic individuals has been questioned. The normal response of ventilation to increasing work can be described by a non-linear rise in ventilation as the exercise intensity increases to near maximal work loads (Jones and Campbell 1982). Cropp and Tanakawa (1977) have described the relationship between ventilation and oxygen uptake for asthmatic and non-asthmatic subjects, examining whether linear or quadratic (parabolic) equations could best describe the relationship. An optimal fit was provided by quadratic regression equations for 12 of the 13 non-asthmatic subjects. Whereas the relationship of only 12 out of the 21 asthmatic

subjects was described best by quadratic equations, with the remaining 9 subjects the rise in ventilation with increasing work loads was linear.

2.12.2 Submaximal Oxygen Uptake.

In addition to the minute ventilation being excessive for the work load in asthmatic individuals, the oxygen cost of the activity may be higher. This may in part be due to the increased oxygen cost of breathing as a result of some pre-exercise obstruction. Therefore, the oxygen cost of an activity may be greater for the asthmatic group due to an increased energy demand by the ventilatory muscles (Wasserman and Whipp 1975). More specifically, in two asthmatic patients, the oxygen uptake was recorded at 10% and 26% higher than the predicted values for oxygen uptake during cycle ergometer work. It was suggested that further work is required to define the relationship between the oxygen cost of work and the abnormality in pre-exercise lung function.

2.12.3 Submaxial Blood Lactate.

Observations that asthmatics accumulated more blood lactic acid at a given work load than non-asthmatics (Barboriak, Sosman, Fink, Maksud and McConnell 1973; Bevegard, Eriksson, Graff-Lonnevig, Kraepelien and Saltin 1971), led to the proposal that lactic acidosis was a possible mechanism for EIA. Although the relationship between EIA and blood lactate was positively confirmed by Fisher (1970), more recent workers have been much more sceptical about these claims. Vassalo (1971) although failing to find a direct relationship between EIA and blood lactate, suggested that EIA may be caused by increased minute ventilation and hypocapnia due to high lactate levels. On the contrary, other investigators have seen no relationship between EIA and blood lactic acid concentration (Chan-Yeung 1971; Silverman, Anderson and Walker 1972). In addition, the observations that asthmatics produce more lactic acid at a given work load compared to non-asthmatics, are unfounded because recent evidence suggests that the higher lactates may be due to their lack of fitness (McFadden 1984). Indeed, a very recent study by Packe, Wiggins, Singh, Nattrass, Wright and Cayton (1987) confirmed that there is no

difference between the blood lactate produced during submaximal treadmill exercise in asthmatics and non-asthmatics of a similar level of habitual activity.

2.12.4 Submaximal Respiratory Exchange Ratio (R).

The body obtains its energy from two substrates, namely fat and carbohydrate. As a guide to which fuel is being utilised the respiratory exchange ratio (R) is calculated (VCO_2 / VO_2). An R value of 0.7 indicates that fat is being metabolised, whereas an R value of 1.0 or over, indicates that all the energy is being supplied by the metabolism of carbohydrate.

It has been suggested that asthmatics may have a problem in metabolising free fatty acids and thus would show a high R value (Barboriak et al 1973). In a study of 5 asthmatic adults and 11 control subjects performing exhaustive cycle ergometer exercise for 12 minutes, plasma free fatty acids were lower immediately after exercise for both groups, but failed to 'rebound' after exercise in the asthmatic group compared to the response in the control group. These results thus suggest that subjects developing EIA may have to rely on CHO as the main fuel for energy, due to the reduced availability of FFA. It was postulated that this may be due to an impaired catecholamine response observed in some asthmatic subjects, as will be discussed in the following section.

When pre exercise pulmonary function is very poor, some asthmatics have been reported to be unable to increase the ventilation sufficiently to effectively eliminate the increased carbon dioxide generated by working muscles (Cropp and Tanakawa 1977). As a result R values would be lower than the actual metabolism of CHO would suggest. Hence, if the asthmatic individuals have a considerable degree of pre-exercise obstruction it is important to take care in interpreting the R values.

2.12.5 Circulating Catecholamines.

Due to the problems with developing a sensitive and specific assay technique for catecholamines it is only recently that adrenaline (AD) and noradrenaline (NA) concentrations have been reported for asthmatics during exercise. Plasma catecholamines are elevated in

response to exercise in non-asthmatic subjects (Barnes et al 1981). To examine whether the adrenergic responses play any part in the pathogenesis of EIA, the catecholamine responses have been compared for reacting and non-reacting asthmatics, and for asthmatics with EIA and non-asthmatics. These studies have yielded conflicting results.

A comparison of 11 reacting and 10 non-reacting asthmatic children (Reinhardt, Nagel, Stemmann and Wegner 1980), has shown that neither group had any change in AD after exercise. However, the group experiencing EIA showed a four fold increase in NA levels, whereas the group not experiencing EIA demonstrated only a 1.5 fold increase in NA. They concluded that EIA originates from alpha receptor stimulation which is mediated by excessive NA release. However, they did state that other factors must also be important, because sodium cromoglycate, which does not act via adrenergic mechanisms, offers protection against EIA. This study is however weakened by the lack of a control group of non-asthmatics. A further study by Zielinski et al (1980) compared reacting and non-reacting asthmatics, in addition to the responses of a small non-asthmatic control group. In the 10 patients developing EIA, AD and NA had risen significantly by the end of exercise, in contrast to the non significant rise for the 10 non-reacting asthmatics. However, for the 4 controls NA had also risen significantly by the end of exercise. Hence, this highlights the need for the asthmatic response to be compared to non-asthmatic response, before definitive conclusions can be offered.

The differences in the adrenergic responses of asthmatics and non-asthmatics has been the focus of various recent studies with asthmatic subjects failing to show a 'normal' rise in AD and NA concentrations with exercise. Using a radioenzymatic technique, Warren et al (1982) observed the catecholamine response of six non-medicated asthmatics and six non-asthmatics one minute after a standard exercise challenge. Adrenaline did not change for the asthmatics compared to the non-asthmatics who showed a three fold increase. Noradrenaline showed a five fold increase for the non-asthmatics, but to less than half this level for the asthmatics. Such a response was similar to that observed, also using radioenzymatic techniques, by Ind et al (1983) and Barnes et al (1981). It has been postulated that the failure of adrenaline to rise to provide a protective effect against the rise of mediators with exercise, such as plasma histamine, results in bronchoconstriction in the asthmatic. However, although the

responses of AD and NA in exercise appear different for asthmatic and non-asthmatic subjects, there seems to be little evidence that they play a direct role in the trigger to EIA:

Ind et al (1983), in addition to confirming no change in AD and only a small change in NA for asthmatics after a short exercise challenge, examined the responses of the EIA and the catecholamines after a second exercise challenge performed 40 minutes after the first. The fall in FEV_1 was 36 $\pm$ 5.5 % and 5.6 $\pm$ 2.1 % for the first and second exercise challenges respectively. However the catecholamine response for either AD and NA after test 1 and test 2 were not different. Therefore, it was concluded that plasma catecholamine levels after exercise do not explain refractoriness to a second exercise test.

Furthermore, Barnes et al (1981), although confirming the reduced sympathoadrenal response to exercise by asthmatics, observed that matched hyperventilation produced a similar degree of bronchoconstriction with no change in circulating catecholamines in either an asthmatic or non-asthmatic group. Thus it was suggested that circulating catecholamines play no direct role in EIA, but may play a permissive role via the mast cell.

To summarize, asthmatics may have rather normal physical performances, whereas others have more or less reduced capacity due to factors related to an impaired respiratory function or to physical inactivity. In addition, although the interelationships between the pulmonary function, maximum oxygen uptake and maximum ventilation values have been speculated upon, this has not been fully examined and comprehensively described.

In addition, the evaluation of the physiological responses of asthmatics to submaximal exercise has revealed that asthmatics may have higher oxygen uptake values, minute ventilation rates and blood lactate concentrations for a given work load, compared to non-asthmatics. In addition, asthmatics may show a reduced sympathoadrenal response to submaximal exercise, although studies have shown conflicting results.

Due to the fear of provoking EIA asthmatics and in particular adults may indeed become inactive. As Jones and Campbell (1982) have commented, the effect of inactivity may be more critical in patients

with impaired lung function, compared to non-asthmatics. This is because the smaller ventilatory reserve of a patient with lung disease may be more readily encroached upon by inefficient usage. Thus, physical training has become a therapeutic tool in the management of lung disease. Thus the next section will consider the effect of physical training on the asthmatic.

2.13 Physical Training and the Asthmatic.

Due to the problem of EIA, some asthmatics in the past were advised by clinicians not to exercise, leading to a decline in the capacity for physical work. However, with the proven ability of asthmatic medication to prevent EIA, asthmatics are now encouraged to take part in all forms of exercise using pre-exercise medication. Hence, exercise programmes are now included in the management of patients with asthma. It has been recommended that the benefits from such programmes should be thought of as having two components, namely the psychological and the physiological (Chai and Falliers 1968). Although the psychological benefits are of importance to the asthmatic, the review will concentrate on the physiological benefit of physical exercise.

Until the 1970's there was little objective evidence to support the inclusion of programmes of physical training in the management of the asthmatic. Although there was good agreement that asthmatics could tolerate well planned activity programmes (Scherr and Frankel 1958;Chai, Falliers, Dietiker and Franz 1967) the benefits claimed were based on subjective rather than objective observations. As Sly, Harper and Rosselot (1972) have commented, the studies failed to show objective benefit, but the psychological adjustments shown seemed sufficiently great to convince the workers of the value of the programme. Hence, the effect of physical training on the asthmatic was since examined more objectively to observe the changes in:

(1) cardio-respiratory fitness,

(2) pulmonary function, and

(3) the degree of exercise-induced asthma.

2.13.1 The Effect of Physical Training on Cardio-Respiratory Fitness.

One of the aims of the participation of asthmatic children or adults in training programmes, is to improve the maximum oxygen uptake, so that daily activities are less demanding. The examination of the physiologic effect of training on the asthmatic has mainly been undertaken using general activity programmes, although there have been a few studies observing the effects of endurance training. The work employing these two type of training will be reviewed.

(a) General Activity Programmes.

Numerous studies have been made on the physiological benefit of general conditioning programmes comprising for example, interval type training including circuit training, gymnastic exercises and games. A variety of results have emerged on the benefits of this type of training on aerobic fitness.

General conditioning programmes in asthmatic children have resulted in improved 'cardiovascular efficiency' as observed by a variety of physiological changes after training. Only a few studies have measured VO_2 max directly, although many studies have documented changes during submaximal exercise similar to those documented for non-asthmatics after a period of physical training (Astrand and Rodahl 1977). Increases in VO_2 max after training have been shown when this parameter has been measured (Oseid and Haaland 1978; Mrzena et al 1976). Measurements during submaximal exercise showing changes after training have included decreases in heart rate (Oseid and Haaland 1978 and Henrikssen, Nielsen and Dahl 1981b and 1983) and lower plasma lactates (Henrikssen et al 1981b) at a given work load. In addition, an increased physical work capacity at a given heart rate (Leisti et al 1979; Svenonius et al 1983) and an improved exercise tolerance (Sly et al 1972; Mallinson, Cockcroft, Burgess and David 1981) after general conditioning programmes have been documented for the asthmatic child. Furthermore an improved post-exercise recovery heart-rate has been documented (Millman, Grundon, Kasch, Wilkerson and Headley 1965). However, on the contrary, Seligman, Randel and Stevens (1970), Vavra, Macek, Mrzena and Spicak (1971), Geubelle, Ernould, Jovanovic (1971) and Graff Lonnevig, Bevegard, Eriksson, Kraepelien and Saltin (1980) have failed to show any physiological benefit of general training

programmes on asthmatic children.

However, the majority of studies agree that asthmatic children can tolerate activity programmes and obtain some physical benefit. Those studies which have not shown physical benefit used ball games and gymnastic exercises as the mode of training (Vavra et al 1971), and very low intensity training comprising walking (Geubelle et al 1971). These types of activities could not be expected to improve the maximum oxygen uptake.

Many of the studies outlined above did not include a control group (Millman et al 1965; Seligman et al 1970; Vavra et al 1971; Geubelle et al 1971; Leisti et al 1979; Mallinson et al 1981), hence placing some doubt on the findings. Where control groups of asthmatic children who did not alter their habitual level of activity were used, a greater change in the aerobic fitness of the trained group compared to the control group was observed (Oseid and Haaland 1978; Henriksen et al 1983; Sly 1972; Svenonius et al 1983). Only one study has compared the asthmatic and non-asthmatic childs' response to training (Mrzena et al 1976). This study showed that the asthmatic group showed a larger increase in VO_2 max than the non-asthmatic group, after the same training. This was thought to be due to the lower level of fitness of the asthmatic group before training.

Although the results from asthmatic children cannot be directly applied to asthmatic adults, similar studies with adults employing general conditioning programmes have yielded the same conclusion: Itkin and Nacman (1966) observed that 75% of the 39 asthmatic adults showed an increase in VO_2 max in response to physical training using calisthenics and sports activities. Furthermore, Hirt (1964) examined the responses of adults with severe asthma to circuit style training, and observed a significant increase in VO_2 max compared to the non-active asthmatic control group. In addition, Afzelius-Frisk et al (1977) examined high intensity intermittent exercise in adults with severe asthma observing a significant increase in VO_2 max, and significant decreases in submaximal heart rate at a given work load. To further examine the effect of the intensity of training, Bundgaard et al (1982b) compared the responses of two groups of asthmatic adults, one performing high intensity work and the other performing low intensity work. They observed that the group involved in high intensity training showed a significant increase in VO_2 max from 27.6 to 30.4 $ml.kg.^{-1}min^{-1}$, whereas the low intensity training group showed

no change. Hence, this study can account for some of the discrepancy in the results of previous training studies employing intermittent exercises, indicating that if the intensity of the exercise is not sufficiently high no change in the VO_2 max can be expected.

Although several studies have shown an increase in VO_2 max or changes in related parameters, the type of training used by many of these investigations is more likely to lead to gains in muscular coordination and strength than improved cardiovascular efficiency. Intermittent exercise compared to continuous exercise is less likely to provoke EIA (Strick 1969 and Morton et al 1982), but is less likely to lead to good improvements of aerobic fitness, compared to activity of a continuous nature.

(b) Continuous (Endurance) Activity.

Training employing activity of a continuous nature has been shown to lead to good improvements in the VO_2 max of previously untrained non-asthmatics (American College of Sports Medicine 1978). However, few studies have documented the safety and physiological effect of activity of training using a continuous activity on the asthmatic. Distance swimming and distance running have been evaluated for asthmatic children, whereas no studies have involved the asthmatic adult.

Although swimming has been recommended as the sport for the asthmatic, little evidence exists documenting the physiologic effect of swimming programmes. Chai and Falliers (1968) and Taylor, Brkich and Herron (1968) both employed swimming training for the asthmatic, but they did not measure the changes in aerobic fitness. Only one study by Fitch and Godfrey (1976) observed the physiologic effect of distance swimming training on a group of asthmatic children. The physical work capacity, at a heart rate of 170 $b.min^{-1}$ on the cycle ergometer, was measured before and after 5 months of swimming training and showed an increase of 11 %. Therefore, despite the test being performed on land, after training in the swimming pool, there appeared to be a good improvement in VO_2 max. Hence, it seems some transfer exists between the physiological changes through swimming training to land based activity, thus supporting swimming as the exercise choice of the asthmatic. However, asthmatics without access to a swimming pool or asthmatics unable to swim would be deprived of a good level of aerobic fitness. Therefore a more recent study examined the safety and

physiologic effect of endurance running training on asthmatic children, because in theory this type of activity is more readily available.

Endurance running of a continuous nature is a more asthmagenic sport compared to swimming (Bar Yishay et al 1982) or intermittent running (Morton et al 1982), and hence it has been the least recommended sport for the asthmatic. However, Nickerson et al (1983) studied the effect of a controlled period of distance running on 15 children with severe asthma. After a control period, the training was performed 4 days a week for a 6 week period with the distance run gradually increased to 3.2 km. The changes in aerobic fitness was measured by the distance run in 12 minutes to reflect the VO_2 max, which was significantly greater after training. They concluded that distance running is safe and can increase the fitness of asthmatic children who are receiving adequate therapy.

In asthmatics not taking pre-exercise medication, training intensities known to improve the physical work capacity may not be tolerated because of the EIA they provoke (Svenonius et al 1983). Thus the need for adequate pre-exercise medication, if full benefit is to be gained from training regimes, is essential (Oseid and Haaland 1978). This will allow the asthmatic to participate to the greatest extent without experiencing EIA. Indeed, all training studies, with asthmatics using pre-exercise medication, have shown a good improvement in aerobic capacity indicating that effective training is possible if EIA is prevented by pre-exercise medication (Oseid and Haaland 1978; Schnall and Landau 1982; Henriksen and Nielsen 1983; Svenonius et al 1983). Indeed, if pre-medicated there seem to be no reasons why swimming should be preferred to dry land exercises.

To evaluate and compare the effects of dry land and swimming training using pre-exercise asthmatic medication, Schnall and Landau (1982) divided a group of 31 asthmatic children into a swimming training group, a dry land training group comprising intermittent exercise, and a group performing both types of exercise. No difference was observed in the degree of EIA induced by the different exercises when the children received pre-exercise medication. In addition, after the 10 week training period a significant reduction in heart rate of the asthmatics occurred while running on the treadmill, for both the dry land and combined activity groups, whereas no significant change was seen for the swimming group. Therefore, they concluded that

provided the asthma was adequately managed, an appropriately planned land based exercise programme would result in similar or greater advantages to those obtained from swimming, without added risk of EIA.

Asthmatics taking pre-exercise medication can obtain physiological benefit from physical training in a similar manner to non-asthmatics. However, the response of the asthmatic adult to endurance running training, which is the most asthmagenic sport but also the most available sport, has not previously been examined.

2.13.2 The Effect of Physical Training on Pulmonary Function.

It is of obvious interest to know whether physical training will change the basal asthmatic condition as reflected by changes in resting pulmonary function. The available studies have shown equivocal results.

Studies on asthmatic children have reported significant increases in the vital capacity after physical training (Millman et al 1965; Petersen and McElhenney 1965). In addition, a residential programme of physical training on asthmatic children (Mallinson et al 1981) has shown significantly higher PEFR and improved clinical status. However, this improvement must be questioned because it may be due to the increased use of medication under supervision or removal from the irritants of the home, in addition to or instead of the influence of physical training. Alternative reasons for an improvement in pulmonary mechanics other than physical training seem quite likely because various studies have shown no significant change in resting pulmonary function after physical training in asthmatic children (Chai and Falliers 1968; Taylor et al 1968; Henriksen et al 1981b; Nickerson et al 1983; Svenonius et al 1983).

The results from studies on asthmatic adults are also ambiguous. Itkin and Nacman (1966) observed an increase in FEV_1 in 16 out of 39 patients and Afzelius-Frisk (1977) observed a slight but significant increase in total lung capacity, FEV_1 and $\%FEV_1$ after training. However, Bundgaard et al (1983) and Hirt (1964) showed no change in pulmonary mechanics after training adult asthmatics.

The general concensus of opinion is that physical training alone will not change lung capacity (Keens 1979). Svenonius et al (1983) have noted that an increase in FEV_1 was largest, though not

significant, in the group using disodium cromoglycate as pre-exercise and maintenance medication. Hence, increased use of and changes in medication, combined with physical training, may lead to an improvement in pulmonary mechanics. The effect of physical training on the severity of EIA has also revealed equivocal results.

2.13.3 The Effect of Physical Training on the Severity of EIA.

An improvement in parameters measuring changes in "cardio-respiratory fitness" have been observed after physical training of the asthmatic by the majority of investigators, but there has been less reported on whether training influences the severity of EIA. Thus there is uncertainty as to whether physical training should be recommended to asthmatic patients to diminish EIA. Physical training may reduce the ventilation rate required to sustain a given work load. Therefore in theory, if the temperature and humidity of the inspired air were kept constant, this reduced minute ventilation may lead to a reduced severity of EIA. Various investigators have aimed to examine this hypothesis, employing a short running test with the asthmatics not taking pre-exercise medication.

There have been a number of studies putting forward claims for the beneficial effect of an improved physical fitness on the severity of EIA. Oseid and Haaland (1978) stated that most children obtaining physiological benefit from regular training programmes, also observed a reduction in the severity of EIA providing that the work load used before and after training was identical. This work was further supported by the findings of Henriksen et al (1981b), with asthmatic children showing a significant decrease in the EIA from 32% to 15% after training. These results were confirmed by a later study with a larger group of asthmatic children (Henriksen and Nielsen 1983), concluding that training has a beneficial effect on EIA.

Appreciating the beneficial effect of pre-exercise medication, Svenonius et al (1983) and Arborelius and Svenonius (1984), examined the effect of training with different pre-exercise medications, on the changes in fitness and EIA. They observed that in each training group, regardless of the pre-exercise drug therapy, the fitness and the degree of EIA after training at the same absolute speed improved. This decrease in EIA was explained by a lower ventilation rate post-training at the same absolute speed. However, it was observed

that for several children EIA was not provoked even at a maximum work load after training implying that a decrease in airway sensitivity had occured. Whether this reduced incidence of EIA was due to the improved physical fitness and/or due to the possibly increased medication, cannot be determined from this study.

However, what has been demonstrated by these studies is that the severity of the EIA is reduced post-training at the same absolute work load, which is thought to be due to the lower ventilation. Less evidence exists as to whether the improved physical fitness will change the basic hyper-reactivity of the airways. As Oseid and Haaland (1978) have stated, this reduction in EIA is the most important effect of the improved aerobic fitness after training, allowing the asthmatic child to participate in physical activities with less discomfort, less bronchospasm and less use of symptomatic medication. There have been no similar findings with asthmatic adults.

On the contrary, various studies have failed to show any change in the severity of EIA after an improvement in physical fitness. Leisti et al (1979) observing asthmatic children, showed an improvement of 11% in the physical working capacity at a heart rate of 180 $b.min^{-1}$ on the cycle ergometer. The peak flow was obtained before and after this cycle test, showing a fall of over 15 % in two children pre-training and a further child (3 in all) post-training, out of 16 asthmatic children. Therefore he concluded that training had no beneficial effect on the submaximal exercise-induced change in PEFR and individual patterns of responses seemed to remain constant. However, in the group Leisti et al (1979) observed, only a small percentage showed an asthmatic response to exercise. The low incidence of EIA among the group was possibly due to the low intensity and long duration of the test for EIA. Other methodological problems existed with other studies: Bundgaard et al (1982b) showed a 10 % increase in VO_2 max in asthmatic adults after high intensity interval type training, without any change in the severity of EIA. The measurement of EIA was performed using free running in the hospital corridor as the exercise challenge, which as the fitness improves would most likely be performed at a higher speed. Hence, the severity of EIA would be affected accordingly.

Other studies failed to appreciate the principle of "specificity of training", so that the exercise challenge test for EIA was not the

same as the type of training performed. Therefore, the gains in fitness would not be reflected in the test employed to assess EIA. Fitch and Godfrey (1976) employing swimming training to improve the physical fitness of asthmatic children, found no change after training in the degree of EIA after an exercise challenge performed at the same absolute running speed on a treadmill. Therefore the frequency and severity of EIA was not altered by regular swimming training. Fitch and Godfrey (1976) questioned whether this confirms that the response to an exercise challenge is a persistent feature of the hyper-responsiveness of the airways of the asthmatic, or merely a good example of the specificity of sports training. Therefore, he suggested that a study should be performed examining the effect of endurance running training on EIA using running as the exercise challenge. In a training study using endurance running, Nickerson et al (1983) showed an improvement in aerobic fitness in asthmatic children, as defined by distance run in 12 minutes, but showed no change in the degree of EIA experienced. However, they had failed to take the advice of Fitch regarding the specificity of training, and had tested for EIA on the cycle ergometer. The ventilation was not changed at the same work load on the cycle ergometer post-training and hence this would suggest that training had not altered the hyper-reponsiveness of the airways because the degree of EIA was the same with the same ventilation. This adds further support to the hypothesis that the reduction in the degree of EIA is the result of a lower ventilation after training, and not changes in the responsiveness of the airways. Thus it is necessary to match the exercise challenge for EIA to the type of training performed, adhering to the principle of specificity of training.

Asthmatics can therefore improve their physical fitness with training, which may in turn lead to a reduction in the severity of EIA. With appropriate medication the asthmatic is now encouraged to perform a wide variety of activities. However, endurance running has not been evaluated as a training mode for the asthmatic adult, and thus merits investigation. The effect of endurance running training on the severity of EIA experienced while running, will also be evaluated. Although no study on asthmatic adults has shown a reduced degree of EIA after physical training it would seem logical that they should benefit in a similar manner to asthmatic children, and hence could lead more normal active lives without experiencing EIA.

It has been shown that asthma does not preclude the development of the VO_2 max with physical training. Thus the available studies documenting the physiological responses to exercise of highly trained asthmatics are reviewed in the following section.

SECTION C - Endurance Running and the Asthmatic

This section will examine the available physiological studies on trained athletes who have asthma. There are however, no extensive studies on the physiological responses of asthmatics to prolonged running. Nevertheless, it is helpful to consider the responses of non-asthmatics to prolonged running in order to appreciate the physiological load which will be placed on the asthmatic in his attempt to meet the challenge of prolonged exercise. In addition, the physiological factors determining success in endurance running for the non-asthmatic will be discussed.

2.14 The Maximum Oxygen Uptake of Endurance Trained Asthmatics.

As was illustrated in the previous section of the review, asthmatics can improve their VO_2 max by training in the same manner as non-asthmatic individuals. For untrained non-asthmatics, maximum oxygen uptake is not normally limited by maximum ventilation but by the transport and uptake of oxygen by the cardio-vascular and muscular systems, respectively (Dempsey 1986). However, endurance running training improves these factors which normally limit VO_2 max, by increasing the oxidative capacity of the skeletal muscle and by increasing the capacity of the cardio-vascular system. Therefore, in well trained athletes the maximum ventilation may become the rate limiting step (Dempsey 1986). As previously documented, in patients with airflow obstruction the maximum ventilation may also pose a limitation on VO_2 max. Thus the effect on the VO_2 max of the combination of airflow obstruction and a highly trained state, merits attention.

Although no study has examined the VO_2 max of groups of well trained asthmatic runners, a study by Mahler et al (1981) examined the physiological responses of 9 runners with airflow obstruction (FEV_1/FVC ratio 63%), to examine whether poor lung function limits VO_2 max. The VO_2 max of these runners was obtained and compared to the VO_2 max values of 9 marathon runners and 9 inactive adults each group with normal lung function. The mean VO_2 max of the runners with airway obstruction was 51.1 $ml.kg.^{-1}min^{-1}$ (range 45.6 - 55.0), which was higher although not significantly than the VO_2 max of the control

group (48.7 ml.kg.$^{-1}$min^{-1}). Marathon runners with normal lung function had a significantly higher VO_2 max (59.1 ml.kg.$^{-1}$min^{-1}) than those runners with airflow obstruction. Thus runners with airflow obstruction only had moderate VO_2 max values, compared to runners with normal lung function.

In one study in which 39 top class athletes all affected by asthma were observed, the maximum oxygen uptake of 15 of these asthmatics was 58.4 $\pm$ 10.7 ml.kg.$^{-1}$min^{-1}, indicating a 'fairly good' VO_2 max (Todaro et al 1984). However, of these 39 athletes only 5 were categorised as participating in sports requiring predominantly 'aerobic' energy metabolism. The extent of the bronchial obstruction (FEV_1/FVC %) did not correlate significantly with the VO_2 max or V_E max. They concluded that bronchial asthma does not preclude participation in competitive activity, even in sports requiring a high VO_2 max. However, the VO_2 max of asthmatics engaged in distance running, has not previously been examined.

The following section will examine the physiological factors determining success in endurance running for non-asthmatics, so that the effect of the potential impairment of VO_2 max in the asthmatic in endurance running can be evaluated.

2.15 Physiological Determinants of Endurance Running Performance.

Many physiological factors have been identified as having influence on success in distance running in non-asthmatic athletes, for example maximum oxygen uptake, the ability to sustain a high % VO_2 max, blood lactate accumulation and running economy.

2.15.1 Maximum Oxygen Uptake.

Success in distance running has often been attributed to having a high maximum oxygen uptake, because observations on internationally ranked endurance athletes have shown that they possess high VO_2 max values (Saltin and Astrand 1967; Wilmore and Brown 1974).

The ability to supply energy by aerobic mechanisms is a dominant factor in the ability to sustain a given running speed. This is because a linear relationship exists between speed and oxygen uptake, and hence those individuals with high VO_2 max values will be able to sustain higher running speeds. Thus many studies were completed in

the 1960's and 1970's to examine the relationship between endurance running performance and VO_2 max.

Costill (1967), recognising that researchers had merely identified the anthropometric and physiological characteristics of elite distance runners and not related them to performance, utilised a battery of sixteen test items to see which correlated best with performance during a 4.7 mile cross country race. Maximum oxygen uptake correlated most strongly with race performance (r=0.82), indicating that 67% of the variation in performance could be accounted for by variations in VO_2 max.

In addition, Foster, Costill, Daniels and Fink (1978) examined the relationship between running performance over 1 to 6 miles with VO_2 max, muscle fibre type and enzyme activities in well trained runners. Running performance was most strongly correlated with VO_2 max, with the relationship increasing with the length on the race (r=0.88 at 6 miles). Similar correlations are observed for longer distances such as the half-marathon (r=0.81) (Williams and Nute 1983) and the marathon (r=0.88) (Maughan and Leiper 1983).

Despite the strong relationship between VO_2 max and endurance performance, it has been proposed that physiological measurements made during submaximal work may be better indicators of endurance exercise capacity (Farrell, Wilmore, Coyle, Billing and Costill 1979). Investigations of various groups of athletes have found that the fractional use of VO_2 max, running economy and blood lactate accumulation can account for more of the variation in performance in distance running than VO_2 max.

2.15.2 Fractional use of VO_2 max.

The ability to sustain a high percentage of VO_2 max is important for distance running performance. The fractional use of VO_2 max in a race can be derived from laboratory treadmill running tests. This approach is valid because there is a good correlation between the oxygen cost of treadmill running and track running, over a wide range of running speeds (McMiken and Daniels 1976).

Observations by Costill, Branan, Eddy and Sparks (1971) on Derek Clayton, the former world record holder for the marathon, had a modest VO_2 max (69.7 $ml.kg.^{-1}min^{-1}$) compared to other world class marathon runners, indicating that VO_2 max alone does not dictate endurance

running performance. It was suggested that success in distance running is dependent on the economical utilisation of a well developed aerobic capacity, and by the ability to use a large %VO_2 max with minimal lactate accumulation. Indeed, Clayton ran the marathon at 86% VO_2 max with a low blood lactate accumulation (2.4mM). During the half-marathon non-asthmatics can use an estimated 79% VO_2 max (Williams and Nute 1983; Farrell et al 1979) with a large range from 69% to 92%. However, for these two studies the fractional use of VO_2 max could not readily account for the differences in race performances, as reflected by a non significant correlations between % VO_2 max utilised and race pace.

It has been suggested that the importance of the fractional use of VO_2 max varies with the length of the race. As running distance is extended, the ability to sustain a high percentage of VO_2 max becomes more important. For example, Davies and Thompson (1979) observed that the relationship between running performance and VO_2 max decreased from 5km to 85km, as the relationship between %VO_2 max and run time increased.

2.15.3 Blood Lactate Accumulation.

Trained individuals have lower blood lactate concentrations during submaximal exercise even at the same relative work load (Williams et al 1967), which will allow them to cover their energy needs more aerobically. Thus, Daniels, Yarborough and Foster (1978) proposed that metabolic parameters measured during submaximal exercise may be a better indicator of endurance exercise capacity than the determination of maximal aerobic power, such that runners may set a race pace that is highly correlated to the accumulation of blood lactate.

Indeed, over a wide range of distances, running speeds at which blood lactate concentrations increase above resting levels have been shown to correlate better with endurance performance than VO_2 max (Farrell et al 1979; Sjodin and Schele 1982; Kumagai et al 1982; Kindermann et al 1979). For example, over the half marathon distance, Williams and Nute (1983) demonstrated a correlation of r=0.877 between race pace and the running speed at 4mM blood lactate (V4mM) indicating that 77% of the variation in performace could be associated with the ability to run at high speed with low blood lactate concentrations, whereas only 66% of the variation in performance could be explained by

VO_2 max.

2.15.4 Running Economy.

Whether differences in running economy, defined as the oxygen cost at a given submaximal running speed, can account for variations in performances in distance running events, has been the subject of many conflicting investigations on non-asthmatics. In the light of the observations that asthmatics with severe pre-exercise obstruction may have a higher oxygen uptake at given submaximal activities (Wasserman and Whipp 1975), it is especially important for the asthmatic that this factor be discussed.

For non-asthmatics there is a linear relationship between running speed and oxygen uptake, at submaximal work loads. This is represented by a very high correlation (approximately r=0.99) between speed and oxygen uptake for individual subjects. However, when data from a group of subjects is pooled, a lower correlation is achieved as reported, for example, by Sjodin and Schele (1982) for experienced male athletes (r=0.87). Therefore, there is some inter-individual variation among non-asthmatic groups of subjects for the oxygen cost of running. Indeed Sjodin and Schele (1982) reported a 15 $ml.kg.^{-1}min^{-1}$ variation for a group of experienced male athletes running at 15 $km.h^{-1}$, although Williams and Nute (1983) reported only a 5.5 $ml.kg.^{-1}min^{-1}$ variation for a group of recreational runners at 14.45 $k.hr^{-1}$.

Running economy is important for distance running performance, because two runners with the same VO_2 max but with markedly different running economies, would be running at different $\%VO_2$ max at a given speed. Whether the differences in running economy are "random" or related to running performance has been examined by various investigators, with conflicting results.

Although considerable variation in running economy existed within a group of 16 well trained distance runners, this factor could not differentiate their 10 mile performances (Costill, Thomason and Roberts 1973). In addition, for recreational runners differences in running economy could not account for the variation in performance over the half marathon (Williams and Nute 1983). Thus, it was claimed that differences in running economy are "random" and of little value in differentiating distance running ability (Costill et al 1973).

However, as Conley and Krahenbuhl (1980) suggest, differences in performance in endurance athletes with similar VO_2 max values may best be explained by differences in running economy. In a more heterogeneous group of 18 male athletes, Farrell et al (1979) examined the relationship of running economy to performance over a wide range of distances from 3.2km to the marathon. Running economy was significantly ($p<0.05$) related to race performance over all distances, although the treadmill velocity at the onset of plasma lactate (OPLA) accounted for the most variation in performance.

Therefore, in non-asthmatics a number of physiological factors can be identified as having influence on endurance running performance. It will be of interest to examine whether these relationships hold true for the asthmatic engaged in endurance running. Numerous studies of non-asthmatic athletes have measured the physiological responses to prolonged exercise, which will be reviewed in the next section.

2.16 The Physiological Responses of Non-Asthmatics to Prolonged Exercise.

Although the physiological responses to short term exercise are well documented for asthmatics, the responses to prolonged exercise such as endurance running have not been evaluated. Thus, the literature documenting the respiratory, cardio-vascular and metabolic responses to prolonged exercise in non-asthmatic athletes, are reviewed in this section.

2.16.1 Respiratory Responses to Prolonged Exercise.

Potentially, asthma poses limitations on the respiratory system. It is therefore particulary relevant to examine the possible additional load that prolonged running may place on the respiratory system of the asthmatic. Thus, the effect of prolonged exercise on the pulmonary function and ventilation rate in the non-asthmatic, will be evaluated.

(a) Pulmonary function.

Although there are numerous studies documenting the physiological demands of long distance running in non-asthmatics, few have observed

the direct effect on the respiratory system.

When measurements of the pulmonary function have been made, marked changes have been obtained after endurance races. Over 50 years ago Gordon, Levine and Wilmaers (1924) observed a 17% reduction in the vital capacity (VC) in 20 runners after the Boston marathon, and Hug (1928) reported similar falls (16-18%) after the 1927 and 1928 Swiss marathons (cited in Mahler et al 1980). Inspite of these large changes in pulmonary function after endurance running, it was not until the 1970's that interest in the area was resumed, which was encouraged by the use of more sensitive pulmonary function tests.

In an attempt to examine the significance of the fall in VC observed by the early workers, and to observe whether present day marathon runners show similar responses, Maron et al (1979) examined the pulmonary function of 13 long distance runners competing in the 1977 Wisconsin Marathon. An 8.6% ($p<0.001$) reduction in the post-race VC was reported, which was accompanied by an equivalent increase in residual volume (RV). Post-race FEV_1 and PEFR were not significantly different compared to pre-race values. However, the FEV_{1-2} sec was reduced by 19.7% ($p<0.01$), indicating that after the race, the expiratory flow was unaffected at high lung volumes, but was decreased at low lung volumes i.e. approximately after 80% of the VC was expelled. Thus it was concluded that the results were compatible with small airway closure occuring at an increased lung volume, which would result in a decreased VC and an increased RV, and was not due to muscular or neuro-muscular fatigue as suggested by earlier workers (Maron et al 1979).

In a shorter road race (20km), Mahler, Snyder and Loke (1980) observed a much smaller but significant decrease in the post race FVC of 4.2%, with the "faster runners" having a significantly greater decrement than the "slower runners" (7.7% vs 2.9% : $p<0.05$). Howver, there were no changes in the mean post race flow rates as measured by FEV_1, FEV_1/FVC ratio, PEFR and the maximum expiratory flow rate at 50% FVC (MEF50). They concluded that as airway obstruction did not develop in these runners, the reduction in FVC may reflect fatigue in the respiratory muscles as a result of glycogen depletion. They offered an explanation for the smaller reduction in FVC observed after 20km than those reported for the marathon, because of the lesser glycogen utilisation due to the shorter distance. Furthermore, they postulated that the greater decrement in the FVC of the "faster

runners" could be explained by their higher intensity of running, leading to a relatively greater depletion of glycogen, compared to the "slower runners". This finding is in contrast to that of Maron et al (1979) who found no correlation between the decrement in the FVC and performance times.

To examine the effect of extreme endurance running on lung function, Moritz, Mahler, Pantalena, Mahler and Loke (1980) observed the FEV_1, FVC, PEFR and flow at 50% of FVC in 15 athletes before and after ultramarathon races (80.6km to 100km). Each parameter was significantly decreased after the race, with repeat testing two and a half hours later still showing significant falls in FVC, PEFR and MEF50. They concluded that since FVC and airflow are dependent on the driving force of the thoracic musculature, post-race changes may reflect fatigue of the respiratory muscles.

Therefore small airway closure (Maron et al 1979) and respiratory muscle fatigue (Mahler et al 1980, Moritz et al 1980) have been suggested as possible mechanisms accounting for the fall in FVC with prolonged exercise in non-asthmatics.

The severity of the decrement has also been shown to be related to the ambient temperature: Mahler and Loke (1981) examined the effect on the pulmonary function of two marathon races completed in widely differing ambient temperatures, in:

(a) 46 runners who completed a marathon in temperatures ranging between -2°C and -4°C and a humidity of 69%, and

(b) 41 runners who completed a marathon in temperatures between 6°C and 8°C, and a humidity of 88%.

The participants in the study did not report any respiratory symptoms. There were significant decreases in the post-race FVC of 3.9% and 5.9% for the runners in the subfreezing and warmer marathons respectively, whereas the FEV_1 did not change for either marathon. However, the PEFR and the flow at 50% of FVC were significantly decreased in the group participating at sub-freezing temperatures, but unchanged when the ambient temperature was above freezing. Thus, they concluded that healthy persons may develop bronchoconstriction during endurance running in subfreezing temperatures.

No intra-race measurements have been made during distance running, and as Maron et al (1979) commented, it is not clear if observations made after endurance races truly reflect events occurring during the race or whether they are strictly post-race phenomenon. Thus it would

be beneficial to make measurements both during and after endurance running to attempt to evaluate the significance of post-exercise measurements.

Therefore, endurance running may cause deterioration in the pulmonary function of non-asthmatics, which may be further enhanced when exercising in sub-freezing conditions. Inspite of this observation, the pulmonary response to prolonged running has not been examined for athletes with asthma. This is suprising since the asthmatic athlete may start exercise with impaired pulmonary function, and have the added risk of EIA especially in cold conditions (Strauss et al 1977). Thus an examination of the effect on the pulmonary function in asthmatic athletes performing prolonged running merits attention.

(b) Ventilation.

It is particularly important to evaluate the response of the ventilation rate of the non-asthmatic to prolonged exercise, for two reasons: Firstly, the airway obstruction in asthma may be limiting the ventilation rate, and secondly, the 'trigger' for exercise-induced asthma is related to the minute ventilation. Thus, in order to evaluate the potential physiological load placed on the asthmatic engaging in endurance running, it is appropriate to examine the changes in the minute ventilation with prolonged running that have been documented for the non-asthmatic.

Although ventilation responds directly to the metabolic demands in short term graded work (Dempsey et al 1977), there is much discussion as to how the ventilation responds during prolonged exercise. The majority of investigators have observed a steady upward drift of ventilation termed the "ventilatory drift" for which various mechanisms have been postulated, whereas others have observed no change in the ventilation rate with prolonged exercise.

Various studies of constant paced exercise have shown ventilatory drift. For example, Martin et al (1981) examined 10 subjects cycling at 66% VO_2 max at a constant rate for 1 hour, and showed a 13% increase in minute ventilation ($p<0.05$) from the first (12 minutes) to the last (61 minutes) observation. This increase in ventilation rate was brought about by an increased breathing frequency ($p<0.05$) with an unchanged tidal volume. Similarly, Hanson et al (1982) examined the physiological responses of 15 well trained runners to 60-70 minutes of

treadmill running at 70-75% VO_2 max. Minute ventilation increased with time, which could be attributed to a 26% increase in breathing frequency. Tidal volume decreased by 10%. This altered respiratory pattern towards rapid shallow breathing as exercise is prolonged, leads to more 'wasteful breathing' requiring an increased total minute ventilation (Martin et al 1979).

However, on the contrary, Swaka, Knowlton and Critz (1980) observed 7 endurance trained males during two 80 minute runs at 70% VO_2 max, 90 minutes apart and found the ventilation rate to be constant throughout each run. Similarly, 7 well trained female athletes showed no significant change in the minute ventilation during 80 minutes of treadmill running at 65% VO_2 max (Gass et al 1983). These findings give support to the observation that trained endurance athletes show less of a rise of ventilation during long term exercise than untrained individuals (Claremont et al 1977), or may be the exercise was not of sufficient duration to show ventilatory drift in these well trained athletes.

Various mechanisms have been proposed attempting to explain the phenomenon of 'ventilatory drift'. Interestingly, there is a parallel rise in core temperature with the rise in ventilation. In an attempt to examine this possible causal relationship between ventilation and temperature, MacDougall, Reddan, Layton and Dempsey (1974) observed the physiological responses to treadmill running at 70% VO_2 max until exhaustion in the following three environmental conditions. (1) normal, (2) hyperthermic, and (3) hypothermic. Significantly prolonged and significantly reduced run times, when compared to the control, were observed in the hypothermal and hyperthermal conditions, respectively. Minute ventilation increased with time under each test condition, with significantly highest V_E values in the hyperthermal condition and lowest in the hypothermal condition. Thus it seemed likely that an increase in core temperature directly leads to an increase in the ventilation during prolonged exercise. However, passive heating of the core temperature does not induce an increase in ventilation (Martin et al 1981), thus casting doubt on the causal link between ventilation and core temperature.

Thus, Martin et al (1981) correlated the 13% increase in ventilation observed during one hour cycling, with other potential or possible mediators. He observed that a slow ventilatory rise occured in the face of the unchanged arterialised venous blood pH, PCO_2,

lactate and VCO_2. However, various mechanisms were postulated as being responsible for the rise in ventilation:

Firstly, the oxygen uptake rose steadily by 8.8% from 12 to 61 minutes ($p<0.05$), and showed a high correlation with the rise in ventilation over time ($r=0.95$:$p<0.01$) (Martin et al 1981). Therefore the rise in ventilation could be attributed to the increased metabolic demands of the muscle. To add support to this theory, the study by Gass et al (1983) which showed no significant change in minute ventilation, also showed no significant change in the oxygen uptake. Hence, if the relationship between the increase in minute ventilation and oxygen uptake is causal, then the absence of a ventilatory drift may be attributed to the unchanged oxygen uptake. On the contrary, this increased oxygen demand as a stimulus for the increased V_E is not supported by the work of Hanson et al (1982) who observed that an increase V_E occured with time, even in some cases as the oxygen uptake decreased.

Secondly, Martin et al (1981) observed that the percentage increase in noradrenaline of 87% from 12 to 61 minutes, with a range from 37 to 191%, was closely correlated with the individual percentage rise of the ventilation over the hour of exercise ($r=0.94$:$p<0.01$). Although it is appreciated that this high correlation offers no proof that a cause and effect relationship exists between them, there is evidence that noradrenaline stimulates ventilation (Heistad et al 1972) and that the levels reached in heavy long term exercise may provide the ventilatory stimulus responsible for the ventilatory drift.

Therefore 'ventilatory drift' with prolonged exercise has been demonstrated by a number of investigators, although the consequences of this are not clear. In non-asthmatics, Hanson et al (1982) has viewed the net effects of hyperventilation in trained runners to be advantageous, since the benefits to pulmonary gas exchange and H+ ion regulation outweigh the expense of some inefficiency in ventilatory work and departure from steady state. In addition, they comment that it is unlikely that the hyperventilation will lead to respiratory muscle fatigue. On the contrary, since the level of breathing is important in determining the perceived rate of exertion (PRE) (Noble et al 1973), it is argued that ventilatory drift may lead to a decreased exercise tolerance (Martin 1981).

Therefore, in non-asthmatics prolonged running may result in

'ventilatory drift', the degree of which may vary due to training status. The mechanisms and the consequences of this phenomenon are not clearly understood. An increased ventilation for the asthmatic may lead to a greater stimulus for EIA or may be difficult due to airway obstruction. 'Ventilatory drift' has not been evaluated for the asthmatic engaging in prolonged exercise, and thus merits careful attention.

2.16.2 Cardio-Vascular Responses to Prolonged Exercise.

To further outline the potential physiological load on the asthmatic performing prolonged endurance exercise, the response of the heart-rate and oxygen uptake of the studies on non-asthmatics to prolonged exercise will now be evaluated.

(a) Heart Rate.

Exercise results in the production of heat, which is dissipated by thermoregulatory processes, predominantly through the mechanism of sweating. Thus an athlete engaged in an endurance activity will lose body fluids which will eventually lead to a fall in plasma volume. This fall in plasma volume leads to a reduction in the venous return, stroke volume and cardiac output, and this, combined with the shunting of blood to the peripheral cutaneous vessels for thermoregulation (Rowell 1974), leads to a compensatory rise in heart-rate. This rise in heart rate or "cardiovascular drift", is commonly seen during prolonged exercise.

The majority of investigations have shown a significant rise in heart rate during prolonged exercise at a given work rate. Martin et al (1981) observing one hour of cycle ergometry at 66% $\dot{V}O_2$ max, showed a 23 beat rise in heart rate ($p<0.05$). An identical increase in heart rate was observed by Saltin and Stenberg (1964), but this was in response to 3 hours of cycle ergometry at 75% $\dot{V}O_2$ max. This increase in heart rate was more marked than the 10% increase in cardiac output because the stroke volume fell from 126 to 114 $ml.beat^{-1}$. Thus the increase in heart rate can be attributed to a fall in stroke volume, which is in turn affected by a fall in plasma volume.

These changes in heart rate seem independent of training status, for example Swaka et al (1979) observing 7 well trained runners found increases in rectal temperature and heart rate and decreases in stroke

volume and cardiac output during the course of an 80 minute treadmill run at 70% of VO_2 max. However, well trained female runners studied by Gass et al (1983) did not show a significant rise in heart-rate during 80 minutes of treadmill running and even had a 1% increase in plasma volume, to explain their lack of "cardio-vascular drift".

(b) Oxygen Uptake.

Oxygen uptake during short term work is a function of the exercise intensity. However, during prolonged exercise at the same work rate, many investigators have found the oxygen demands of the activity to increase, whereas other investigators have reported no change. This apparent discrepancy in the findings may be accounted for by the differences in the duration and intensity of the exercise of each study, or partly due to the differences in training status of the groups studied, as discussed below:

It has been suggested that a 5% to 10% increase in the oxygen required for a given work rate occurs when exercise is prolonged (Hartley 1977), and this seems to be independent of the work load or type of exercise employed. Experimental evidence from numerous investigators support this finding (Saltin and Stenberg 1964; Martin et al 1981; MacDougall et al 1974).

A number of possible mechanisms have been proposed to account for this increase in VO_2 and so apparent decrease in the mechanical efficiency, during prolonged exercise. Firstly, Hartley (1977) proposed that the increasing contribution of fat to supply the energy demands as exercise is prolonged, will lead to a greater demand of oxygen to supply the energy required. Secondly, an increased energy demand for peripheral circulation and sweat gland activity for thermoregulatory control, may lead to a greater oxygen uptake (MacDougall et al 1974). Thirdly, a loss of mechanical coordination with fatigue may lead to the recruitment of 'less efficient' muscle fibres (Rowell 1969). Fourthly, increased energy demands of the respiratory muscles may increase the oxygen uptake.

On the contrary, the studies with trained athletes of Swaka et al (1979) and Gass et al (1983) showed no change in the oxygen uptake. The investigators claimed that the unchanged oxygen demands is a result of the balance between increases in running efficiency and fatty acid oxidation. Therefore, these studies indicate that well trained athletes seem to be able to hold the oxygen demands in "steady

state" during prolonged exercise, or alternatively the duration of the exercise was not sufficiently long enough to show significant rises in the oxygen uptake with well trained individuals.

During competitive races in the field, very little information on oxygen uptake has been obtained, with the exception of a study by Maron, Horvath, Wilkerson and Gliner (1976) of two experienced athletes during a marathon. Expired air was collected at three mile intervals, and on analysis it was found that the oxygen uptake actually decreased with time while running at similar rates and covering similar terrain during the latter part of the race.

The majority of investigations have shown increases in heart-rate and oxygen uptake with prolonged constant-paced running, although the mechanisms accounting for these changes are unclear. An examination of these cardio-vascular responses to proloned running in trained asthmatics has not been evaluated and thus merits attention.

2.16.3 Metabolic Responses to Prolonged Exercise.

Although there is much information and some consensus of opinion on the metabolic responses during prolonged exercise in non-asthmatic subjects, there is no such information on asthmatic individuals. Therefore, the metabolic responses to prolonged running of the non-asthmatic athlete will be discussed, which will aid a future comparison with the response of the asthmatic athlete.

(a) Respiratory Exchange Ratio [R].

The body obtains its energy from two substrates, namely fat and carbohydrate, with the preferred fuel for exercise of a moderate intensity being carbohydrate. This is because fat cannot supply the body with energy at as fast a rate as carbohydrate, and thus in all but the lowest intensity exercise, carbohydrate is the preferred fuel. Carbohydrate for muscle metabolism, is stored as muscle and liver glycogen.

Research has shown that as exercise is prolonged a metabolic shift towards fat metabolism occurs. Early work by Costill (1970a) observed the responses of two experienced distance runners performing two hours of treadmill running from 55% to 67% of VO_2 max. The R value decreased

from 0.88 at 10 minutes, to 0.80 at 120 minutes, indicating a metabolic shift from 61% to 33% carbohydrate. This was further shown in female athletes by Gass et al (1983). As the glycogen stores become reduced, the body is forced to utilise fat as the substrate for energy production, eventually leading to the inability to provide energy at an adequate rate leading to fatigue. This will be the cause of the cessation of exercise in constant work conditions, or alternatively will explain the reduction in work rate in race conditions.

(b) Blood Lactate.

The accumulation of blood lactic acid during muscular activity is considered as an indicator of the degree of anaerobic metabolism and has become associated with 'exhaustion' in athletic activities. However, this popular association is unfounded for endurance events because studies have shown low blood lactate levels at the point of exhaustion in prolonged exercise.

The accumulation of blood lactate depends on the intensity of the activity, and the state of training. Indeed, field and laboratory assessment by Costill (1970a) on well trained distance runners during a series of races of various lengths, has revealed an inverse curvilinear relationship between the length of the competitive race and blood lactate concentrations. Therefore, blood lactate concentrations decrease as the length of the activity increases. At all distances the post-exercise lactate was found to be related to the $\%VO_2$ max utilised, which agrees with many other investigations (Astrand, Hallback, Hedman and Saltin 1963; Saltin and Stenberg 1964; Gohil et al 1982; Gass et al 1983). It was concluded that for trained runners when the oxygen requirements were less than 70% VO_2 max, little or no lactate accumulated. Thus it is unlikely that blood lactate will play a major role in fatigue in long distance running.

In addition to elevating VO_2 max, training for competitive distance running appears to permit a greater fraction of that capacity to be utilised without the accumulation of blood lactate. Indeed recent evidence has suggested that well trained elite runners may be able to race at higher blood lactate concentrations than less well trained runners (Williams et al 1984).

(c) Blood Glucose.

Blood glucose is used as an energy source to supplement the glycogen stores of the working muscles in exercise. Indeed, the contribution of blood glucose to the energy demands during prolonged running has been estimated as being just over 12% by Hall, Braaten, Bolton, Vranic and Thoden (1983). Goldstein (1961) has claimed that the increase in the muscle uptake of glucose is promoted by some activator of the glucose transport system, a humoral factor not confined to the muscle, this activator in turn is stimulated by muscular contraction.

Due to the utilisation in exercise, blood glucose would be rapidly depleted unless continuously renewed by the liver. The regulation of blood glucose is necessary because blood glucose is the main fuel for the brain and CNS and thus if it were not regulated then there would be an impairment of the function of these vital organs (Wahren et al 1971). It has been estimated that during submaximal exercise, 75% of the glucose production comes from glycogenolysis, with 25% from gluconeogenesis (the conversion of lactate and pyruvate into glucose) (Wahren 1977). As the duration of the exercise increases and the liver glycogen concentration decreases, the contribution to glucose production from gluconeogenesis may increase to 45% of the total.

The response of the blood glucose during prolonged exercise is well researched. Blood glucose concentrations rise at the start of exercise, which is probably caused by an elevated rate of hepatic glycogenolysis due to exercise-induced increases in catecholamine concentrations (Hall et al 1983). As exercise is prolonged the blood glucose may fall due to a mismatch between the rate of production of glucose from the liver and uptake by the muscles. Sanders (1964) has postulated two possible reasons to account for the fall in blood glucose. Firstly, a drop in the hepatic glucose output, which gained support from Ahlborg, Felig, Hagenfeldt, Hendler and Wahren (1974). Secondly, an increase in the utilisation of glucose in the muscle. This was supported by Lavoie et al (1982), who stated that hypoglycaemia during prolonged exercise is most likely caused by an increased glucose uptake by the muscles as muscle glycogen becomes depleted.

Hypoglycaemia has been defined by Felig et al (1982) as a blood glucose concentration of less than 2.5mM. Studies of blood glucose concentrations have revealed equivocal findings as to whether

hypoglycaemia is inevitable at the end of prolonged exercise. A further area of controversy exists as to whether the cessation of exercise is a necessary consequence of hypoglycaemia.

The early work of Christensen and Hansen (1939) observed the cessation of cycling at 67% VO_2 max occured when blood glucose fell. Thus a low blood glucose or hypoglycaemia has been associated with fatigue in long distance running. However, recent studies have questioned whether exhaustion is necessarily associated with low blood sugar. Felig et al (1982) observed that of the 19 males cycling to exhaustion at 60-65% VO_2 max, 10 experienced hypoglycaemia. However, when the blood glucose concentration of these 10 males fell below 2.5mM, they were still able to cycle for a further 15 to 70 minutes. Although cycling to exhaustion seems to cause hypoglycaemia in a significant number of subjects, running to exhaustion on a treadmill has not had the same effect. Hall et al (1983) had seven subjects attempt to run a marathon on a treadmill, and even at the point of exhaustion (21 to 24 miles) no hypoglycaemia was present. Similarly, Costill (1970a) observed no hypoglycaemia in two well trained athletes during an exhaustive two hour treadmill run. Thus, these studies suggest that hypoglycaemia is not necessarily linked with exhaustion, nor is the cessation of exercise a necessary consequence when hypoglycaemia is evident. As Costill (1984) has succinctly stated, blood glucose is only one source of carbohydrate for muscle metabolism during exercise. Thus hypoglycaemia and exhaustion only coincide when the endogenous carbohydrate supplies are also depleted.

(d) Free Fatty Acids (FFA).

The concentration of free fatty acids (FFA) governs the rate of diffusion into the muscle (Newsholme 1982), and thus the FFA concentration in the blood will influence the rate of FFA utilisation. Thus, the rate of uptake and oxidation of FFA by the working muscles is proportional to their plasma concentrations (Armstrong, Steele, Altszuler, Dun, Bishar and De Boos 1961). If FFA are to supply the energy demands of the muscle during submaximal exercise, a high rate of diffusion of FFA will be necessary. However, rarely do the FFA concentrations reach very high levels and thus the energy demands come from a combination of carbohydrate and fat, the relative proportions of which are determined by the concentration of the FFA.

Indeed, artificially increasing the concentration of FFA in rats has

been shown to improve endurance and lead to higher blood glucose and muscle glycogen concentrations at the end of exercise, compared to the control rats (Hickson et al 1977). Thus, raising the FFA inhibits glycolysis which in turn delays the onset of fatigue by a carbohydrate sparing effect.

During exercise the FFA concentrations are dependent on the intensity and duration of the exercise. For example, up to an exercise intensity of 70-80% of VO_2 max, plasma FFA concentration increases proportionately with the exercise intensity, whereas a negative correlation is found between the rise in FFA and blood lactate (Pruett 1970).

Therefore the question which remains to be answered is whether these respiratory, cardio-vascular and metabolic responses to prolonged exercise are similar in asthmatics to those in non-asthmatics.

CHAPTER 3

GENERAL METHODS

3.1 Subjects.

3.1.1 Untrained Asthmatics.

The 'untrained' asthmatic subjects investigated in these studies were volunteers from the student population of Loughborough University and from the general public in the Leicestershire area. The general public were advised about the project in local newspapers and on local radio. The general practitioner of each asthmatic was given details of the investigations to be undertaken. These 'untrained' asthmatics were not engaged in endurance running training, although a number were involved in other recreational activities.

3.1.2 Trained Asthmatics.

The trained asthmatic individuals investigated in these studies were all seriously engaged in endurance running training and competed regularly in endurance running events. They were recruited from an advertisement placed in the running magazine "Athletics Weekly", which is available nationwide. Sixteen asthmatic athletes from England, Scotland and Wales visited the laboratory for physiological and asthmatic assessment.

3.1.3 Untrained Non-Asthmatics.

Untrained non-asthmatic individuals were recruited from the students and staff at Loughborough University. None of these were actively engaged in endurance running training, although many took part in other sporting activities.

3.1.4 Trained Non-Asthmatics.

Trained non-asthmatic athletes were volunteers from the students and staff of Loughborough University and from a local athletics club.

3.2 Design, Construction and Calibration of Equipment.

3.2.1 Physical Characteristics of Subjects.

(a) Height.

A Harpenden stadiometer was used to obtain the height of each subject who were measured in bare feet.

(b) Weight.

Weight was obtained using a set of balance scales (Avery Ltd., model 3306ABV) with a capacity of 120kg and accurate to the nearest 50gm. They had been factory calibrated and rechecked regularly. Subjects were weighed wearing shorts (males) and shorts and shirt (females).

(c) % Body Fat.

In accordance with the methods and calculations of Durnin and Wormesley (1974) the percent body fat was obtained. This involved taking skin fold measurements at four sites on the right hand side of the body (biceps, triceps, subscapular and suprailliac) with skinfold calipers (Harpenden).

3.2.2 Assessment of Lung Function.

(a) Dry Spirometer.

A dry spirometer (Vitalograph Ltd.) was used to obtain the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC), in litres (BTPS). Each subject performed the manoeuvre until consistent readings were obtained (i.e. two readings for FEV_1 within 100 ml). FEV_1 was expressed as a percentage of the FVC (FEV_1%).

Predicted normal values for FEV_1 and FVC were obtained from the prediction nomograms in the Vitalograph manual based on the work of Kamburoff and Woitowitz (1972). The predicted values are based on the sex, age and height of each subject.

(b) Peak Flow Meter.

A Mini-Wright peak flow meter (Clement Clarke International Ltd.), as developed by Wright and McKerrow (1959), was used to obtain the peak expiratory flow rate (PEFR) measured in $l.min^{-1}$. The best of three trials was recorded as the subjects PEFR.

Predicted normal values, based on age and height, were obtained

from the nomogram of Gregg and Nunn (1973).

(c) Diary Cards.

Diary cards on which to record twice daily PEFR values and asthma symptom scores were completed by a number of asthmatics in these experiments. The diary card is shown in Appendix 1.

3.2.3 Equipment for Exercise Testing.

(a) Treadmill.

Motor driven treadmills (Quinton and Woodway), which were calibrated by the manufacturers and checked regularly, were used for all running tests. They had a range of speeds from 0 to 7 $m.s^{-1}$ and elevation range from 0 to 40%. In accordance with the test procedure, the speed of the treadmill could be altered by a hand held switch, either by the investigator or by the subject running on the treadmill. The treadmills were linked to a micro-computer (Pet Commodore) for which a programme had been written so that the time, speed and distance covered could be continuously displayed on the screen, with the added facility that a print out of the results could be obtained at 30 second intervals.

(b) Heart Rate.

After careful preparation of the skin (cleaning using a Mediswab and mild abrasion), four electrodes (Red Dot, 3M products Ltd) were applied to the chest in the following positions:

i. top of the sternum,
ii. right side of the thorax, approximately over the 5th rib,
iii. left side of the thorax, approximately over the 5th rib,
iv. clavicle region (earth electrode).

Leads from a heart rate monitor (Rigel Cardiac Memory Monitor, model 302) were attached to the electrodes. Heart rate ($b.min^{-1}$) and an ECG profile on an oscilloscope were continuously displayed. The heart rate monitor was linked into the micro-computer (Pet Commodore), so that heart rate was recorded at 30 second intervals throughout the tests.

(c) Subjective Ratings.

The Borg (1973) rating scale of perceived exertion, comprising a 15 point scale from 6 to 20 on a continuum of very very light to very very hard was used to obtain subjective ratings of the exercise intensity from each subject during exercise.

(d) Expired Air Collection Equipment.

A light weight (65gm), low resistance (3 cm H_2O at 300 $l.min^{-1}$) one way respiratory valve with a small dead space (80ml) designed in this laboratory and based on the specifications of Jakeman and Davies (1979) was used. A broad flanged rubber mouthpiece was attached to this valve. Low resistance, wide bore (30mm) flexible tubing (Falconia; Baxter, Woodhouse and Taylor) approximately 1m to 1.5m in length, connected the valve to a two-way tap (Harvard Equipment), which was used to open or close a 150 litre capacity Douglas bag (Harvard Equipment). A nose clip was used by the subject during all expired air collections.

(e)Breathing Frequency (Bf).

A small temperature probe was inserted and sealed into the one way respiratory valve, and this was linked to a chart recorder via an amplifier. The increase in temperature of the expired air on exhalation is thus amplified and recorded, thus recording each breath. The paper on the chart recorder was set at a known speed so that breathing frequency (Bf) in breaths per minute, could then be calculated. Tidal volume (Vt) can then be computed in the following way:

$$Vt\ (l) = \frac{V_E\ (l.min^{-1})}{Bf}$$

(f) Environmental Conditions.

A barometer was used to obtain the barometric pressure at the time of the gas analysis. A whirling hygrometer (Brannan Thermometers) was used to obtain the temperature and humidity of the laboratory environment.

3.2.4 Blood Sampling Equipment.

(a) Capillary Samples.

Samples of capillary blood from the thumb were taken from each subject before and during exercise without having to stop the runner. Alcohol swabs were used to clean the thumb before and after pricking the thumb with a sterilised lancet (Boehringer Mannheim). Duplicate capillary blood samples for the determination of blood lactate and blood glucose (25 ul) were collected from the thumb in calibrated

micro-pipettes (Acupette Pipettes; Scientific Industries Ltd.). The blood was deproteinized in 250 ul of 2.5% perchloric acid, centrifuged and then frozen at -20° C, for later analysis.

(b) Venous Blood Samples.

Venous blood samples were taken from an ante-cubital vein with the subject seated. The blood was placed in heparinised tubes and then centrifuged to obtain the plasma, which was then stored at -20°C for later analysis.

From the venous blood duplicate 20 ul samples were taken and mixed with 5ml Drabkins solution for the determination of haemoglobin concentration. In addition, triplicate samples of venous blood were placed in heparinized capillary tubes for the measurement of haematocrit. The tubes were plugged using miniseal clay blocks (Scientific Industries Ltd.), centrifuged for 10 minutes in a micro-haematocrit centrifuge (Hawksley). Values were then calculated with a micro-haematocrit reader (Hawksley).

Using the values for haemoglobin and haematocrit, the percentage change in the plasma volume was calculated, using the methods described by Dill and Costill (1974).

3.3 Analyses of Test Measurements.

3.3.1 Analysis of Expired Air.

The standard method of calculating oxygen uptake, carbon dioxide production, and ventilation was used, details of which are shown in Appendix 2. Calculations to obtain the derived parameters of respiratory exchange ratio, ventilatory efficiency and oxygen pulse are also given in Appendix 3.

The equipment used for the analysis of expired air is described below.

(a) Gas analysers.

A digital paramagnetic oxygen analyser (Taylor Servomex Model 570A) was used to measure the percentage of oxygen in expired air. An infrared carbon dioxide analyser (Mines Safety Appliances Ltd., Lira Model 303) was used to determine the percentage of carbon dioxide in the expired air. The analyser was used in conjunction with a calibration curve supplied by the manufacturer.

The oxygen and carbon dioxide analysers were calibrated before every expired air analysis, using a null gas (100% nitrogen), room air and a gas of known oxygen and carbon dioxide concentration.

(b) Gas Volume Meter.

A dry gas meter (Parkinson Cowan Ltd.), calibrated by the manufacturers and in the laboratory using a 600 litre Tissot spirometer (Collins Ltd.), was used to determine the volume of expired air. The air from the Douglas bag was drawn through the dry gas meter (Parkinson-Cowan Ltd.) using a small pump.

The temperature of the expired air was obtained using an Edale thermistor (type 2984, Model C), fitted to the inlet tube of the gas meter. The barometric pressure in the laboratory was also noted at the time of the gas analysis.

3.3.2 Analysis of Blood Samples.

(a) Capillary Blood.

Blood lactate was analysed using a modification of Olsen's (1971) fluorimetric procedure, for which the coefficient of variation was 3.0% (Williams and Nute 1981). Blood glucose was analysed using a colourimetric method, analysed photometrically using an Eppendorf Photometer (Maughan 1982).

Haemoglobin was measured in accord with the cyanmethaemoglobin, colourimetric method of Van Kampen (1961).

(b) Venous Blood.

The 10 ml venous blood samples obtained from an antecubital vein were centrifuged, and then the plasma divided into two. One sample was stored appropriately for the analysis of plasma catecholamines, and the other sample was stored appropriately for the analysis of plasma free fatty acids and plasma glycerol.

Plasma catecholamines (adrenaline and noradrenaline) were determined using liquid chromatography with electrochemical detection, in accordance with modifications of the methods of Bioanalytical Systems Ltd. and Davies, Kissinger and Shoup (1981). The coefficient of variation of the methods to determine adrenaline and noradrenaline were 5.9% and 3.5%, respectively.

Plasma free fatty acids was analysed using a modification of the photometric, colourimetric assay of Chromy, Gerger, Voznicek, Krombholzova and Musil (1977) and plasma glycerol measured using a

fluorimetric assay modified from Laurell and Tibbling (1966).

Full details of these assays are given in appendices 4 to 9.

3.4 Test Details.

A series of three treadmill running tests were performed on all subjects involved in each of the studies:

3.4.1 Maximum Oxygen Uptake Test.

Maximum oxygen uptake was determined during uphill treadmill running using a modification of the protocol of Taylor, Buskirk and Henschel (1955), employing the Douglas bag procedure for the collection of expired air. This procedure, involving subjects running at a constant speed up an ever increasing gradient until subjective exhaustion was preferred to the protocols employing increasing speeds, for safety reasons. The test-retest reliability coefficient of 0.95 was obtained by Taylor et al (1955) in 69 determinations of VO_2 max by this method.

After weight was obtained and ECG electrodes applied, the subject was informed of the maximal effort demanded by the test and the requirement of the subject to give a signal with the index finger to indicate that he or she could run for only one more minute, during which a sample of expired air would be collected. A brief warm up was allowed, and then the subject was connected to the heart rate monitor. A running speed was selected according to the running ability of the subject.

The speed of the treadmill was held constant throughout the test, with the grade of the treadmill being increased by 2.5% (from an initial 3.5%) every three minutes. Expired air collections were made from minutes 1:45 to 2:45 in the three minutes at each grade, and during the final minute of exercise. Heart rate was monitored continuously throughout the test and the maximum heart rate obtained. The treadmill run time was recorded.

Expired air was analysed for the percentages of oxygen and carbon dioxide and the ventilation obtained for each gas collection. Using the Haldane technique, oxygen uptake and carbon dioxide production were determined (Appendix 2). The highest value obtained for oxygen

uptake was taken as the subjects maximum oxygen uptake (VO_2 max), when the following criteria were satisfied:

(a) Subjective exhaustion, and

(b) a respiratory exchange ratio (VCO_2/VO_2) greater than 1.15.

3.4.2 Submaximal Running Test (Speed-Lactate).

A submaximal running test was employed to determine each subjects relationship between running speed, oxygen uptake and blood lactic acid accumulation.

The subjects arrived at the laboratory having fasted for at least 3 hours. Their weight was obtained and ECG electrodes applied. A pre-exercise capillary blood sample was taken from a pre-warmed thumb: Duplicate 25ul and 20ul capillary tubes collected blood for the determination of blood lactate and haemoglobin respectively.

A continuous running protocol on a level treadmill was employed involving 4 minutes at each of 4 speeds, in a sequence of slowest to fastest. The speeds were selected to elicit approximately 60, 70, 80 and 90 $\%VO_2$ max for each subject. Expired air was collected during the final minute of each 4 minute at each speed. Without slowing the treadmill duplicate 25ul blood samples for the determination of blood lactate, were obtained from the thumb every four minutes at the end of the four minutes at each running speed. At the end of the sixteen minutes the treadmill was slowed down, during which time the last blood sample was taken.

Heart rate was monitored at 30 second intervals throughout the test. The mean of the heart rates collected during the minute of expired air collection, was calculated. Ratings of perceived exertion were obtained during the period of gas collection (Borg 1973).

Expired air was analysed for the percentage of oxygen and carbon dioxide and the volume of ventilation obtained. From this information oxygen uptake and carbon dioxide production at each speed, was calculated. A regression equation and Pearson product moment correlation, describing the relationship between running speed and oxygen uptake ($ml.kg.^{-1}min^{-1}$) for each subject, was obtained. Using a computer programme, the running speed, VO_2 ($ml.kg.^{-1}min^{-1}$) and $\%VO_2$ max at blood lactate concentrations of 2mM and 4mM, were obtained.

3.4.3 Exercise-Induced Asthma Test.

Subjects were requested to go without the following asthmatic medication for these specified periods prior to the test for exercise-induced asthma:

(a) Bronchodilator treatment - 8 hours.
(b) Sodium cromoglycate - 24 hours.
(c) Theophylline preparations - 24 hours.

Inhaled steroids (beclomethasone dipropionate) were continued as normal.

Resting dry spirometer and peak flow recordings were made, and if they were not more than 15% lower than the values previously obtained for the subject and above 60% of predicted normal, then the test was allowed to proceed.

The ECG electrodes were applied and the subject was attached to the heart rate monitor. The test involved running on the treadmill for 2 minutes at a warm up speed, and then 6 minutes at a faster speed selected to elicit approximately 80% VO_2 max (Wilson and Evans 1981). The perceived rate of exertion was obtained throughout the test and noted during the final minute. A one minute sample of expired air was collected during the final minute of the test. Immediately after the cessation of exercise and 5, 10, 15 and 20 minutes post-exercise, dry spirometer (FEV_1) and peak flow recordings were made.

A physician was in attendance throughout the test, and oxygen was available if required. If the subject became very asthmatic, the test was terminated and a bronchodilator was administered, usually through a "spacer" device. In order to evaluate whether EIA was induced, the percentage fall in the FEV_1 from resting values was calculated, as follows:

$$\% \text{ Fall } FEV_1 = \frac{\text{Pre Exercise } FEV_1 - \text{Lowest Post Exercise } FEV_1}{\text{Pre Exercise } FEV_1} \times 100$$

A percentage fall of FEV1 of over 10% is confirmation of EIA (Anderson 1983).

CHAPTER 4

A COMPARISON OF UNTRAINED ASTHMATIC AND NON-ASTHMATIC MALE ADULTS.

4.1 Introduction.

There is a surprisingly small amount of literature comparing the circulatory, ventilatory and metabolic responses to exercise in asthmatics and non-asthmatics (McFadden 1984a). Potentially, asthmatics may have a low exercise tolerance, either because the airway obstruction associated with the asthma may affect the maximum cardio-respiratory response to exercise (Fitch and Godfrey 1976), or alternatively the inactivity which may follow from a fear of provoking EIA may retard the development of the cardio-respiratory system (McFadden 1984a).

In studies that have compared the maximum physiological responses of asthmatic and non-asthmatic children, the results were conflicting. Bevegaard et al (1976) reported a normal maximum cardio-respiratory response to exercise, whereas Cropp and Tanakawa (1977) reported an adverse effect of asthma on the maximal response to exercise. There have been no studies, however, which have made a direct comparison of the maximum exercise capacity of asthmatic and non-asthmatic adults.

There is also evidence that the physiological responses in untrained asthmatics may be impaired during submaximal exercise. Firstly, the oxygen cost of a given activity has been found to be greater for asthmatics compared to non-asthmatics (Wasserman and Whipp 1975; Cropp and Tanakawa 1977). This was thought to be due to an increased oxygen cost of breathing. Secondly, some studies have shown that asthmatics have higher blood lactate concentrations at the same submaximal absolute work loads, compared to non-asthmatics (Silverman et al 1972b, Barboriak et al 1973), although more recent evidence does not support this (Packe et al 1987). Despite these findings there have been no studies comparing the physiological responses of groups of asthmatics and non-asthmatics at the same relative work loads, that is at the same $\%VO_2$ max.

The aim of this study was to compare the physiological responses of asthmatics and non-asthmatics, firstly, to maximal exercise and subsequently to submaximal exercise both at the same absolute and

relative exercise intensities. The subjects were chosen so that the current level of activity was similar for the two groups and thus any differences may be attributed to the asthma per se, rather than differences in the habitual level of activity.

4.2 Methods.

4.2.1 Subjects.

Seventeen untrained male asthmatic adults from the student and general public populations were tested. These individuals had all volunteered to be subjects in endurance running training studies. The baseline observations made before the running training, so that each subject was in an "untrained" state, were used for comparison. The responses of the asthmatics were compared to 17 male non-asthmatic adults, whose habitual levels of activity and ages were similar to those of the asthmatic group.

4.2.2 Laboratory Testing.

The VO_2 max and "speed-lactate" treadmill tests, were performed by each subject to measure the circulatory, ventilatory and metabolic responses to both maximal and submaximal exercise. The details of these tests are given in the General Methods (Chapter 3).

Prior to the VO_2 max test, the subjects lung function was measured using dry spirometry (FEV_1, FVC, and FEV_1/FVC%) before and after their usual pre-exercise medication for all of the asthmatic group, and for 10 of the non-asthmatic group. The lung function was expressed as a percentage of predicted normal (Kamburoff and Woitowitz 1972).

4.2.3 Statistics.

A students 't' test (unpaired) was used to analyse the difference between the asthmatic and non-asthmatic groups. The lung function and the physiological responses during both the maximal and submaximal exercise, were compared. The paired 't' test was used to analyse the change in lung function with pre-exercise medication, for the asthmatic group. The Pearson product moment correlation was used to analyse the relationships between the VO_2 max, V_E max and the lung function (FEV_1 percent predicted).

4.3 Results.

4.3.1 Physical Characteristics.

The asthmatic and non-asthmatic groups were reasonably well matched for age, height and weight (Table 4.1). Table 4.2 shows the lung function of the asthmatics (without medication) and the non-asthmatics, obtained before the VO_2 max test. The FEV_1 and FVC, expressed as a percentage of predicted normal, were significantly lower for the asthmatic group compared to the non-asthmatic group. Using the categorisation of Cropp and Tanakawa (1977), the airway obstruction for the asthmatics (FEV_1 percent predicted), could be categorised as normal for 12; mild for 3; moderate for 1; and marked for 1.

Prior to the maximal and submaximal treadmill running tests the asthmatics took their usual pre-exercise medication. For the majority of the asthmatics, this was either salbutamol (Ventolin) or sodium cromoglycate (Intal or Intal compound), taken singly or in combination. The mean FEV_1, prior to the VO_2 max test was increased from 3.88 $\pm$ 0.86 to 4.08 $\pm$ 0.83 litres for the asthmatics after their usual pre-exercise medication. This represented a small increase (5%) in the FEV_1 from baseline. The FEV_1 with pre-exercise medication, expressed as a percent of predicted, was still significantly lower for the asthmatics compared to the non-asthmatics (85.5 $\pm$ 12.3 % vs 100.5 $\pm$ 14.2 %, $p<0.01$).

4.3.2 Maximal Exercise.

Table 4.3 shows the results from the maximal exercise test. The mean VO_2 max was significantly lower for the asthmatics compared to the non-asthmatics (47.0 $\pm$ 5.9 vs 51.7 $\pm$ 5.0 $ml.kg.^{-1}min^{-1}$, $p<0.05$). In addition, the lowest VO_2 max values were obtained for asthmatic subjects. Maximum ventilation rate (V_E max) was significantly lower for the asthmatics compared to the non-asthmatics (117 $\pm$ 22 vs 142 $\pm$ 14 $l.min^{-1}$ BTPS, $p<0.01$). The range of the values for V_E max was much greater for the asthmatic group. Maximum heart rate was lower for the asthmatics compared to the non-asthmatics, but the difference was not significant. However, the respiratory exchange ratio (R), which is often taken as evidence that VO_2 max has been reached, was significantly lower for the asthmatics compared to the non-asthmatics (1.13 $\pm$ 0.07 vs 1.18 $\pm$ 0.05, $p<0.05$).

Graphs of the relationships between VO_2 max, V_E max and the percent predicted FEV_1(with medication), are shown for both groups. There was a significant correlation between the percent predicted FEV_1 and the V_E max achieved for the asthmatic group, such that those with a lower percent predicted FEV_1 have a lower V_E max ($r=0.701$, $p<0.01$ - Figure 4.1a). A significant correlation was found between VO_2 max and V_E max for the asthmatic group, showing that the lower the maximum ventilation the lower the VO_2 max ($r=0.598$, $p<0.05$ - Figure 4.2a). A further significant though modest correlation was found between VO_2 max and the percent predicted FEV_1 for the asthmatic group ($r=0.502$, $p<0.05$ - Figure 4.3a). The non-asthmatic group showed no significant relationships between these parameters (Figures 4.1b, 4.2b and 4.3b).

An example of the pattern of response to maximum exercise of an asthmatic with marked airflow obstruction (FEV_1 55.8% predicted) compared to an asthmatic with near normal lung function (FEV_1 94.8% predicted), is given (Figure 4.4). The ventilation rate for the asthmatic with severe pre-exercise obstruction did not increase significantly as maximum exercise was approached, although the oxygen uptake did show a further increase, attributed to an increased extraction of oxygen from the inspired air. In addition, the respiratory exchange ratio fell as the exercise intensity approached maximum for the asthmatic with severe pre-exercise obstruction, suggesting that this asthmatic was unable to increase the ventilation sufficiently to eliminate the carbon dioxide generated by the working muscles. In contrast, the asthmatic with an FEV_1 near predicted normal, shows a normal response to maximum exercise, with increases in minute ventilation and respiratory exchange ratio as the exercise intensity increases.

4.3.3 Submaximal Exercise.

In addition to a comparison of the maximum physiological responses to exercise of the asthmatic and non-asthmatic groups, a comparison of selected physiological responses were made for submaximal exercise, at a reference running speed (2.75 $m.s^{-1}$) and at the same relative exercise intensity (75% VO_2 max).

Table 4.4 shows a summary of the physiological responses at a reference running speed equivalent to 2.75 $m.s^{-1}$ for the asthmatic and non-asthmatic groups. This running speed was chosen to compare the groups because all subjects, asthmatic and non-asthmatic, ran at

ranges of treadmill speeds during the submaximal test which encompassed 2.75 $m.s^{-1}$. There were statistically significant differences between the groups for certain measurements. The asthmatics showed higher blood lactate concentrations (3.86 ± 1.59 vs 2.61 ± 1.12 mM, $p<0.05$), poorer ventilatory equivalent (25.0 ± 2.6 vs 21.7 ± 2.6 l, $p<0.001$), increased fraction of oxygen left in expired air (16.9 ± 0.5 % vs 16.3 ± 0.5 %, $p<0.01$) and reduced percentage of carbon dioxide exhaled into expired air (3.95 ± 0.46 vs 4.48 ± 0.39, $p<0.01$), when compared to the non-asthmatics. The oxygen uptake expressed as a percentage of VO_2 max at 2.75 $m.s^{-1}$ was, however, higher for the asthmatic group (76.8%), compared to the non-asthmatic group (70.1%).

Further comparison of the results shows that when the physiological responses were compared at the same relative exercise intensity (75% VO_2 max) (Table 4.5), the blood lactate concentration was not different for the asthmatics compared with the non-asthmatics. However, the other significant differences found between the asthmatics and non-asthmatics at the reference running speed, persisted, when compared at the same relative exercise intensity.

The ventilatory equivalent or the ventilation required to obtain one litre of oxygen, was significantly greater for the asthmatics compared to the non-asthmatics at 75 % VO_2 max (25.0 ± 2.6 vs 22.4 ± 2.1 l, $p<0.01$). In addition, the fraction of oxygen in the expired air (FeO_2%) was significantly higher for the asthmatics compared to the non-asthmatics at 75% VO_2 max (16.92 ± 0.46 % vs 16.44 ± 0.40 %, $p<0.01$). Furthermore, the percentage of carbon dioxide in the expired air ($FeCO_2$%) at 75% VO_2 max was significantly lower for the asthmatics compared to the non-asthmatics (3.95 ± 0.43 % vs 4.43 ± 0.36 %, $p<0.01$).

The above data has given statistical comparisons of selected physiological responses to submaximal exercise of untrained asthmatic and non-asthmatic males at 2.75 $m.s^{-1}$ and at 75% VO_2 max. The responses over a range of submaximal running speeds for the asthmatic and non-asthmatic group of selected physiological variables are shown graphically.

The oxygen cost of running at a range of submaximal running speeds is shown in Figure 4.5, indicating no difference between the asthmatics using pre-exercise medication, and the non-asthmatics. Nevertheless, the variation within the asthmatic group in terms of

oxygen requirements at 2.75m.s^{-1} were large (27.7 to 40.5 ml.kg.$^{-1}$min^{-1}). These individual subject variations for the oxygen cost of running within the asthmatic group were not significantly correlated to the percent predicted FEV_1 (r=0.064 : ns).

Figure 4.6a shows the blood lactate concentrations over a range of submaximal running speeds. The asthmatic group showed a significantly higher blood lactate concentration at a running speed of 2.75 m.s^{-1} when compared to the non-asthmatic group. When the running speed is expressed as a %VO_2 max, however, the blood lactate concentrations between the asthmatic and non-asthmatic groups were not different (Figure 4.6b).

Figures 4.7a and 4.7b show the relationship of heart rate with both running speed and %VO_2 max, respectively. At any given percentage of VO_2 max, heart rate is slightly lower for the asthmatic group compared to the non-asthmatics, which may be a reflection of the lower maximum heart rate of the asthmatic group. Figure 4.8 shows that at any given running speed, ventilation is slightly higher, although not significantly so at 2.75 m.s^{-1}, for the asthmatic group. The large intra subject variation in the ventilation required at a 2.75 m.s^{-1} (45.7 to 100.7 l.min^{-1} BTPS) was not correlated to the percent predicted FEV_1 (r=0.120 : ns).

Table 4.1. The physical characteristics of the groups of untrained asthmatic and non-asthmatic males (mean ± SD).

	Non-Asthmatics (n=17)	Asthmatics (n=17)
Age (years)	26.5 ± 9.4	23.5 ± 7.4
Range	20 - 55	16 - 41
Height (m)	1.79 ± 0.04	1.78 ± 0.08
Range	1.72 - 1.88	1.61 - 1.90
Weight (kg)	74.6 ± 8.4	69.6 ± 10.3
Range	55.5 - 87.5	54.2 - 89.55

Table 4.2. Lung function values of the untrained asthmatic and non-asthmatic males. Values are without medication and shown as a percentage of predicted normal (mean ± SD).

	Non-Asthmatics (n=10)	Asthmatics (n=17)
VC (1.BTPS)		
Actual	5.79 ± 0.64	5.06 ± 1.02
% of Predicted	104.0 ± 14.6	91.2 ± 15.2 *
FEV_1 (1.BTPS)		
Actual	4.73 ± 0.62	3.88 ± 0.86
% of Predicted	100.5 ± 14.2	81.4 ± 15.0 **
$FEV_1/FVC\%$		
Actual	81.9 ± 8.5	77.1 ± 12.5

Statistically significant difference between asthmatics and non-asthmatics: * $p<0.05$, ** $p<0.01$

Table 4.3. The physiological characteristics of the untrained asthmatic and non-asthmatic males obtained in response to the maximum oxygen uptake test (mean ± SD).

	Non-Asthmatics (n=17)	Asthmatics (n=17)
VO_2 max ($l.min^{-1}$)	3.85 ± 0.53	3.26 ± 0.53 **
Range	2.83 - 4.93	2.56 - 4.14
VO_2 max ($ml.kg.^{-1}min^{-1}$)	51.7 ± 5.0	47.0 ± 5.9 *
Range	40.6 - 57.8	35.2 - 57.4
H.R. max.($beat.min^{-1}$)	194 ± 12	188 ± 8
Range	164 - 209	173 - 203
V_E max.($l.min^{-1}$ BTPS)	142.3 ± 14.3	117.0 ± 21.9 **
Range	122.7 - 181.7	74.7 - 164.6
R max.	1.18 ± 0.05	1.13 ± 0.07 *
Range	1.10 - 1.30	0.96 - 1.25

Statistically significant difference between non-asthmatic and asthmatic groups: * $p<0.05$ ** $p<0.01$

Table 4.4. A comparison of selected physiological measurements for untrained asthmatic and non-asthmatic males, at a reference running speed of 2.75 $m.s^{-1}$ (mean ± SD).

	Non-Asthmatics (n=15)	Asthmatics (n=17)
$\dot{V}O_2$ ($ml.kg.^{-1}min^{-1}$)	35.5 ± 2.1	35.8 ± 3.9
% $\dot{V}O_2$ max	70.1 ± 6.4	76.8 ± 11.8
$\dot{V}CO_2$ ($ml.kg.^{-1}min^{-1}$)	33.9 ± 1.8	34.4 ± 4.2
$\dot{V}_E$ ($l.min^{-1}$ BTPS)	68.5 ± 10.2	73.9 ± 11.5
Heart Rate ($beat.min^{-1}$)	157 ± 14	163 ± 17
Blood Lactate (mM)	2.61 ± 1.12	3.86 ± 1.59*
R ($\dot{V}CO_2/\dot{V}O_2$)	0.95 ± 0.04	0.96 ± 0.04
Ventilatory Equivalent	21.7 ± 2.6	25.0 ± 2.6***
FeO_2%	16.3 ± 0.5	16.9 ± 0.5**
$FeCO_2$%	4.48 ± 0.39	3.95 ± 0.46**

Statistically significant difference between asthmatic and non-asthmatic groups: ***$p<0.001$, **$p<0.01$, *$p<0.05$

Table 4.5. A comparison of selected physiological measurements for the untrained asthmatic and non-asthmatic males, at running speeds equivalent to 75% VO_2 max (mean ± SD).

	Non-Asthmatics (n=15)	Asthmatics (n=17)
Blood Lactate (mM)	3.29 ± 1.03	3.51 ± 0.74
Ventilatory Equivalent	22.4 ± 2.1	25.0 ± 2.6**
FeO_2%	16.4 ± 0.4	16.9 ± 0.5**
$FeCO_2$%	4.43 ± 0.36	3.95 ± 0.43**

Statistically significant difference between asthmatic and non-asthmatic groups: **$p<0.01$

Figure 4.1a

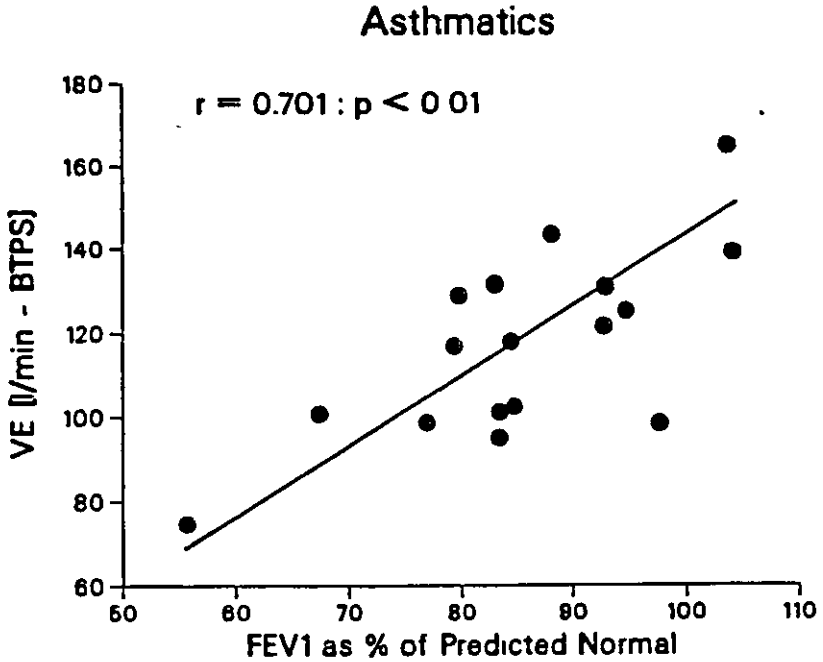
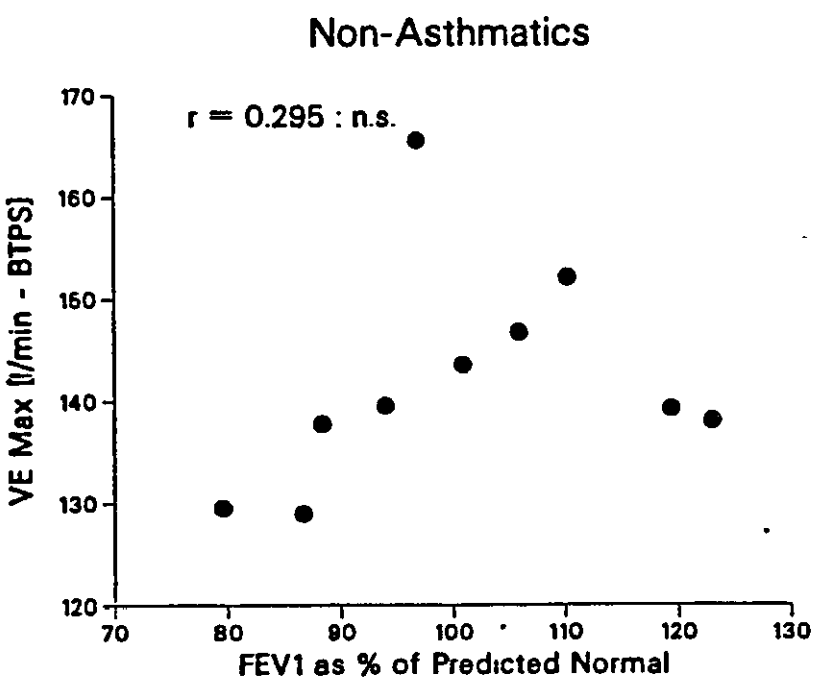


Figure 4.1b



Figures 4.1a and 4.1b. The relationship of the FEV_1, expressed as a percentage of predicted normal values, to the maximum ventilation rate for the untrained asthmatics [4.1a] and non-asthmatics [4.1b].

Figure 4.2a

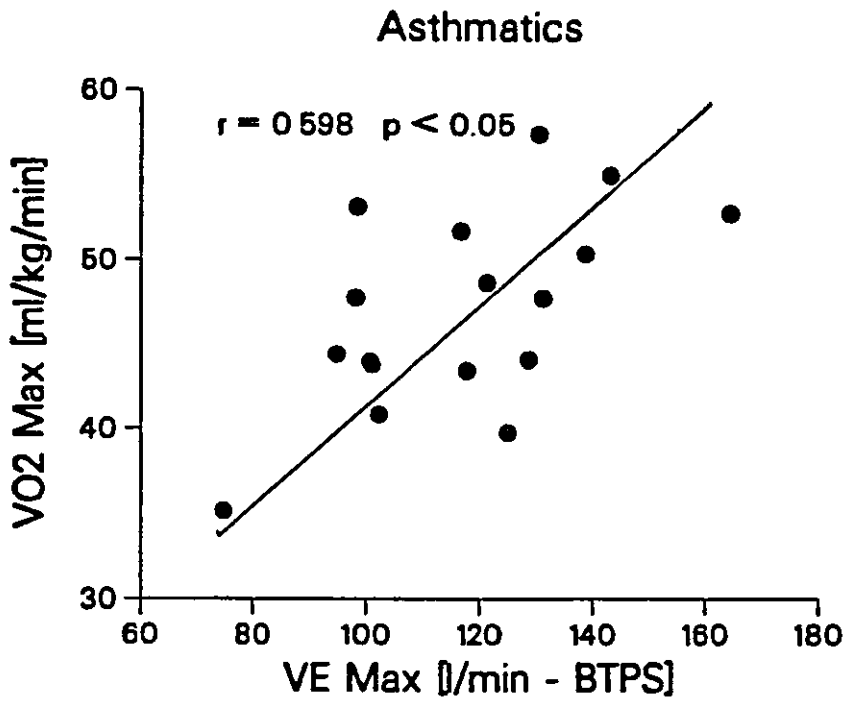
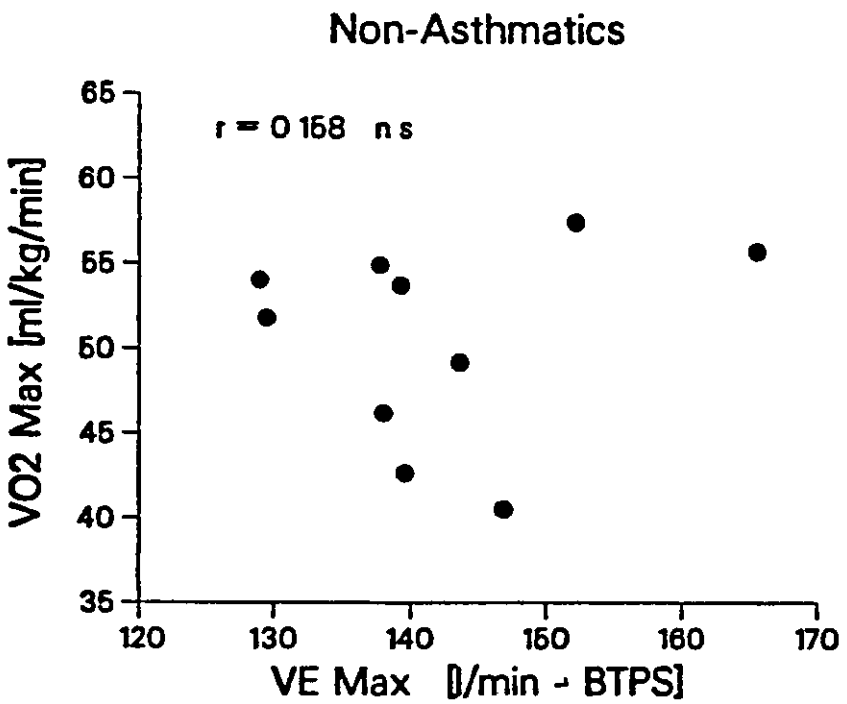


Figure 4.2b



Figures 4.2a and 4.2b. The relationship of the maximum ventilation rate to the maximum oxygen uptake for the untrained asthmatics [4.2a] and non-asthmatics [4.2b].

Figure 4.3a

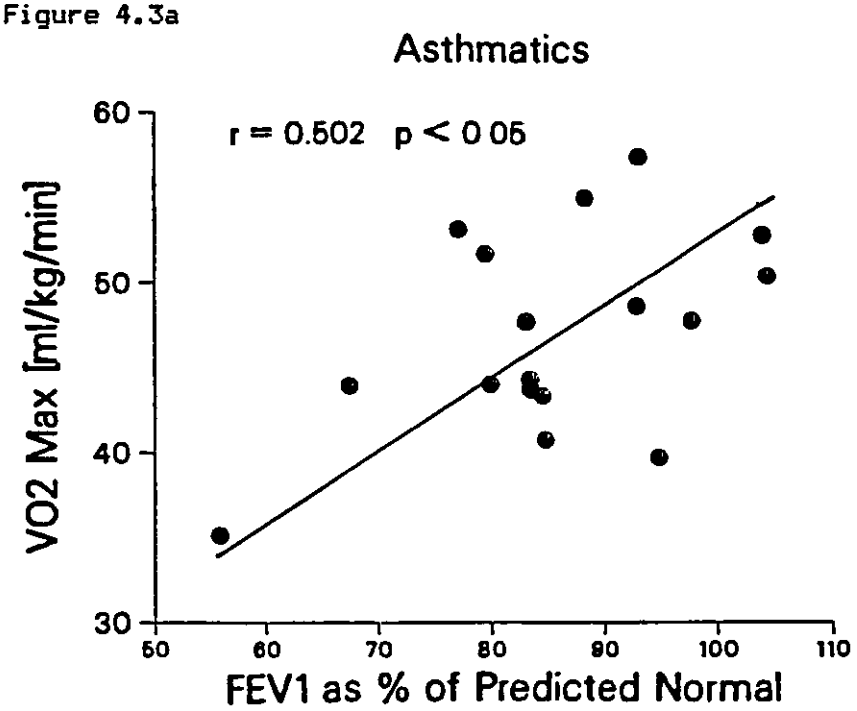
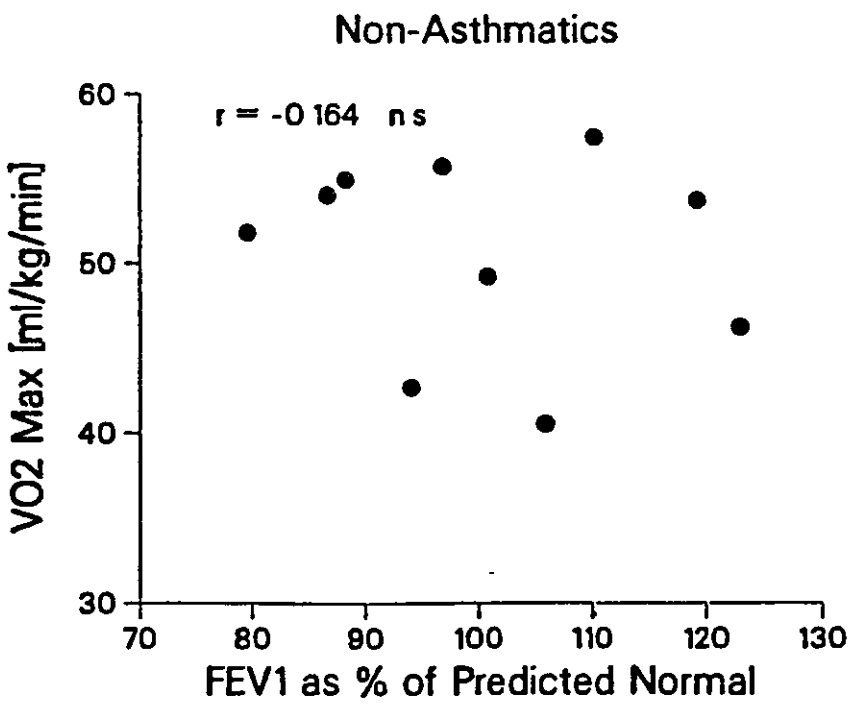


Figure 4.3b



Figures 4.3a and 4.3b. The relationship of the FEV_1, expressed as a percentage of predicted normal values, to the maximum oxygen uptake for the untrained asthmatics [4.3a] and non-asthmatics [4.3b]

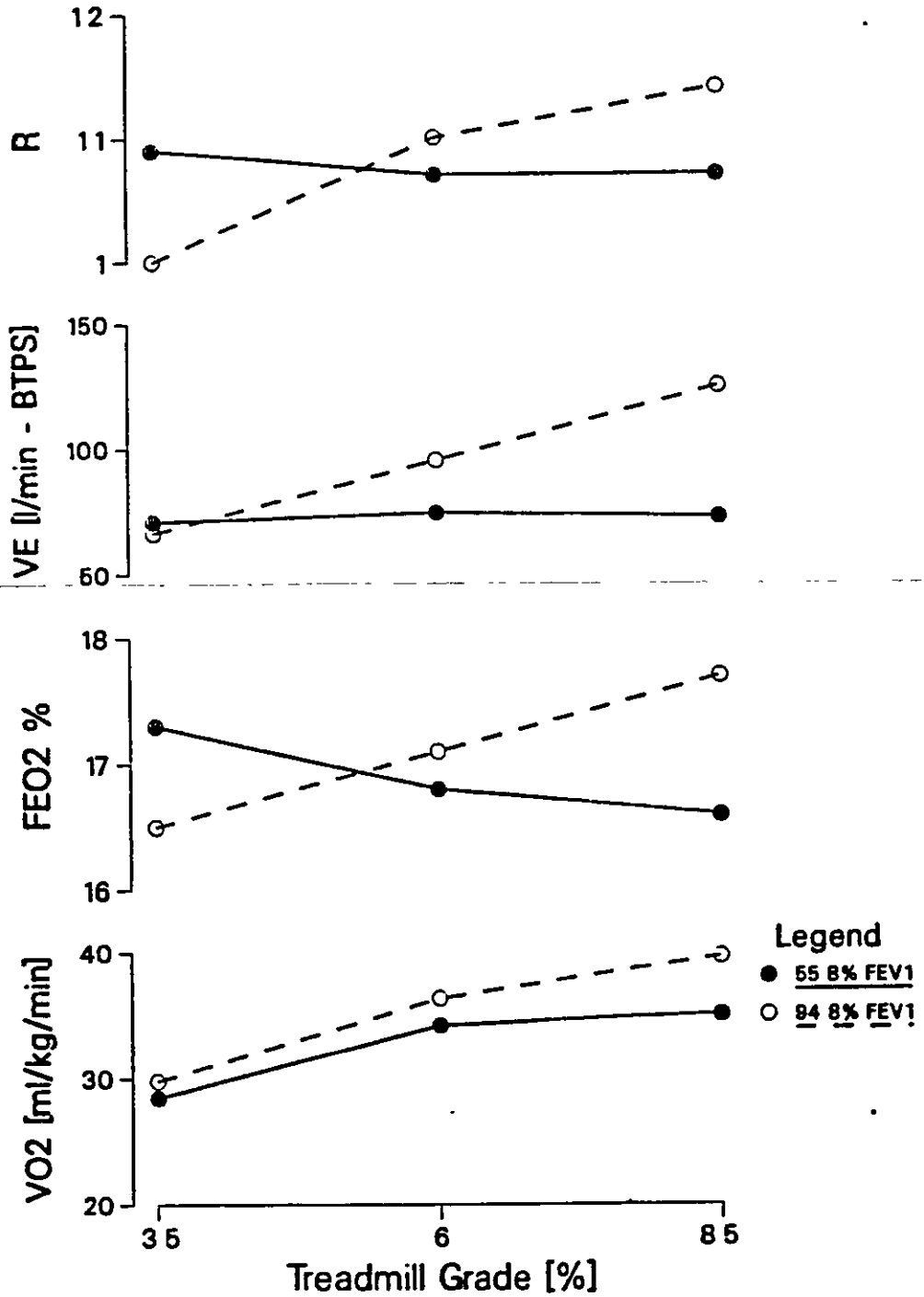


Figure 4.4. Selected physiological responses to the maximum oxygen uptake test for an asthmatic with severe airway obstruction and an asthmatic with normal lung function (FEV_1 55.8% and 94.8% predicted, respectively).

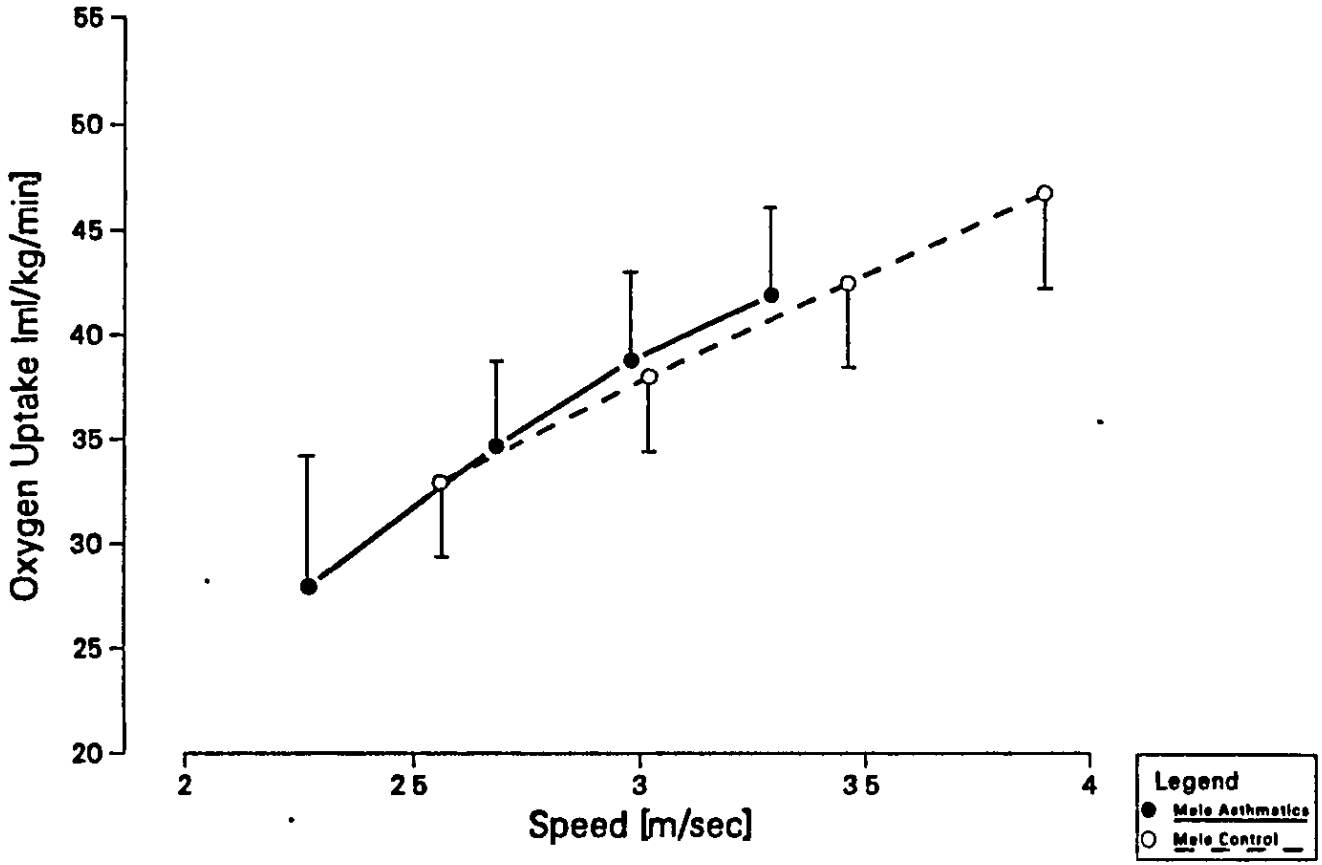


Figure 4.5. The oxygen uptake at a range of submaximal running speeds for the untrained asthmatic and non-asthmatic groups.

Figure 4.6a

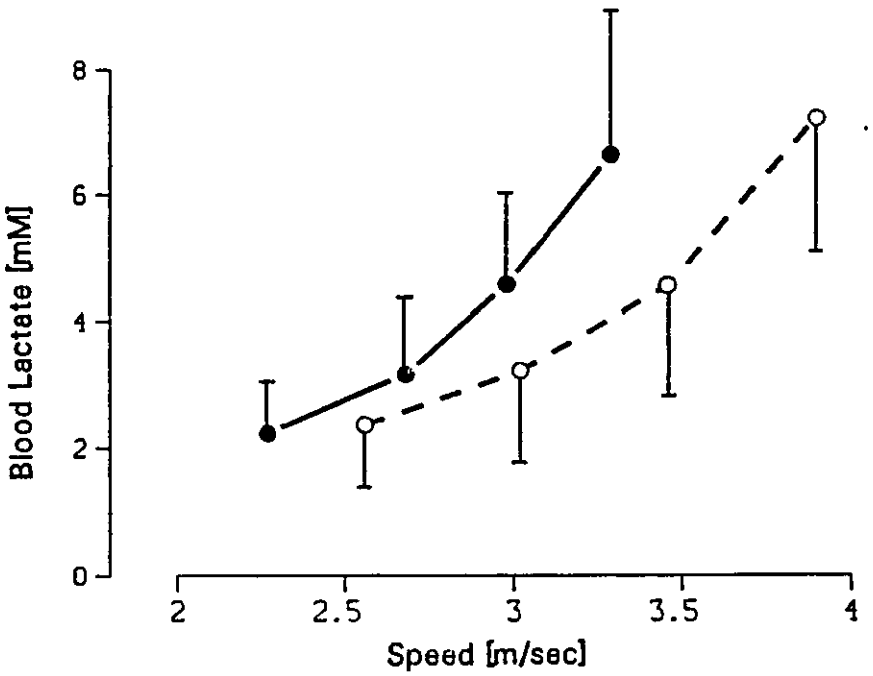
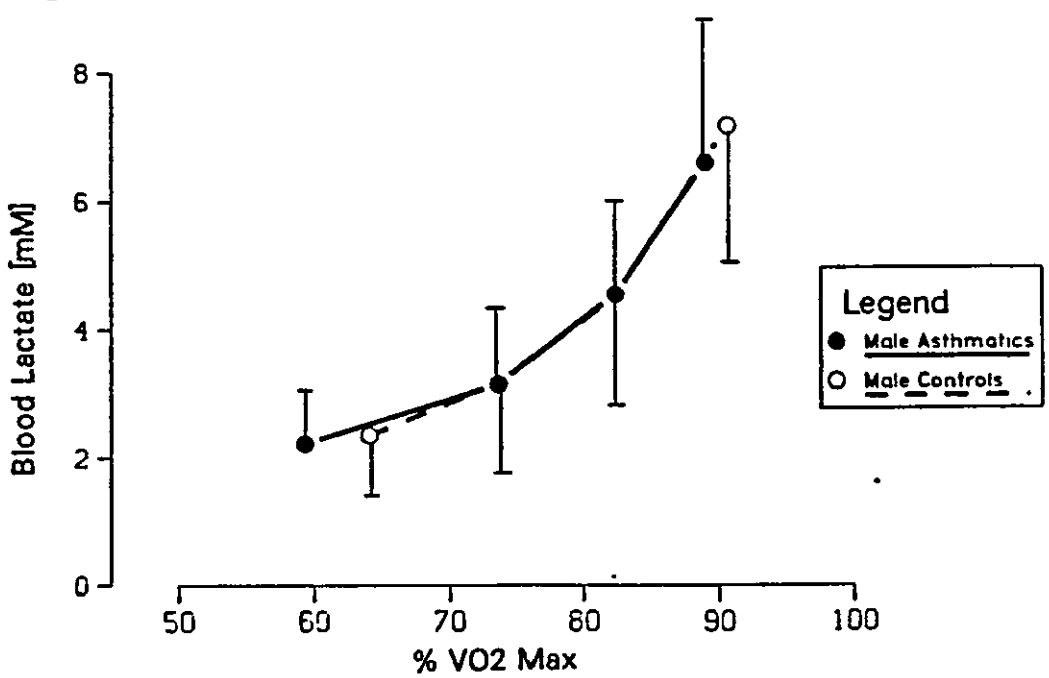


Figure 4.6b



Figures 4.6a and 4.6b. The blood lactate concentration in relation to running speed (4.6a) and $\%VO_2$ max (4.6b), for the untrained asthmatic and non-asthmatic groups.

Figure 4.7a

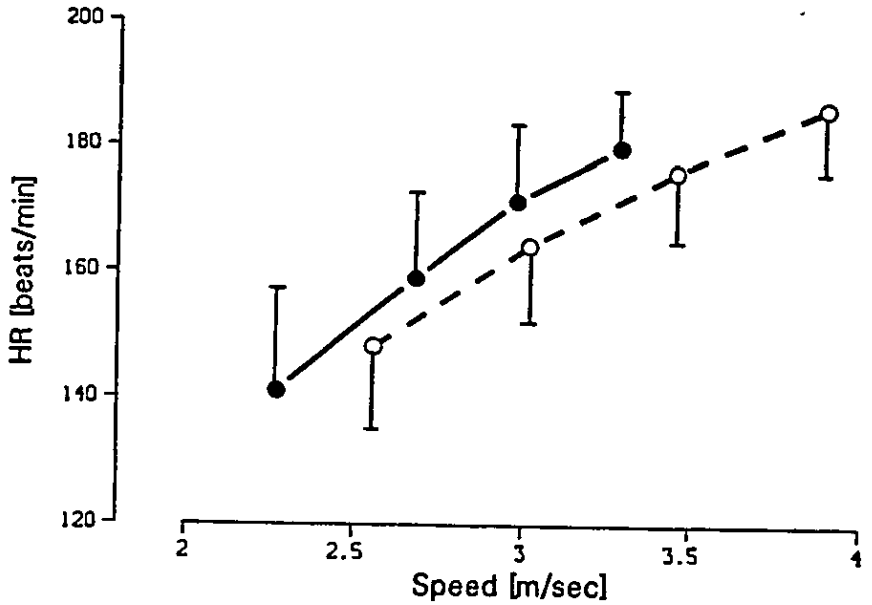
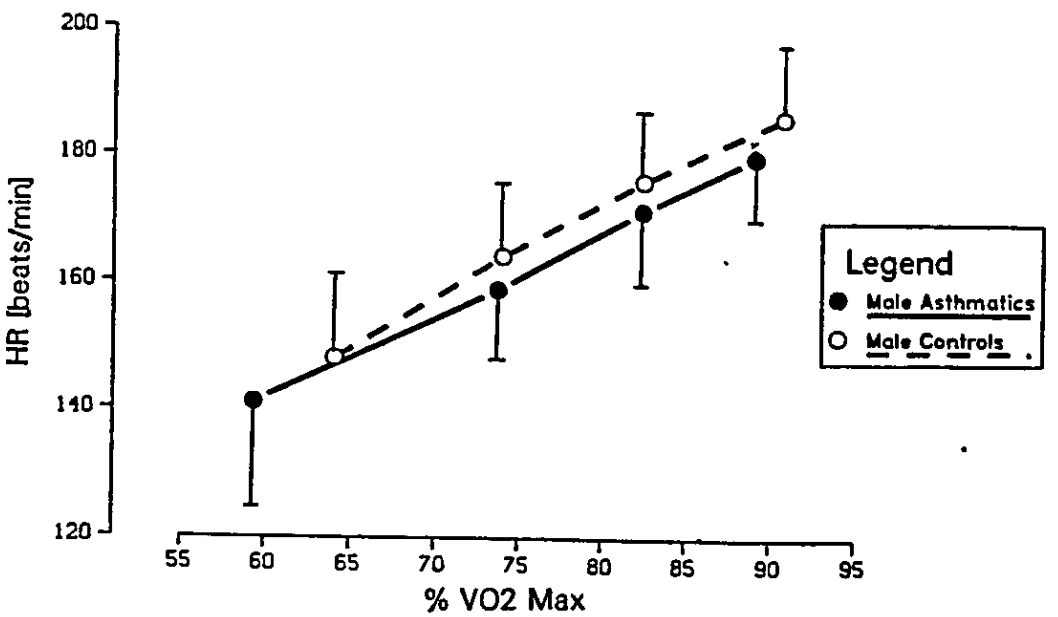


Figure 4.7b



Figures 4.7a and 4.7b. The heart rate in relation to running speed (4.7a) and $\%VO_2$ max (4.7b), for the untrained asthmatic and non-asthmatic groups.

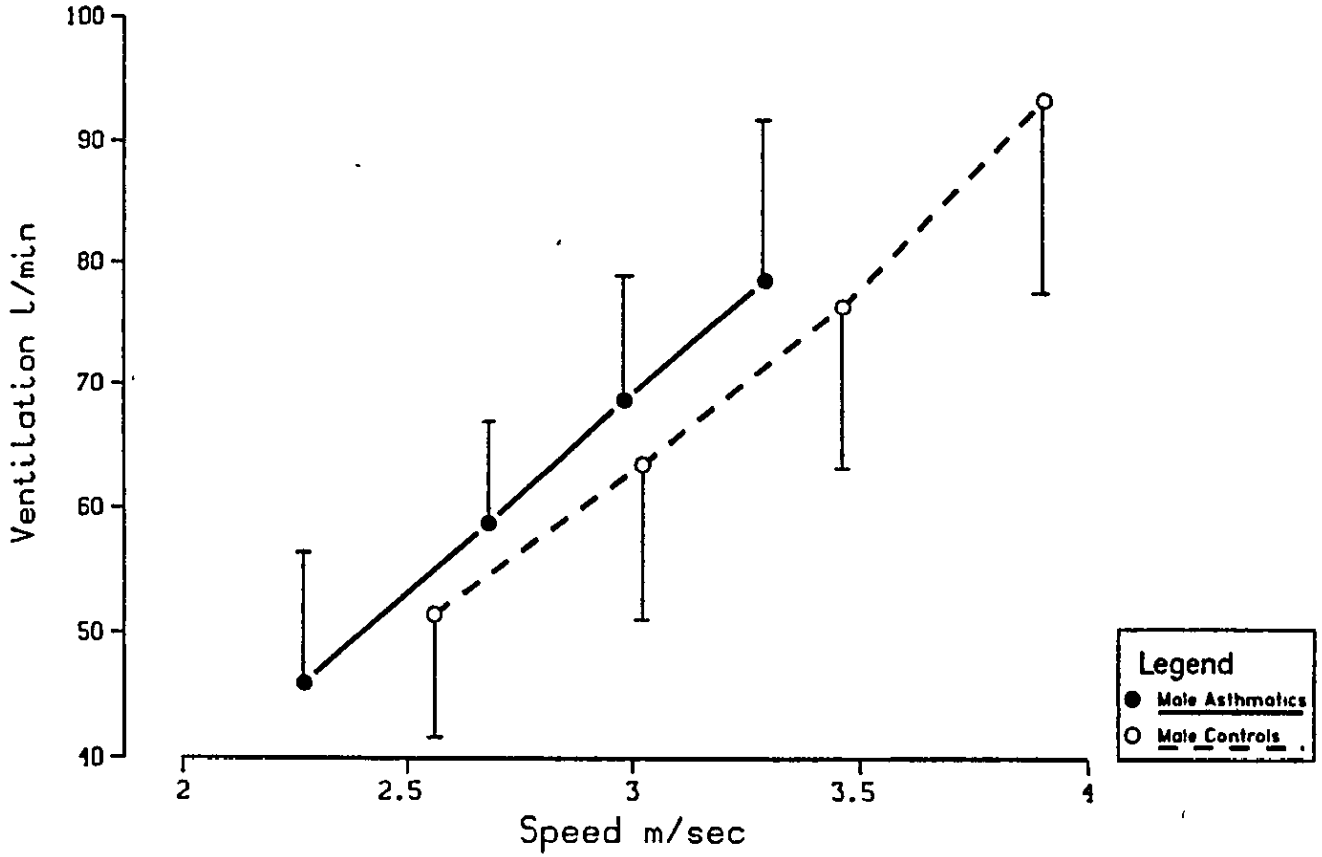


Figure 4.8. The ventilation rate at a range of submaximal running speeds, for the untrained asthmatic and non-asthmatic groups.

4.4 Discussion.

It has been suggested that any differences in the physiological measurements between asthmatics and non-asthmatics is likely to be due to inactivity resulting from a fear of provoking EIA (McFadden 1984a). The purpose of this study was, therefore, to compare the physiological responses to maximal and submaximal treadmill running of groups of untrained asthmatic and non-asthmatic male adults with similar levels of habitual activity. The two groups were therefore reasonably well matched for the dependent variables, including activity levels, age and sex, and thus any difference observed on exercise could be majorly attributed to the airway obstruction in the asthmatic group.

The asthmatic group took their normal pre-exercise medication prior to the treadmill running tests to minimise exercise-induced asthma. The baseline airway obstruction for the group of asthmatics under investigation was essentially mild, with a mean FEV_1 81.4 percent predicted. This is confirmed by the classification of the asthma using the criteria of Cropp and Tanakawa (1977) with the majority of the asthmatics being classified as having "mild" asthma. Within the asthmatic group, however, there were a few individuals with more severe airway obstruction. The effect of the prescence and the severity of airflow obstruction on the maximum and submaximal response to exercise in the asthmatic group, is discussed below.

4.4.i Maximal Exercise

The maximum oxygen uptake of untrained individuals is usually limited by the cardiac output and the oxidative capacity of the skeletal muscles, and not by the ventilation rate (Dempsey 1986). In individuals with airflow obstruction, however, the maximum ventilation may be reduced and thus may become the rate limiting step in determining VO_2 max. Inspite of only a modest degree of pre-exercise airway obstruction, the maximum ventilation attained by the asthmatic group was significantly reduced compared to the non-asthmatic group (117.0 ± 21.9 vs 142.3 ± 14.3 $l.min^{-1}$ BTPS). This would indicate that the airflow obstruction is limiting the maximum ventilation rate, which may be adversely affecting the VO_2 max.

The asthmatic group showed significantly lower values for VO_2 max, compared to the non-asthmatic group (47.0 ± 5.9 vs 51.7 ± 5.0

$ml.kg.^{-1}min^{-1}$. Inspite of the reduced VO_2 max of the asthmatic group compared to the non-asthmatic group in this study, the mean value obtained for VO_2 max is still considerably higher than that quoted by other studies for asthmatic male adults (Bundgaard et al 1982b; Ingemann-Hansen et al 1980). This is partly due to the nature of the exercise test, as Bundgaard et al (1982b) employed cycle ergometry (which is known to result in a lower VO_2 max than treadmill running), and partly due to the slightly older population of asthmatics investigated by Ingemann-Hansen et al (1980). In addition, many of the asthmatics in the present study, although not endurance trained, were reasonably active, and not hospitalised as quoted in other reports.

This would suggest that the asthmatics in this study have a slightly impaired maximal response to exercise compared to the non-asthmatic group. The lower VO_2 max of the asthmatic group compared to the non-asthmatic group may be associated with the lower V_E max, which in turn may be influenced by the airway obstruction of the asthmatic group. It has been suggested by Cropp and Tanakawa (1977) that there must be a considerable deterioration in lung function before the asthmatic cannot increase the ventilation adequately in response to exercise, and the threshold has been placed at an FEV_1 of 60% of the predicted normal. Indeed, the results from the present study confirm that the asthmatic with the poorest FEV_1 (55% predicted) did show an impaired ventilatory response to maximal exercise, with failure to increase the ventilation rate as maximum exercise was approached, and consequently achieved a low VO_2 max. The significant correlations between measurements of lung function (FEV_1 percent predicted), maximum ventilation and maximum oxygen uptake, however, may suggest some impairment in the maximal response to exercise in asthmatics even when this "threshold" for the degree of airway obstruction has not been reached.

It has been demonstrated that the greater the decrement in FEV_1 the lower both the V_E max and VO_2 max. In addition, V_E max and VO_2 max were positively correlated, such relationships not observed for the non-asthmatic group. This would suggest that the severity of the basal airflow obstruction influences the V_E max, and subsequently limits the VO_2 max. When low VO_2 max values have been reported for hospitalised asthmatics, this may therefore be due to the presence of asthma alone supporting the views of Fitch and Godfrey (1976), and not necessarily due to the inactivity of the asthmatic individual as has been

suggested by McFadden (1984a). These correlations would suggest that impairment of the V_E max and VO_2 max may occur even when FEV_1 is only slightly below predicted normal, with the severity of the impairment related positively to the severity of airflow obstruction.

The significantly lower respiratory exchange ratio (R) values during maximum exercise of the asthmatic group suggests that the asthmatics were less able to expel the carbon dioxide produced. This observation agrees with the proposal by Cropp and Tanakawa (1977), who stated that when pre-exercise pulmonary function is very poor, some asthmatics are unable to increase the ventilation rate sufficiently to effectively eliminate the increased carbon dioxide generated by the muscles. In asthmatics, with marked airflow obstruction it may not therefore be appropriate to use a respiratory exchange ratio value of over 1.15 (Issekutz et al 1962) as one of the main determinants to establish that VO_2 max has been reached.

4.4.2 Submaximal Exercise.

Previous studies have failed to equate the level of exercise intensity for the asthmatic and non-asthmatic groups. Hence, in the present study comparisons both at the same absolute running speed, and at the same $\%VO_2$ max have been made between the asthmatic and non-asthmatic groups.

Wasserman and Whipp (1975), and Cropp and Tanakawa (1977) indicated that the oxygen cost and ventilatory demands of a given activity was greater for asthmatics compared to the non-asthmatics, due to an increased oxygen cost of breathing. The results of the present study contradicted these findings, showing no significant difference in the oxygen cost of running or the ventilation required at a given treadmill speed between the two groups. Nor was the oxygen uptake or ventilation rate required by each subject correlated to the degree of airflow obstruction (FEV_1 % predicted). This discrepancy with the results of previous studies may be explained by the fact that the asthmatic group were all taking their normal pre-exercise medication, protecting them from EIA. Due to the relatively modest degree of airflow obstruction the oxygen cost of breathing may not necessarily be elevated for this group. Furthermore, the individual subject variations in oxygen uptake and ventilation rates at a given speed may be more a function of other factors such as training status and running style, than the severity of airway obstruction.

In addition, the cardiac response to submaximal exercise appears similar for medicated asthmatics and non-asthmatics. This assessment has focused purely on heart rate, and the effect of asthmatic medication on cardiac arrythmias during exercise for example, has not been evaluated.

Although the absolute ventilation rate required at a given running speed is not different between asthmatics and non-asthmatics, subtle differences in the respiratory responses to exercise were observed in this study. The asthmatic group had both a poorer ability to extract oxygen from the inspired air (F_EO_2%) and expel carbon dioxide during exercise (F_ECO_2%), compared to non-asthmatics. This is reflected in the significantly poorer ventilatory equivalent of the asthmatic group at both the same absolute and relative work loads. This poorer gas exchange of the untrained asthmatic compared to the non-asthmatic, may be due to mucous plugging or ventilation/perfusion mismatch as a result of airway narrowing. Thus the asthmatic exercises under less efficient ventilatory conditions, a finding which agrees with the work of Cropp and Tanakawa (1977) with asthmatic children.

The metabolic changes during exercise in asthmatics, and in particular the response of blood lactate as a 'index' of anaerobic metabolism, are uncertain. Silverman and Anderson (1972b) and Barboriak et al (1973) claimed that the blood lactic acid accumulation was greater for asthmatics compared to non-asthmatics, and speculated that this may be a factor which is associated with triggering the asthma. In the present study, although the blood lactate concentration for the asthmatics was significantly higher at the same absolute work load, there was no difference between the groups when compared at the same relative exercise intensity (75% VO_2 max). Indeed the differences in the blood lactate at the same absolute running speed can be associated with the lower VO_2 max of the asthmatic group and not the asthma per-se. Thus, failure of the early workers to compare the blood lactate concentrations of asthmatics and non-asthmatics at the same relative exercise intensity has led to erroneous speculations about blood lactate being a possible trigger factor associated with EIA. The higher blood lactate concentrations observed at the same absolute running speed in this and previous studies, is a reflection of the lower level of VO_2 max of the asthmatics compared to the non-asthmatics.

4.5 Summary.

The VO_2 max and V_E max values for the asthmatic group were statistically lower compared to the non-asthmatic group with a similar level of habitual activity. Significant relationships of the FEV_1 percent predicted with VO_2 max and V_E max, suggest that the severity of the pre-exercise obstruction will adversely affect the maximal physiological responses to exercise.

The oxygen uptake and ventilation rate at a given submaximal running speed were not significantly different for the asthmatic group compared to the non-asthmatic group. However, blood lactate concentrations were significantly higher at the same running speed for the asthmatics compared to the non-asthmatics, although this difference disappeared when the blood lactate concentrations were compared at the same relative exercise intensity. In contrast, the ventilatory equivalent, the oxygen extraction from inspired air and the removal of carbon dioxide into expired air were all significantly poorer for the asthmatics compared to the non-asthmatics, both at the same absolute and relative work loads. Thus the asthmatic exercises under impaired ventilatory conditions.

CHAPTER 5

THE PHYSIOLOGICAL CHARACTERISTICS OF ASTHMATIC ENDURANCE RUNNERS.

5.1 Introduction.

Long distance running is an aerobic activity requiring an adequate supply of oxygen for the working muscles. The asthmatic may be at a disadvantage to compete in endurance running when compared to the non-asthmatic, for two main reasons.

Firstly, the airflow obstruction associated with the asthma may pose limits on the VO_2 max. The previous chapter has shown that in untrained asthmatics, especially with increasingly severe asthma, the VO_2 max may be impaired at the ventilatory level. In addition, physical training may lead to the maximum ventilation becoming the rate limiting step in determining VO_2 max in non-asthmatics (Dempsey 1986). Thus the effects of airflow obstruction and a well trained state may enhance the limitation of the ventilation rate on VO_2 max in well trained asthmatics.

Secondly, for a number of reasons distance running is more likely to provoke EIA than other forms of exercise. Endurance running involves prolonged hyperventilation, often in cold air, conditions which are known to provoke the asthma (Strauss et al 1977). In addition, activity of a continuous nature is more likely to provoke asthma than activity of an intermittent nature (Morton et al 1982). For these reasons endurance running is not considered the most suitable activity for the asthmatic.

Nevertheless, asthmatics do participate successfully in endurance running at an elite level (Fitch 1975b), and at a 'recreational' level (London Marathon statistics). There have been no studies, however, that evaluate the physiological response to exercise or the race performances of well trained asthmatic runners. Previously it has been demonstrated that mild airway obstruction does not prevent the successful completion of a marathon with appropriate training, but in this study by Mahler et al (1981b) only one subject gave a history of previous asthma. A further study of a group of 39 top class Italian athletes identified as having bronchial asthma, none were found to be engaged in endurance running (Todaro et al 1984). There is therefore a

need to examine the physiological responses to maximum and submaximal treadmill exercise in a group of asthmatic long distance runners.

Many factors have been shown to influence success in distance running in non-asthmatic athletes, for example VO_2 max (Foster, Daniels and Yarborough 1977), the percentage utilisation of VO_2 max (Davies and Thompson 1979), plasma lactate accummulation (Farrell et al 1979; Williams and Nute 1983) and running economy (Conley and Krahenbuhl 1980). Whether these physiological parameters have similar relationships with endurance racing performance for the asthmatic athlete is unknown, and thus will also be evaluated.

Although VO_2 max is a good indicator of the maximum physiological responses to exercise, the ability to undertake prolonged exercise should be defined independently of this parameter. "Endurance fitness" must include an examination of the percentage of VO_2 max that can be sustained for a prolonged period. In this study performance data from recent races of asthmatic athletes will be evaluated in relation to the physiological responses obtained during treadmill running.

There were two main aims of this study. The first was to examine the physiological responses of a group of asthmatic endurance running trained athletes to maximum and submaximal treadmill exercise. The results were compared to those of the untrained asthmatics previously described in Chapter 4. The second aim was to examine the "endurance fitness" of the asthmatic athletes by evaluating their performance over a half-marathon in relation to their laboratory data.

5.2 Methods.

5.2.1 Subjects.

An advertisement was placed in the running magazine "Athletics Weekly" asking for asthmatic endurance runners to contact the department. Numerous replies were received and to each reply a questionnaire was sent, to obtain information about their asthmatic and athletic history. The questions concerning the asthma obtained information on the duration of their asthma; known precipitating factors to the asthma (i.e. exercise, dust, animals, pollen or others); and their daily and pre-exercise asthmatic medication. From the questions concerning the athletic history, the weekly mileage,

performance times for the half-marathon and full marathon, and details of most recent races, were obtained for each athlete.

Sixty eight asthmatic athletes (57 males) returned the questionnaires. Asthmatic athletes who on the basis of their questions fulfilled the following criteria, were invited to visit the laboratory:

(a) A history of EIA.

(b) Taking regular asthmatic medication.

(c) A commitment to endurance running, with recent performance times in long distance races i.e. half-marathon or marathon.

Sixteen asthmatic athletes visited the laboratory and underwent a series of treadmill running tests designed to assess their physiological and asthmatic responses to exercise.

5.2.2 Laboratory Testing.

A one day study was carried out on each asthmatic athlete. The percentage body fat was obtained for each athlete from skinfold measurements (Durnin and Wormesley 1974), in addition to the haemoglobin concentration, height, weight and age. Asthmatic medication was witheld for at least 6 hours before arrival at the laboratory. None were on long term bronchodilators.

The following treadmill tests were completed by each subject, each of which are described more fully in the general methods (Chapter 3). The treadmill speeds for these tests were selected according to running ability obtained from performance times.

(a) Subjects were familiarised to treadmill running. Subsequently they performed the treadmill test without pre-exercise medication, to assess for EIA.

(b) After a recovery period, a treadmill VO_2 max test modified from Taylor (1955) was performed.

(c) After at least a 2 hour rest without food (to ensure that blood lactate levels had returned to near baseline), each subject performed a continuous running test at four submaximal running speeds ("speed-lactate test"). For each athlete, the treadmill speed, VO_2, and $\%VO_2$ max at blood lactate concentrations of 2mM were obtained. The oxygen uptake at a treadmill velocity of $4m.s^{-1}$ was used as a reference speed to assess each individuals running economy.

Lung function measurements (spirometry and PEFR) were made before exercise, with and without asthmatic medication, and 10 minutes post

exercise, for both the VO_2 max and "speed-lactate" test. The resting pulmonary function values without asthmatic medication, were expressed as a percentage of the predicted normal.

5.2.3 Running Performance : A Physiological Perspective.

Eleven of the sixteen asthmatic athletes had recent performance times for a competitive half-marathon race. An estimate of the average oxygen cost of running the outdoor half-marathon was obtained from each individuals regression equation describing the relationship between treadmill speed and oxygen uptake, and this was then expressed in absolute terms ($ml.kg.^{-1}min^{-1}$) and as a percentage of each individuals VO_2 max. In addition, an estimate of the ventilation rate and percentage of maximum ventilation utilised during the half-marathon was calculated from the submaximal treadmill running test.

5.2.4 Statistics.

The results from these asthmatic athletes were compared to those obtained from the 17 untrained male asthmatics, previously described in Chapter 4. The pooled 't' test was used to compare the physiological responses of the trained and untrained asthmatic groups. A Pearson product moment correlation was used to analyse the relationships between pertinent physiological variables.

Pearson product moment correlations between half-marathon performance (race pace and estimate of the % VO_2 max utilised), and all pertinent physiological and asthmatic parameters, were obtained to determine the physiological determinants of distance running performance for this group of asthmatic athletes. To further account for the variation in performance times and $\%VO_2$ max utilised for the half-marathon, multiple regression analysis was also employed.

5.3 Results

5.3.1 Physical Characteristics.

The physical characteristics, running experience and duration of asthma for the sixteen male asthmatic athletes are shown in Table 5.1. The group had a mean age of 35 years, had been running seriously for nine years and were currently training an average of 82 kilometres per week (50 miles). The asthmatic athletes had a percentage body fat of 12.2 $\pm$ 3.8 and a haemoglobin concentration of 15.1 $\pm$ 0.9 $g.dl^{-1}$. Each athlete had a history of asthma, with 12 of the group having had symptoms since childhood, and the remaining 4 having had a 'late onset' of asthma. Each athlete was on regular daily and pre-exercise medication, taking maintenance (Intal, Intal Compound) and / or bronchodilator therapy (Ventolin, Berotec, Exirel, Bricanyl, Intal Compound), with 3 subjects also taking inhaled steroid medication (Becotide, Becloforte).

5.3.2 Pulmonary Function.

Table 5.2 shows the lung function values of the trained and untrained asthmatic groups, obtained after their asthmatic medication had been withheld. The lung function measures, expressed as a percentage of predicted normal, and the FEV_1/FVC ratio, were similar. There was no significant difference between the lung function of the groups. On the basis of abnormalities in pulmonary function as indicated by the percent predicted FEV_1) (Cropp and Tanakawa 1977), the severity of asthma of the 16 trained asthmatics was classified as normal in 7, mild in 5, moderate in 1 and marked in 3. Again this is similar to the asthmatic conditions of the untrained group of asthmatics, of which 7 were classified as normal, 8 as mild, 1 as moderate and 1 as marked. Thus the severity of asthma of the two groups was comparable.

5.3.3 Maximal Exercise.

Table 5.3 shows the results from the VO_2 max test for the trained and untrained asthmatic groups groups. The mean VO_2 max of the trained group was significantly higher than the untrained asthmatic group (61.8 $\pm$ 6.3 vs 47.0 $\pm$ 5.9 $ml.kg.^{-1}min^{-1}$, $p<0.01$). The highest value of VO_2 max obtained by one of the asthmatics of 70.9 $ml.kg.^{-1}min^{-1}$, is

consistent with the values obtained for elite performers. The maximum ventilation rate reached during the VO_2 max test for the trained asthmatic group was 20 litres higher ($p<0.05$) than the untrained asthmatic group. Maximum heart rate and maximum respiratory exchange ratio (R) were not significantly different for the trained and untrained asthmatic groups. However, for both groups the mean R value was below the 1.15 required to confirm that VO_2 max had been attained (Issekutz et al 1962), with individuals having very low R values as indicated by the lowest values in each group.

Each subject took their usual pre-exercise medication prior to the maximum exercise test. For the group of asthmatic athletes the pre-exercise medication increased the FEV_1 from 3.42 $\pm$ 0.79 to 3.77 $\pm$ 0.78 litres, an increase of 10.2%. The FEV_1 was similar 10 minutes after exercise (3.60 $\pm$ 0.91 l - BTPS), thus the pre-exercise medication had been successful in preventing EIA for the asthmatic athletes.

5.3.4 Submaximal Exercise.

The second of the running tests involved an examination of the physiological parameters at submaximal running speeds of trained and untrained asthmatics. The groups were compared at the same relative exercise intensity (75% VO_2 max).

Figure 5.1a shows that the oxygen cost of running over a range of running speeds was slightly lower for the trained compared to the untrained asthmatics. Due to the lack of a common running speed between the two groups, the oxygen uptake at the fourth running speed in the submaximal test was expressed as $ml.kg^{-1}.metre^{-1}$, to allow statistical comparison between the groups. The trained asthmatic group had a significantly lower oxygen uptake per kilogram of body weight per metre of ground covered compared to the untrained asthmatic group (0.196 $\pm$ 0.013 vs 0.214 $\pm$ 0.021 $ml.kg^{-1}.metre^{-1}$, $p<0.01$). Although the correlation between running speed and oxygen uptake for each asthmatic athlete was almost perfect (range $r = 0.991$ to 1.00), the lower correlation for the whole group ($r = 0.935$) indicates that there was some variation in the oxygen uptake within the asthmatic group. Indeed the variation in the running economy, defined here as the oxygen uptake at a running speed of 4 $m.s^{-1}$, was large ranging from 40.7 to 53.1 $ml.kg.^{-1}min^{-1}$. Figure 5.1b shows the oxygen uptake expressed as a percentage of the VO_2 max, over the range of running

speeds. This confirms that any given running speed represents a much lower relative exercise intensity for the trained asthmatics compared to the untrained asthmatics.

Heart rate, although lower at a specific speed for the trained group compared to the untrained group, was not significantly different when compared at a given $\%\dot{V}O_2$ max (Figures 5.2a and 5.2b). The trained asthmatics had a lower blood lactate concentration at a given running speed and even at the same relative exercise intensity (Figures 5.3a and 5.3b). At 75% $\dot{V}O_2$ max, the blood lactate concentration was significantly lower for the trained group compared to the untrained group (2.00 $\pm$ 0.48 vs 3.51 $\pm$ 0.74 mM, $p<0.01$).

The ventilation rate at specific speeds were lower for the trained asthmatics when compared to the untrained asthmatics, whereas at a given $\%\dot{V}O_2$ max the trained group had a higher ventilation rate (Figures 5.4a and 5.4b). Due to the lower ventilation rate at a given speed, the ventilation rate equivalent to an oxygen uptake of one litre per minute (ventilatory equivalent) is less for trained asthmatics, compared to untrained asthmatics (Figure 5.5a). However, at 75% $\dot{V}O_2$ max, there was no significant difference between the ventilatory equivalent for the trained and the untrained asthmatic groups (24.2 $\pm$ 1.9 vs 25.0 $\pm$ 2.6 litres) (Figure 5.5b).

The respiratory exchange ratio was lower for the trained group at the same absolute work load (Figure 5.6a), whereas there was no significant difference when compared at the same relative work load (Figure 5.6b). The extraction of oxygen from the inspired air was not different for the two groups, as indicated by the similar $\%F_EO_2$ at 75% $\dot{V}O_2$ max (16.9 $\pm$ 0.5 % vs 16.8 $\pm$ 0.3 %). In addition, there was no significant difference in the fraction of carbon dioxide in the expired air ($\%F_ECO_2$) for the untrained and trained asthmatics at 75% $\dot{V}O_2$ max (3.95 $\pm$ 0.43 % vs 4.00 $\pm$ 0.28 %).

As for the maximum test each subject took their usual pre-exercise medication prior to the submaximal exercise test. For the group of asthmatic athletes the pre-exercise medication increased the FEV_1 from 3.68 $\pm$ 0.77 to 3.81 $\pm$ 0.79 litres, an increase of 3.5%. The FEV_1 was slightly lower for the asthmatic athletes 10 minutes after exercise (3.54 $\pm$ 0.77 l - BTPS), although the difference from resting measurements was not significant.

5.3.5 Exercise-Induced Asthma.

The results from the non-medicated running test to examine for EIA, are given in Table 5.4 for the asthmatic athletes. Taking a fall of 10% in FEV_1 as an indicator of exerise-induced asthma (Anderson 1983), 13 out of the 15 athletes tested had EIA, suggesting an incidence of EIA among asthmatic athletes of 87%. In the present study three of the athletes took a bronchodilator to reverse the EIA provoked by the test, before the 20 minutes of post-exercise recordings were completed. The response of the FEV_1, after the exercise challenge, is shown in Figure 5.7a for the 12 athletes who did not require asthmatic medication.

The severity of EIA, expressed as the largest percentage post-exercise fall of FEV_1 and PEFR from pre-exercise values, was 23.6 $\pm$ 12.7 % and 22.6 $\pm$ 14.4 % respectively. There was a large variation in the severity of EIA which ranged up to a 48.4% fall in FEV_1. The physiological demands of the test for the group showed that it required 79% VO_2 max, a ventilation rate of 93.1 $l.min^{-1}$ (BTPS), and a heart rate of 167 beats per minute. There was much variation in the physiological responses to the test for individual subjects. However, the degree of EIA was not significantly correlated with the level of exercise intensity achieved i.e. % VO_2 max ($r=-0.122$), ventilation rate ($r=-0.433$) or heart rate ($r=-0.324$). However, the fall in the FEV_1 was moderately correlated with the severity of pre-exercise airway obstruction (percent predicted FEV_1) ($r=-0.551$, $p < 0.05$). However, it is appreciated that the same absolute fall will be a different magnitude of EIA if the pre-exercise FEV_1 values are very different. For example, for two asthmatics who experienced decreases in FEV_1 of 0.44 litres and 0.48 litres, this represented markedly different percentage decreases in FEV_1 from pre-exercise (35.5% and 11.6%). Indeed, when the absolute fall in FEV_1 was correlated with the percent predicted FEV_1 no significant correlation emerged ($r=-0.011$).

However, as previously mentioned, the normal pre-exercise medication protected the asthmatic athletes from EIA for the maximal and submaximal tests. Figure 5.7b shows the FEV_1 before and after the test performed without asthmatic medication, compared to the response of the FEV_1 to the maximal and submaximal exercise tests when pre-exercise asthmatic medication was taken.

5.3.6 Relationships Between the Physiological Characteristics.

The relationships between various parameters from the maximal, submaximal, and non-medicated running tests for the asthmatic athletes are given as a correlation matrix in Table 5.5. The pre-exercise FEV_1 (with medication) expressed as a percent of predicted, is taken as a measure of the resting abnormality in lung function. The fall in FEV_1 after the running test without asthmatic medication is used as a measure of the degree of EIA. The percent predicted FEV_1 was significantly correlated with VO_2 max ($r=0.518$; $p<0.05$) and with maximum ventilation ($r=0.694$; $p<0.01$) for the asthmatic athletes. These correlation values are similar to those obtained for the untrained asthmatic group ($r=0.502$; $p<0.05$ and $r=0.701$; $p<0.01$, respectively). Thus, as for the untrained asthmatics, the further the FEV_1 from predicted the lower the VO_2 max and V_E max. In addition, VO_2 max was highly correlated with V_E max for the asthmatic athletes ($r=0.779$; $p<0.01$), although not so strongly correlated for the untrained asthmatic group ($r=0.598$; $p<0.05$). The interrelationship between V_E max, VO_2 max and percent predicted FEV_1 are shown for the asthmatic athletes in Figures 5.8a, 5.8b and 5.8c.

Furthermore, the percent predicted FEV_1 was negatively correlated with the $\%VO_2$ max at which 2mM blood lactate accumulated ($r=-0.568$; $p<0.05$) (Figure 5.9). This suggests that the individuals whose FEV_1 was below predicted normal (and thus for whom VO_2 max and V_E max may be limited), could compensate for this by being able to exercise at a high $\%VO_2$ max with lower blood lactate concentrations.

5.3.7 Half-Marathon Performance.

A recent outdoor performance time over a half-marathon was available for 11 of the asthmatic athletes (Table 5.6). The mean half-marathon time of 82.36 $\pm$ 8.76 minutes, was consistent with the VO_2 max (60.0 $\pm$ 5.9 $ml.kg.^{-1}min^{-1}$), of which the group utilised an estimated 81.9 $\pm$ 4.0 $\%VO_2$ max during the half-marathon. The relationships between half-marathon race pace and the $\%VO_2$ max utilised, with all pertinent physiological variables are shown in Table 5.7.

5.3.8 The Physiological Determinants of Half-Marathon Race Pace.

Race pace correlated significantly with VO_2 max ($r=0.881$; $p<0.01$) (Figure 5.10a). However, the highest correlation with race pace was

with the treadmill running speed equivalent to blood lactate concentrations of 2mM (V2mM) ($r=0.971$; $p<0.01$), indicating that 94% of the variation in half-marathon performance times for the asthmatic athletes could be accounted for by differences in blood lactate accumulation at submaximal running speeds (Figure 5.10b).

In addition, other factors were important in distinguishing between performances over the half-marathon. Running economy, defined here as the oxygen uptake required to run on the treadmill at a speed of 4 $m.s^{-1}$, correlated significantly with race pace ($r=-0.693$; $p<0.05$). In addition, when the running economy at 4 $m.s^{-1}$ was expressed as a $\%VO_2$ max the correlation was further improved ($r=-0.919$; $p<0.01$), hence indicating that the fractional use of oxygen at a given speed taking into consideration both VO_2 max and running economy, was important in determining running performance over the half-marathon. These relationships are shown in Figures 5.11a and 5.11b.

The ability to run at a high $\%VO_2$ max did not discriminate between the half-marathon performances in this group of asthmatic athletes, as indicated by the non-significant correlation between $\%VO_2$ max utilised and race pace ($r=0.113$) (Figure 5.12a). Moreover, the ability to utilise a high oxygen uptake regardless of what $\%VO_2$ max it represents, seemed to be very important for performance as illustrated by the highly significant correlation between the estimated average oxygen cost of the run and race pace ($r=0.924$; $p<0.01$) (Figure 5.12b). In addition, the maximum ventilation was also significantly correlated with race pace ($r=0.580$; $p<0.05$). However, as previously illustrated with the total group and further highlighted by this sub-group of 11, a relationship exists between maximum ventilation and VO_2 max ($r=0.785$; $p<0.01$), hence the association of race pace and maximum ventilation was not surprising.

Multiple regression analysis showed that other factors added to the highest correlation with performance (V2mM) were unable to explain more of the variation in the half-marathon performance times of the asthmatic athletes (Table 5.8).

5.3.9 The Physiological Determinants of the % VO_2 max Utilised during the Half-Marathon.

The fractional use of VO_2 max by the asthmatic athletes over the half-marathon distance varied widely within the group (range 77% to

92% VO_2 max). The $\%VO_2$ max sustained in the race was positively correlated with the $\%VO_2$ max at 2mM blood lactate ($r=0.817$; $p<0.01$) as illustrated in Figure 5.13a. Thus the ability to sustain a high $\%VO_2$ max is associated with the ability to supply the energy needs more aerobically. In addition, a highly significant negative correlation of $r=-0.800$ ($p<0.01$) between the % VO_2 max utilised in the half-marathon and the percent predicted FEV_1 (Figure 5.13b) emerged. Hence, subjects with low FEV_1 values, were able to run at a high $\%VO_2$ max during the half-marathon. To further support this the percent predicted FEV_1 and the $\%VO_2$ max at a blood lactate concentration of 2mM were significantly correlated ($r=-0.647$, $p<0.05$), indicating those subjects with low FEV_1 values accumulated 2mM blood lactate at higher $\%VO_2$ max (Figure 5.13c).

Multiple regression analysis showed that the 67% of the variation in the $\%VO_2$ max utilised in the half-marathon accounted for by the $\%VO_2$ max at 2mM blood lactate, could be increased to 80% when the percent predicted FEV_1 was added (Table 5.8).

Table 5.1. The physical characteristics, running experience and asthmatic history for the group of endurance trained asthmatics.

	mean ± SD	Range
Age (yrs)	35.0 ± 8.6	22 - 48
Height (m)	1.76 ± 0.06	1.64 - 1.84
Weight (kg)	66.0 ± 4.4	58.4 - 72.5
Duration of Running (yrs)	9.2 ± 7.2	3 - 25
Running Training (km/week)	82 ± 22	56 - 121
Duration of Asthma (yrs)	25 ± 16	2 - 46

Table 5.2. Lung function measures of trained and untrained asthmatic males. Values are without medication and are shown as a percentage of predicted normal (mean ± SD).

	Trained n=16	Untrained n=17
VC (l BTPS)		
Actual	4.82 ± 0.83	5.06 ± 1.02
% Predicted	94.0 ± 16.0	91.2 ± 15.2
FEV_1 (l BTPS)		
Actual	3.33 ± 0.94	3.88 ± 0.86
% Predicted	77.5 ± 18.2	81.4 ± 15.0
FEV_1/FVC %		
Actual	68.7 ± 13.1	77.1 ± 12.5
PEFR ($l.min^{-1}$)		
Actual	471 ± 122	511 ± 77
% Predicted	75.3 ± 19.0	85.5 ± 13.6

Table 5.3. The physiological characteristics of the trained and untrained asthmatic males obtained in response to the maximum oxygen uptake test (mean ± SD).

	Trained (n=16)	Untrained (n=17)
VO_2 max ($l.min^{-1}$)	4.07 ± 0.43	3.26 ± 0.53 **
Range	3.29 - 4.78	2.56 - 4.14
VO_2 max ($ml.kg.^{-1}min^{-1}$)	61.8 ± 6.3	47.0 ± 5.9 **
Range	50.0 - 70.9	35.2 - 57.4
HR max ($b.min^{-1}$)	186 ± 11	188 ± 8
Range	168 - 205	173 - 203
V_E max ($l.min^{-1}$-BTPS)	138.7 ± 24.7	117.0 ± 21.9 *
Range	93.9 - 181.0	74.7 - 164.6
R max (VCO_2 / VO_2)	1.12 ± 0.05	1.13 ± 0.07
Range	1.05 - 1.22	0.96 - 1.25

Denotes significant difference between trained and untrained asthmatic groups: ** $p<0.01$: * $p<0.05$

Table 5.4. The physiological responses and degree of exercise-induced asthma to the non-medicated running test for the group of endurance trained asthmatic runners (n=15).

	mean ± SD	Range
Speed ($m.s^{-1}$)	4.25 ± 0.48	3.5 - 5
VO_2 ($ml.kg.^{-1}min^{-1}$)	49.3 ± 6.4	37.5 - 59.2
% VO_2 max	79.4 ± 6.2	66.5 - 91.2
V_E ($l.min^{-1}$ - BTPS)	93.1 ± 21.0	60.2 - 134.0
HR ($b.min^{-1}$)	167 ± 9	153 - 185
% Fall FEV_1 Post Exercise	23.6 ± 12.7	7.4 - 48.4
% Fall PEFR Post Exercise	22.6 ± 14.4	1.6 - 46.5

Table 5.5. The relationships between selected physiological responses obtained during the maximal, submaximal and non-medicated running tests for the asthmatic athletes.

	FEV_1 % Predicted	Degree* of EIA	VO_2 max $ml.kg.^{-1}min^{-1}$	V_E max $l.min^{-1}$	V2mM $m.s^{-1}$	$\%VO_2$ max 2mM
Degree of EIA (% Fall FEV_1)	-0.314					
VO_2 max ($ml.kg.^{-1}min^{-1}$)	0.518*	-0.476				
V_E max ($l.min^{-1}$)	0.694**	-0.458	0.779**			
V2mM ($m.s^{-1}$)	0.333	-0.557*	0.712**	0.540*		
% VO_2 max (2mM)	-0.568*	-0.094	-0.019	-0.231	0.426	
VO_2 (4 $m.s^{-1}$)	-0.232	0.286	0.143	-0.053	-0.450	-0.052

Significant correlations: ** $p<0.01$ * $p<0.05$

* Degree of EIA : % fall in FEV_1 post-exercise, from resting FEV_1.

Table 5.6. Run time and estimated percentages of the VO_2 max and V_E max utilised, for an outdoor half-marathon for 11 asthmatic runners.

	mean ± SD	Range
HALF-MARATHON		
Time (mins)	82.36 ± 8.76	69.37 - 94.00
Race Pace ($m.s^{-1}$)	4.32 ± 0.49	3.74 - 5.07
VO_2 ($ml.kg^{-1}min^{-1}$)	49.2 ± 4.8	42.4 - 55.8
% VO_2 max Utilised	81.9 ± 4.0	77.0 - 91.5
V_E ($l.min^{-1}$-BTPS)	99.7 ± 13.6	80.9 - 121.5
%V_E max Utilised	76.0 ± 7.2	63.5 - 86.2

Table 5.7. Pearson product moment correlations between running speed and the estimated $\%VO_2$ max utilised for the outdoor half-marathon, with relevant physiological responses obtained during treadmill running.

Parameter	Half Marathon Race Pace ($m.s^{-1}$)	$\%VO_2$ max Utilised
VO_2 max ($ml.kg.^{-1}min^{-1}$)	0.881**	-0.246
V_E max ($l.min^{-1}$ - BTPS)	0.580*	-0.628*
$\%V_E$ max Utilised	-0.056	0.737*
VO_2 (4 $m.s^{-1}$)	-0.693*	0.120
$\%VO_2$ (4 $m.s^{-1}$)	-0.919**	0.259
V2mM ($m.s^{-1}$)	0.971**	0.037
VO_2 (2mM) ($ml.kg.^{-1}min^{-1}$)	0.892**	0.108
$\%VO_2$ (2mM)	0.216	0.817**
VO_2 Utilised ($ml.kg.^{-1}min^{-1}$)	0.924**	0.226
% FEV_1 of Predicted Normal	0.383	-0.800**
Degree of EIA	-0.643*	-0.182

* $p<0.05$ ($r>0.576$)

** $p<0.01$ ($r>0.768$)

Table 5.8. The use of multiple correlations of the running speed and the %VO_2 max utilised during the outdoor half-marathon, with physiological measurements made during treadmill running.

Run Speed in Half Marathon

Variable	Multiple r	r^2 %
V2mM ($m.s^{-1}$)	0.971	94.3%
+ VO_2 max ($ml.kg.^{-1}min^{-1}$)	0.972	94.5%
+ VO_2 ($4m.s^{-1}$) ($ml.kg.^{-1}min^{-1}$)	0.975	95.1%
+ EIA (% fall FEV_1)	0.975	95.1%

% VO_2 max in Half Marathon

Variable	Multiple r	r^2 %
%VO_2 max (2mM)	0.817	66.7%
+ FEV_1 % Predicted	0.896	80.3%

Figure 5.1a

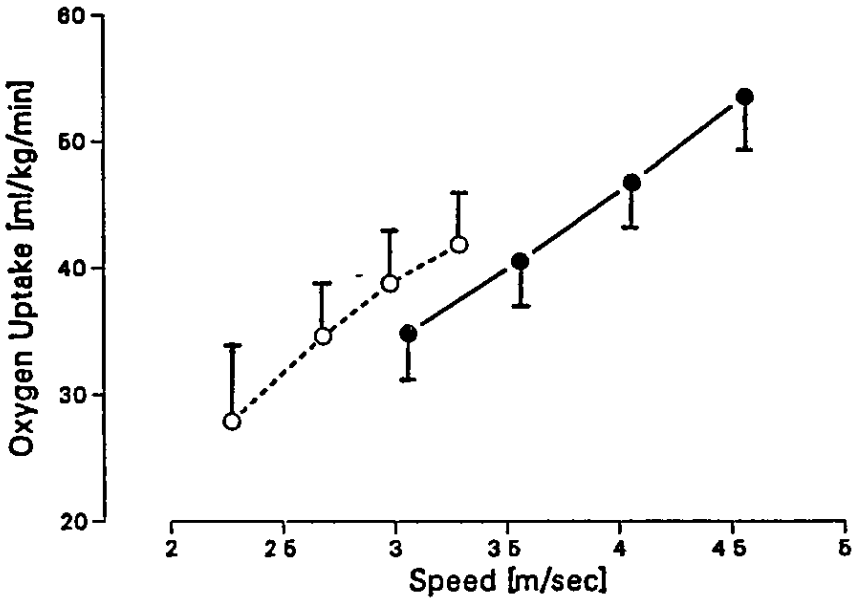
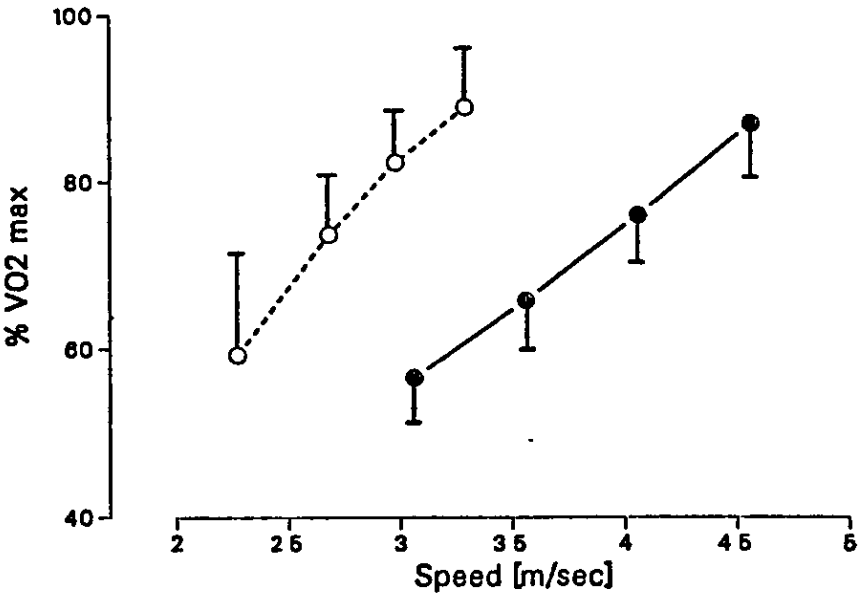
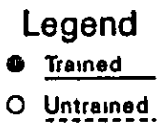


Figure 5.1b





Figures 5.1a and 5.1b. The oxygen uptake [5.1a] and the $\%VO_2$ max [5.1b] at a range of submaximal running speeds, for the untrained and trained asthmatic groups.

Figure 5.2a

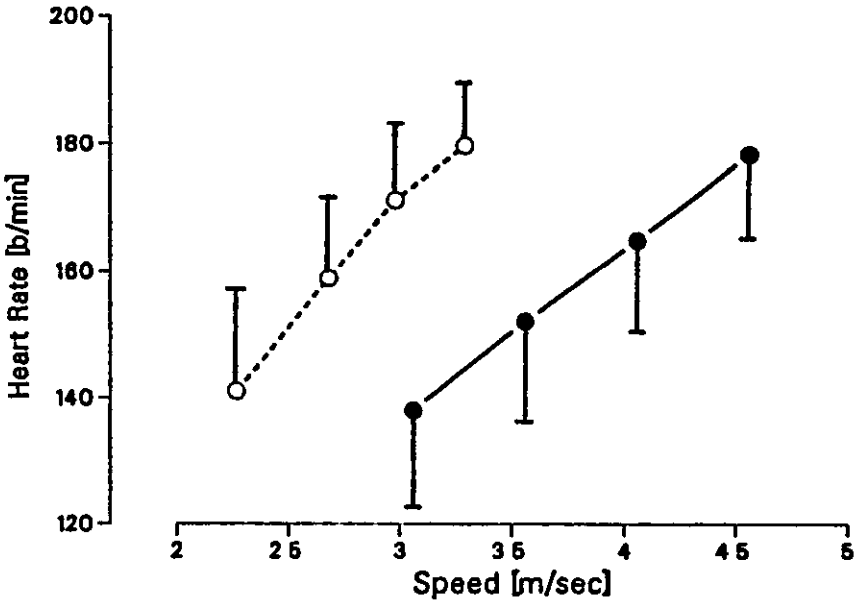
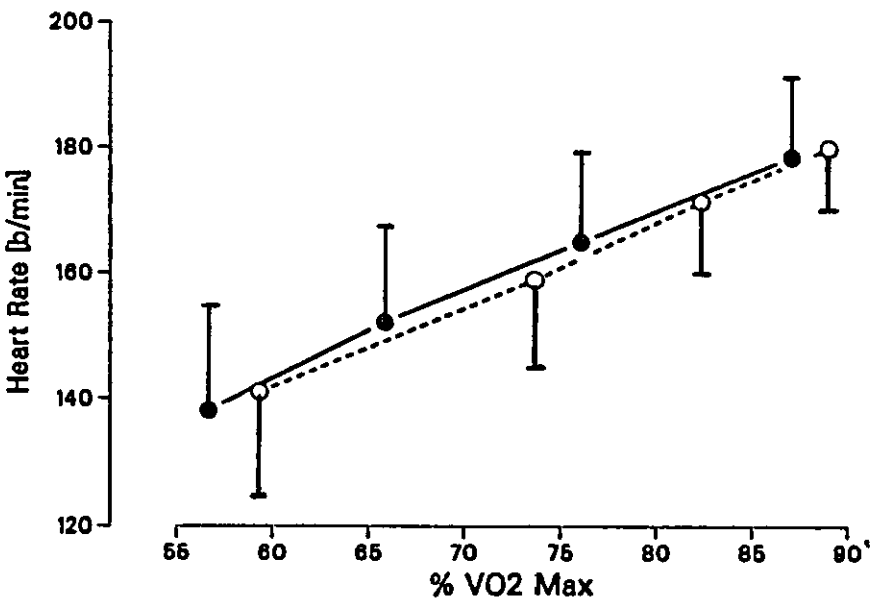


Figure 5.2b



Legend
● Trained
○ Untrained

Figures 5.2a and 5.2b. The heart rate in relation to running speed (5.2a) and $\%VO_2$ max (5.2b), for the untrained and trained asthmatic groups.

Figure 5.3a

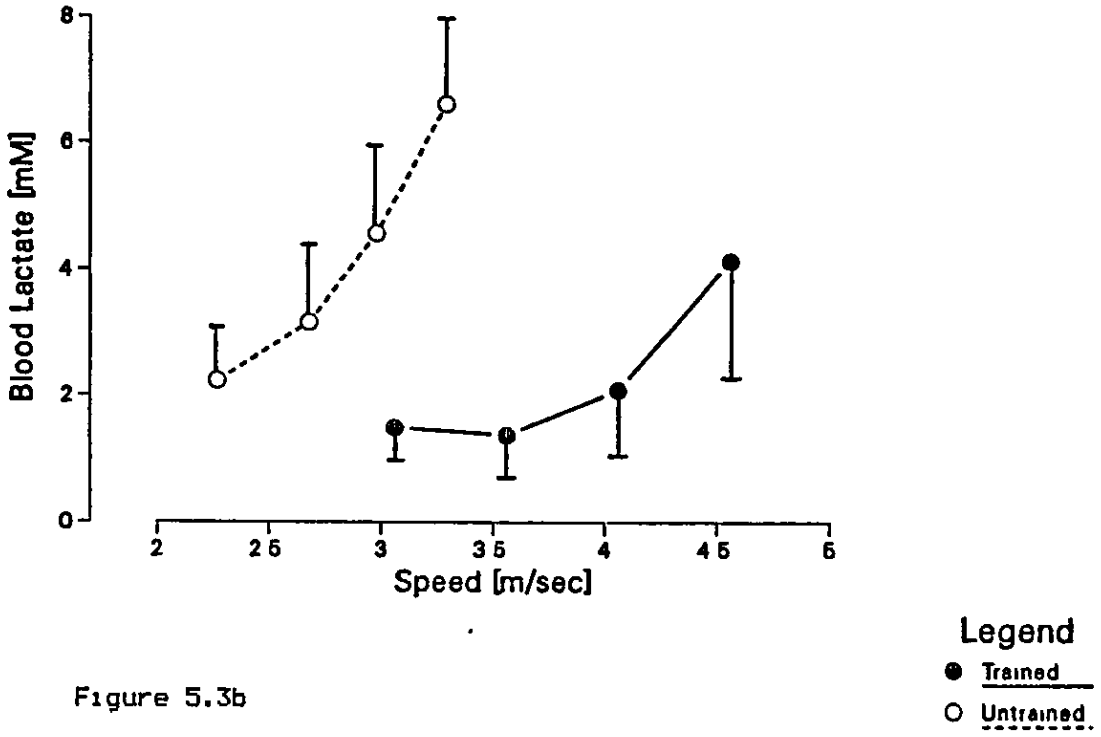
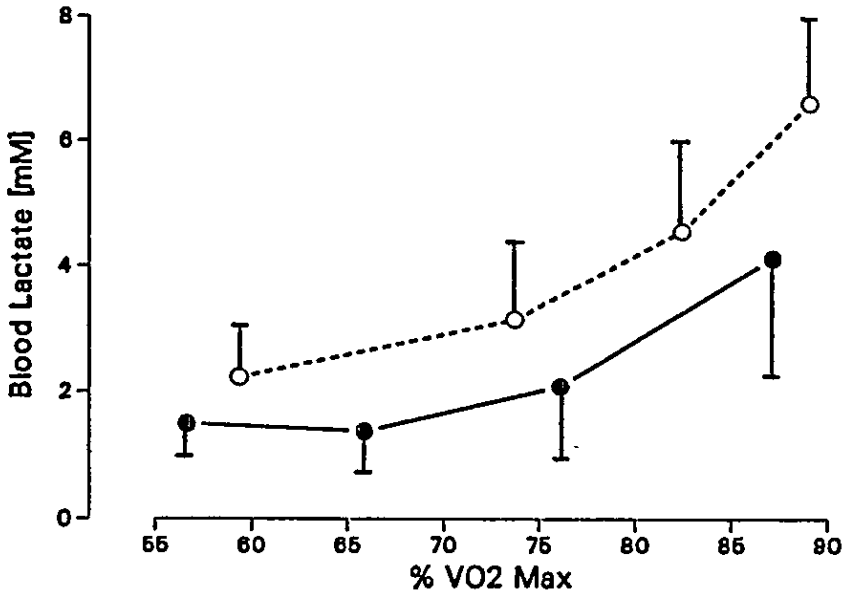


Figure 5.3b



Figures 5.3a and 5.3b. The blood lactate concentration in relation to running speed (5.3a) and $\%VO_2$ max (5.3b), for the untrained and trained asthmatic groups.

Figure 5.4a

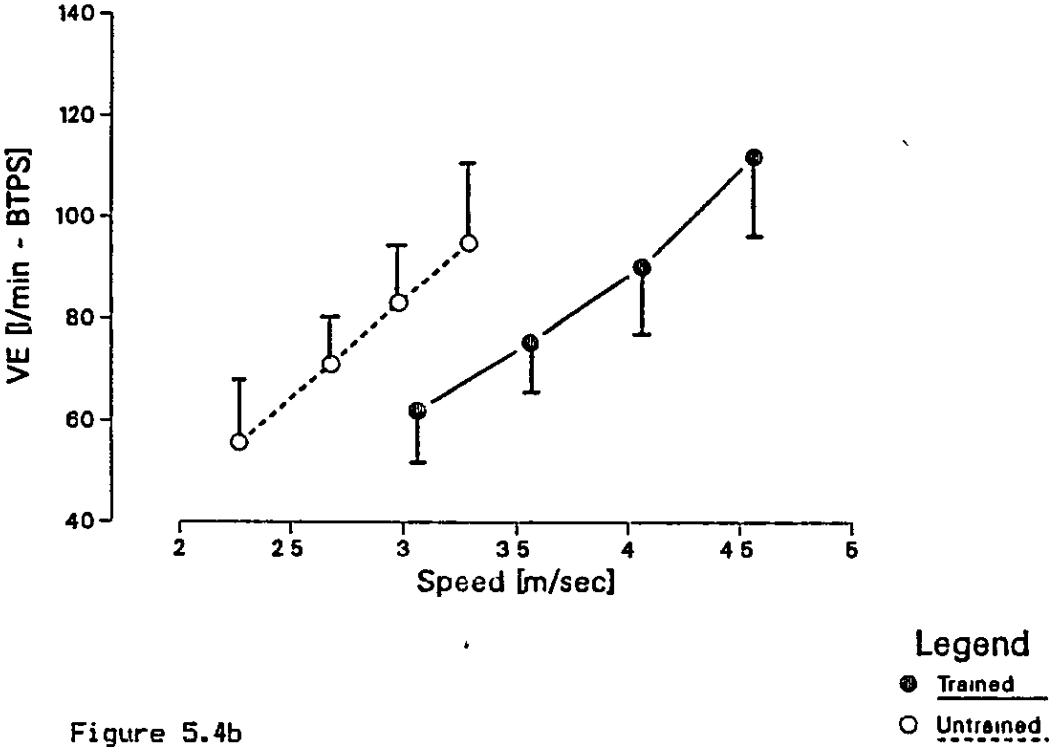
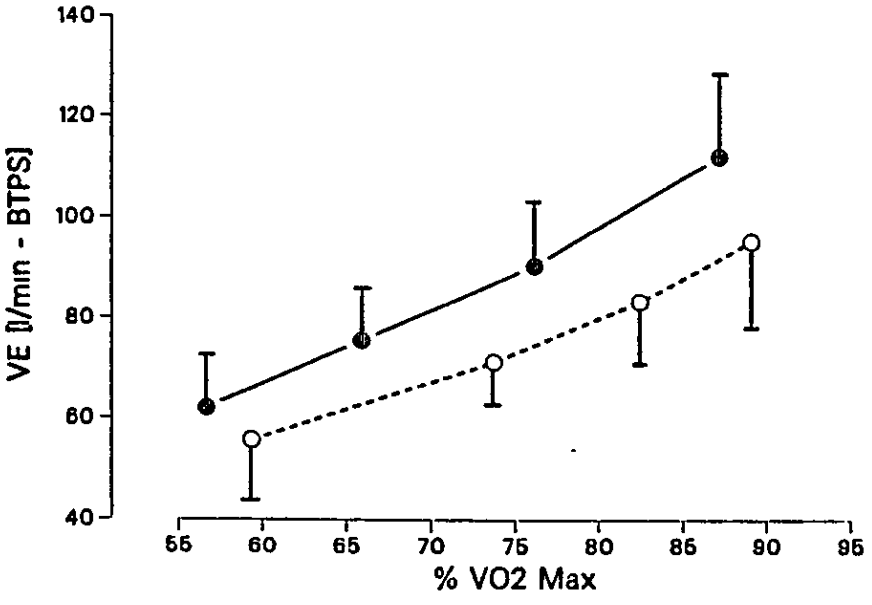


Figure 5.4b



Figures 5.4a and 5.4b. The ventilation rate in relation to running speed (5.4a) and $\%VO_{2}$ max (5.4b), for the untrained and trained asthmatic groups.

Figure 5.5a

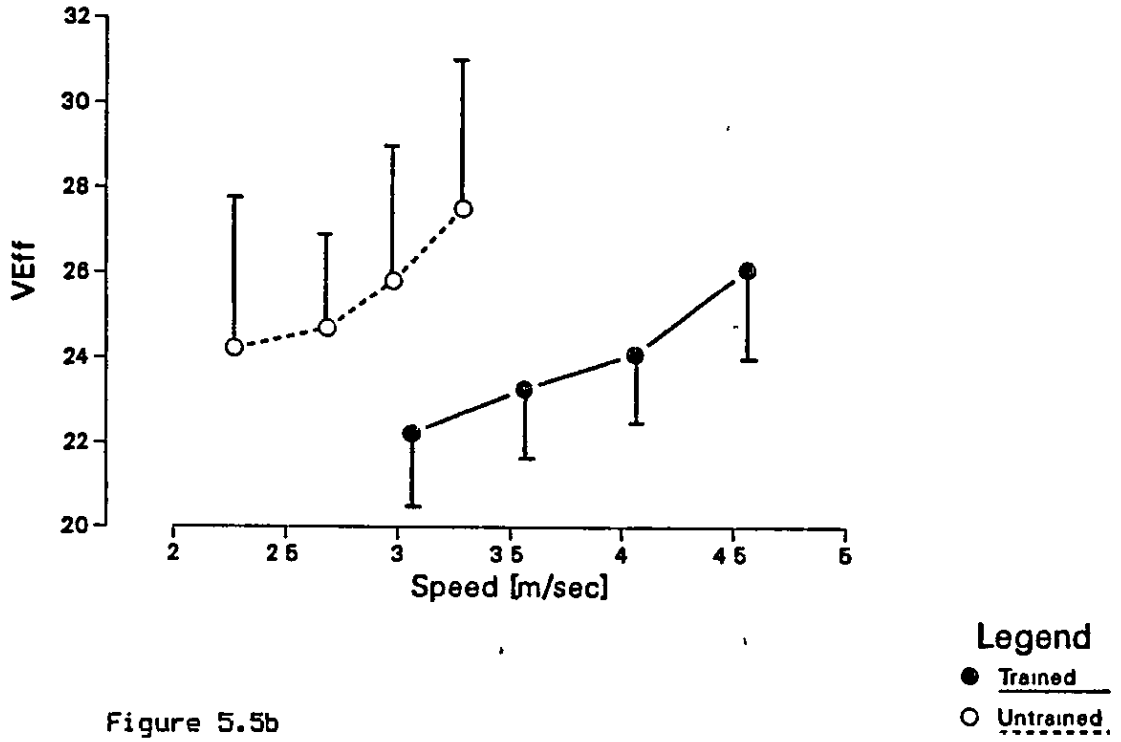
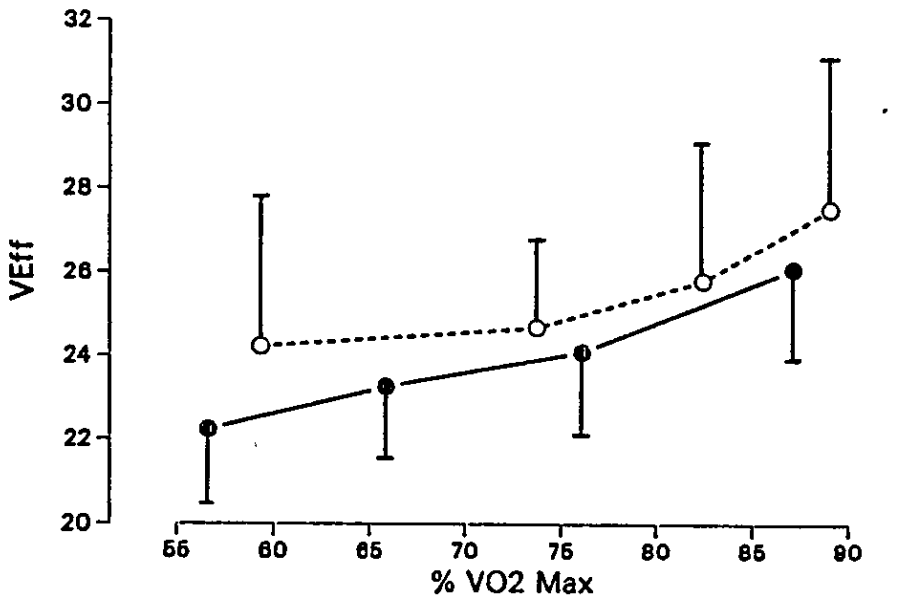


Figure 5.5b



Figures 5.5a and 5.5b. The ventilatory equivalent in relation to running speed (5.5a) and $\%VO_2$ max (5.5b), for the untrained and trained asthmatic groups.

Figure 5.6a

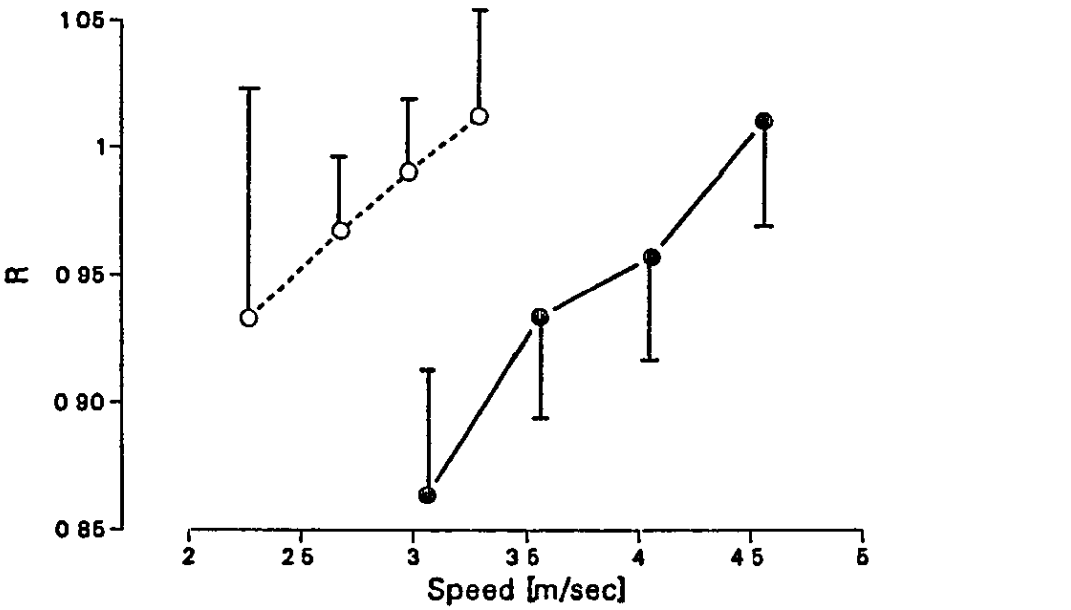
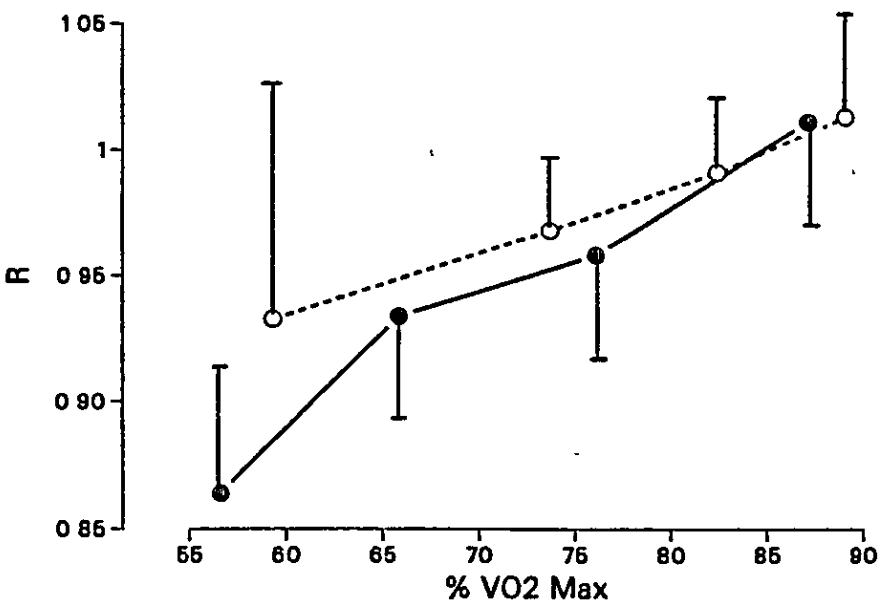


Figure 5.6b



Figures 5.6a and 5.6b. The respiratory exchange ratio in relation to running speed (5.6a) and $\%VO_2$ max (5.6b), for the untrained and trained asthmatic groups.

Figure 5.7a

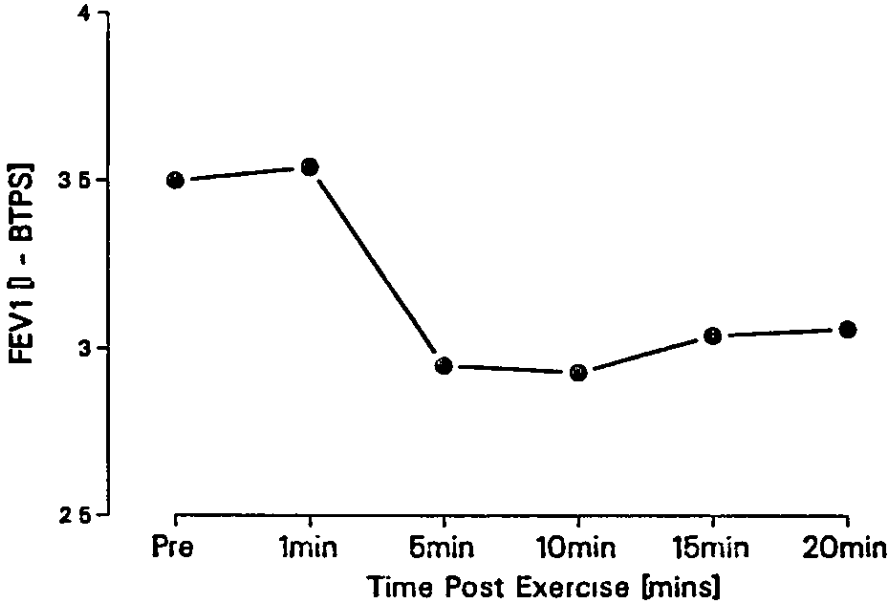
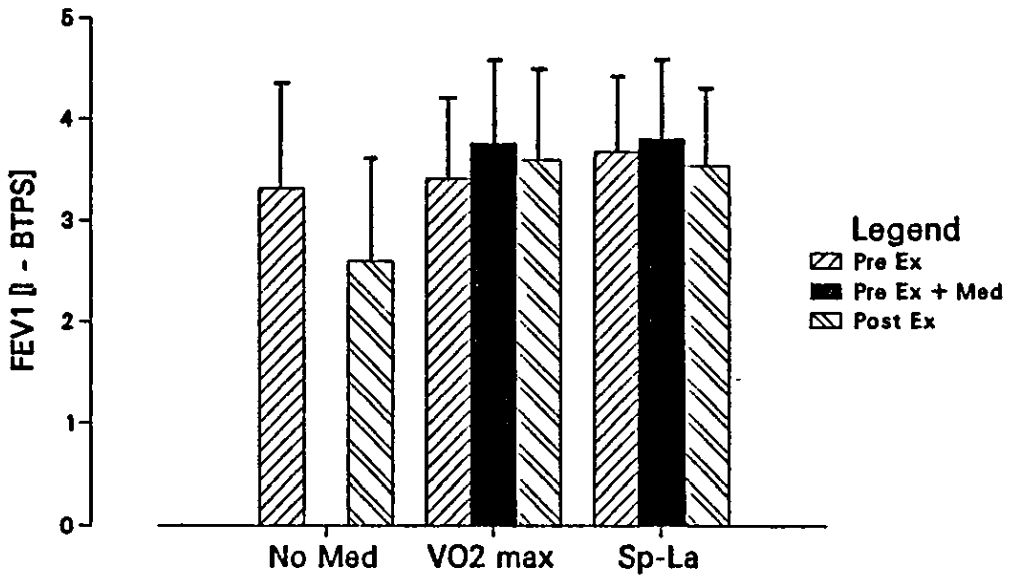


Figure 5.7b



Figures 5.7a and 5.7b. The FEV_1 before and after the non-medicated running test (5.7a), and after the maximum and speed-lactate tests when medication was taken pre-exercise (5.7b), for the asthmatic athletes.

Figure 5.8a

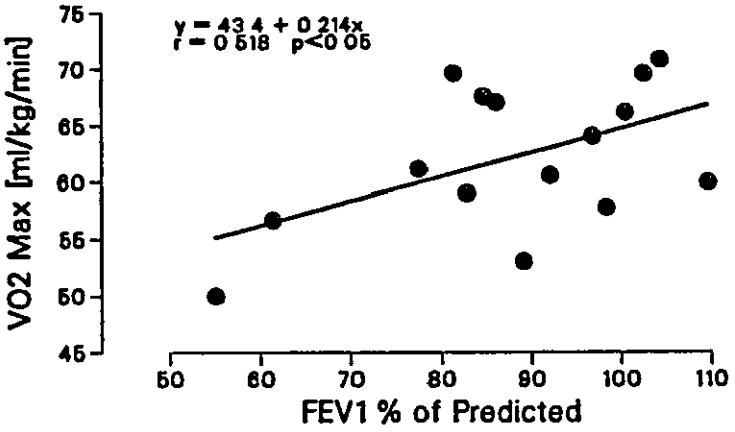


Figure 5.8b

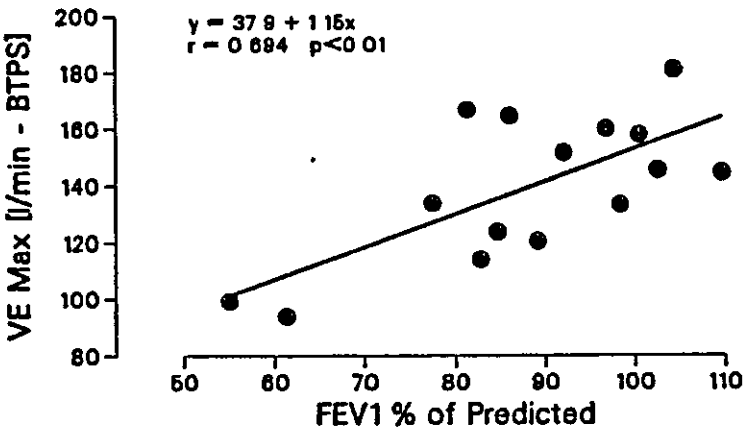
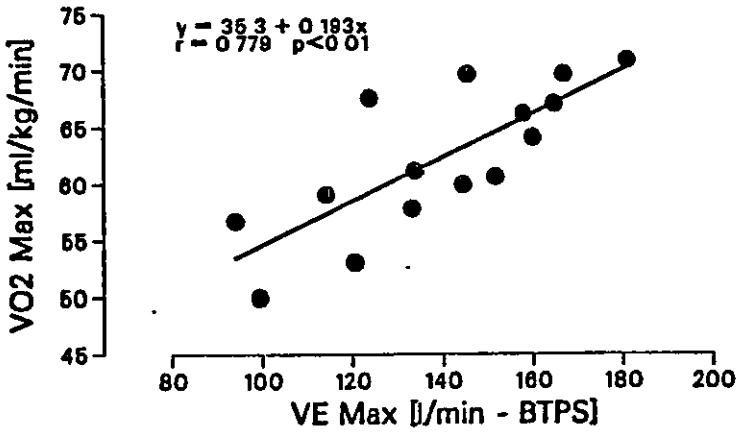


Figure 5.8c



Figures 5.8a, 5.8b and 5.8c. The relationships between VO_2 max, V_E max and the FEV_1 expressed as a percentage of the predicted normal, for the asthmatic athletes.

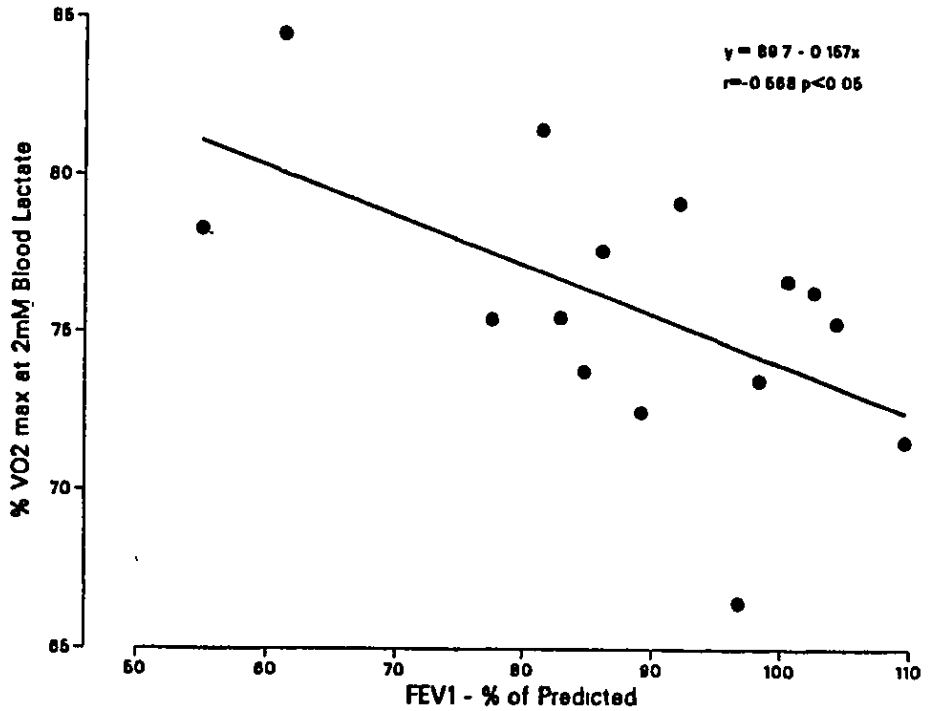


Figure 5.9. The relationship of the FEV_1 expressed as a percentage of the predicted normal, and the $\%VO_2$ max at a blood lactate concentration of 2mM, for the asthmatic athletes.

Figure 5.10a

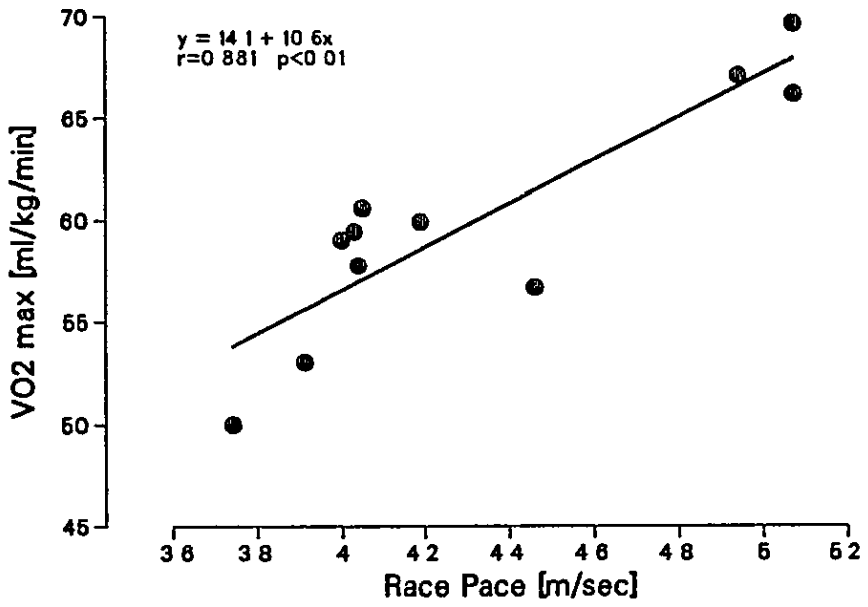
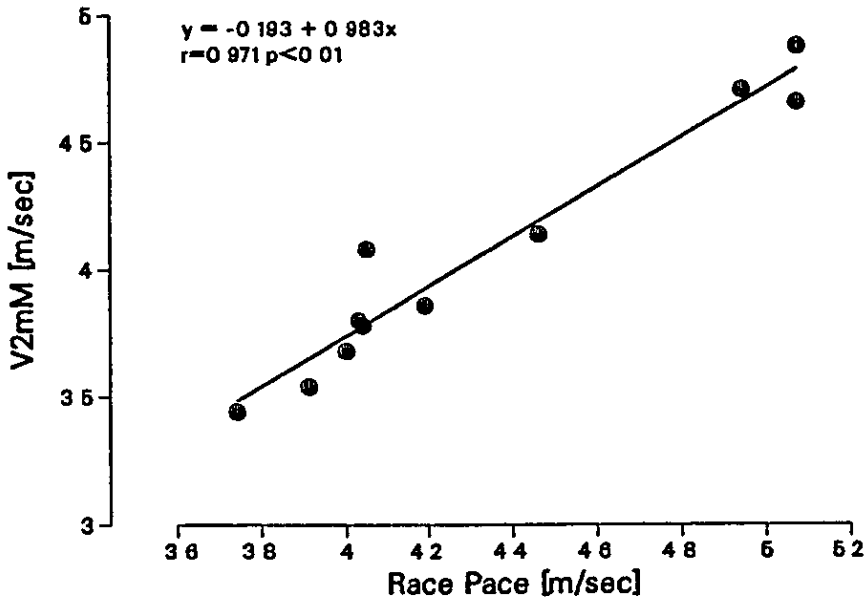


Figure 5.10b



Figures 5.10a and 5.10b. The relationship between the outdoor half-marathon running speed, with VO_2 max (5.10a) and with the running velocity at a blood lactate concentration of 2mM (5.10b), for the asthmatic athletes.

Figure 5.11a

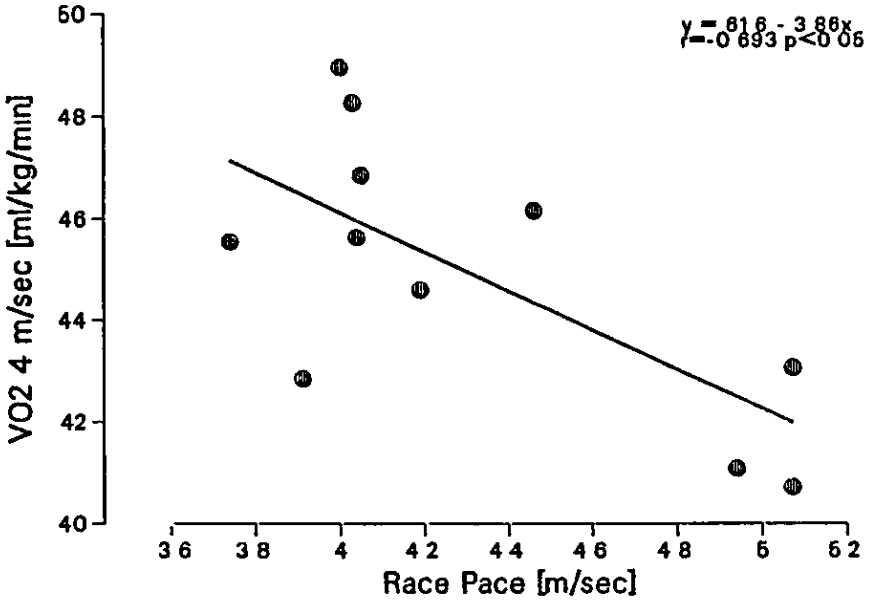
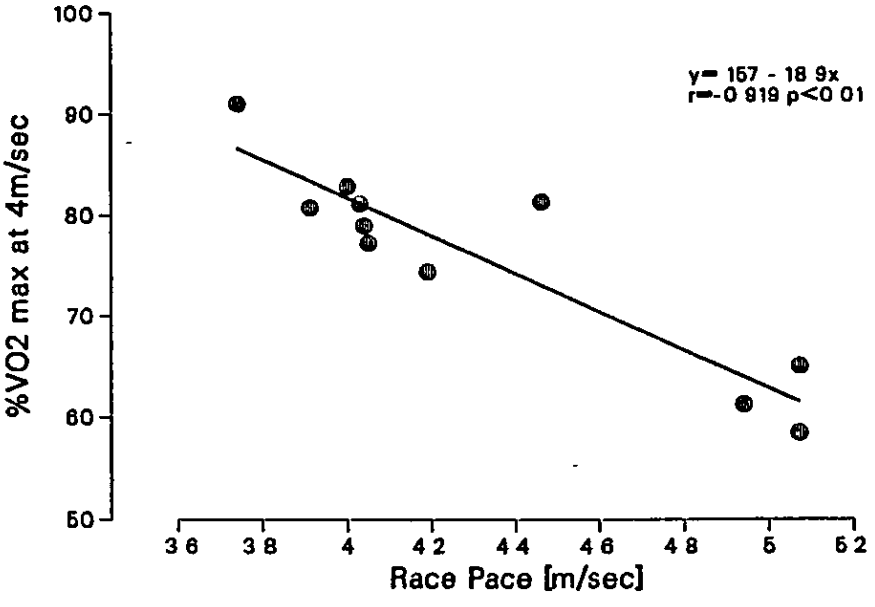


Figure 5.11b



Figures 5.11a and 5.11b. The relationship of half-marathon running speed with running economy (VO_2 at a running speed of $4m.s^{-1}$) (5.11a) and with the $\%VO_2$ max at $4m.s^{-1}$ (5.11b), for the asthmatic athletes.

Figure 5.12a

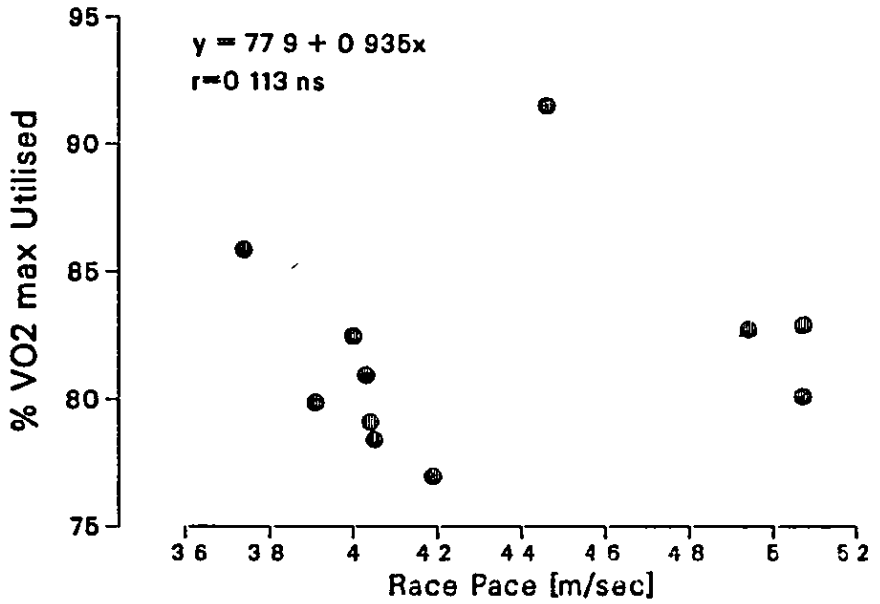
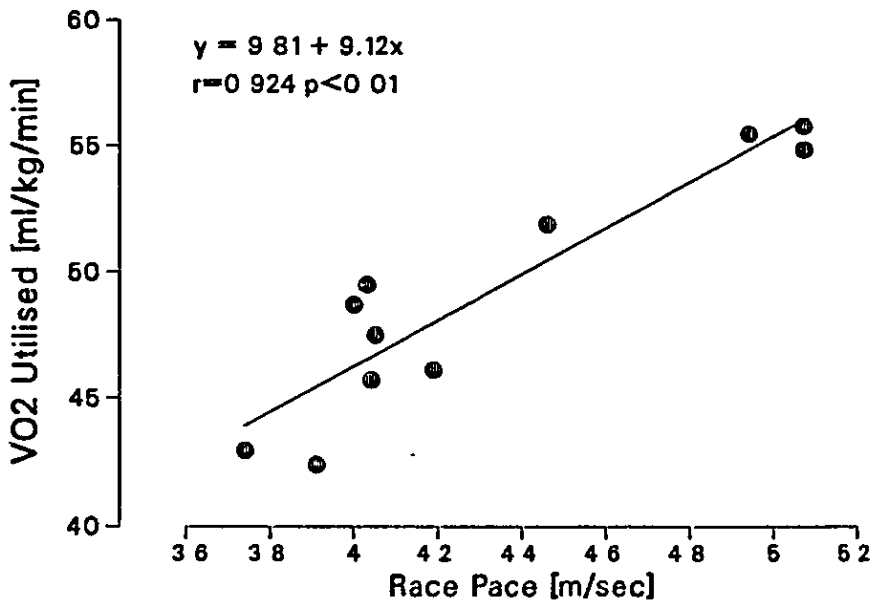


Figure 5.12b



Figures 5.12a and 5.12b. The relationship of the half-marathon running speed with the percentage of VO_2 max (5.12a) and with the absolute oxygen uptake (5.12b) utilised during the half-marathon, for the asthmatic athletes.

Figure 5.13a

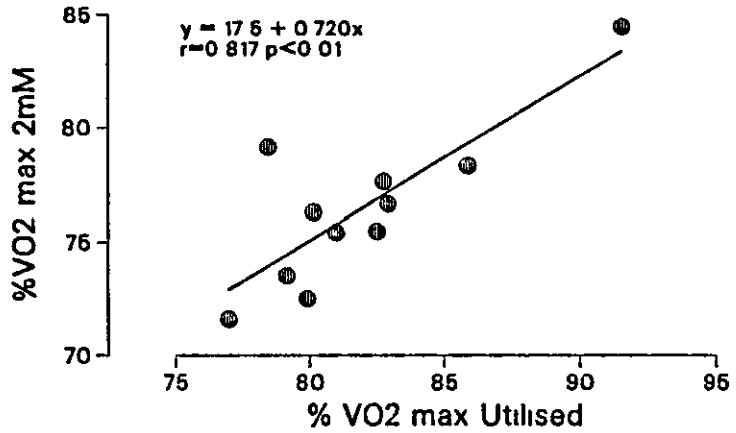


Figure 5.13b

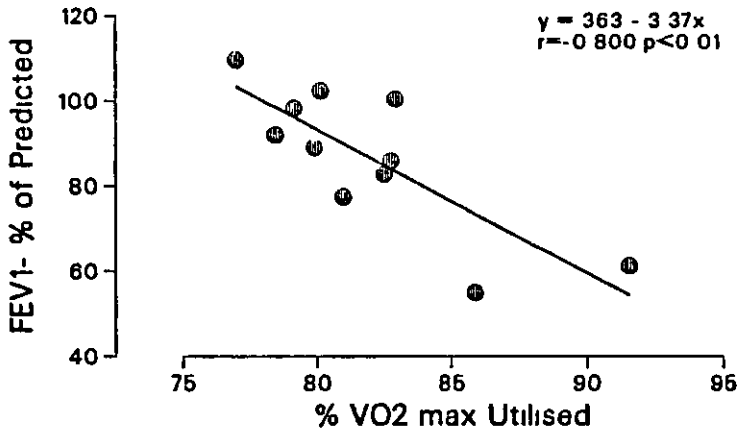
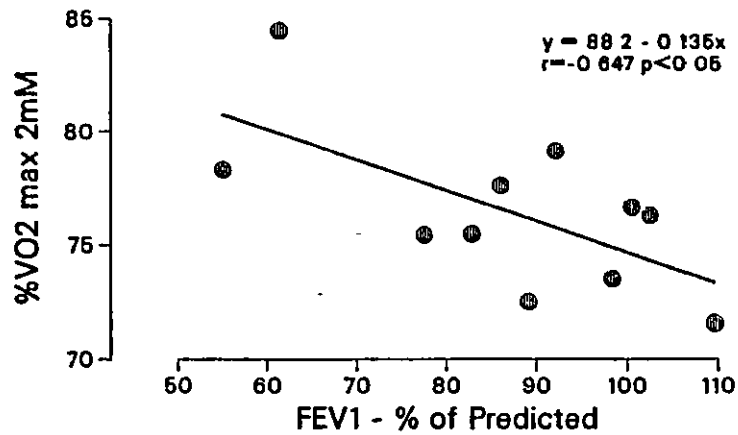


Figure 5.13c



Figures 5.13a, 5.13b and 5.13c. The relationship between the $\%VO_2$ max utilised during the half-marathon, the $\%VO_2$ max at 2mM blood lactate and the FEV_1 expressed as a percentage of predicted normal, for the asthmatic athletes.

5.4 Discussion.

The group of asthmatic athletes studied were all on regular asthmatic medication, were known asthmatics for several years, and were currently involved in endurance running training. Laboratory tests supported the medical diagnosis of asthma, confirming a degree of airflow obstruction (FEV_1 77.5 $\pm$ 18.2 percent predicted) and exercise-induced asthma in 13 out of the 15 athletes tested. To evaluate whether the asthmatic is at a disadvantage in endurance running this study evaluated the physiological responses to maximal and submaximal exercise of these trained asthmatics. Their responses were compared to the untrained asthmatics discussed in Chapter 4, whose severity of asthma was comparable. The endurance running performance over a half-marathon of this group of asthmatic athletes was also evaluated in the light of laboratory data.

5.4.1 Maximal Exercise.

The mean maximum oxygen uptake for the group of asthmatic athletes of 61.8 $\pm$ 6.3 $ml.kg.^{-1}min^{-1}$ was significantly higher than that observed for the untrained group of asthmatics (47.0 $ml.kg.^{-1}min^{-1}$), and considerably higher than that observed by other investigators studying untrained asthmatic males (Ingemann-Hansen et al 1980, Bundgaard et al 1982b). The value reported by Todaro et al (1984) for elite asthmatic athletes, albeit not endurance runners of 58.4 $\pm$ 10.7 $ml.kg.^{-1}min^{-1}$ was similar to that observed for the present group. The VO_2 max of the group of asthmatic athletes compared very favourably with those of a group of eight non-asthmatic recreational runners of 59.9 $\pm$ 4.6 $ml.kg.^{-1}min^{-1}$ (Williams and Nute 1983). Although the mean value for the group did not reach the high values for VO_2 max of 70 $ml.kg.^{-1}min^{-1}$ reported for groups of elite distance runners (Costill 1970a, Costill et al 1970b, Maron et al 1976), there were six asthmatics who had VO_2 max values in excess of 65 $ml.kg.^{-1}min^{-1}$. Therefore, this group of elite and recreational athletes have shown a well developed "aerobic capacity" inspite of their asthma.

The large range of VO_2 max (50 to 70 $ml.kg.^{-1}min^{-1}$) within the group of asthmatic athletes was accompanied by a wide variation in the pre-exercise airflow obstruction (55.0 to 109.6 percent predicted FEV_1). Due to the successful inhibition of EIA by pre-exercise

medication for the asthmatic athletes, maximum exercise did not result in an increase in the pre-exercise airflow obstruction. Thus the physiological responses to the maximum test were examined in relation to the variation in the pre-exercise pulmonary abnormalities.

In untrained non-asthmatics, the VO_2 max is not normally limited by the ventilation rate but more by the capacity for oxygen transport and the oxygen utilisation by the muscle (Dempsey 1986). However, it has been previously demonstrated in Chapter 4 that airflow obstruction may impair the maximum physiological responses to exercise of untrained asthmatics, leading to a reduced V_E max and as a consequence a reduced VO_2 max. Thus with airflow obstruction the ventilation rate may be the rate limiting step in determining VO_2 max. In addition, physical training in non-asthmatics improves the factors that normally limit VO_2 max so that the maximum ventilation becomes a more rate limiting step in determining VO_2 max (Dempsey 1986). Therefore with airflow obstruction and a highly trained state the ventilation rate may become more critical in dictating VO_2 max, and thus merits attention.

For this group of asthmatic athletes, the severity of the bronchial obstruction (percent predicted FEV_1) correlated positively with the VO_2 max and V_E max. The correlations were similar to those reported in the untrained asthmatics (Chapter 4). Therefore, those individuals with more severe airflow obstruction, had lower values for the maximum oxygen uptake and maximum ventilation. This observation for asthmatic athletes is consistent with the findings of Spiro et al (1975) who observed that the exercise ventilatory capacity is highly correlated with the FEV_1 in patients with chronic respiratory disorders. Hence, as with untrained asthmatics, more severe bronchial obstruction seems to limit the maximum physiological response to exercise in trained asthmatics. These significant correlations are inconsistent with the findings of Todaro et al (1984) who observed no significant correlations between lung function measures (FEV_1, FVC and FEV_1/FVC%) and VO_2 max and V_E max for a group of asthmatic athletes from a variety of sports.

In theory, for reasons discussed above, the maximum ventilation may pose greater limits on the VO_2 max of trained asthmatics compared to untrained asthmatics, with comparable degrees of airflow obstruction. Without measurements of the oxygen saturation, it is difficult to say whether the ventilation rate is more critical in determining VO_2 max. However, the correlation between the VO_2 max and the V_E max for the

asthmatic athletes ($r=0.779$, $p<0.01$), is higher than the same correlation obtained for the untrained asthmatics ($r=0.598$, $p<0.05$). Thus it is tentatively suggested that the maximum ventilation may be playing a more critical role in determining VO_2 max in well trained asthmatics with airflow obstruction, compared to untrained asthmatics with a similar level of airflow obstruction.

5.4.2 Submaximal Exercise.

In preference to VO_2 max, submaximal blood lactate concentrations are good indicators of the training status. The blood lactate concentrations were significantly lower for the trained asthmatics, compared to the untrained asthmatics both at the same speed and at the same $\%VO_2$ max. This finding is similar to that observed for non-asthmatics during submaximal exercise, with trained individuals having lower blood lactate levels than untrained individuals at the same speed (Holloszy 1973) and at the same relative work load (Williams et al 1967, Saltin and Karlsson 1971). Thus the asthmatic athletes have shown a similar adaptation to training as non-asthmatics. The lower blood lactate of the trained group would mean that aerobic metabolism could cover a greater proportion of the energy needs of the working muscle.

For the group of asthmatic athletes the severity of airflow obstruction (percent predicted FEV_1) was negatively correlated with the $\%VO_2$ max at which a blood lactate concentration of 2mM accumulated ($r=-0.568$, $p<0.05$). Thus the asthmatic athletes in whom the airflow obstruction was most severe, and in whom VO_2 max may as a consequence be impaired, have developed their submaximal fitness by being able to exercise at a high $\%VO_2$ max with low blood lactate concentrations. This is an adaptation to endurance running training in a group whose VO_2 max may be limited by airflow obstruction.

The trained asthmatics have a significantly lower oxygen uptake when expressed as $ml.kg.^{-1}metre^{-1}$, compared to the untrained asthmatics. The airflow obstruction is similar for the asthmatic and non-asthmatic groups and thus it is unlikely that differences in the oxygen cost of breathing could account for this. It is suggested that training has improved the running economy of the asthmatic athletes. This is consistent with the findings of studies of non-asthmatics which have shown that trained runners require less oxygen at a given submaximal runing speed compared to untrained subjects (Bransford and

Howley 1977, Mayhew et al 1979). The lower oxygen demands of trained athletes has been attributed to an increased running efficiency associated with years of endurance running training (Mayhew 1977).

Although blood lactate concentrations were reduced at a given $\%VO_2$ max for the trained asthmatics compared to the untrained group, no difference could be found between untrained and trained asthmatics for various other physiological parameters at a given $\%VO_2$ max during submaximal running. It has been previously observed that untrained asthmatics had a significantly poorer ventilatory equivalent, a reduced extraction of oxygen from inspired air and a lower ability to expel carbon dioxide at the same $\%VO_2$ max compared to untrained non-asthmatics (Chapter 4). For these parameters, the trained and untrained asthmatics showed no significant difference indicating that these factors may be inherent in the physiology of the asthmatic, and may not be improved by training.

Therefore, this trained asthmatic group showed a good aerobic fitness as defined by VO_2 max and submaximal blood lactate concentrations, despite having bronchial obstruction and EIA. Endurance fitness, however, is defined as the ability to sustain a high $\%VO_2$ max over a prolonged period. Therefore, the race performance over a half-marathon for the asthmatic athletes, was examined.

5.4.3 Endurance Running Performance

The recent performance times from races over the half-marathon distance for eleven of the asthmatic athletes were analysed in relation to their physiological responses obtained from the laboratory tests. The justification allowing the estimation of the oxygen cost of outdoor running from treadmill data, is based on the work of McMiken and Daniels (1976), who found a good correlation between the oxygen uptake of track and treadmill running over a wide range of running speeds. However, it must be appreciated that the value for the $\%VO_2$ max utilised during the half-marathon, gives an average, and that uphill and downhill sections may demand an oxygen uptake greater and lower than the average for the race (Maron et al 1976).

The average half-marathon time for the sub-group of eleven asthmatics with recent race performance times (82.36 $\pm$ 8.76 min) are consistent with what would be expected from the VO_2 max of the group (60.0 $\pm$ 5.9 $ml.kg.^{-1}min^{-1}$). The percentage of VO_2 max utilised during the half-marathon for the asthmatic athletes, estimated from treadmill

data, was 81.9 ± 4.0 %. This is similar to that utilised by non-asthmatic recreational runners during races of similar lengths of 79 %VO_2 max observed by Williams and Nute (1983) and Farrell et al (1979). Therefore, the asthmatic group were able to sustain a high %VO_2 max over a prolonged period, suggesting that asthma does not preclude the development "endurance fitness". It is concluded that mild to moderate asthmatics using pre-exercise asthmatic medication can become proficient performers in long distance races with appropriate training.

5.4.4 The Physiological Determinants of Endurance Running Performance.

For the asthmatic athletes the wide range of half-marathon times (69 to 94 minutes) was comparable to the large range of VO_2 max values (50.0 to 70.9 $ml.kg.^{-1}min^{-1}$). In the present study the VO_2 max values correlated strongly with race pace ($r=0.881$), which agrees with the work of various investigators studying similar groups of non-asthmatic recreational runners performing the half-marathon (Williams and Nute 1983), and 19.3km (Farrell et al 1979). Hence a high VO_2 max is required to run at a fast pace for the half-marathon. Although the fractional use of VO_2 max varied widely during the half-marathon (77.0% to 91.5%), it seemed not to be important in determining the differences in performance within the asthmatic group ($r=0.113$, ns), agreeing with the findings in non-asthmatic runners (Farrell et al 1979, Williams and Nute 1983). Although the fractional use of VO_2 max over the half-marathon was not useful as a discriminator of performance, it is still biologically important. Indeed, with a more homogeneous population in terms of VO_2 max, it is likely that the fractional utilisation of VO_2 max would be a more important discriminator of performance.

The relationship between the absolute oxygen utilisation at race pace with the half-marathon running speed was highly significant ($r=0.924$). This indicates that for both asthmatic and non-asthmatic (Farrell et al 1979) athletes, performance over the half-marathon is related to the ability to maintain a large oxygen consumption regardless of what %VO_2 max it represents. This relationship is obtained because of the linear relationship between oxygen uptake and running speed.

Running economy, defined here as the oxygen consumption for a submaximal treadmill velocity of $4m.s^{-1}$, showed a range of 8

ml.kg.$^{-1}$min^{-1} for the asthmatic athletes. This range was larger than that shown by Williams and Nute (1983) of 5.5 ml.kg.$^{-1}$min^{-1}, and less than that shown by Sjodin and Schele (1982) of 15 ml.kg^{-1}min^{-1}. Whether this range of running economies, for the asthmatic athletes, are random or have any relevance to running performance has been examined. For the group of asthmatic athletes, race pace was moderately and negatively correlated with running economy at 4 m.s^{-1} ($r=-0.693$:$p<0.05$), indicating that the fastest runners utilised the least oxygen at 4 m.s^{-1}. This observation suggests that running economy plays a part in distinguishing between performance over the half-marathon for the asthmatic athletes. This observation is consistent with studies of non-asthmatic runners (Farrell et al 1979, Conley and Krahenbuhl 1980). The correlation with half-marathon performance is further improved to $r=-0.919$ ($p<0.01$) if the oxygen uptake at a speed of 4m.s^{-1} is expressed at a percentage of VO_2 max. Therefore, the fractional use of VO_2 max at a set running speed gives a better indication of performance than does VO_2 max or running economy alone, as was observed by Costill et al (1973).

Although VO_2 max and running economy are both important determinants of endurance running performance, it has been proposed by Daniels et al (1978) that the metabolic parameters measured during submaximal exercise are better indicators of endurance exercise capacity. For example, submaximal lactate accumulation has been proposed as a measure of submaximal fitness (Sjodin and Schele 1982). Indeed, for this group of asthmatic athletes, the highest single correlate with the half-marathon race pace was with the treadmill velocity equivalent to a blood lactate concentartion of 2mM (V2mM), accounting for over 94% of the differences in performance. This agrees with several investigations on non-asthmatic athletes, which have observed that the running speed at which blood lactate increases above resting levels correlates best with endurance running performance over a wide range of distances (Farrell et al 1979, Kumagai et al 1982, Sjodin and Schele 1982, Williams and Nute 1983). It appears, therefore, that runners set a pace that is highly correlated to the accumulation of blood lactate.

The addition of other variables to V2mM failed to significantly raise the multiple regression correlation coefficient. This is consistent with the work of Farrell et al (1979) who showed that other parameters added to the treadmill velocity at 4mM blood lactate,

failed to account for more variation in performance times of non-asthmatic runners. Therefore, asthmatics have shown similar correlations with race performance and various physiological parameters as non-asthmatic runners.

5.4.5 The Physiological Determinants of the $\%VO_2$ max Utilised.

In this study the ability to run at a high $\%VO_2$ max could not discriminate between half-marathon performances. However, endurance fitness has recently been defined as the ability to sustain a high percentage of VO_2 max, and hence the fractional use of VO_2 max during the half-marathon merits further investigation. In the present study, the range of the $\%VO_2$ max sustained over the half-marathon varied widely from 77.0% to 91.5% VO_2 max. This wide variation in the $\%VO_2$ max sustained was not random but could be associated with the ability to provide the energy needs by aerobic metabolism, as indicated by the correlation between the $\%VO_2$ max utilised and the $\%VO_2$ max at a blood lactate concentration of 2mM ($r=0.817$:$p<0.01$). Thus the higher the $\%VO_2$ max at 2mM blood lactate concentration, the higher $\%VO_2$ max sustained during prolonged exercise. This study supports the findings observed with non-asthmatics that the $\%VO_2$ max sustained over a prolonged period is largely dependent on the capacity of the muscle to cover their energy needs by aerobic metabolism (Williams and Nute 1983).

In addition, the percent predicted FEV_1 was negatively correlated with the ability to sustain a high $\%VO_2$ max ($r=-0.800$,$p<0.01$). Therefore, those athletes with a low FEV_1 in relation to predicted normal, were able to sustain a high $\%VO_2$ max. As previously indicated, a poor FEV_1 may limit the maximum physiological parameters, and hence to counteract this limitation these subjects have developed their "endurance fitness" to be able to utilise a higher $\%VO_2$ max during prolonged running. This is further supported by the significant correlation between the percent predicted FEV_1 with the $\%VO_2$ max at a running speed equivalent to a concentration of blood lactate concentration of 2mM. Thus, with appropriate training, asthmatic athletes with severe airflow obstruction are able to develop a higher degree of "endurance fitness", as indicated by the ability to sustain a high $\%VO_2$ max, when compared to asthmatic athletes with near normal lung function. This adaptation is similar, though not as extreme, to the training adaptations reported by Coyle et al (1983) showing that

cardiac patients with limitations on their VO_2 max were able to exercise at intensities close to VO_2 max with low blood lactate concentrations.

5.5 Summary.

Mild to moderate asthma does not grossly impair the ability to develop good aerobic fitness with appropriate training, as illustrated by measurements of VO_2 max and blood lactate accumulation at submaximal running speeds. However, with increasing severity of airway obstruction, the V_E max and thus the VO_2 max may be adversely affected.

Asthmatics, who have undergone appropriate training, can complete distance running events such as the half-marathon. Moreover, the performance times and the $\%VO_2$ max utilised during the half-marathon would suggest that asthmatics can compete successfully and sustain a similar $\%VO_2$ max over the distance, compared to non-asthmatic athletes. Asthma, therefore, does not preclude the development of a high degree of "endurance fitness".

The race pace over the half-marathon for the asthmatic athletes was most highly correlated to the accumulation of blood lactate at submaximal running speeds, which agrees with similar published reports for non-asthmatics. The fractional use of VO_2 max over the half-marathon was most strongly associated with the ability to supply the energy needs by aerobic metabolism ($\%VO_2$ max at a blood lactate concentration of 2mM). Asthmatic athletes with more severe airflow obstruction, adapt to the possible limitations on VO_2 max by being able to sustain a higher $\%VO_2$ max over the half-marathon compared to asthmatics with near normal lung function.

CHAPTER 6

THE RESPONSE OF ASTHMATIC AND NON-ASTHMATIC ATHLETES TO A TREADMILL HALF-MARATHON.

6.1 Introduction.

The previous chapter demonstrated that asthma does not preclude the successful completion of a half-marathon and thus the development of a high degree of endurance fitness. Endurance running, however, is a sport likely to provoke exercise-induced asthma because it involves prolonged hyperventilation often in cold conditions (Strauss et al 1977). Despite the number of asthmatics engaged in endurance running, the physiological responses to and safety of asthmatics during and after prolonged running has not been documented.

Pre-exercise medication has been shown to inhibit or minimise EIA in the majority of asthmatics (Fitch 1986), although the effectiveness of the drugs have been evaluated only during short-term exercise. Whether pre-exercise medication can provide protection from asthma for very prolonged exercise, such as running a half-marathon, is not known. In addition, the clinical observation that asthmatics can "run through" their asthma (Fitch and Godfrey 1976) is interesting and can be investigated by examining the response of the asthmatic to an extended treadmill run.

Although the performance from outdoor distance races can be interpreted in the light of the physiological responses obtained during treadmill running as in the previous chapter, this approach yields limited information. It is technically difficult to measure the physiological responses in an outdoor race. Endurance 'racing' conditions were therefore simulated on a treadmill, enabling a comparison of the physiological responses of groups of asthmatic and non-asthmatic athletes to a half-marathon. The half-marathon distance was selected because this is a frequently run distance, and the asthmatic group had recent outdoor performance times available to compare with the treadmill race.

6.2 Methods.

6.2.1 Subjects.

From the initial 16 male asthmatic athletes tested for fitness and indices of asthma in the laboratory (Chapter 5), six volunteered to run a half-marathon on the treadmill. This sub-group of 6 asthmatic athletes were similar the total group in terms of VO_2 max (59.1 $\pm$ 5.4 vs 61.8 $\pm$ 6.3 $ml.kg.^{-1}min^{-1}$); severity of EIA (26.3 $\pm$ 12.1 vs 23.6 $\pm$ 12.7 % fall FEV_1); and baseline airflow obstruction before pre-exercise medication (71.3 $\pm$ 20.1 vs 77.5 $\pm$ 18.2 percent predicted FEV_1). Six non-asthmatics were matched as closely as possible to these asthmatics, in terms of running experience and age.

6.2.2 Baseline Laboratory Testing.

All subjects performed 3 preliminary treadmill running tests, to determine VO_2 max; the relationship between blood lactic acid and running speed; and the degree of exercise-induced asthma. The methodology for these tests is as described in the General Methods (Chapter 3).

6.2.3 Treadmill Half-Marathon.

On the day of the half-marathon time trial each subject arrived at the laboratory in a fasted state. After preliminary measurements, each athlete raced half-marathon on the treadmill (13.11 miles i.e. 21.1 kilometres). The treadmill was instrumented so that the subject could control their own speeds, with the choice of speed along with the distance run being continuously monitored by a computer interfaced with the treadmill. The following protocol was employed:

(a) Pre-exercise lung function measurements were made (FVC, FEV_1 and PEFR). These recordings were made before and after their normal pre-exercise medication for the asthmatic group.

(b) With the subject seated the following samples were taken:

(i) A 5 minute resting sample of expired air.

(ii) Capillary blood from the thumb for the determination of blood lactate and blood glucose concentrations.

(iii) A 10 ml venous blood sample from an antecubital vein for the determination of the haematocrit, haemoglobin, catecholamines (adrenaline and noradrenaline), plasma free fatty acids and plasma

glycerol concentrations.

(c) As a warm-up the subject performed 5 minutes running at a speed selected to elicit 60% VO_2 max.

(d) Using a hand held switch to alter the speed of the treadmill, each subject 'raced' the half-marathon. Knowledge of running pace, time elapsed and distance covered was available throughout the run, from a computer screen.

(e) Water and a sponge for external cooling purposes were available. The volume of water consumed and the ambient temperature and humidity were recorded throughout the half-marathon.

(f) A series of measurements were made at 1.5km,4km,8km,12km,16km and 20km during the run as follows:

(i) One minute collections of expired air were made into Douglas bags.

(ii) Duplicate 25 ul capillary blood samples from the thumb for blood lactate and glucose concentrations.

(iii) FEV_1 was recorded whilst running as the best of two trials.

(iv) Breathing frequency.

(v) Heart rate was recorded throughout the half-marathon and displayed continuously on an oscilloscope.

(g) On completion of the half-marathon, capillary blood from the thumb and a 10 ml venous blood sample from an antecubital vein, were obtained. Using the haemoglobin and haematocrit values obtained before and after the half-marathon, the percentage change in the plasma volume was calculated, using the methods described by Dill and Costill (1974).

(h) After the half-marathon the FEV_1 and PEFR were measured at 5 minute intervals for 20 minutes.

(i) Body weight was obtained both before and after the run.

In addition to pre-exercise medication, each subject was free to take asthmatic medication during the run and at the end of the run, as required.

One of the six asthmatic subjects performed two treadmill half-marathon time trials using different pre-exercise asthmatic medications. The protocol was identical to that described above for each treadmill half-marathon.

6.2.4 Statistics.

A pooled 't' test was used to compare the responses of the asthmatic and non-asthmatic groups, to the preliminary tests and to the half-marathon. The paired 't' test was used to examine any changes in the various physiological parameters recorded before, during and after the treadmill half-marathon of each group separately. The Pearson product moment correlation was used to examine the choice of running speed by examining the relationships between a variety of physiological responses measured at 4km. To analyse for changes from 4km to 20km, trend analysis (Page 1963) was performed on the physiological responses to the half-marathon for the asthmatic and non-asthmatic groups separately.

6.3 Results.

6.3.1 Physiological Characteristics.

The physiological characteristics of age, height, weight and VO_2 max were not significantly different for the asthmatic and non-asthmatic athletes who performed the treadmill half-marathon (Table 6.1). The running speed and $\%VO_2$ max at reference blood lactate concentrations of 2mM and 4mM from the submaximal running test, are shown in Table 6.2. There was no significant difference between the speed and $\%VO_2$ max at these reference blood lactate concentrations, for the asthmatic and non-asthmatic groups. Moreover, selected physiological characteristics at a running speed of 4 $m.s^{-1}$ were not different for the trained asthmatic and non-asthmatic groups (Table 6.3).

Table 6.4 gives the individual results of the exercise challenge without asthmatic medication, which shows a 26.3% fall in FEV_1 for the asthmatic runners, whereas only a 0.2% change for the non-asthmatic group. The FEV_1, FVC and $FEV_1/FVC\%$ obtained before the half-marathon prior to taking asthmatic medication are shown in absolute terms and as a percent of predicted for both the asthmatic and non-asthmatic groups (Table 6.5). The FEV_1 percent predicted and the $FEV_1/FVC\%$ were significantly lower for the asthmatic group when compared to the non-asthmatic group.

Each asthmatic had a history of asthma which was present in childhood, and all were on daily medication. The asthmatic history of the runners, along with the daily medication, and medication taken

before and during the half-marathon are shown in Table 6.6. A variety of medications were taken before exercise but each asthmatic took at least one bronchodilator. Sodium cromoglycate (Intal or Intal Co.) was taken before exercise by 3 of the asthmatic athletes. Four of the asthmatics required medication during the half-marathon and took salbutamol (Ventolin), whereas the other two asthmatics did not require extra medication during the half-marathon.

6.3.2 Treadmill Half-Marathon Performance.

The times for the treadmill half-marathon and recent performance times in an outdoor half-marathon race, are shown for the asthmatic and non-asthmatic athletes in Table 6.7. There was no significant difference between the time taken to run the treadmill and outdoor half-marathons for the asthmatic group. An average of the $\%VO_2$ max utilised throughout the run was calculated from the expired air collections during the half-marathon. The time taken to run the half-marathon and the $\%VO_2$ max utilised were not significantly different for the asthmatic and non-asthmatic groups.

6.3.3 Laboratory Conditions for the Treadmill Half-Marathon.

Table 6.8 shows that the laboratory conditions of temperature and humidity were not significantly different between the groups but varied widely from trial to trial. The fluid intake, the changes in body weight and changes in plasma volume, were not significantly different between the groups. The percentage changes in body weight were modest, with an average decrease of 2.5% and 2.7% for the asthmatic and non-asthmatic groups respectively, representing a mean change in body weight for the 12 runners of 2.6 $\pm$ 0.2 kg. The fluid (water) intake during the half-marathon varied widely ranging from 0 to 306 ml with a mean for the whole group of 99 $\pm$ 93 ml. In addition, the changes in plasma volume, calculated using haemoglobin and haematocrit values, ranged from +2.7 to -7.7 % with a total mean response of -1.8 $\pm$ 2.8 % for the 12 athletes.

6.3.4 Lung Function Responses to the Half-Marathon.

Each asthmatic athlete took their preferred pre-exercise medication prior to the half-marathon (Table 6.6), which slightly increased the mean FEV_1 from 3.45 $\pm$ 0.76 to 3.59 $\pm$ 0.82 litres (4.1% increase).

Tables 6.9 and 6.10 give the values for the FEV_1 during and after

the treadmill half-marathon for both the asthmatic and non-asthmatic groups. Figure 6.1 shows the percent changes from pre-exercise values of the FEV_1 during and after the half-marathon for the asthmatic and non-asthmatic groups. Although the asthmatic group, showed a decrease in FEV_1 during and after the half-marathon, the changes from the resting values were not significantly different. This is due to the large variation in the responses within the asthmatic group. Four asthmatics did not experience significant asthma in response to the half-marathon (Figure 6.2a), whereas two asthmatics (4 and 5) experienced had marked changes in the FEV_1 both during and after the half-marathon (Figure 6.2b). The non-asthmatic group experienced a significantly lower FEV_1 during the half-marathon compared to pre-exercise values, but the mean post-exercise values were not significantly different to the pre-exercise response.

After the 20 minute post-exercise recordings of the FEV_1 the two asthmatics who experienced marked bronchoconstriction took 200ug of salbutamol (Ventolin) from an inhaler and then the FEV_1 was recorded after 15 minutes. Asthmatic number 4 had a pre-exercise FEV_1 of 3.65 litres, which dropped to 2.83 litres 20 minutes after the half-marathon and was only slightly reversed to 2.90 litres after the inhalation of salbutamol. Similarly, asthmatic number 5 had a resting FEV_1 of 2.93 litres, which had dropped to 2.42 litres after 20 minutes of recovery and was only 2.60 litres after the administration of the bronchodilator.

6.3.5 Metabolic Responses to the Half-Marathon.

The blood lactate concentrations during the half-marathon are shown in Table 6.11, showing a varied response between subjects. The mean values of the blood lactate concentrations for the asthmatic and non-asthmatic groups were not significantly different (Figure 6.3a). Likewise the blood glucose concentrations shown in Table 6.12 for each subject, indicate a large variation in the responses. No athlete experienced hypoglycaemia, defined as a blood glucose concentration of less than 2.5mM. Two non-asthmatics, however, did have a reduction in their blood glucose concentrations at the end of the half-marathon. The mean response for the blood glucose concentrations of the asthmatic and non-asthmatic groups are illustrated in Figure 6.3b. Although there were no significant difference between the blood glucose values for the groups, the asthmatic group showed higher blood

glucose concentrations throughout the run. This was mainly due to the greater rise in blood glucose of two of the asthmatic runners.

The catecholamine (noradrenaline (NA) and adrenaline (AD)) responses to the half-marathon for the asthmatic (n=6) and non-asthmatic (n=4) groups are shown in Figure 6.4a and 6.4b. For the asthmatic group, NA and AD showed a highly significant increase from pre-exercise values, representing 10 fold and 7 fold changes respectively. The non-asthmatic group showed a similar response but due to the large intra-group variation, only the NA showed a significant change. In addition, there was no significant difference between groups for the pre-exercise, post-exercise and changes in either NA or AD. The individual values for NA and AD are shown in Table 6.13, showing the varied response. There were no major differences in the response of NA and AD for the asthmatics who did and did not bronchoconstrict.

The asthmatic and non-asthmatic groups showed a significant increase in FFA and plasma glycerol concentrations, with no significant difference in the magnitude of the response between groups (Figures 6.5a and 6.5b), although the variation in the response between subjects was large (Table 6.14).

6.3.6 The Cardio-Respiratory Responses to the Half-Marathon.

The mean values for various cardio-respiratory responses to the half-marathon, together with trends over time, are shown in Tables 6.15 and 6.16 for the asthmatic and non-asthmatic groups. Running speed was slightly but not significantly higher for the asthmatics throughout the half-marathon, but there was no difference between the groups in terms of the $\%VO_2$ max utilised (Fig. 6.6). Heart rate was significantly lower at 12km and 16km for the asthmatics compared to the non-asthmatics (Fig. 6.7a), although there was no difference when expressed as a percentage of the maximum heart rate. Trend analysis showed a significant increase in heart rate ($p<0.001$) for both groups over the half-marathon. Ventilation rate was lower, though not significantly so, for the asthmatic group throughout the half-marathon (Fig. 6.7b) and showed an upward trend for both the asthmatics ($p<0.001$) and non-asthmatics ($p<0.05$). The lower ventilation rate of the asthmatic group was accompanied by a lower (but not significant) breathing frequency, rather than any difference in tidal volume (Figs. 6.8a and 6.8b). No difference in the ventilatory equivalent between

the groups was evident (Fig. 6.9a). Nor was there any difference between the groups in the metabolism of fat and carbohydrate, as illustrated by the similar respiratory exchange ratio (R) (Fig. 6.9b). Both groups showed a trend towards a lowering of the R values throughout the half-marathon, indicating an increased metabolism of fat with time.

6.3.7 The Physiological Examination of the Choice of Running Speed.

To examine the choice of running pace, the relationships between individual values for selected physiological parameters at a distance of 4km into the run, were correlated with the pre-exercise medicated lung function values. It was envisaged that each subject should have selected their preferred running pace by the time 4km had been completed. The FEV_1 percent predicted and the $FEV_1/FVC\%$, were correlated with relevant physiological parameters for both the asthmatic and non-asthmatic groups (Table 6.17). For the asthmatic group the physiological parameters at 4km were significantly correlated with the $FEV_1/FVC\%$ but not with FEV_1 percent predicted. A low $FEV_1/FVC\%$ was significantly associated with a low breathing frequency and good ventilatory equivalent. In addition, the $FEV_1/FVC\%$ was significantly and negatively correlated with tidal volume. In addition the poorer the pre-exercise air-flow obstruction, the higher the percentages of VO_2 max and V_E max utilised during the half-marathon. The non-asthmatic group did not show such relationships.

6.3.8 Two Half-Marathons by one Asthmatic Using Different Pre-Exercise Medications.

One of the asthmatic runners (4), who experienced marked bronchospasm during and after the half-marathon, elected to race a second half-marathon using a different combination of pre-exercise medications which he sometimes used to prevent EIA in long distance races. The first half-marathon (Run 1) was performed using sodium cromoglycate (Intal) and salbutamol (Ventolin) pre-exercise. The second half-marathon (Run 2) was performed using aminophylline (Phyllocontin) in addition to the pre-exercise treatment taken in Run 1. The asthmatic took three 225 mg slow-release Phylloncontin capsules, one the night before the half-marathon, one on waking and one pre-exercise. This dosing regime had previously been adopted by

this asthmatic prior to long distance races. Table 6.18 shows the results from the two half-marathons. The performance times for the two runs were similar, being run in 85.48 minutes and 87.52 minutes, utilising an average of 75.6% and 74.0% VO_2 max, respectively.

The response of the FEV_1 under the two experimental conditions is shown in Figure 6.10 indicating that this asthmatic experienced his asthma during both runs, but at a much later stage in run 2. The severity of the EIA was greater in run 2 with a 58.1% maximum fall in FEV_1 compared to 33.7% in run 1. After run 1 the FEV_1 started to recover immediately, but the FEV_1 continued to fall in the post-exercise period after run 2. The FEV_1 stayed low, despite taking salbutamol during the half-marathon, and in addition the FEV_1 did not recover immediately despite further salbutamol after exercise. For example, after run 1 the FEV_1 rose from 2.83 to 2.90 litres 15 minutes after the inhalation of 200ug salbutamol. Furthermore, after run 2 the FEV_1 rose from 1.76 to 2.04 litres 15 minutes after the same dose of bronchodilator, which was still much lower than the pre-exercise FEV_1 of 3.41 litres. The FEV_1 one and a half hours after the end of run 2 with many extra doses of the bronchodilator inhaler, however, was elevated above the resting value (3.55 litres).

The running speed and oxygen uptake throughout the two half-marathons, are shown in Figure 6.11a and 6.11b. The running speed and the oxygen uptake were reduced when the EIA increased in severity in both half-marathons. The heart rate was much higher in run 2 with aminophylline despite the slightly slower running speed (Figure 6.12a). Indeed, the heart-rate was higher than the maximum heart-rate recorded in response to the maximum oxygen uptake test (183 beats.min^{-1}) for a substantial part of run 2 (4km to the end of the half-marathon). In contrast, the minute ventilation was similar for the two runs (Figure 6.12b). Figures 6.13a and 6.13b shows the breathing frequency and tidal volume for the two runs. With the onset of the asthma tidal volume was much reduced, with breathing frequency slightly elevated despite a reduction in minute ventilation. The ventilatory equivalent was not different for the two runs (Figure 6.14a), whereas the oxygen pulse was lower on run 2 with aminophylline (Figure 6.14b).

Figures 6.15a and 6.15b shows the responses of the blood lactate and blood glucose concentrations during the two runs. Blood glucose was lower for run 2 with aminophylline compared to run 1, whereas

blood lactate was not consistently different. In addition, the response of the catecholamines (adrenaline and noradrenaline) during run 1 were very much greater when compared to the response of run 2 with aminophylline. In addition the change from pre-exercise values in the plasma concentrations of FFA and glycerol after the half-marathon were much lower for run 1 compared to run 2 (Table 6.18).

The laboratory conditions were somewhat different, being warmer and less humid for run 2. Regardless of these differences in environmental conditions, the weight losses and changes in plasma volume were not markedly different after the two runs for this subject (Table 6.18).

Table 6.1. The physiological characteristics of the male asthmatic and non-asthmatic treadmill half-marathon runners, obtained in response to the maximum oxygen uptake test.

	Age (yr)	Height (m)	Weight (kg)	VO_2 max ($ml.kg.^{-1}min^{-1}$)	HR max ($b.min^{-1}$)	V_E max ($l.min^{-1}$-BTPS)
Asthmatics						
1	31	1.80	65.9	60.6	188	151.5
2	44	1.84	66.7	61.1	201	133.8
3	36	1.79	72.2	66.2	177	157.8
4	48	1.67	63.95	59.9	183	144.5
5	44	1.77	65.85	50.0	171	99.3
6	41	1.72	58.9	56.7	178	93.9
mean	40.7	1.77	65.6	59.1	183	130.1
± SD	6.2	0.06	4.3	5.4	11	27.3
Non-Asthmatics						
1	31	1.82	75.9	54.0	183	160.5
2	34	1.78	69.9	57.2	187	144.5
3	33	1.69	65.75	61.6	186	132.2
4	30	1.90	72.4	65.3	179	147.2
5	46	1.65	54.2	62.0	188	122.4
6	44	1.71	74.2	53.6	184	134.3
mean	36.3	1.76	68.7	58.9	185	140.2
± SD	6.9	0.09	8.0	4.7	3	13.4

Table 6.2. The running speed and $\%VO_2$ max at 2mM and 4mM blood lactate concentrations, for the asthmatic and non-asthmatic treadmill half-marathon runners.

	V2mM ($m.s^{-1}$)	V4mM ($m.s^{-1}$)	$\%VO_2$ max 2mM	$\%VO_2$ max 4mM
Asthmatics				
1	4.08	4.5	79.1	89.2
2	3.80	4.26	75.4	85.7
3	4.66	5.24	76.7	85.9
4	3.86	4.52	71.6	83.5
5	3.44	3.93	78.3	89.6
6	4.14	4.61	84.5	94.2
mean	4.00	4.51	77.6	88.0
±SD	0.41	0.43	4.3	3.8
Non-Asthmatics				
1	3.62	4.16	77.1	88.4
2	3.50	4.05	67.7	80.8
3	4.47	4.71	80.0	86.0
4	4.61	5.22	76.9	92.3
5	4.01	4.57	69.8	82.4
6	3.61	3.95	71.9	81.3
mean	3.97	4.44	73.9	85.2
±SD	0.48	0.48	4.8	4.6

Table 6.3. A comparison of physiological responses for the asthmatic and non-asthmatic treadmill half-marathon runners, at a reference running speed of 4 $m.s^{-1}$ (mean ± SD).

	Asthmatics (n=6)	Non-Asthmatics (n=6)
VO_2 ($ml.kg.^{-1}min^{-1}$)	45.8 ± 1.8	43.2 ± 3.1
% VO_2 max	78.1 ± 8.5	74.1 ± 10.6
VCO_2 ($ml.kg.^{-1}min^{-1}$)	44.0 ± 3.5	44.1 ± 6.1
Ventilation ($l.min^{-1}$-BTPS)	86.9 ± 9.5	89.7 ± 21.6
Heart Rate ($b.min^{-1}$)	159 ± 12	160 ± 13
Respiratory Exchange Ratio	0.96 ± 0.06	1.02 ± 0.08
Ventilatory Equivalent	23.9 ± 1.7	24.6 ± 2.7
% FEO_2	16.8 ± 0.3	16.8 ± 0.4
% $FECO_2$	4.07 ± 0.29	4.18 ± 0.28

Table 6.4. The physiological responses and changes in the FEV_1 for the test performed without asthmatic medication, for asthmatic and non-asthmatic treadmill half-marathon runners.

	Speed $m.s^{-1}$	VO_2 $ml.kg^{-1}min^{-1}$	$\%VO_2$ max	V_E BTPS $l.min^{-1}$	HR $b.min^{-1}$	Pre FEV_1	Post FEV_1	% Change FEV_1
Asthmatics								
1	4.25	49.3	81.4	106.1	166	4.30	2.65	-38.4
2	4.0	46.9	76.8	85.0	165	2.70	1.74	-35.6
3	5.0	56.9	85.9	115.0	165	3.28	2.50	-23.8
4	4.25	46.9	78.3	95.1	175	3.13	2.63	-16.0
5	3.5	37.5	75.1	60.2	153	1.24	0.80	-35.5
6	4.50	51.7	91.2	76.6	163	2.15	1.96	-8.8
mean	4.25	48.2	81.4	89.7	164	2.80	2.05	-26.3
± SD	0.50	6.4	20.0	6.1	7	1.04	0.72	12.1
Non-Asthmatics								
1	4.0	45.7	84.6	125.4	162	4.80	4.78	-0.4
2	4.25	49.6	86.7	121.6	175	4.65	4.68	0.7
3	4.5	49.4	80.2	89.6	168	3.79	3.76	-0.8
4	5.25	59.9	91.8	129.0	169	6.05	5.79	-4.3
5	4.75	55.4	89.4	105.6	156	2.75	2.86	4.0
mean	4.55	52.0	86.5	114.2	166	4.41	4.37	-0.2
± SD	0.48	5.6	4.5	16.4	7	1.23	1.11	3.0

Table 6.5. Lung function values prior to the treadmill half-marathon for the asthmatics (without medication) and the non-asthmatics. (Actual and percent predicted shown).

	VC (1-BTPS)		FEV_1 (1-BTPS)		$FEV_1/VC\%$
	Actual	% Pred.	Actual	% Pred.	Actual
Asthmatics					
1	4.95	89.4	4.52	97.0	91.3
2	5.07	92.7	3.27	74.3	64.5
3	6.20	117.0	3.85	87.5	62.1
4	5.43	129.9	3.81	114.4	70.2
5	4.85	97.0	2.74	68.5	56.5
6	4.75	100.6	2.48	64.4	52.2
mean	5.21	104.4	3.45	84.4 *	66.1 *
± SD	0.54	15.7	0.76	19.1	13.8
Non-Asthmatics					
1	5.49	95.8	4.86	100.8	88.5
2	5.29	99.8	4.68	105.6	88.5
3	5.08	107.2	4.06	102.0	88.5
4	7.12	113.6	5.91	113.4	83.0
5	3.98	95.7	3.00	89.6	75.4
6	5.19	113.6	4.13	112.2	79.6
mean	5.36	104.3	4.44	103.9	83.9
±SD	1.01	8.3	0.97	8.7	5.5

* $p<0.05$: Denotes significant difference between asthmatics and non-asthmatics.

Table 6.6. The asthmatic history and medication taken before and during the treadmill half-marathon for the asthmatic athletes.

	Age (yr)	Yrs of Asthma	Daily Medication	Medication for Half Marathon Before	During (mins)
1	31	30	Becotide/Berotec	Berotec	-
2	44	39	Becotide/Ventolin	Ventolin	Ventolin (8,19)
3	36	34	Ventolin	Ventolin	Ventolin (38)
4	48	46	Becloforte/Intal Ventolin	Intal Ventolin	Ventolin (58,66,76)
5	44	40	Becotide/Intal Co. Ventolin	Intal Co. Ventolin	Ventolin (18,43,62,77)
6	41	40	Intal Co.	Intal Co.	-
mean	41	38			
±SD	6	6			

Table 6.7. Half-marathon times (treadmill and outdoor) and the average running speed, and $\%VO_2$ max utilised during the treadmill half-marathon, for the asthmatic and non-asthmatic athletes.

	Treadmill (min)	Outdoor (min)	Speed ($m.s^{-1}$)	Average $\%VO_2$ max
Asthmatics				
1	87.60	86.78	4.01	71.9
2	82.23	87.35	4.28	79.3
3	71.25	69.42	4.94	79.1
4	85.48	84.00	4.11	78.2
5	98.68	94.00	3.56	82.5
6	80.53	78.87	4.37	84.0
mean	84.30	83.40	4.21	79.2
±SD	9.03	8.43	0.45	4.2
Non-Asthmatics				
1	91.63		3.84	83.7
2	101.02		3.48	76.2
3	83.72		4.20	71.7
4	74.52		4.72	82.0
5	77.52		4.54	84.9
6	97.12		3.62	76.3
mean	87.59		4.07	79.2
±SD	10.7		0.50	5.2

Table 6.8. Laboratory conditions, fluid intake, and changes in body weight and plasma volume for the asthmatic and non-asthmatic groups during the treadmill half-marathon.

	Asthmatics			Non-Asthmatics		
	mean	± SD	Range	mean	± SD	Range
Temperature						
°C	18.1	± 2.0	15.4 - 20.5	16.6	± 1.9	13.4 - 18.9
Humidity						
%	60.5	± 7.1	53 - 73	64.2	± 12.5	48 - 83
Weight (kg)						
Pre	65.7	± 4.9	58.5 - 72.4	69.2	± 8.7	53.4 - 76.4
Post	64.1	± 4.7	57.2 - 70.4	67.4	± 8.4	52.1 - 74.5
% Change	-2.5	± 0.2	-2.3 - -2.8	-2.7	± 0.2	-2.3 - -3.1
Haemoglobin ($g.dl^{-1}$)						
Pre	15.8	± 0.9	14.6 - 17.3	14.9	± 0.9	13.3 - 15.8
Post	15.9	± 0.9	14.7 - 17.0	15.3	± 1.0	13.6 - 16.5
Haematocrit (%)						
Pre	45.8	± 2.0	43.0 - 48.5	43.8	± 2.7	40.5 - 48
Post	46.4	± 2.8	42.5 - 49.5	43.1	± 2.7	39.3 - 47
Plasma Volume						
% Change	-2.2	± 3.4	-7.7 - 2.7	-1.2	± 2.0	-2.9 - 1.8
Fluid Intake						
(ml)	93	± 91	0 - 222	106	± 103	28 - 306

Table 6.9. The FEV_1 recorded pre-exercise (with medication), and during the treadmill half-marathon, for the asthmatic and non-asthmatic athletes (litres).

			Distance in Half-Marathon					
	REST	W-Up	1.5Km	4Km	8Km	12Km	16Km	20Km
Asthmatics								
1	4.55	4.37	4.30	4.37	4.29	4.13	3.86	3.83
2	3.58	3.53	3.42	3.47	3.27	3.48	3.44	3.41
3	4.41	4.28	4.22	4.19	4.31	4.32	4.17	4.35
4	3.65	3.73	3.59	3.57	3.49	2.98	2.42	2.42
5	2.93	3.16	3.10	2.82	2.77	2.55	2.55	2.49
6	2.43	2.44	2.57	2.63	2.64	2.51	2.63	2.60
mean	3.59	3.59	3.53	3.51	3.46	3.33	3.18	3.18
±SD	0.82	0.72	0.66	0.70	0.72	0.78	0.75	0.80
Non-Asthmatics								
1	4.86	4.84	4.69	4.82	4.65	4.42	4.08	4.10
2	4.68	4.35	4.01	3.92	3.84	3.94	4.10	3.79
3	4.06	3.81	3.72	3.86	3.97	4.00	3.86	3.45
4	5.91	5.57	5.60	5.57	5.49	5.62	5.50	5.16
5	3.00	3.02	2.97	3.03	3.03	3.03	3.05	3.12
6	4.13	3.78	3.80	3.67	3.77	3.69	3.97	3.92
mean	4.44	4.23*	4.13*	4.15	4.13	4.12*	4.09*	3.92*
±SD	0.97	0.90	0.91	0.90	0.85	0.87	0.79	0.70

* $p<0.05$: Denotes significant difference from pre-exercise values.

Table 6.10. The FEV_1 recorded for 20 minutes after the treadmill half-marathon for the asthmatic and non-asthmatic athletes.

	Time Post-Exercise				
	Pre Ex.	5 min	10 min	15 min	20min
Asthmatics					
1	4.55	4.31	4.28	4.28	4.37
2	3.58	3.37	3.42	3.41	3.44
3	4.40	4.21	4.22	4.22	4.35
4	3.65	2.66	2.72	2.65	2.83
5	2.93	2.05	2.00	2.26	2.42
6	2.43	2.32	2.40	2.42	2.58
mean	3.59	3.15	3.17	3.21	3.33
±SD	0.82	0.97	0.96	0.90	0.87
Non-Asthmatics					
1	4.86	4.60	4.58	4.59	4.72
2	4.68	4.50	4.45	4.64	4.71
3	4.06	3.71	3.91	4.05	3.88
4	5.91	6.03	6.07	5.90	5.91
5	3.00	3.21	3.20	3.13	3.16
6	4.13	4.15	4.06	4.11	4.10
mean	4.44	4.37	4.38	4.40	4.41
±SD	0.97	0.97	0.96	0.91	0.94

Table 6.11. Blood lactate concentration [mM] during the treadmill half-marathon for the asthmatic and non-asthmatic runners.

	Distance in Half-Marathon								
	Rest	1.5km	4km	8km	12km	16km	20km	End	Trend
Asthmatics									
1	1.05	2.91	2.52	2.64	1.66	8.11	7.40	7.40	
2	0.78	3.29	3.85	4.15	4.79	7.22	6.30	3.92	
3	0.74	3.17	4.29	5.94	4.76	3.80	6.83	4.96	
4	0.81	3.44	4.01	4.78	5.50	4.20	4.41	5.24	
5	1.04	2.88	3.20	3.32	2.84	3.71	2.50	2.16	
6	0.79	3.25	4.86	3.25	3.06	2.70	2.89	3.00	
mean	0.87	3.16	3.79	4.01	3.77	4.96	5.06	4.45	ns
± SD	0.14	0.22	0.83	1.21	1.47	2.17	2.09	1.86	
Non-Asthmatics									
1	1.14	4.52	4.34	7.03	5.88	4.21	3.99	4.05	
2	0.47	5.51	7.31	6.14	4.67	2.17	3.50	2.81	
3	0.78	1.19	1.80	1.48	3.04	3.04	2.64	1.96	
4	0.84	2.60	1.97	1.84	2.66	2.74	3.11	3.03	
5	0.97	4.95	5.29	5.87	6.02	6.35	6.83	8.34	
6	0.47	2.19	2.28	2.82	3.94	3.89	7.15	6.14	
mean	0.78	3.49	3.83	4.20	4.37	3.73	4.54	4.39	ns
± SD	0.27	1.73	2.21	2.43	1.41	1.48	1.95	2.41	

Table 6.12. Blood glucose concentration (mM) during the treadmill half-marathon for the asthmatic and non-asthmatic runners.

	Distance in Half-Marathon								
	Rest	1.5km	4km	8km	12km	16km	20km	End	Trend
Asthmatics									
1	4.72	4.27	4.20	4.65	3.69	3.92	5.18	5.18	
2	4.15	4.70	5.39	5.31	5.06	4.91	3.68	5.77	
3	4.21	5.17	6.50	9.27	10.60	9.76	6.98	7.55	
4	4.71	5.59	6.86	9.03	10.38	11.48	10.04	9.85	
5	5.38	5.11	5.45	6.01	5.89	5.59	5.22	5.27	
6	4.68	5.38	6.53	6.81	7.04	5.54	4.08	4.23	
mean	4.64	5.04	5.82	6.85	7.11	6.87	5.86	6.31	ns
± SD	0.44	0.48	1.00	1.92	2.84	3.02	2.35	2.05	
Non-Asthmatics									
1	4.08	4.04	3.72	4.09	3.95	3.38	2.82	2.87	
2	4.43	5.42	6.48	6.33	3.92	2.57	2.90	3.31	
3	5.12	5.17	5.84	6.28	7.32	7.46	6.37	5.95	
4	3.89	4.25	4.87	4.31	4.09	4.19	4.21	4.29	
5	5.09	5.42	6.09	7.19	8.19	8.52	8.30	8.19	
6	4.07	4.33	4.37	4.29	4.37	4.31	4.22	4.32	
mean	4.45	4.77	5.23	5.42	5.31	5.07	4.80	4.82	ns
± SD	0.54	0.63	1.08	1.34	1.92	2.37	2.14	1.96	

Table 6.13. The noradrenaline and adrenaline concentrations before and after the treadmill half-marathon, for the asthmatic and the non-asthmatic runners.

	NA Pre	NA Post	Change	AD Pre	AD Post	Change
		($nmol.l^{-1}$)			($nmol.l^{-1}$)	
Asthmatics						
1	3.08	35.33	32.25	0.49	4.03	3.54
2	2.39	15.48	13.09	0.54	2.71	2.17
3	2.14	23.68	21.54	0.45	3.50	3.05
4	1.52	33.80	32.28	1.26	6.95	5.69
5	1.61	19.19	17.58	0.41	3.47	3.06
6	4.52	31.89	27.37	0.28	3.62	3.34
mean	2.54	26.56***	24.02	0.57	4.05***	3.48
±SD	1.12	8.28	7.93	0.35	1.49	1.18
Non-Asthmatics						
1	3.14	12.63	9.49	0.57	11.35	10.78
3	2.88	28.93	26.05	0.45	1.35	0.90
4	2.19	22.52	20.33	0.97	3.27	2.30
6	2.14	37.44	35.30	0.24	3.83	3.59
mean	2.59	25.38*	22.79	0.56	4.95	4.39
±SD	0.50	10.50	10.80	0.31	4.40	4.40

Significant difference between pre and post values: * $p<0.05$
*** $p<0.001$

Table 6.14. The plasma free fatty acid and plasma glycerol concentrations before and after the treadmill half marathon, for the asthmatic and the non-asthmatic runners.

	FFA [mM]			Glycerol [mM]		
	Pre	Post	Change	Pre	Post	Change
Asthmatics						
1	0.27	1.05	0.78	0.06	0.36	0.30
2	0.16	0.89	0.73	0.06	0.37	0.31
3	0.22	0.62	0.40	0.06	0.55	0.49
4	0.37	0.46	0.09	0.08	0.36	0.28
5	0.15	0.54	0.39	0.05	0.28	0.23
6	0.18	0.39	0.21	0.06	0.18	0.12
mean	0.23	0.66*	0.43	0.06	0.35**	0.29
±SD	0.08	0.26	0.28	0.01	0.12	0.12
Non-Asthmatics						
1	0.22	0.91	0.69	0.05	0.37	0.32
3	0.32	0.49	0.17	0.07	0.43	0.36
4	0.30	0.58	0.28	0.07	0.35	0.28
5	0.31	1.16	0.85	0.08	0.43	0.35
6	0.10	0.57	0.47	0.04	0.51	0.47
mean	0.25	0.74*	0.49	0.06	0.42***	0.36
±SD	0.09	0.28	0.28	0.02	0.06	0.07

Significant difference pre and post half-marathon: * $p<0.05$
** $p<0.01$
*** $p<0.001$

Table 6.15. The speed, oxygen uptake, $\%VO_2$ max, heart rate and respiratory exchange ratio during the treadmill half-marathon for the asthmatic and non-asthmatic groups (mean ± SD).

		Distance in Half-Marathon							
	Rest	W-Up	1.5km	4km	8km	12km	16km	20km	Trend
Speed ($m.s^{-1}$)									
Asth x	-	3.04	4.26	4.25	4.26	4.19	4.17	4.21	ns
±SD	-	0.25	0.49	0.49	0.51	0.46	0.42	0.59	
Non-Asth x	-	3.17	4.13	4.16	4.12	4.13	4.08	3.98	ns
±SD	-	0.20	0.41	0.40	0.42	0.48	0.54	0.58	
VO_2 ($ml.kg.^{-1}min^{-1}$)									
Asth x	2.75	31.6	45.9	46.0	46.6	47.0	46.4	48.4	ns
±SD	0.59	2.5	4.5	5.2	4.8	4.3	2.5	4.9	
Non-Asth x	2.82	33.3	46.0	47.3	46.6	47.0	46.8	46.4	ns
±SD	0.37	3.4	5.0	5.4	4.8	5.3	6.4	6.9	
$\%VO_2$ max									
Asth x	4.73	53.6	77.7	77.9	78.97	79.7	78.9	81.9	ns
±SD	1.17	3.7	5.1	6.8	6.4	4.8	5.9	3.7	
Non-Asth x	4.79	56.8	78.1	80.4	79.0	79.6	79.3	78.4	ns
±SD	0.56	7.8	7.2	7.7	5.0	5.4	6.9	7.2	
Heart Rate ($b.min^{-1}$)									
Asth x	-	119	157	163	165	168	171	174	*** ^{i}
±SD	-	14	10	10	8	6	4	8	
Non-Asth x	-	134	165	171	176	178	178	177	*** ^{i}
±SD	-	6	8	9	9	7	5	9	
Respiratory Exchange Ratio (R)									
Asth x	0.940	0.912	0.992	0.980	0.973	0.963	0.943	0.965	* ^{d}
±SD	0.04	0.03	0.04	0.04	0.04	0.05	0.06	0.04	
Non-Asth x	0.905	0.931	0.996	0.992	0.978	0.971	0.948	0.936	*** ^{d}
±SD	0.05	0.04	0.05	0.04	0.03	0.04	0.04	0.05	

Page trend analysis: * $p<0.05$, *** $p<0.001$
^{i} : increase, ^{d} : decrease.

Table 6.16. The ventilation rate, breathing frequency, tidal volume and ventilatory equivalent during the treadmill half-marathon for the asthmatic and non-asthmatic groups.

		Distance in Half-Marathon							
	Rest	W-Up	1.5Km	4Km	8Km	12Km	16Km	20Km	Trend
V_E ($l.min^{-1}$ - BTPS)									
Asth x	10.5	59.7	89.5	93.3	95.1	97.0	96.1	106.5	*** ↑
± SD	1.4	6.5	9.8	10.4	13.3	13.4	12.4	21.3	
Non-Asth x	9.9	64.7	95.8	101.6	104.3	105.2	103.2	100.7	* ↑
± SD	1.3	14.1	16.7	17.2	17.6	14.7	14.8	13.8	
Breathing Frequency ($breath.min^{-1}$)									
Asth x	15.8	29.5	37.3	40.3	41.8	42.7	45.5	48.7	*** ↑
± SD	3.0	7.1	6.7	9.5	9.6	9.6	8.0	9.0	
Non-Asth x	15.4	29.8	41.3	43.3	46.8	47.7	48.5	48.3	* ↑
± SD	1.9	7.5	9.4	8.8	5.6	7.3	9.2	8.2	
Tidal Volume (l - STPD)									
Asth x	0.56	1.69	2.01	1.97	1.93	1.92	1.77	1.82	* ↓
± SD	0.09	0.22	0.23	0.31	0.34	0.29	0.13	0.25	
Non-Asth x	0.54	1.88	2.00	1.95	1.85	1.85	1.80	1.78	ns
± SD	0.11	0.61	0.59	0.49	0.31	0.36	0.38	0.43	
Ventilatory Equivalent									
Asth x	48.1	24.0	24.7	25.7	25.8	26.0	26.1	27.6	*** ↑
± SD	4.8	1.2	1.5	1.7	1.1	1.3	1.6	2.3	
Non-Asth x	42.7	23.2	25.2	25.9	26.8	26.9	26.5	26.2	ns
± SD	4.2	2.4	3.4	3.2	2.9	2.2	1.7	2.3	

Page trend analysis: * $p<0.05$, *** $p<0.001$
↑ : increase, ↓ : decrease.

Table 6.17. The relationship between selected resting lung function values, and various physiological parameters at 4Km into the treadmill half-marathon, for the asthmatic and the non-asthmatic groups.

Asthmatics

	FEV_1 %Pred	$\%FEV_1$	$\%\dot{V}_E$ max	$\%\dot{V}O_2$ max	fB ($b.min^{-1}$)	Vt (l)
$\%FEV_1$ (FEV_1/VC)	0.694					
$\%\dot{V}_E$ max	-0.940**	-0.867*				
$\%\dot{V}O_2$ max	-0.514	-0.912**	0.773*			
fB ($b.min^{-1}$)	0.440	0.908**	-0.634	-0.788*		
Vt (l)	-0.179	-0.809*	0.429	0.751	-0.905**	
$\dot{V}_E$ Equivalent	0.456	0.823*	-0.653	-0.777*	0.705	-0.832*

Non-Asthmatics

	FEV_1 %Pred	$\%FEV_1$	$\%\dot{V}_E$ max	$\%\dot{V}O_2$ max	fB ($b.min^{-1}$)	Vt (l)
$\%FEV_1$ (FEV_1/VC)	0.340					
$\%\dot{V}_E$ max	-0.381	-0.506				
$\%\dot{V}O_2$ max	-0.514	0.325	-0.378			
fB ($b.min^{-1}$)	-0.734	0.048	0.143	0.480		
Vt (l)	0.638	0.503	-0.493	0.131	-0.739	
$\dot{V}_E$ Equivalent	-0.434	0.320	0.305	0.569	0.629	-0.170

Pearson product moment correlations: * $p<0.05$; ** $p<0.01$

Table 6.18. Running performance and blood metabolites from two treadmill half-marathons performed by an asthmatic athlete (4), using different pre-exercise medications.

		Run 1	Run 2
Pre-Exercise Asthmatic Drugs		Intal Ventolin	Intal Ventolin Phyllocontin
Ventolin During (min)		58,66,76	85
Time (min)		85.48	87.52
Speed ($m.s^{-1}$)		4.11	4.02
% VO_2 max		75.6	74.0
Laboratory Temperature (°C)		16.6	18.9
Laboratory Humidity (%)		73	53
Water Intake (ml)		0	90
Weight (kg)	Pre-	62.2	61.6
	Post-	60.6	60.1
	%Change	2.6	2.4
Haemoglobin ($g.dl^{-1}$)	Pre-	15.24	16.95
	Post-	15.05	16.84
Haematocrit (%)	Pre-	44.5	48.7
	Post-	46.5	48.3
Plasma Volume	%Change	-2.4	-1.7
Noradrenaline ($nmol.l^{-1}$)	Pre-	1.52	3.17
	Post-	33.80	16.36
	Change	32.28	13.15
Adrenaline ($nmol.l^{-1}$)	Pre-	1.26	0.41
	Post-	6.95	1.81
	Change	5.69	1.40
Free Fatty Acids (mM)	Pre-	0.37	0.59
	Post-	0.46	1.17
	Change	0.09	0.58
Glycerol (mM)	Pre-	0.08	0.10
	Post-	0.36	0.47
	Change	0.26	0.37

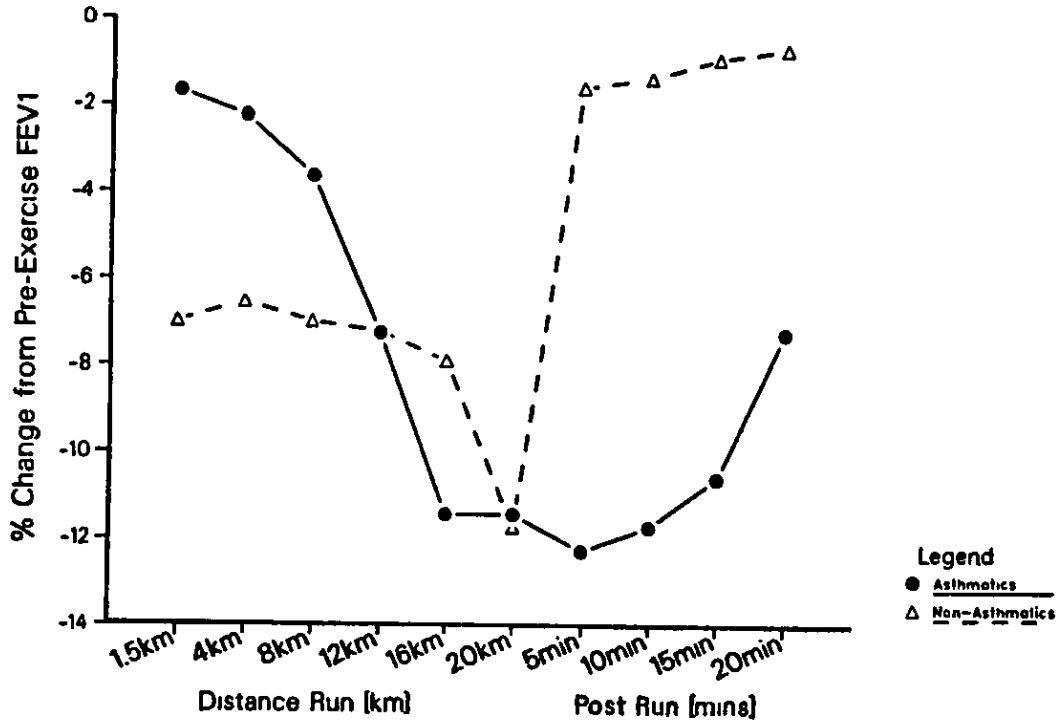


Figure 6.1. The FEV_1, expressed as a percentage of the pre-exercise value, during and after the half-marathon for the asthmatic and non-asthmatic groups.

Figure 6.2a

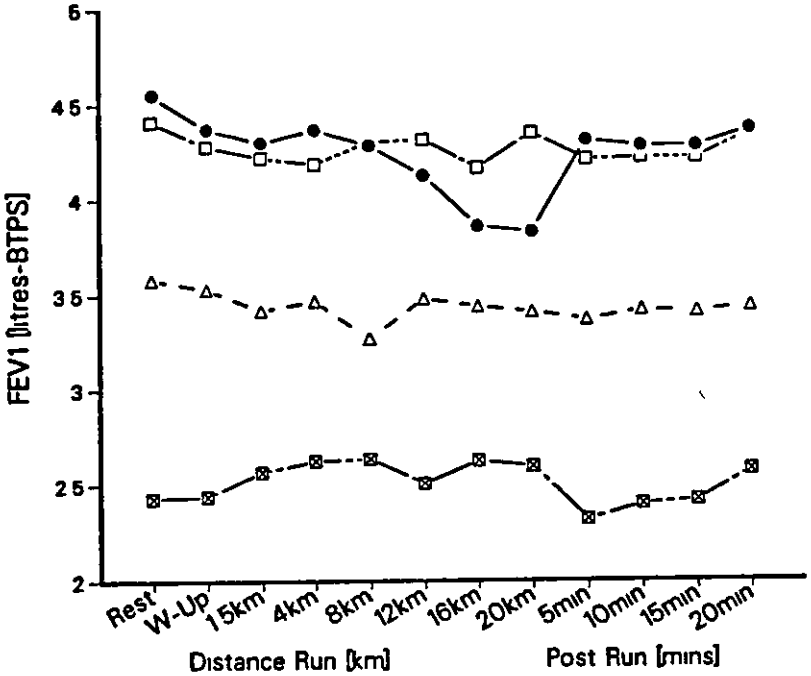
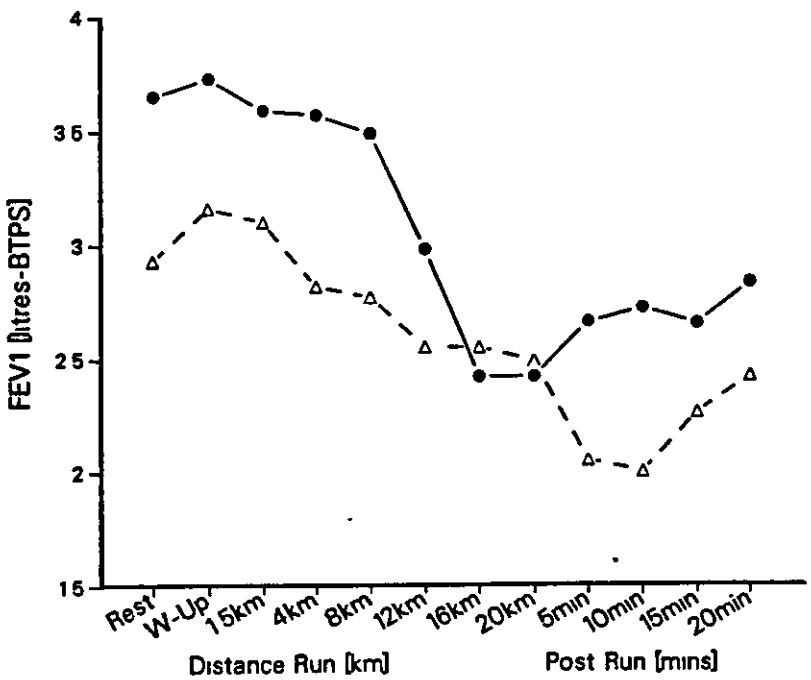


Figure 6.2b



Figures 6.2a and 6.2b. The FEV_1 for the four asthmatics who did not experience asthma (6.2a) and for the two asthmatics who did experience asthma (6.2b), during and after the half-marathon.

Figure 6.3a

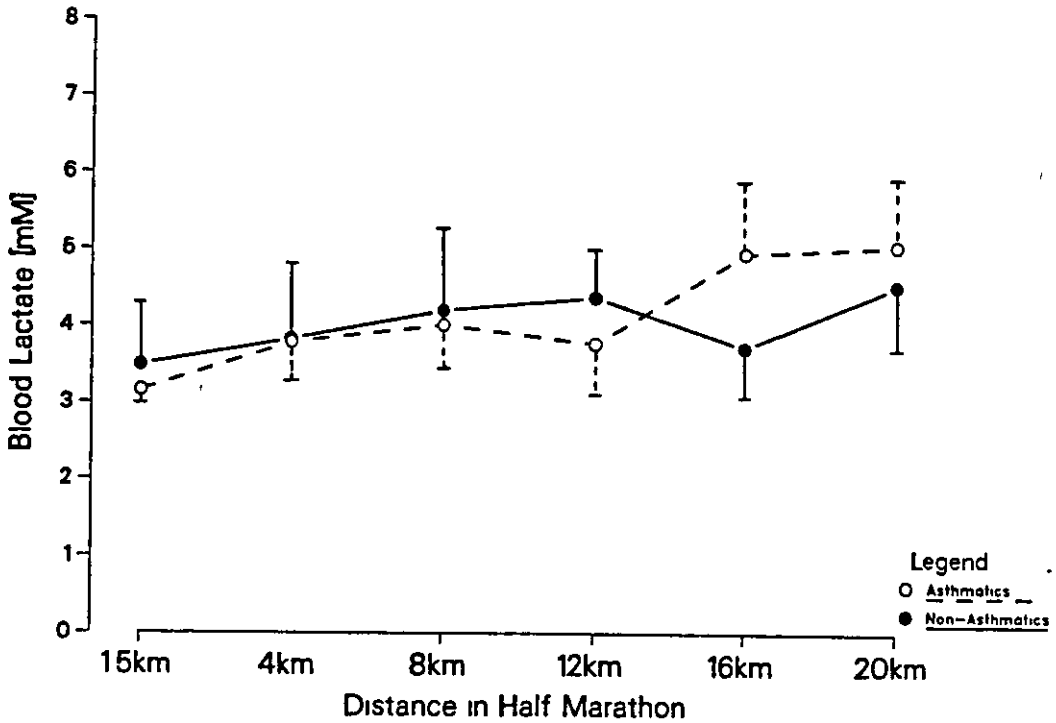


Figure 6.3b

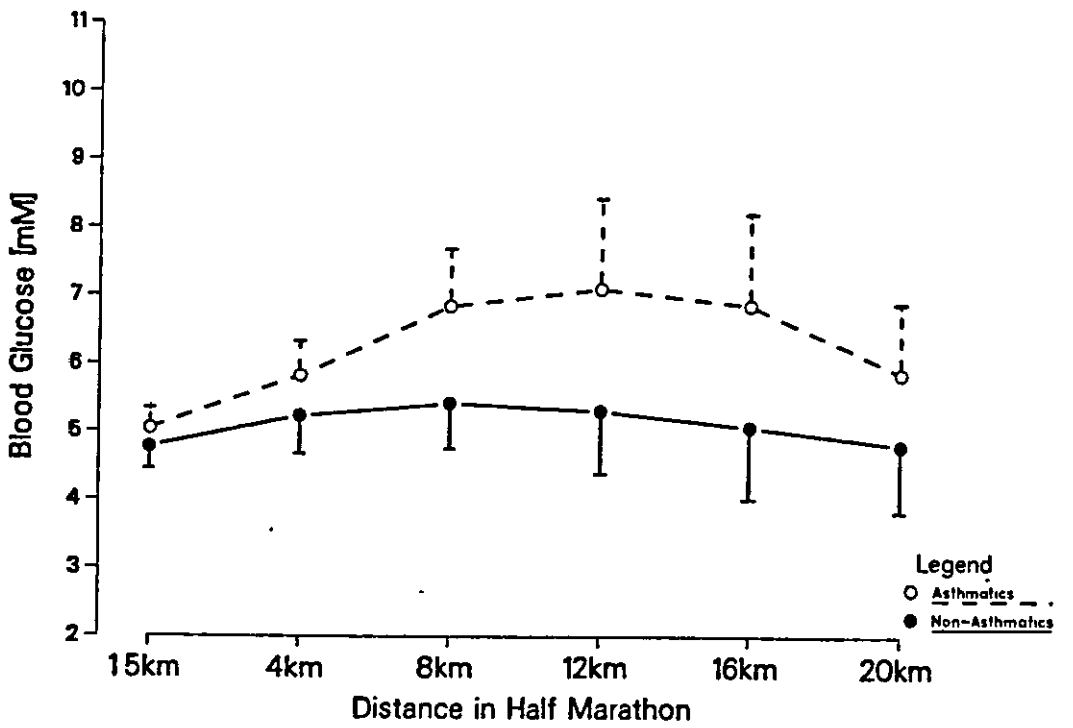


Figure 6.3a and 6.3b. The blood lactate (6.3a) and blood glucose (6.3b) concentrations during the half-marathon, for the asthmatic and the non-asthmatic groups.

Figure 6.4a

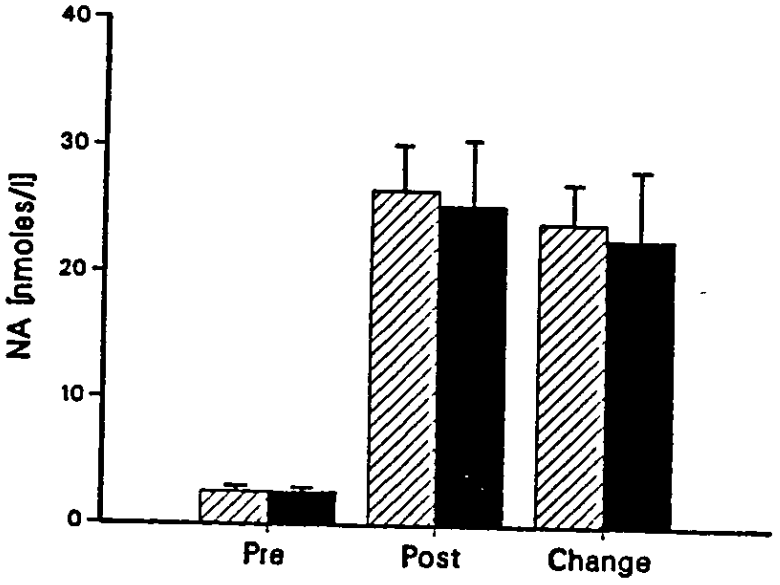
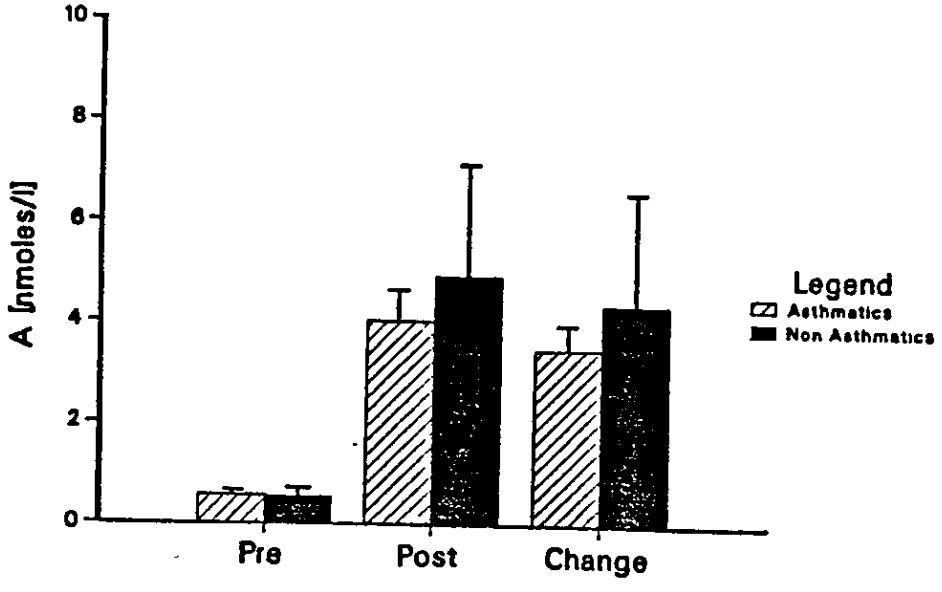


Figure 6.4b



Figures 6.4a and 6.4b. The adrenaline (6.4a) and noradrenaline (6.4b) concentrations before and after the half-marathon, for the asthmatic and the non-asthmatic groups.

Figure 6.5a

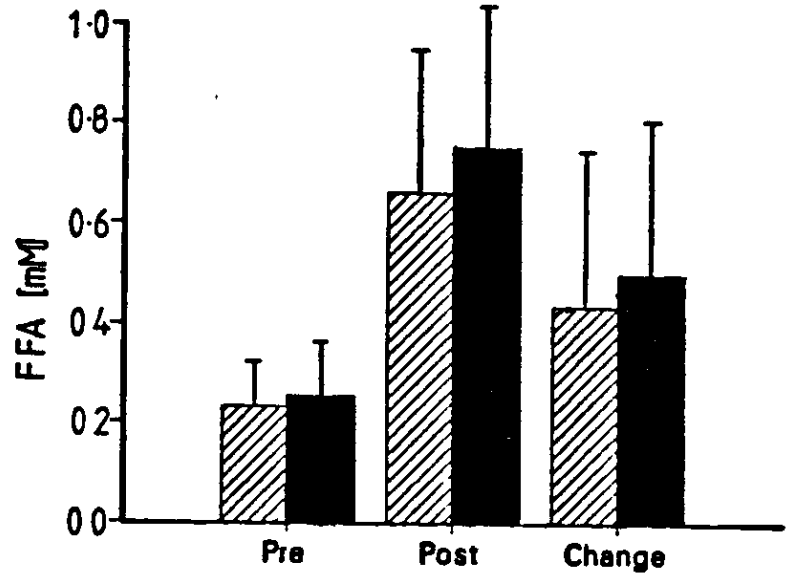
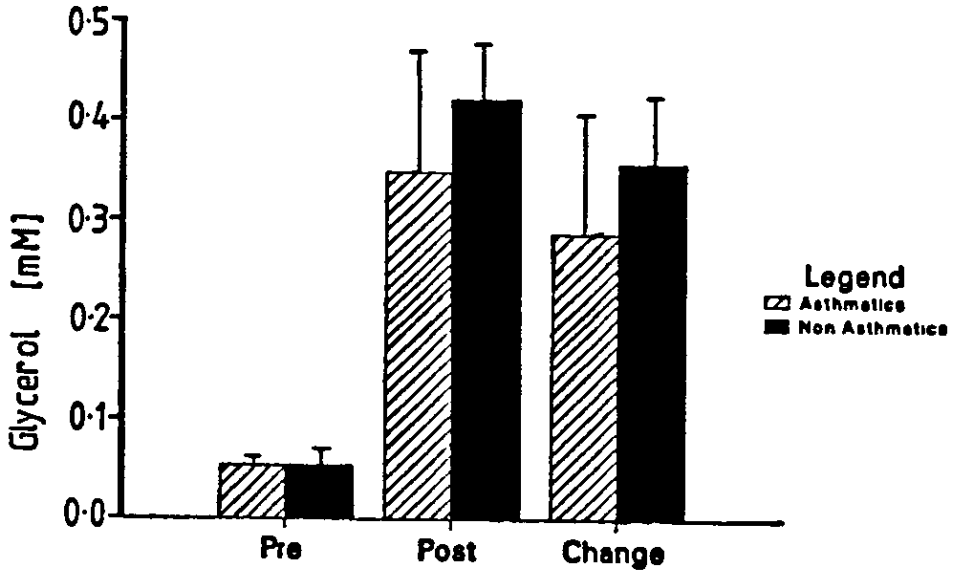


Figure 6.5b



Figures 6.5a and 6.5b. The plasma free fatty acid (6.5a) and plasma glycerol (6.5b) concentrations before and after the half-marathon, for the asthmatic and the non-asthmatic groups.

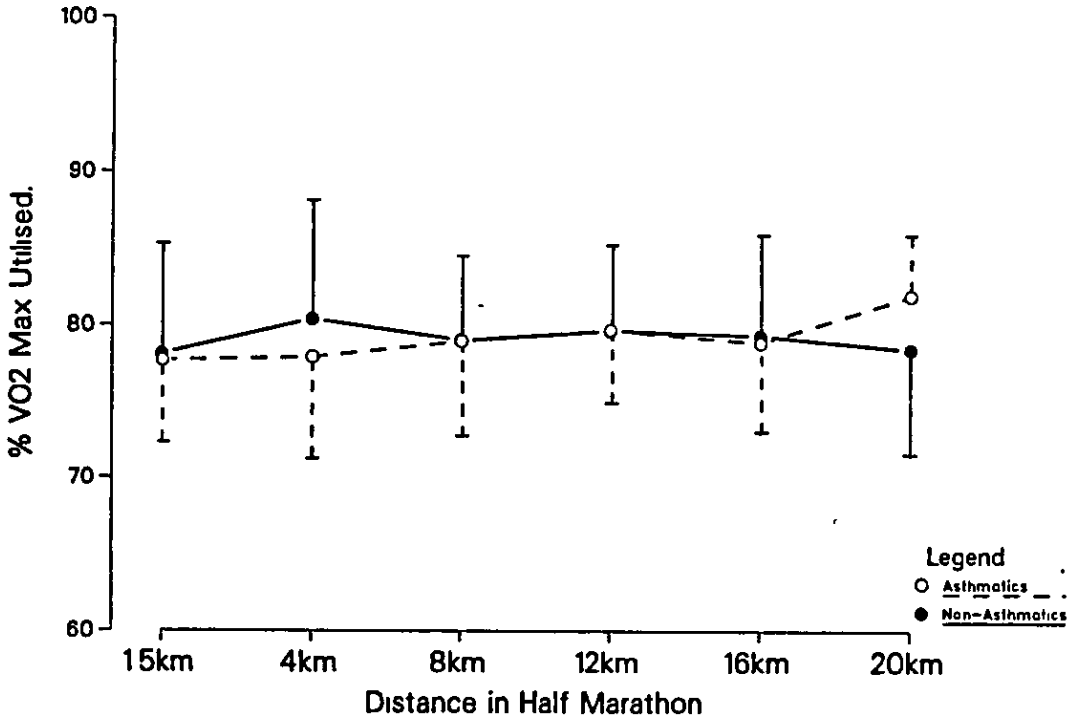


Figure 6.6. The $\%VO_2$ max utilised during the half-marathon, for the asthmatic and the non-asthmatic groups.

Figure 6.7a

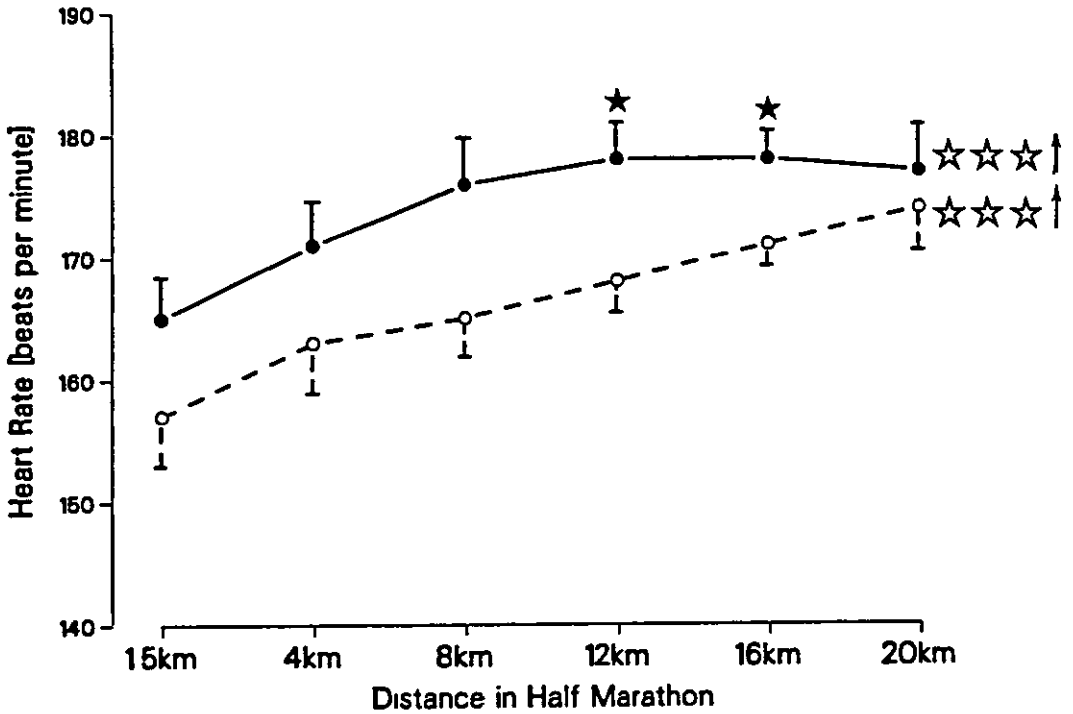
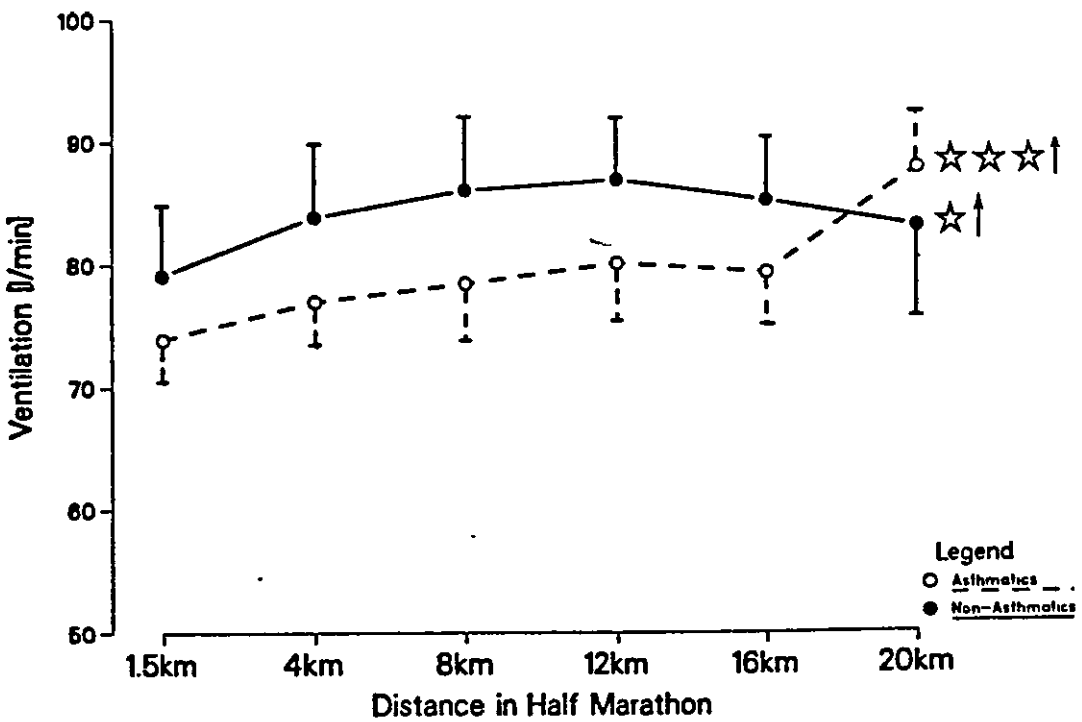


Figure 6.7b



Figures 6.7a and 6.7b. The heart rate (6.7a) and ventilation rate (6.7b) during the half-marathon, for the asthmatic and the non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆☆ $p<0.001$

Denotes significant difference between asthmatic and non-asthmatic groups: ★ $p<0.05$

Figure 6.8a

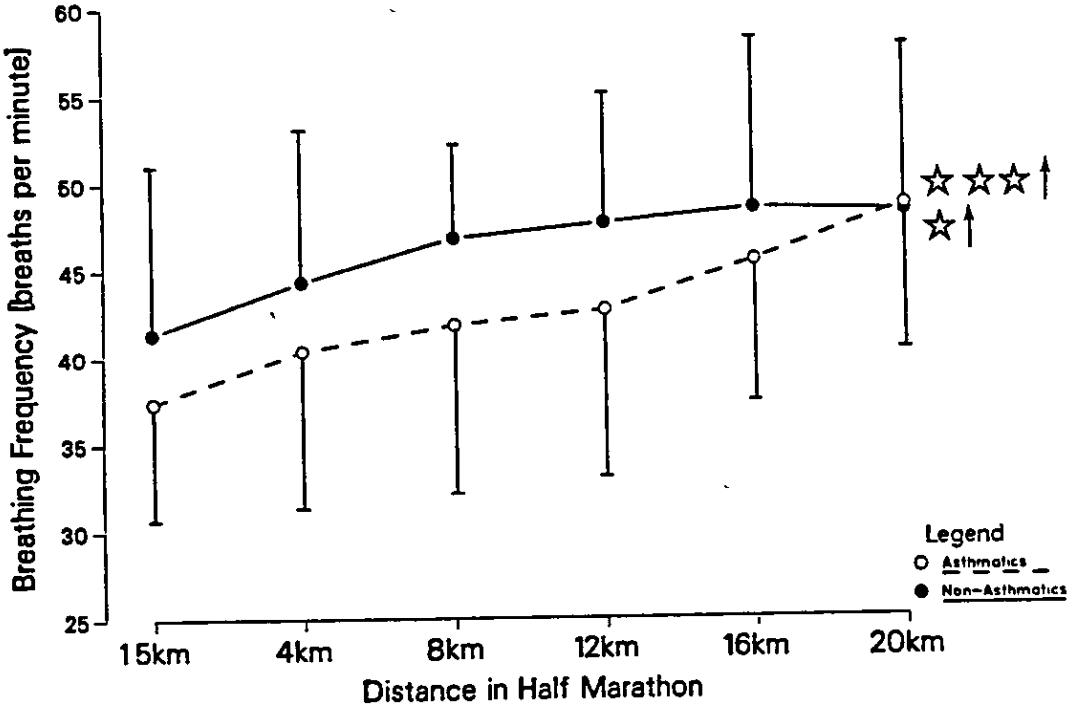
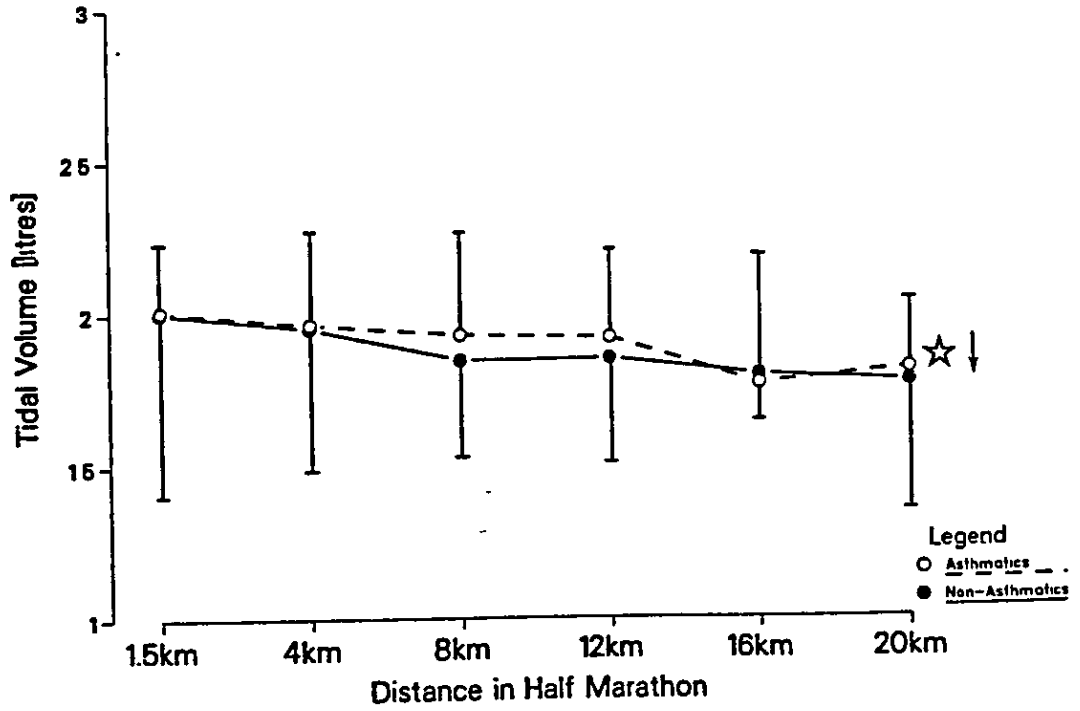


Figure 6.8b



Figures 6.8a and 6.8b. The breathing frequency (6.8a) and the tidal volume (6.8b) during the half-marathon, for the asthmatic and the non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆☆ $p<0.001$

Figure 6.9a

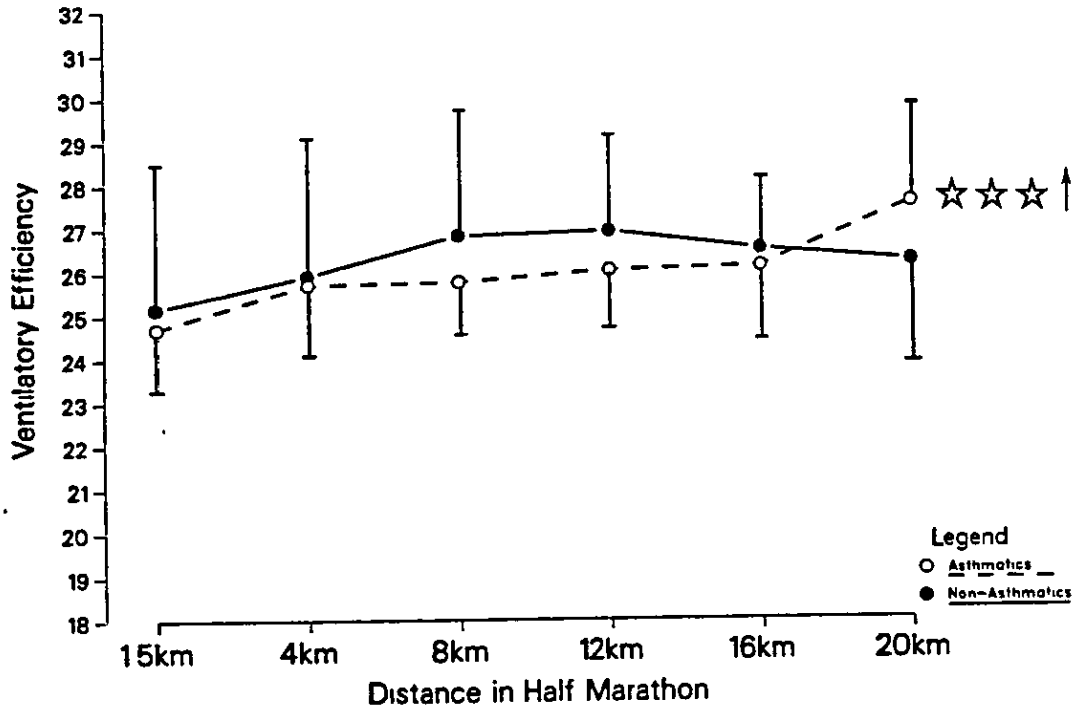


Figure 6.9b

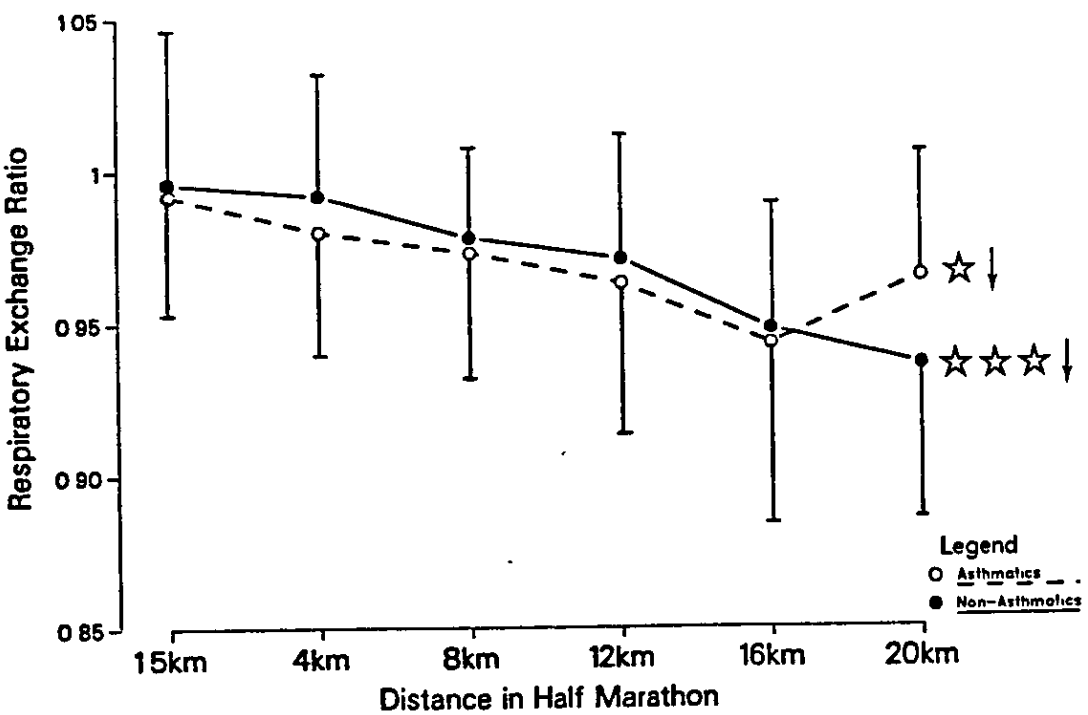


Figure 6.9a and 6.9b. The ventilatory equivalent (6.9a) and the respiratory exchange ratio (6.9b) during the half-marathon, for the asthmatic and the non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆☆ $p<0.001$

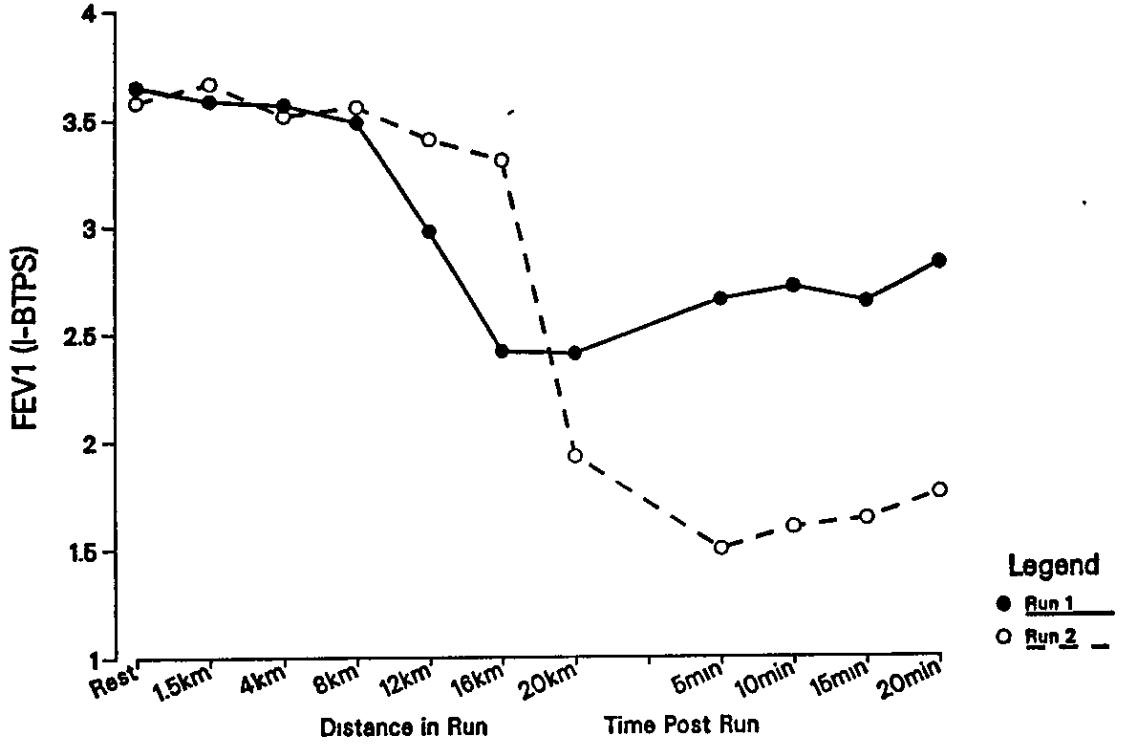


Figure 6.10. The response of the FEV_1 during and after the two half-marathons performed by one asthmatic (4) taking different pre-exercise medications.

Figure 6.11a

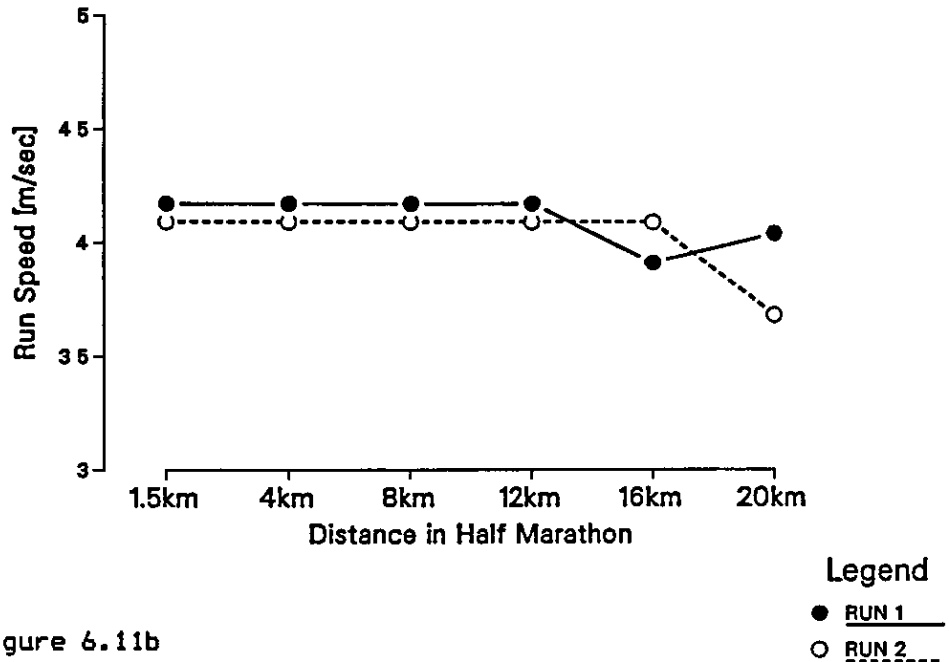
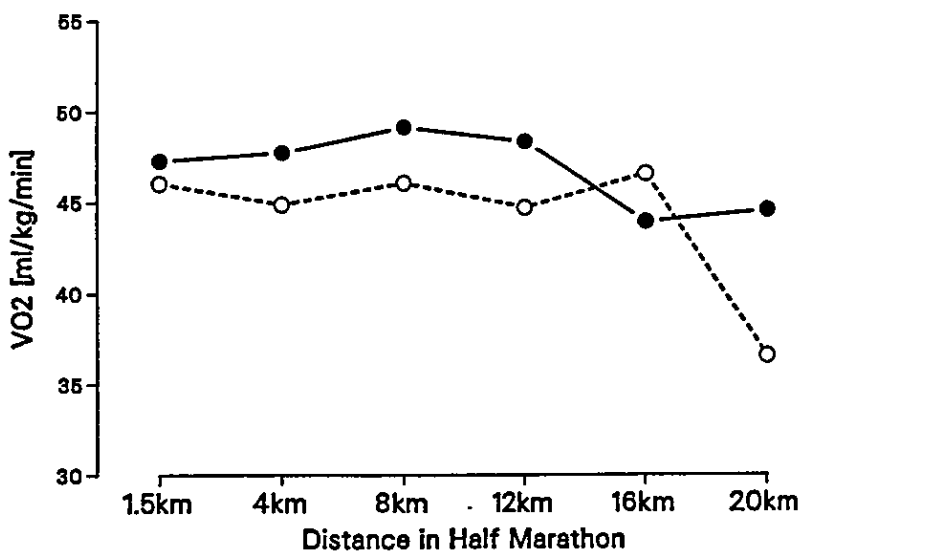


Figure 6.11b



Figures 6.11a and 6.11b. The running speed (6.11a) and the oxygen uptake (6.11b) for the two half-marathons performed by one asthmatic(4) taking different pre-exercise medications.

Figure 6.12a

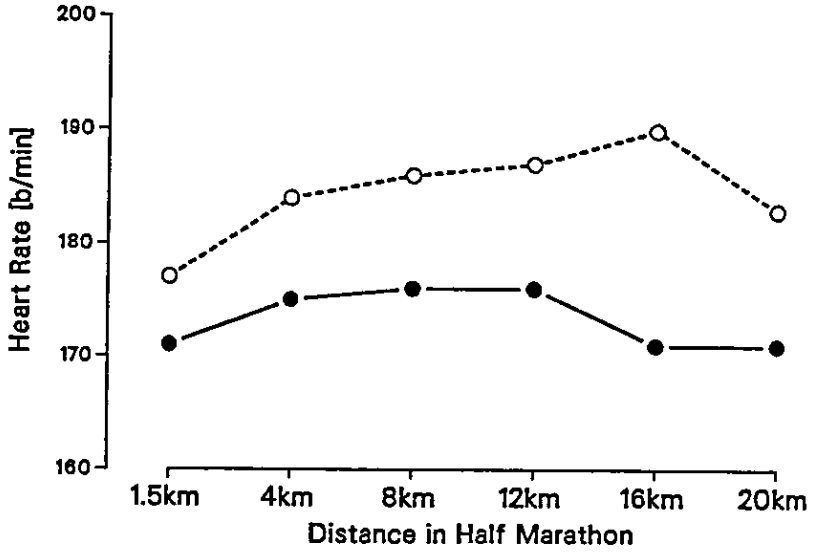
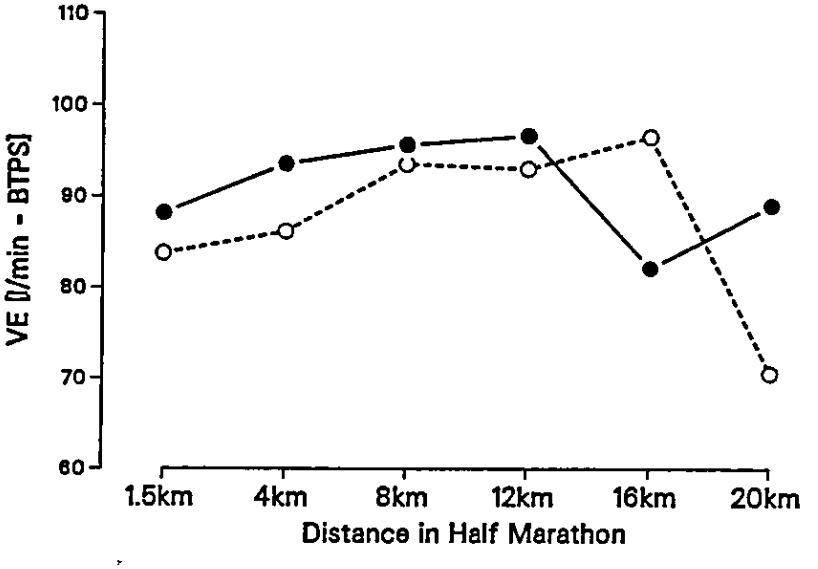
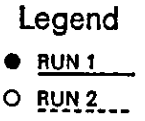


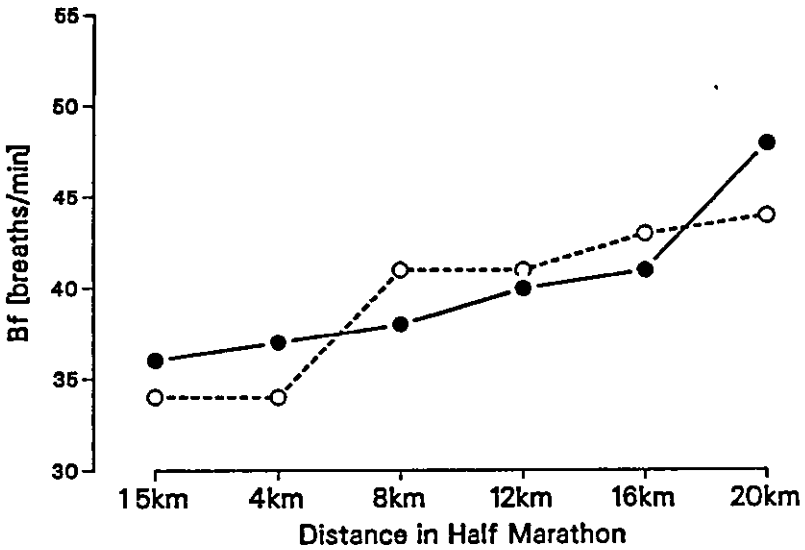
Figure 6.12b





Figures 6.12a and 6.12b. The heart rate (6.12a) and ventilation rate (6.12b) for the two half-marathons performed by one asthmatic (4) taking different pre-exercise medications.

Figure 6.13a



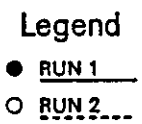
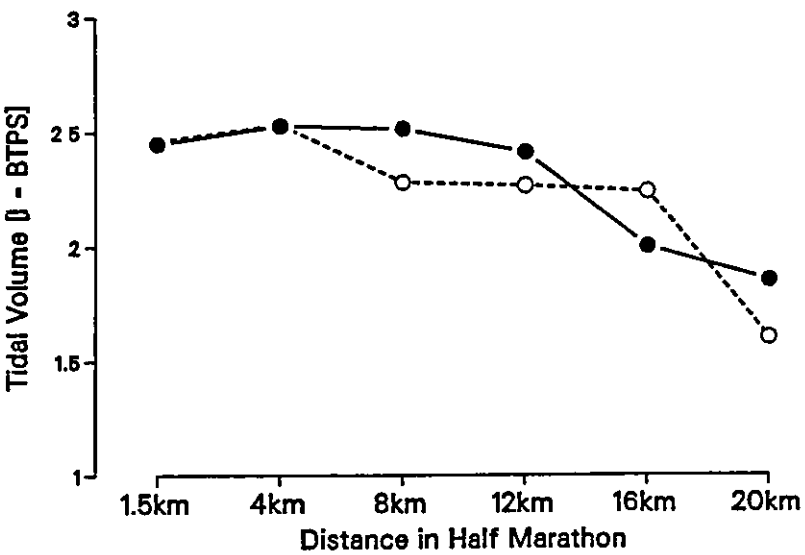


Figure 6.13b



Figures 6.13a and 6.13b. The breathing frequency (6.13a) and the tidal volume (6.13b) for the two half-marathons performed by one asthmatic (4) taking different pre-exercise medications.

Figure 6.14a.

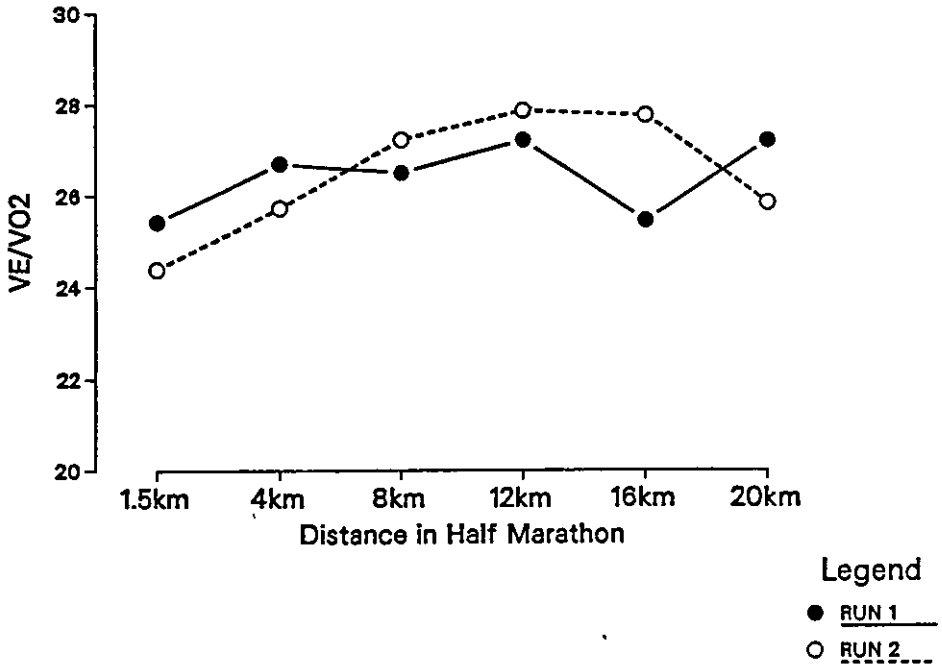
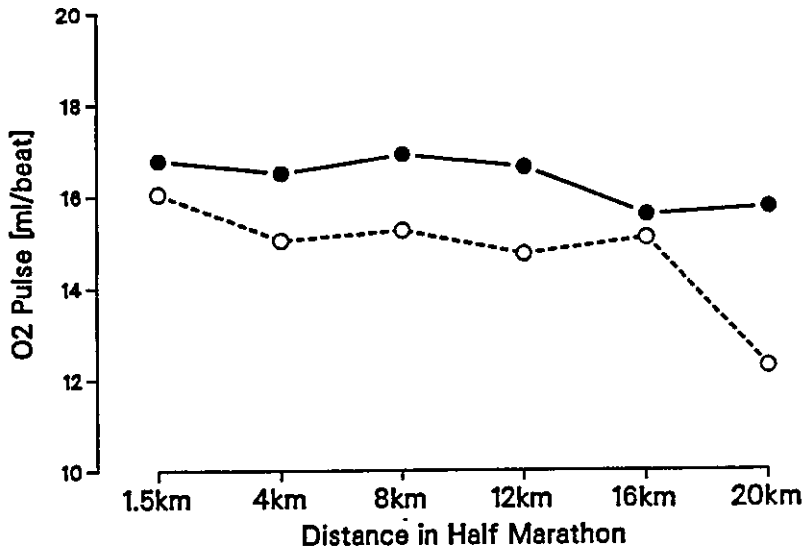


Figure 6.14b.



Figures 6.14a and 6.14b. Ventilatory equivalent (6.14a) and oxygen pulse (6.14b) for the two half-marathons performed by one asthmatic (4) taking different pre-exercise medications.

Figure 6.15a

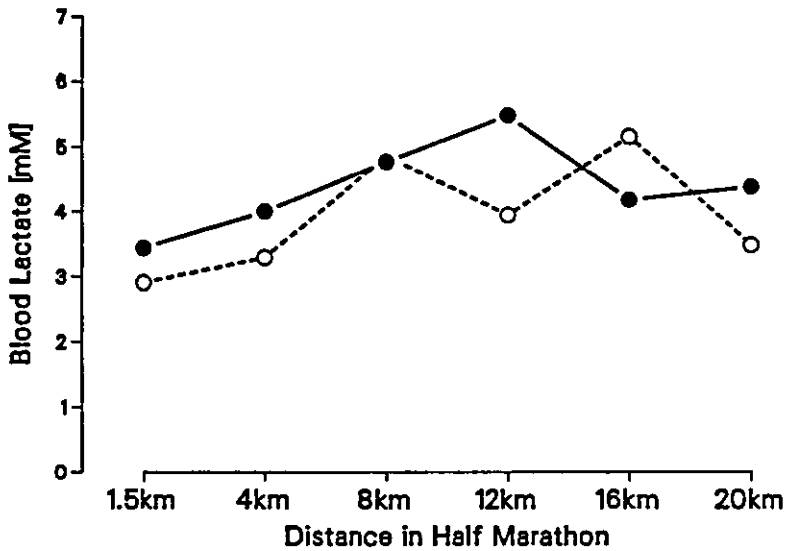
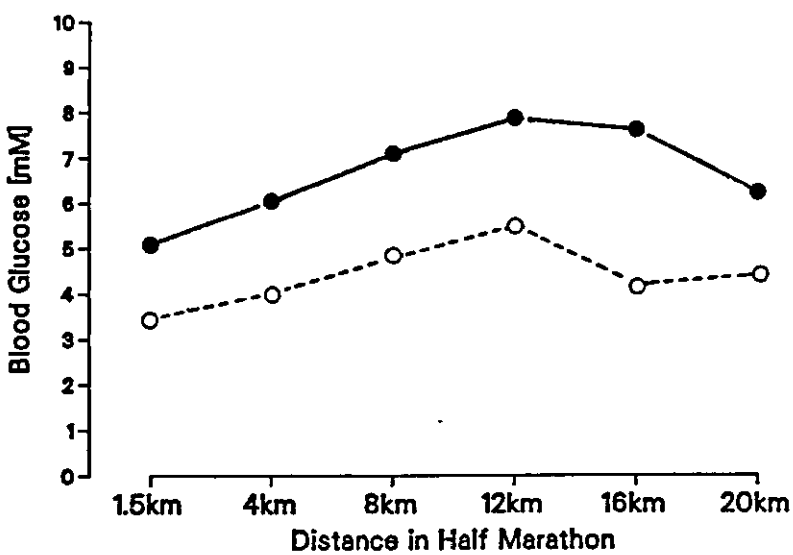
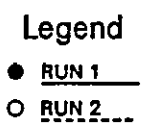


Figure 6.15b





Figures 6.15a and 6.15b. Blood lactate (6.15a) and blood glucose (6.15b) concentrations for the two half-marathons performed by one asthmatic (4) taking different pre-exercise medications.

6.4 Discussion.

The physiological responses to a treadmill half-marathon race for a group of asthmatic athletes, taking their normal pre-exercise medication, were compared with those of a similar group of non-asthmatic athletes. The groups were matched for age and running experience, comprising of a mixture of elite and recreational runners. The mean VO_2 max, and the running speed and $\%VO_2$ max at blood lactate concentrations of 2mM and 4mM, were similar. The asthmatic and non-asthmatic groups were therefore well matched for cardio-respiratory fitness. The asthmatic group had EIA after the short non-medicated running test and their lung function, obtained before the half-marathon (FEV_1 percent predicted and the $FEV_1/FVC\%$), was significantly poorer compared to the non-asthmatic group.

The main findings from this study were the similar cardio-respiratory and metabolic responses to the half-marathon of the asthmatic and non-asthmatic groups. However, the response of the lung function to the half-marathon between the asthmatic and non-asthmatic groups, and within the asthmatic group, were different.

6.4.1 Half-Marathon Performance.

The performances in the treadmill half-marathon were not significantly different in terms of the times or $\%VO_2$ max utilised for the asthmatics and non-asthmatics, with both groups utilising an average of 80% VO_2 max for the entire half-marathon. This fractional use of the maximal oxygen uptake is similar to that observed for a group of recreational runners (78%) performing a half-marathon (Williams and Nute 1983) and similar to the estimated oxygen uptake obtained for an outdoor half-marathon for the asthmatic athletes (Chapter 5). This finding confirms that asthma does not preclude the development of good endurance fitness. In addition, the similar treadmill and outdoor half-marathon performance times for the asthmatic group would suggest that 'racing' conditions had been successfully simulated on the treadmill.

Within the asthmatic group, the physiological responses at 4km into the half-marathon varied according to the severity of the pre-exercise airflow obstruction. Athletes with increased pre-exercise airflow obstruction (reduced $FEV_1/FVC\%$) had reduced breathing frequency and

increased tidal volume resulting in a good ventilatory equivalent. In addition, those asthmatics with more severe pre-exercise obstruction were able to work at a higher $\%VO_2$ max. This is consistent with the observations for the asthmatic athletes engaged in an outdoor half-marathon (Chapter 5). As we have seen in the previous chapter, the maximum parameters (V_E max and VO_2 max) are limited for asthmatics with more severe airflow obstruction. Thus these athletes have adapted their submaximal fitness through training, to ensure they are able to exercise at a higher $\%VO_2$ max. This type of adaptation supports the work of Coyle et al (1983) with cardiac patients.

6.4.2 Lung Function Responses to the Half-Marathon.

The control of exercise-induced asthma is essential if the asthmatic is to participate safely in physical activity and without respiratory disadvantage in sport (Fitch 1986). In the half-marathon the pre-exercise medication adequately protected four of the six asthmatic athletes from EIA.

Although the non-asthmatics showed a lower FEV_1 during the half-marathon compared to resting values, the FEV_1 returned spontaneously to near pre-exercise levels after exercise. This immediate reversibility would suggest that the non-asthmatics were unable to reproduce a pre-exercise FEV_1 whilst running on the treadmill rather than any bronchospasm per-se. Of the four asthmatic subjects not affected by asthma, three were able to reproduce pre-exercise FEV_1 values throughout the half-marathon. This would indicate that respiratory muscle fatigue (if this can be associated with the ability to produce a near normal FEV_1), occurred to a greater extent in the non-asthmatics than the asthmatics free from an exacerbation of their asthma. The work of Gorski et al (1978) in rats, stated that exercise causes a reduction in the glycogen levels of the respiratory muscles, and so the decrease in the FEV_1 observed by the non-asthmatic group may have been related to a reduction in the glycogen content of the respiratory muscles. In addition, endurance running training for the asthmatic athlete may have served to increase the aerobic capacity of the respiratory muscles, possibly leading to higher glycogen levels and thus allowing asthmatics free from EIA, to obtain a near pre-exercise FEV_1 while exercising.

Two asthmatics did, however, experience a fall in FEV_1 both during

and after exercise, suggesting that asthma had been provoked. Therefore, the pre-exercise medication, comprising both salbutamol and sodium cromoglycate for these two athletes, failed to protect them from EIA for the entire duration of the run. Furthermore, the addition of aminophylline to the pre-exercise treatment for one of these asthmatics failed to reduce the severity of EIA in a second treadmill half-marathon. Although theophylline has been shown to be useful in the inhibition of EIA (Ellis 1984a), this failed to give added protection when aminophylline was used in the combination therapy for this asthmatic. Thus, the recent suggestion by Fitch (1986) that inhibition of EIA is achieved in most asthmatics by pre-exercise aerosol beta-2 agonists, supplemented by sodium cromoglycate and/or theophylline, cannot be supported when the exercise is prolonged.

With the onset of EIA the running speed was reduced and thus the performance of these asthmatics would be impaired. Indeed, the requirement for maximum performance necessitates optimum respiratory function and in this situation reversal of the asthma. However, despite a reduction in running speed and the use of a bronchodilator, EIA could not be reversed while running. It would seem that once the EIA produces a noticeable fall of FEV_1, it is not possible to "run through" the asthma as suggested by Fitch and Godfrey (1976), even with the help of a bronchodilator. Furthermore, the possibility of immediately reversing the EIA provoked during prolonged exercise is questionable, since it was demonstrated that a bronchodilator failed to immediately reverse the asthma after the half-marathon.

These observations suggest that the asthmatic will be at a disadvantage in endurance running if EIA is provoked during competition. More importantly the results must question the safety of the participation of the asthmatic in competitive endurance running, if pre-exercise medication does not afford full protection from EIA.

6.4.3 The Cardio-Respiratory Responses to the Half-Marathon.

The heart-rate was significantly lower for the asthmatic group during the half-marathon when compared to the non-asthmaic group. This difference was however a function of the lower maximum heart-rate of the asthmatic group since there was no difference between the groups when the heart-rate was expressed as a percentage of the maximum. The ventilation, although lower for the asthmatic group, was not

significantly different between groups. The components of ventilation, breathing frequency and tidal volume, were not significantly different between the groups. The breathing frequency, however, was approximately 5 breaths.min^{-1} lower for the asthmatics suggesting a more 'controlled' pattern of breathing. The similar ventilatory efficiency of the groups would indicate that the breathing pattern developed by the asthmatic group was as efficient at gas exchange compared to the non-asthmatics. The response of these cardio-respiratory parameters over time was also observed.

It has been well documented that during constant paced running at a speed above 70% VO_2 max a gradual rise in heart rate or cardiovascular drift occurs (Saltin and Stenberg 1964). If individuals are allowed to self select their running pace, as during the present study, a steady increase in heart rate for the asthmatic and the non-asthmatic groups was also shown. This increase in heart rate may be compensating for the decrease in stroke volume, associated mainly with changes in the redistribution of cardiac output for temperature regulation.

Endurance events require effective temperature regulation during rather than after exercise. The loss of heat is mainly effected by sweat mechanisms, leading to a loss of fluid. To offset this loss of body fluid through sweating, athletes are recommended to take in liquid. However, the water intake during the half-marathon of 99ml, fell well short of the recommendations of Sinclair et al (1983), of one litre of fluid per hour during endurance exercise. However, under competitive conditions it is impossible to drink this quantity of fluid while running, and thus the fluid intake may do little to balance the fluid loss (Costill et al 1970b). Although the fluid intake during the half-marathon was low, the changes in plasma volume and body weight were minimal and not related to the amount of fluid consumed.

After the half-marathon a small fall in plasma volume of 1.8% was observed, indicating that a half-marathon does not place such severe demands on plasma volume changes as would a marathon (Myhre et al 1982). Indeed, the mean group reduction in body weight of 2.6% or any of the individual subject values, do not approach the value of 4% associated with dehydration (Astrand and Saltin 1964). Our results are very comparable with those observed by Colt et al (1978) who observed a 2.3% change in body weight for 10 males in a 10 mile race. In addition, there was no support for the direct relationship between the

changes in plasma volume and body weight suggested by Costill et al (1976).

In addition to cardio-vascular drift, the groups also showed ventilatory drift as indicated by an increase in ventilation rate over the half-marathon. This increase in ventilation rate has been viewed as being advantageous by benefiting pulmonary gas exchange or H+ ion regulation, which outweighs any inefficiency in ventilatory work (Hanson et al 1982). In contrast the increased ventilation has been considered as detrimental to performance because the sensed level of breathing is an important part of a runners perceived rate of exertion (Martin et al 1981).

In asthmatics the trigger to EIA is associated with the ventilation rate (Deal et al 1979), and thus the net increase in ventilation must be considered harmful for the asthmatic. Up to 16Km the asthmatic group showed only an 8% increase in ventilation rate, so it is possible that asthmatic runners may alter their running speed according to their level of ventilation. It was not until the last expired air collection at 20Km that any marked increase in ventilation was observed, when if the asthma was induced, the end of the run was near. The non-asthmatic group did not show a marked increase in ventilation, with the ventilation rate decreasing as the speed of the treadmill was reduced in the later stages of the run. Therefore, during race conditions in which the subject can change the running speed, the ventilatory drift does not seem as pronounced as in steady speed running (Hanson et al 1982).

The similar cardiac and ventilatory responses of the groups to the half-marathon would suggest that the asthmatic is not at a disadvantage in endurance running.

6.4.4 The Metabolic Responses to the Half-Marathon.

Blood lactate concentrations during the half-marathon was not significantly different for the asthmatic and non-asthmatic groups. The values obtained at the end of the run of approximately 5mM were similar to those obtained by Williams and Nute (1983) during a field study on half-marathon running. The range of responses between subjects was large, with the subjects selecting race speeds that elicited blood lactate concentrations of between 1.2mM and 5.5mM at 1.5Km. However, two non-asthmatic subjects had blood lactate concentrations of 5.5mM and 4.5mM at 1.5km had to slow down

considerably in the later stages of the half-marathon. This would indicate that for these two asthmatics the selection of pace was incorrrect, and perhaps muscle glycogen may be a limiting factor in the half-marathon when incorrect pacing is employed. This is in contrast to the observations of Costill (1973) who concluded that for a 10 mile race, albeit a slightly shorter distance, muscle glycogen was not a limiting factor. In contrast, a very well trained non-asthmatic selected a speed which accumulated 4.9mM of blood lactate at 1.5Km, and was able to maintain this speed for the entire run. Due to the large range of blood lactate concentrations observed during racing conditions, fitness should be related to the ability to utilise a high percentage of VO_2 max, regardless of the accumulation of blood lactate.

The blood glucose responses to the half-marathon were not significantly different for the asthmatic and non-asthmatic groups. Both groups showed an early rise in blood glucose concentrations during the half-marathon, possibly caused by an elevated rate of hepatic glycogenolysis due to raised catecholamine levels with the onset of exercise (Hall et al 1983). The blood glucose fluctuated around this elevated level for all but two of the subjects, throughout the half-marathon ensuring both an adequate blood glucose supply for fuel for vital organs, and fuel to the muscle as muscle glycogen levels are reduced. No athlete experienced hypoglycaemia as defined by a blood glucose concentration of less than 2.5mM (Felig et al 1982). Thus the fatigue experienced at the end of the half-marathon race was not necessarily associated with low blood glucose for this group of athletes, this being in agreement with other investigations (Hall et al 1983, Felig et al 1982).

The elevated, though not significantly different, blood glucose concentrations of the asthmatics compared to the non-asthmatics could mainly be attributed to the hyperglycaemic response of two asthmatics. Their elevated response may be explained by the effects of salbutamol (Neville et al 1977), although not all asthmatics taking salbutamol demonstrated abnormally high blood glucose concentrations. Adrenaline has a role in regulating muscle glycogenolysis (Richter 1984, Jansson et al 1986), and thus any differences in the blood glucose concentrations may be associated with differences in the response of adrenaline to exercise. Indeed, the highest adrenaline level obtained within the asthmatic group (5.69 $nmol.l^{-1}$) was observed for the

asthmatic with the highest blood glucose concentration (9.85mM) at the end of exercise. In contrast, the non-asthmatic with the highest adrenaline (10.78 $nmol.l^{-1}$) had the lowest blood glucose concentration (2.87mM) at the end of exercise. This non-asthmatic was forced to reduce his running speed at the end of exercise due to fatigue, and therefore the lower blood glucose level may be accounted for by reduced glycogen levels.

The changes in plasma catecholamines with distance running have not been well documented either for asthmatic or non-asthmatic subjects. In the present study, there was no difference in the resting concentrations of adrenaline and noradrenaline in the asthmatics and non-asthmatics. The catecholamine concentrations of the asthmatics were, however, slightly higher than those reported by other investigators (Warren et al 1982), possibly due to anticipation of exercise. During the half-marathon large changes in the NA (10 fold) and AD (7 fold) from pre-exercise levels were observed for the asthmatic group, with their responses not significantly different from those of the non-asthmatics. This would give support to the idea that there is no difference between the adrenergic responses of the asthmatic and the non-asthmatic, agreeing with the work of Beil et al (1977), Chryssanthopulus et al (1978) and Zieluiski et al (1980) in short-term exercise. The magnitude of the catecholamine responses for the asthmatic compared to previous studies, utilising the standard 6-8 minute exercise test, was much greater due to the longer duration of activity. In addition, the catecholamines were similar for the two asthmatics who did bronchoconstrict and compared to those of the four asthmatics who did not bronchoconstrict. This would support the view that catecholamines do not play a direct role in the pathogenesis of EIA (Barnes et al 1981b). Indeed, the response of the catecholamines of the subject who ran two treadmill half-marathons were markedly different, yet EIA still occurred. However, in the half-marathon where the response of the catecholamines was greater, the FEV_1 did not fall further when exercise ended, whereas when the catecholamines were lower FEV_1 fell further after exercise had stopped. Thus higher catecholamine levels may prevent a further fall in the FEV_1 after exercise.

It has been suggested that asthmatics may have a problem in the mobilization of free fatty acids (FFA), and therefore may have to rely upon carbohydrate as an energy source (Barboriak et al 1973). The rate

of uptake and oxidation of FFA by the working muscle is proportional to the plasma FFA concentration (Armstrong et al 1961). Therefore, the post-exercise FFA levels should give a reflection of the degree to which FFA are supplying the energy demands. Both the asthmatic and non-asthmatic groups showed a significant increase in plasma FFA, and a corresponding increase in plasma glycerol after the half-marathon. However, there was no difference in the response of FFA or glycerol to suggest that asthmatics had a reduced ability to utilise FFA. Indeed, the R value reflecting the substrates utilised, was not significantly different for the asthmatic and non-asthmatic groups. In addition, both groups demonstrated an increased reliance on fat as the substrate, as the half-marathon progressed as illustrated from the respiratory exchange ratio.

There were no significant differences between the metabolic responses of the asthmatic and non-asthmatic groups to suggest that the asthmatic is at a disadvantage in endurance running.

6.4.5 The Effect of Asthmatic Medication on the Physiological Responses to the Half-Marathon.

From the design of the study it is not possible to determine the effect of the medication alone on the physiological responses observed in the asthmatic group. An assessment of the physiological effects of aminophylline (theophylline ethylenediamine) can be drawn from the results of the asthmatic who performed two half-marathons, with and without aminophylline, in addition to disodium cromoglycate and salbutamol before each test. Although theophylline has never been considered to have an "ergogenic" effect to enhance performance, it does have a number of extra-pulmonary effects such as enhancement of cardiac and respiratory muscle function which therefore merits further attention (Ellis 1984b). As Aubier et al (1981) have demonstrated, aminophylline concentrations in the therapeutic range of 10 to 20 ug/ml (13 $\pm$ 0.9 ug/ml) improves diaphragmatic contractility in non-asthmatics, rendering the diaphragm less susceptible to fatigue. Despite theophylline having been found to have no effect on the maximum exercise performance of healthy men (Elliot 1985), aminophylline may still benefit endurance running perfomance. However, the similar half-marathon performances both with and without aminophylline, would suggest that theophylline does not have an ergogenic effect during distance running for this asthmatic. Further

work is required in non-asthmatics before definite conclusions can be made on the possible ergogenic effect of theophylline in distance running. There were, however, large differences in the physiological responses between the two half-marathons performed with and without aminophylline.

The higher heart-rate and lower oxygen pulse during the half-marathon when aminophylline was taken is consistent with the work in exercise of Elliot et al (1985). Ogilvie et al (1977) found that at rest, an increased heart rate with aminophylline was not accompanied by any change in the stroke volume, but was accompanied by vasodilation of the skeletal muscle vascular bed of the forearm. On the basis of these findings Elliot et al (1985) explained the increased heart rate on exercise as a physiological response to maintain an adequate oxygen supply to the muscle, this being necessary due to the reduced arteriovenous oxygen content difference produced by vasodilatation.

There were also differences in the metabolic responses to the half-marathon in the presence of aminophylline. For the half-marathon with aminophylline, both lower adrenaline and blood glucose concentrations, and higher free fatty acid concentrations were observed, when compared to the half-marathon without aminophylline. Theophylline is an inhibitor of phosphodiesterase, the enzyme responsible for the breakdown of cAMP. Cyclic AMP acts as a "second messenger" mediating the effects of the hormones involved in muscle and liver glycogenolysis, adrenaline and glucagon. Thus elevated cAMP levels in the presence of theophylline may account for the differences in the metabolic responses between the two half-marathons.

The lower adrenaline concentrations at the end of the half-marathon may be a negative feedback mechanism consequent on the elevated cAMP levels due to the presence of theophylline. Alternatively, the lower adrenaline and noradrenaline levels with aminophylline may be partly due to a greater clearance by the liver consequent on the elevated heart-rate. Despite the much reduced adrenaline concentrations with aminophylline, the blood glucose concentrations showed a normal rise during both half-marathons. This may suggest that elevated cAMP levels with theophylline have allowed adequate glycogenolysis to maintain the blood glucose concentrations. The slightly higher blood glucose concentrations for the first half-marathon compared to the second half-marathon with aminophylline, was probably due either to the

elevated adrenaline levels for the first run, and / or due to the increased use of the beta-2 agonist, salbutamol, during run 1 (Neville et al 1977).

Cyclic AMP also acts as a mediator to hormones other than those involved in carbohydrate metabolism, for example in lipolysis. An increase in cAMP, activates a protein kinase that in turn phosphorylates and activates a second enzyme, triglyceride lipase. This lipase then catalyses the degradation of stored triglycerides into fatty acids, which are then released into the blood (Bowmans and Rand 1982). The concentration of free fatty acids after the half-marathon was higher for the run with aminophylline, and thus the effect of increased cAMP may increase fat mobiliation. An increased metabolism of fat may lead to a glycogen sparing effect and thus the effect of theophylline on substrate mobilisation must be examined in the light of the possible ergogenic effect of theophylline in endurance exercise.

6.5 Summary.

The similar cardio-respiratory and metabolic responses to the half-marathon of the asthmatic and non-asthmatic groups would suggest that the asthmatic, adequately protected from EIA by pre-exercise medication, should not be at a disadvantage in endurance running. Therefore, airway obstruction, which does not worsen with exercise, does not inhibit the endurance running performance of the asthmatic who has undergone appropriate training.

Standard pre-exercise asthmatic medication, however, may not totally inhibit EIA in endurance racing condition. Asthmatics may experience EIA during and after prolonged running, therefore questioning the safety of the participation of the asthmatic in distance running and placing the asthmatic at respiratory disadvantage in this sport.

CHAPTER 7

THE PHYSIOLOGICAL RESPONSES OF ASTHMATIC AND NON-ASTHMATIC ATHLETES TO A 2 HOUR TREADMILL RUN AT 70% VO_2 MAX.

7.1 Introduction.

The previous chapter described the physiological responses of the asthmatic athlete during an endurance 'race'. The study showed that the effect on the cardiac, ventilatory and metabolic systems to the treadmill half-marathon were similar for the asthmatic and non-asthmatic athletes. Although the physiological effects of more controlled exercise conditions, such as prolonged constant speed running, are well documented for non-asthmatics (Chapter 2), there is no such information on the asthmatic athlete. The aim of the present study was to compare the responses of asthmatic and non-asthmatic athletes to prolonged exercise at the same relative exercise intensity.

The previous study (Chapter 6) observed that, despite the use of pre-exercise medication, asthma may still be provoked under competitive conditions. When EIA developed during the treadmill half-marathon, the asthmatic was forced to reduce his running speed. The consequences of developing bronchoconstriction alone could not therefore be determined. Should an athlete develop EIA during the prolonged run, this approach will allow an examination of the physiological effects of the fall in FEV_1 during exercise.

This study compared the cardio-respiratory and metabolic responses of asthmatic athletes (with pre-exercise medication) and non-asthmatic athletes subjected to 2 hours of constant speed treadmill running. The speed was selected to obtain 70% of each individuals VO_2 max, both groups being exercised at the same relative exercise intensity.

7.2 Methods.

7.2.1 Subjects.

Four asthmatic and four non-asthmatic endurance trained runners volunteered for the study to examine the physiological and metabolic responses to a 2 hour run. The asthmatic and non-asthmatic athletes had similar running experience and were of a similar training status at the time of this study.

7.2.2 Baseline Laboratory Testing.

Each subject performed 3 preliminary treadmill tests to measure VO_2 max, the relationship between running speed and blood lactate concentration, and the incidence and severity of EIA. The details of these tests are reported in Chapter 3 (General Methods).

The regression equation for the relationship between the running speed and the oxygen uptake from the 'speed-lactate' test, was obtained for each subject. Using this regression equation and the VO_2 max, the treadmill running speeds required to elicit 60% (warm-up speed) and 70% (2 hour run) of VO_2 max, were obtained for each asthmatic and non-asthmatic athlete.

7.2.3 Two Hour Treadmill Run at 70% VO_2 max.

After an overnight fast, each subject completed a 2 hour treadmill run at 70% VO_2 max. The following protocol was adopted:

(a) Pre-exercise lung function measurements were made at rest by dry spirometry (Vitalograph) to obtain FVC and FEV_1, and PEFR for the asthmatic and non-asthmatic groups. The asthmatics repeated these measurements 10 minutes after taking their usual pre-exercise medication.

(b) With the subject seated the following samples were taken:

(i) A 5 minute resting sample of expired air.

(ii) Capillary blood samples, for the determination of blood lactate and blood glucose, were obtained from the thumb of a pre-warmed hand.

(iii) A 10ml venous blood sample from an ante-cubital vein was obtained for the determination of haematocrit, haemoglobin and catecholamines (adrenaline and noradrenaline).

(c) A five minute 'warm-up' at a speed selected to elicit

approximately 60% VO_2 max, was completed by each subject. A one minute sample of expired air was taken at the end of the warm-up period.

(d) The treadmill speed was then adjusted to the speed required to elicit 70% VO_2 max. This speed was held constant for 2 hours. The time elapsed and distance covered was visible to the athlete.

(e) Sponges for external cooling purposes, and drinking water were available throughout the run. The total volume of liquid drunk during the 2 hour run was recorded. Throughout the run the temperature and humidity were noted, and the mean values for the laboratory conditions over the 2 hour period were calculated.

(f) A series of collections were made at 15 minute intervals during the 2 hours:

(i) One minute samples of expired air collected in Douglas bags.

(ii) Duplicate 25ul capillary blood samples from the thumb for the determination of blood lactate and blood glucose.

(iii) FEV_1 was recorded as the best of two trials whilst running.

(iv) Breathing frequency, allowing in addition the derivation of tidal volume.

(v) Heart rate was recorded continuously throughout the run and displayed continuously on an oscilloscope.

(g) On completion of the 2 hour run a 10ml venous blood sample from an antecubital vein was obtained, for the determination of haemoglobin, haematocrit and catecholamines (adrenaline and noradrenaline). Using the haemoglobin and haematocrit values obtained before and after the 2 hour run, the percentage change in the plasma volume was obtained using the calculations described by Dill and Costill (1974).

(h) The FEV_1 was recorded at 5 minute intervals for 20 minutes after the 2 hour run.

(i) Body weight was obtained both before and after the run.

7.2.4 Statistics.

Due to the small number of subjects (n=4) statistical analyses are restricted. In an attempt to examine any differences between the asthmatic and non-asthmatics groups the mean values over the 2 hour run are shown graphically. The response of the variables over time were examined using Page's trend analysis (Page 1963), for both the asthmatic and non-asthmatic groups.

7.3 Results.

7.3.1 Physiological Characteristics.

The physical and physiological characteristics of the four asthmatic and the four non-asthmatic endurance runners are shown in Table 7.1. The mean VO_2 max for the asthmatic group (55.8 $\pm$ 4.7 $ml.kg.^{-1}min^{-1}$) was lower than that for the non-asthmatic group (63.4 $\pm$ 4.8 $ml.kg.^{-1}min^{-1}$). This difference in the maximum oxygen uptake for the two groups is not critical because the aim of the study was to compare the physiological responses of the asthmatic to the non-asthmatic group at the same relative exercise intensity (i.e. 70% of each individuals VO_2 max), regardless of the absolute running speed.

Table 7.2 shows the running speed and the $\%VO_2$ max at blood lactate concentrations of 2mM and 4mM. The similar mean values of the $\%VO_2$ max at these reference blood lactate concentrations, indicates that the groups had developed similar levels of submaximal fitness.

The results from the running test without asthmatic medication (Table 7.3), illustrates that the non-asthmatic group did not develop EIA as reflected by only a 3.6% fall in the FEV_1, whereas the asthmatic group exhibited a range of responses. One asthmatic (4) did not complete the test because his pre-exercise FEV_1 was only 34% of predicted normal. Exercise-induced asthma was confirmed in one of the asthmatics who showed at least the 10% fall in FEV_1 required to confirm EIA (Anderson 1983). The remaining two asthmatics were borderline for the diagnosis of EIA on this occasion, but had shown unequivocable falls in FEV_1 in previous tests. One of these individuals had recently modified his asthmatic medication adding beclomethasone dipropionate (Becotide), and thus this may have reduced the hyperreactivity of his airways during the exercise challenge. The peak flow values of this subject while changing treatment are shown in Appendix 10.

Each asthmatic took daily and pre-exercise medication (Table 7.4). In addition, one athlete took medication during the 2 hour run. Table 7.5 shows the lung function values before and after their pre-exercise medication, prior to the 2 hour run. The values are expressed as a percentage of the predicted normal for each subject. The non-asthmatic group had an FEV_1 within normal limits, whereas without

medication all asthmatics had an FEV_1 below 80% of the predicted normal value. It is of note that one asthmatic had a very low FEV_1 (28% predicted), which was increased with pre-exercise medication (52% predicted)

7.3.2 Two Hour Run at 70% VO_2 max.

Each athlete ran at a speed, calculated from previous treadmill tests, to elicit 70% VO_2 max (Table 7.6). The average oxygen uptake over the 2 hour run revealed that this had been successfully achieved, with the asthmatic and non-asthmatic groups running at 70.8 $\pm$ 1.3 and 70.4 $\pm$ 2.8 $\%VO_2$ max, respectively.

The laboratory conditions for the 2 hour run, the fluid intake and changes in body weight and plasma volume are shown in Table 7.7. Both groups had a small fluid intake and approximately a 3% fall in body weight, after the two hour run. In addition, the 2 hour run resulted in falls in plasma volume of 7.8% for the asthmatics and 5.9% for the non-asthmatics.

7.3.3 Lung Function Responses to the 2 Hour Run.

The FEV_1 during and after the 2 hour run are shown in Tables 7.8 and 7.9, respectively. The mean responses of the FEV_1 are shown in Figure 7.1. Three of the non-asthmatics experienced no marked reduction in the FEV_1 either during or after the 2 hour run. One non-asthmatic (1) did, however, experience a reduction in the FEV_1 of over 20%, although FEV_1 returned to pre-exercise levels post-exercise. One non-asthmatic (4) experienced bronchodilation both during and after the 2 hour run. The mean response for the asthmatic group showed a fall in the FEV_1 both during and after the 2 hour run. Two asthmatics (2 and 4) experienced a lowering of the FEV_1 during exercise, which was further reduced post-exercise, with a maximum decrease of 30% and 39% respectively. The mixed response of the FEV_1 for the four asthmatics is illustrated in Figures 7.2a and 7.2b.

7.3.4 Metabolic Response to the 2 Hour Run.

Blood lactate values showed a similar pattern for both groups, with concentrations fluctuating around 2mM for the 2 hour run (Figure 7.3a). Table 7.10 shows the response of each subject, however Page's trend analysis revealed no significant trend with time.

The blood glucose concentration was similar for the asthmatic and

non-asthmatic groups (Figure 7.3b). Table 7.11 shows the blood glucose concentration for each subject. It can be seen that one of the asthmatics (3) showed an unexplained fall in the blood glucose at the onset of exercise, which influences the mean results for this group. Although both groups showed a slight lowering of blood glucose at the end of the 2 hour run, no subject appeared to develop hypoglycaemia as defined by a blood glucose concentration less than 2.5mM. Indeed over the 2 hour run, there was no significant trend in blood glucose concentrations for either group.

The response after the 2 hour run of the plasma catecholamines, adrenaline and noradrenaline, were similar for the asthmatic and non-asthmatic groups (Table 7.12). Increases, from resting values of approximately 500% for both adrenaline and noradrenaline occurred for both groups (Figures 7.4a and 7.4b).

7.3.5 The Cardio-Respiratory Responses to the 2 Hour Run.

The mean values for selected cardio-respiratory variables together with the results from the Page trend analysis to illustrate significant change over time, are shown in Tables 7.13 and 7.14.

The oxygen cost of the 2 hour run showed a slight upward trend for both the asthmatics (7.1% increase) and non-asthmatics (3.6% increase) (Figure 7.5a). The oxygen cost of the 2 hour run was higher for the non-asthmatic group compared to the asthmatics, as a consequence of their higher running speeds. However, there was little difference in the oxygen uptake when expressed at a percentage of VO_2 max (Figure 7.5b). The ventilation rate, expressed in absolute terms and as a percentage of V_E max, are shown in Figures 7.6a and 7.6b. A small but significant upward drift of the ventilation rate of 4.6% and 6.9% was observed for the asthmatic and non-asthmatic groups, respectively. The non-asthmatics showed a higher absolute ventilation rate than the asthmatics, but this was not different when expressed as a percentage of maximum ventilation rate. As a result of the concurrent increase in both VO_2 and V_E, the ventilatory equivalent remained unchanged for the duration of the 2 hour run (Figure 7.7a). The respiratory exchange ratio (R) was not different for the asthmatic and non-asthmatic groups throughout the 2 hour run (Figure 7.7b). From this we can conclude that the contributions of the substrates, fat and carbohydrate, to energy metabolism were similar.

The increase in the ventilation rate was brought about by a

significant increase in breathing frequency over time for the non-asthmatic group (13.3%) and to a lesser extent for the asthmatic group (9.6%) (Figure 7.8a). Indeed, tidal volume decreased significantly over the 2 hour run for the non-asthmatics, although the asthmatic group experienced no such change (Figure 7.8b).

The breathing patterns were different for the asthmatic and non-asthmatic groups running at 70% VO_2 max. Breathing frequency was lower for the asthmatic group, although there were no apparent differences between the groups in the tidal volume. Thus, the asthmatics, in order to achieve a tidal volume comparable to that of the non-asthmatics, had a slower breathing frequency. The tidal volume was a much greater percentage of the FEV_1, for the asthmatic group when compared with the non-asthmatic group (Figure 7.9).

The heart rate of the asthmatic group was lower than that of the non-asthmatic group, although there was no difference when expressed as a percentage of maximum heart rate (Figure 7.10a and 7.10b). The asthmatic and non-asthmatic groups both showed significant increases in the heart rate over time. In addition, the oxygen pulse (millilitres of oxygen per heart beat) showed a significant downward trend over time, for both groups (Figure 7.11).

Table 7.1. The physiological characteristics of the asthmatic and non-asthmatic athletes who completed the 2 hour treadmill run, in response to the maximum oxygen uptake test.

	Age yrs	Height m	Weight kg	VO_2 max $l.min^{-1}$	$ml.kg.^{-1}min^{-1}$	V_E max $l.min^{-1}$	HR max $b.min^{-1}$
Asthmatics							
1.	44	1.84	66.05	4.06	61.5	132.5	184
2.	44	1.77	65.25	3.76	57.6	121.3	172
3.	43	1.76	69.4	3.67	52.8	131.0	176
4.	41	1.72	59.7	3.05	51.1	86.0	174
mean	43.0	1.77	65.1	3.64	55.8	117.6	177
±SD	1.4	0.05	4.0	0.42	4.7	21.7	5
Non-Asthmatics							
1.	36	1.69	60.35	3.70	61.2	134.5	187
2.	30	1.90	72.35	5.10	70.5	149.2	181
3.	46	1.65	53.6	3.31	61.8	120.7	183
4.	43	1.80	76.8	4.62	60.1	163.8	185
mean	38.8	1.76	65.8	4.18	63.4	142.1	184
±SD	7.2	0.11	10.7	0.82	4.8	18.6	3

Table 7.2. The running speed and $\%VO_2$ max at 2mM and 4mM blood lactate concentrations, for the asthmatic and non-asthmatic runners who completed the 2 hour run.

	V2mM ($m.s^{-1}$)	V4mM ($m.s^{-1}$)	V2mM ($\%VO_2$ max)	V4mM ($\%VO_2$ max)
Asthmatics				
1.	4.29	4.65	80.8	89.6
2.	3.57	4.03	74.1	82.5
3.	3.68	4.19	79.4	90.7
4.	3.88	-	80.5	-
mean	3.86	4.29	78.7	87.6
±SD	0.32	0.32	3.1	4.5
Non-Asthmatics				
1.	3.72	4.19	74.6	84.6
2.	4.95	5.25	83.8	89.6
3.	4.16	4.75	67.2	82.6
4.	3.86	4.24	78.6	85.8
mean	4.17	4.61	76.0	85.7
±SD	0.55	0.50	7.0	2.9

Table 7.3. The physiological responses and changes in the FEV_1 to the non-medicated running test, for the asthmatics and non-asthmatics who completed the 2 hour run.

	$\dot{V}O_2$ $ml.kg.^{-1}min^{-1}$	$\%\dot{V}O_2max$	$\dot{V}_E$ $l.min^{-1}$	HR $b.min^{-1}$	Pre-FEV_1	Post-FEV_1	% Change FEV_1
Asthmatics							
1.	44.0	71.4	84.8	151	3.36	3.08	-8.3
2.	37.7	65.4	58.8	133	1.92	1.25	-34.9
3.	43.0	81.5	83.2	157	2.98	2.70	-9.4
4.	-	-	-	-	1.29 *	-	-
mean	41.6	72.8	75.6	147	2.75	2.34	-17.5
± SD	3.4	8.1	14.6	12	0.75	0.97	15.1
Non-Asthmatics							
1.	48.2	78.7	101.2	159	3.12	3.00	-3.8
2.	59.9	84.9	129.0	169	6.05	5.79	-4.3
3.	44.8	72.5	69.3	162	3.15	3.02	-4.1
4.	45.1	75.1	81.8	160	4.35	4.25	-2.3
mean	49.5	77.8	95.3	163	4.17	4.02	-3.6
± SD	7.1	5.4	26.0	5	1.38	1.32	0.9

* Did not perform test due to a low resting FEV_1.

Table 7.4. The asthmatic history and the medication taken before and during the 2 hour treadmill run at 70% VO_2 max for the asthmatic athletes.

	Age (Yrs)	Yrs of Asthma	Daily Medication	Medication for 2 hr Run Before	During (mins)
1	44	39	Becotide/Ventolin	Ventolin	-
2	44	40	Becotide/Intal Co. Ventolin	Intal Co. Ventolin	Ventolin (16,32,88)
3	43	2	Exirel, Intal	Exirel, Intal	-
4	41	40	Intal Co.	Intal Co. Ventolin	-
mean	43	30			
±SD	1.4	19			

Table 7.5. Lung function of the asthmatic (pre and post medication) and non-asthmatic groups prior to the 2 hour treadmill run at 70% VO_2 max. Values are given in absolute terms and as a percentage of predicted normal (in brackets).

	FEV_1		FVC		FEV_1%	
	1-BTPS (% Pred)		1-BTPS (% Pred)			
	Pre Med.	Post Med.	Pre Med.	Post Med.	Pre Med.	Post Med.
Asthmatics						
1.	3.25(73.9)	3.48(79.1)	4.87(89.0)	5.09(93.1)	66.7	68.4
2.	1.98(49.5)	2.85(71.3)	3.96(79.2)	4.88(97.6)	50.0	58.4
3.	3.06(76.9)	3.26(81.9)	5.00(101.4)	5.07(102.8)	61.2	64.3
4.	1.08(28.1)	1.99(51.7)	2.83(60.0)	4.25(90.0)	38.2	46.8
mean	2.34(57.1)	2.90(71.0)	4.17(82.4)	4.82(95.9)	54.0	59.5
±SD	1.01(22.9)	0.66(13.6)	1.00(17.5)	0.39(5.6)	12.6	9.4
Non-Asthmatics						
1.	3.11(80.8)		3.77(81.1)		82.5	
2.	5.90(113.2)		6.40(102.1)		92.2	
3.	3.09(92.2)		4.12(99.0)		75.0	
4.	4.27(101.7)		5.62(108.1)		76.0	
mean	4.09(97.0)		4.98(97.6)		81.4	
±SD	1.33(13.8)		1.24(11.6)		7.9	

Table 7.6. The running speed, distance covered, and the average oxygen uptake for the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic runners.

	Run Speed ($m.s^{-1}$)	Distance (km)	VO_2 ($ml.kg.^{-1}min^{-1}$)	$\%VO_2$ max
Asthmatics				
1.	3.78	27.2	43.7	71.0
2.	3.47	25.0	41.8	72.6
3.	3.36	24.2	36.8	69.7
4.	3.40	24.5	35.8	69.9
mean	3.50	25.2	39.5	70.8
±SD	0.19	1.4	3.8	1.3
Non-Asthmatics				
1.	3.48	25.1	42.8	69.9
2.	4.29	30.9	47.0	66.7
3.	4.20	30.2	45.3	73.2
4.	3.61	26.0	43.3	72.0
mean	3.90	28.1	44.6	70.4
±SD	0.41	2.9	1.9	2.8

Table 7.7. Laboratory conditions, fluid intake, and changes in body weight and plasma volume for the 2 hour treadmill run at 70% VO_2 max for the asthmatic and non-asthmatic athletes.

	Temp. °C	Humidity %	Fluid (ml)	Weight Loss (kg)	%Change Weight	%Change Plasma Vol.
Asthmatics						
1.	22.0	77	279	2.4	-3.6	11.3
2.	18.6	78	388	1.75	-2.7	-1.3
3.	21.0	56	114	2.4	-3.5	-8.5
4.	19.3	69	233	1.5	-2.5	-10.0
mean	20.2	70	254	2.0	-3.1	-7.8
±SD	1.6	10	113	0.5	0.6	4.5
Non-Asthmatics						
1.	22.0	59	216	1.75	-2.9	-4.1
2.	19.6	70	88	2.5	-3.5	-8.8
3.	20.3	60	20	2.0	-3.7	-2.8
4.	21.7	55	306	2.65	-3.5	-7.8
mean	20.9	61	158	2.0	-3.4	-5.9
±SD	1.1	6	128	0.4	0.3	2.9

Table 7.8. The FEV_1 before and during the 2 hour treadmill run at 70% VO_2 max for the asthmatic and the non-asthmatic athletes.

	Running Time [mins]									
	Rest	W-Up	15'	30'	45'	60'	75'	90'	105'	120'
Asthmatics										
1.	3.48	3.48	3.36	3.37	3.25	3.20	3.37	3.35	3.40	3.41
2.	2.85	3.10	2.36	2.38	2.49	2.58	2.40	2.43	2.48	2.54
3.	3.26	3.09	3.00	2.98	3.02	2.96	3.00	2.92	2.77	3.25
4.	1.99	2.20	2.21	1.99	1.96	1.86	1.84	1.79	1.86	1.82
mean	2.90	2.97	2.73	2.68	2.68	2.65	2.65	2.62	2.63	2.76
±SD	0.66	0.54	0.54	0.61	0.58	0.59	0.67	0.67	0.64	0.73
Non-Asthmatics										
1.	3.11	2.90	2.40	2.52	2.45	2.83	2.82	2.81	2.90	2.79
2.	5.90	5.51	5.38	5.40	5.52	5.25	5.57	5.26	5.37	5.40
3.	3.09	2.97	2.92	2.87	2.95	2.98	2.95	2.87	2.96	3.03
4.	4.27	4.74	4.62	4.62	4.70	4.65	4.76	4.89	4.80	4.87
mean	4.09	4.03	3.83	3.85	3.91	3.93	4.03	3.96	4.01	4.02
±SD	1.33	1.30	1.40	1.38	1.45	1.21	1.36	1.30	1.27	1.31

Table 7.9. The FEV_1 recorded for 20 minutes after the 2 hour treadmill run at 70% VO_2 max for the asthmatic and non-asthmatic athletes.

	Time in Recovery				
	Pre Ex.	5 min	10 min	15 min	20min
Asthmatics					
1.	3.48	3.53	3.52	3.55	3.55
2.	2.85	2.00	2.18	2.31	2.65
3.	3.26	3.25	3.28	3.07	3.18
4.	1.99	1.21	1.38	1.38	1.27
mean	2.90	2.50	2.59	2.58	2.66
±SD	0.66	1.09	1.00	0.95	1.00
Non-Asthmatics					
1.	3.11	3.10	3.09	3.05	3.00
2.	5.90	5.73	5.85	5.84	5.58
3.	3.09	3.17	2.97	3.20	2.98
4.	4.27	4.76	4.62	4.85	4.72
mean	4.09	4.19	4.13	4.24	4.07
±SD	1.33	1.28	1.37	1.35	1.30

Table 7.10. Blood lactate concentrations (mM) before and during the 2 hour treadmill run at 70% VO_2 max for the asthmatic and non-asthmatic athletes.

	Running Time (mins)									
	Rest	15'	30'	45'	60'	75'	90'	105'	120'	Trend
Asthmatics										
1.	0.70	0.94	1.28	1.07	2.50	0.75	1.91	1.21	1.97	
2.	0.62	1.53	3.70	2.45	2.15	1.53	1.81	1.35	1.50	
3.	1.68	1.31	1.75	2.16	1.06	4.11	1.68	3.64	3.32	
4.	0.89	0.96	1.58	1.17	1.83	1.07	2.90	2.84	2.40	
mean	0.97	1.19	2.08	1.71	1.89	1.87	2.08	2.26	2.30	ns
±SD	0.49	0.29	1.10	0.70	0.61	1.53	0.56	1.18	0.77	
Non-Asthmatics										
1.	0.86	1.95	2.18	2.14	1.19	1.52	1.39	1.54	1.52	
2.	0.77	0.99	1.40	1.26	1.11	1.19	1.55	1.87	1.51	
3.	0.93	1.56	1.43	1.25	1.37	1.23	1.35	1.39	1.69	
4.	0.95	1.78	3.09	3.32	2.49	2.66	3.40	3.44	3.76	
mean	0.88	1.57	2.03	1.99	1.54	1.65	1.92	1.81	2.12	ns
±SD	0.08	0.42	0.80	0.98	0.64	0.69	0.99	0.47	1.10	

Table 7.11. Blood glucose concentrations (mM) before and during the 2 hour treadmill run at 70% VO_2 max for the asthmatic and non-asthmatic athletes.

	Running Time (mins)									
	Rest	15'	30'	45'	60'	75'	90'	105'	120'	Trend
Asthmatics										
1.	3.99	4.47	4.52	4.32	4.33	4.47	4.11	3.95	3.57	
2.	5.18	5.80	6.15	5.76	5.58	5.23	5.40	5.74	5.68	
3.	5.88	2.96	3.54	4.16	4.34	4.03	4.19	4.32	4.01	
4.	4.46	4.59	4.67	4.71	4.59	4.43	4.15	4.25	4.01	
mean	4.88	4.46	4.72	4.74	4,71	4.54	4.46	4.57	4.32	ns
±SD	0.83	1.16	1.08	0.72	0.59	0.50	0.63	0.80	0.93	
Non-Asthmatics										
1.	4.79	4.69	4.67	4.84	4.70	4.65	4.61	4.47	4.71	
2.	3.53	4.10	3.82	3.81	3.70	3.61	3.41	3.42	3.27	
3.	4.29	4.93	5.05	5.24	5.09	4.89	4.55	4.38	4.15	
4.	4.31	4.70	4.90	4.79	4.61	4.44	4.48	4.12	4.00	
mean	4.23	4.61	4.61	4.67	4.53	4.40	4.26	4.10	4.03	ns
±SD	0.52	0.35	0.55	0.61	0.59	0.56	0.57	0.48	0.59	

Table 7.12. The noradrenaline and adrenaline concentrations before and after the 2 hour treadmill run at 70% VO_2 max, for the asthmatic and non-asthmatic athletes.

	NA [nmol.l^{-1}]			A [nmol.l^{-1}]		
	Pre	Post	Change	Pre	Post	Change
Asthmatics						
1.	1.60	10.27	8.67	0.15	3.06	2.91
2.	2.02	15.25	13.23	0.33	1.18	0.85
3.	1.97	13.75	11.78	0.28	1.23	0.95
4.	3.10	14.22	11.12	0.20	0.64	0.44
mean	2.17	13.37	11.20	0.24	1.53	1.29
±SD	0.65	2.16	1.90	0.08	1.06	1.10
Non-Asthmatics						
1.	2.35	10.01	7.66	0.32	1.17	0.85
2.	2.11	14.66	12.55	0.22	2.98	2.76
3.	2.50	13.29	10.79	0.17	1.22	1.05
4.	2.45	19.64	17.19	0.27	1.31	1.04
mean	2.35	14.40	12.05	0.25	1.67	1.43
±SD	0.17	4.00	3.98	0.07	0.88	0.89

Table 7.13. The changes in the physiological variables, VO_2, HR, O_2 pulse, VCO_2 and R, during the 2 hour run at 70% VO_2 max for the asthmatic and non-asthmatic groups.

	Rest	Running Time (mins) 15'	30'	45'	60'	75'	90'	105'	120'	
VO_2 ($ml.kg.^{-1}min^{-1}$)										
Asthmatics										
mean	3.48	38.2	38.6	39.7	39.3	39.9	40.1	40.0	40.4	***^{i}
±SD	0.36	2.8	4.0	3.3	3.7	3.4	4.4	4.2	5.5	
Non-Asthmatics										
mean	2.59	43.7	44.2	44.2	44.4	44.9	44.9	45.1	45.3	*^{i}
±SD	0.44	1.3	1.3	1.7	2.7	2.3	2.6	2.4	2.1	
Heart rate ($b.min^{-1}$)										
Asthmatics										
mean	-	142	147	148	149	151	154	156	159	***^{i}
±SD	-	6	7	6	6	7	8	7	7	
Non-Asthmatics										
mean	-	153	156	158	158	160	162	163	166	***^{i}
±SD	-	4	6	5	3	4	5	6	4	
Oxygen Pulse ($ml.beat^{-1}$)										
Asthmatics										
mean	-	17.5	17.1	17.5	17.2	17.2	16.9	16.7	16.5	***^{d}
±SD	-	1.8	2.1	2.2	2.2	2.0	2.0	2.2	2.3	
Non-Asthmatics										
mean	-	18.9	18.7	18.5	18.5	18.5	18.2	18.2	17.9	***^{d}
±SD	-	3.8	3.5	3.6	3.5	3.6	3.6	3.7	2.9	
VCO_2, ($ml.kg.^{-1}min^{-1}$)										
Asthmatics										
mean	2.91	33.3	33.9	33.6	33.6	34.6	34.4	34.3	34.5	***^{i}
±SD	0.39	3.0	3.8	3.3	3.7	3.4	3.9	3.5	4.5	
Non-Asthmatics										
mean	2.20	38.6	38.5	38.5	38.5	38.6	39.0	39.2	40.0	***^{i}
±SD	0.51	2.5	2.8	2.9	3.4	3.1	2.7	2.1	2.9	
R										
Asthmatics										
mean	0.834	0.870	0.878	0.846	0.854	0.865	0.858	0.857	0.855	
±SD	0.053	0.023	0.025	0.021	0.027	0.030	0.007	0.029	0.022	
Non-Asthmatics										
mean	0.847	0.884	0.870	0.870	0.867	0.859	0.869	0.870	0.883	
±SD	0.094	0.040	0.042	0.035	0.038	0.047	0.045	0.022	0.048	

Page trend analysis: * $p<0.05$, ** $p<0.01$, *** $p<0.001$
^{i} : increase ^{d} : decrease

Table 7.14. The changes in the physiological variables, V_E, ventilatory equivalent, Bf, V_t and V_t / FEV_1 ratio, during the 2 hour run at 70% VO_2 max for the asthmatic and non-asthmatic groups.

	Rest	Running Time (mins) 15'	30'	45'	60'	75'	90'	105'	120'	
V_E ($l.min^{-1}$ BTPS)										
Asthmatics										
mean	11.4	71.5	72.1	73.6	72.7	73.4	71.5	73.7	74.9	*↑
±SD	1.0	10.3	11.6	12.2	12.6	12.0	12.0	12.6	13.5	
Non-Asthmatics										
mean	9.2	82.3	82.3	83.1	84.4	85.6	84.7	86.2	87.6	***↑
±SD	1.5	11.1	11.8	12.7	13.0	12.0	11.3	10.4	9.5	
Ventilatory Equivalent (l)										
Asthmatics										
mean	41.7	23.7	23.7	23.5	23.4	23.3	22.6	23.3	23.5	
±SD	4.5	0.8	0.7	1.1	1.0	1.0	0.8	0.9	1.2	
Non-Asthmatics										
mean	45.4	23.9	23.6	23.9	24.1	24.2	24.0	24.3	24.6	
±SD	6.3	2.6	2.5	2.9	2.6	2.6	1.9	2.5	1.0	
Breathing Frequency (breaths.min^{-1})										
Asthmatics										
mean	13.5	32.0	33.0	33.8	34.0	33.8	33.5	34.5	34.8	*↑
±SD	3.9	6.5	5.9	7.5	8.2	6.7	7.3	7.3	5.9	
Non-Asthmatics										
mean	16.1	42.0	43.3	42.0	44.5	44.8	45.0	46.3	46.8	***↑
±SD	4.0	13.0	13.0	14.1	11.4	12.7	8.8	12.0	10.2	
V_t (l - STPD)										
Asthmatics										
mean	0.748	1.862	1.811	1.821	1.789	1.806	1.778	1.776	1.778	
±SD	0.265	0.120	0.113	0.138	0.148	0.100	0.123	0.142	0.116	
Non-Asthmatics										
mean	0.496	1.727	1.663	1.756	1.649	1.679	1.605	1.627	1.615	*↓
±SD	0.171	0.551	0.486	0.557	0.501	0.530	0.404	0.501	0.449	
V_t / FEV_1 %										
Asthmatics										
mean	33.1	85.7	85.2	86.0	86.1	87.1	87.2	86.0	82.7	
±SD	14.8	21.7	19.9	23.8	26.7	24.6	26.8	22.9	23.0	
Non-Asthmatics										
mean	14.7	55.3	53.3	55.4	50.9	50.9	50.1	49.3	49.2	
±SD	1.8	2.9	5.5	6.8	2.9	4.7	4.7	4.0	4.1	

Page trend analysis: * $p<0.05$, ** $p<0.01$, *** $p<0.001$
↑ : increase ↓ : decrease

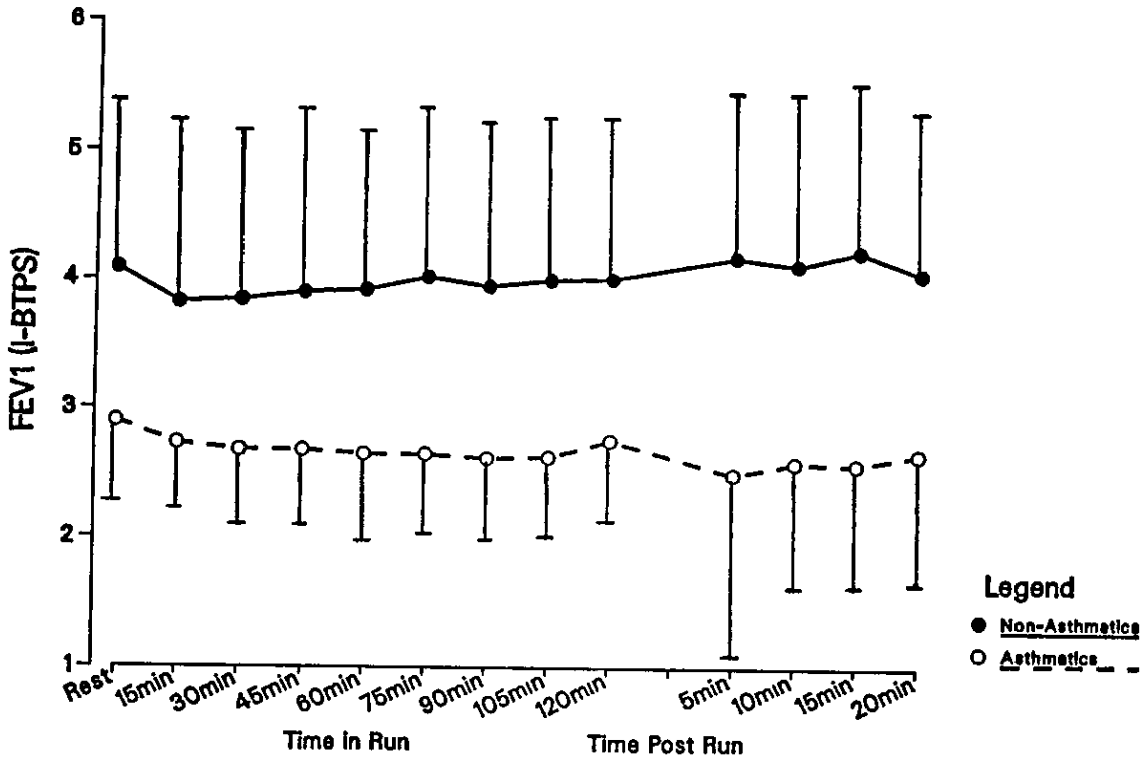


Figure 7.1. The FEV_1 during and for 20 minutes after the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Figure 7.2a

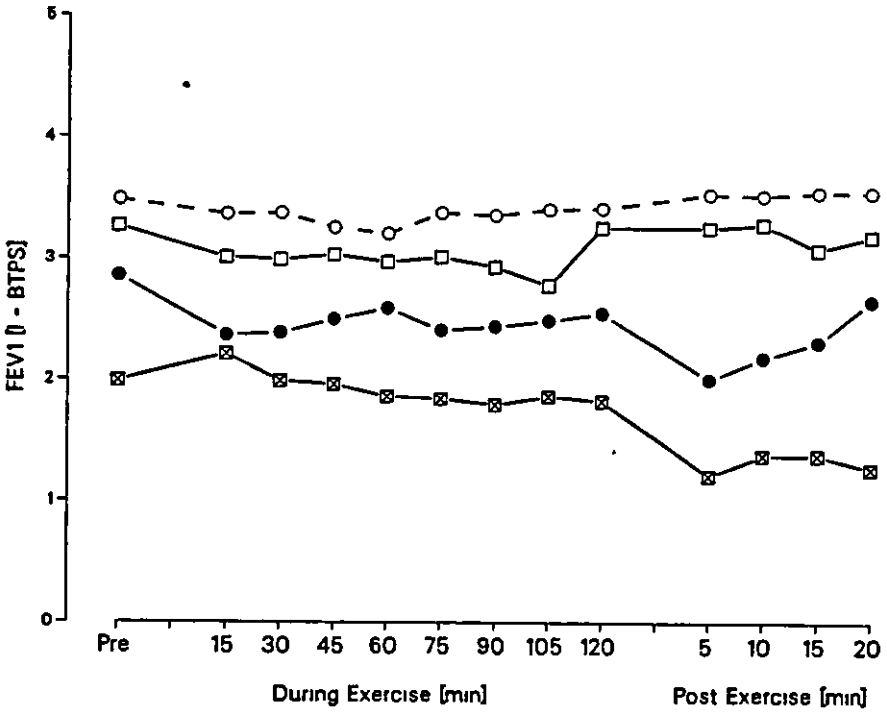
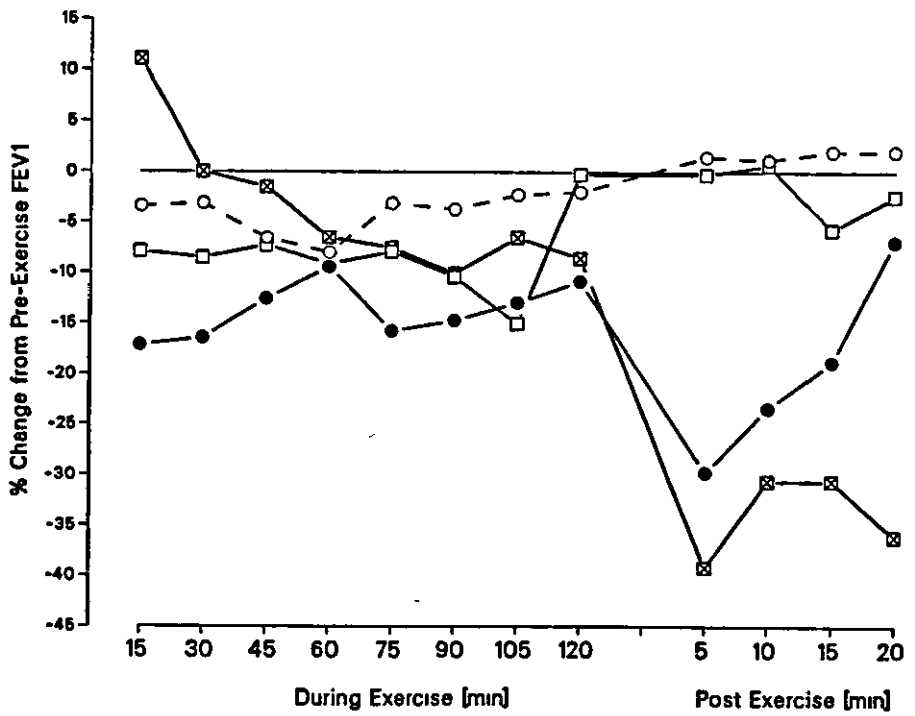


Figure 7.2b



Figures 7.2a and 7.2b. The FEV_1 during and for 20 minutes after the 2 hour run at 70% VO_2 max, shown in litres (7.2a) and as a percentage change from the pre-exercise value (7.2b), for the four asthmatic runners.

Figure 7.3a

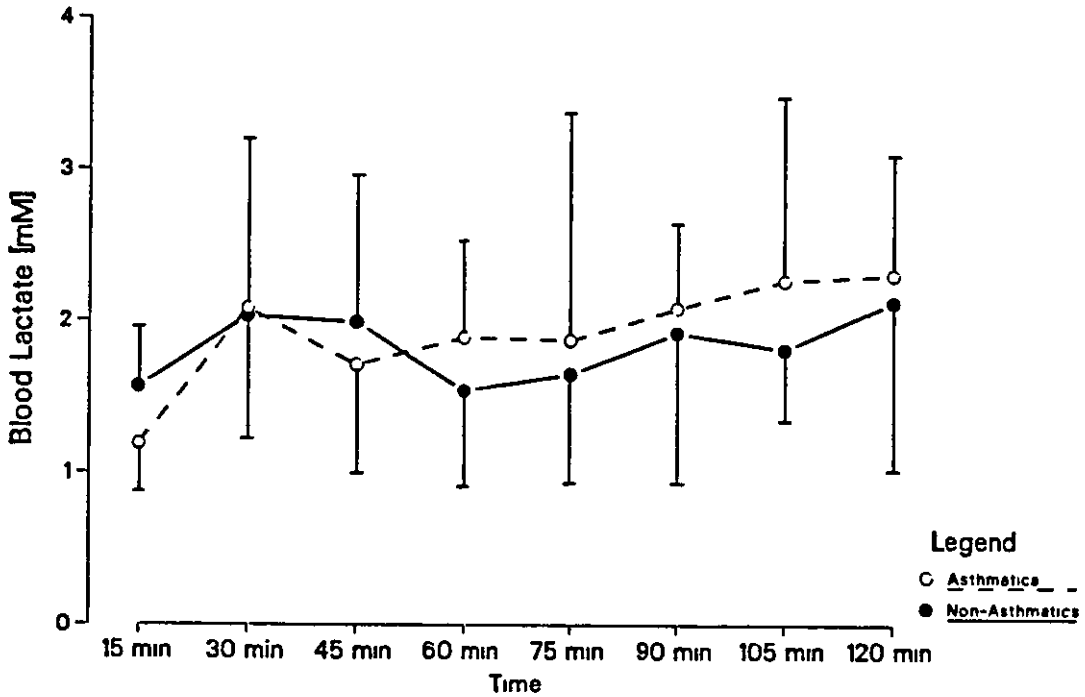
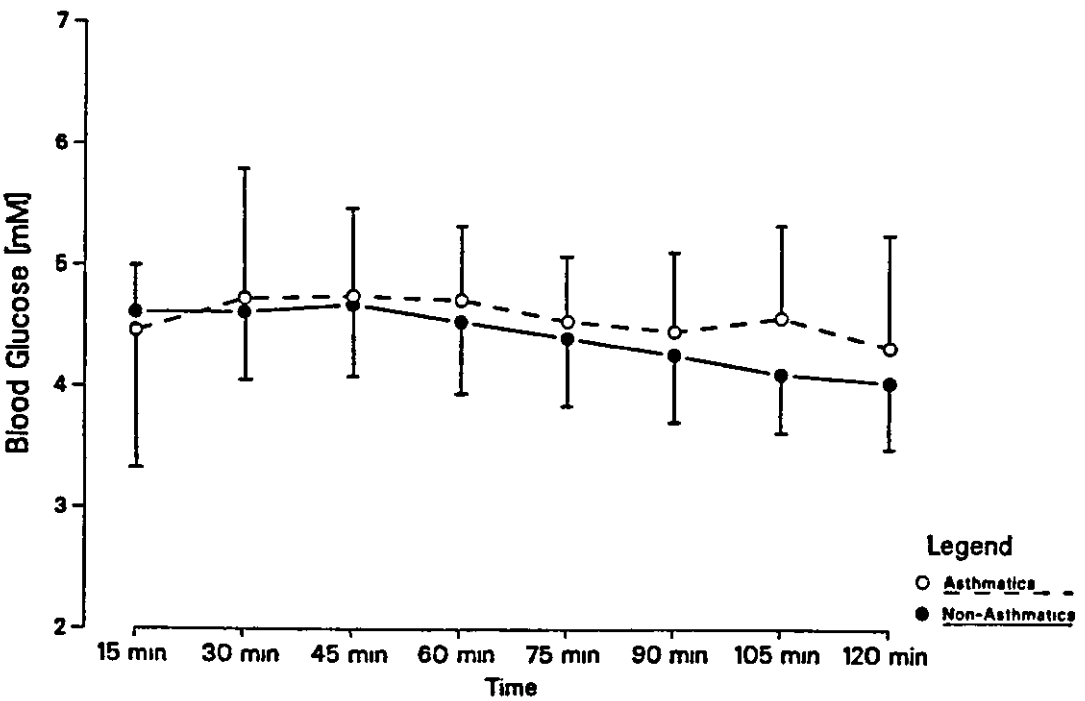


Figure 7.3b



Figures 7.3a and 7.3b. The blood lactate (7.3a) and blood glucose (7.3b) concentrations during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Figure 7.4a

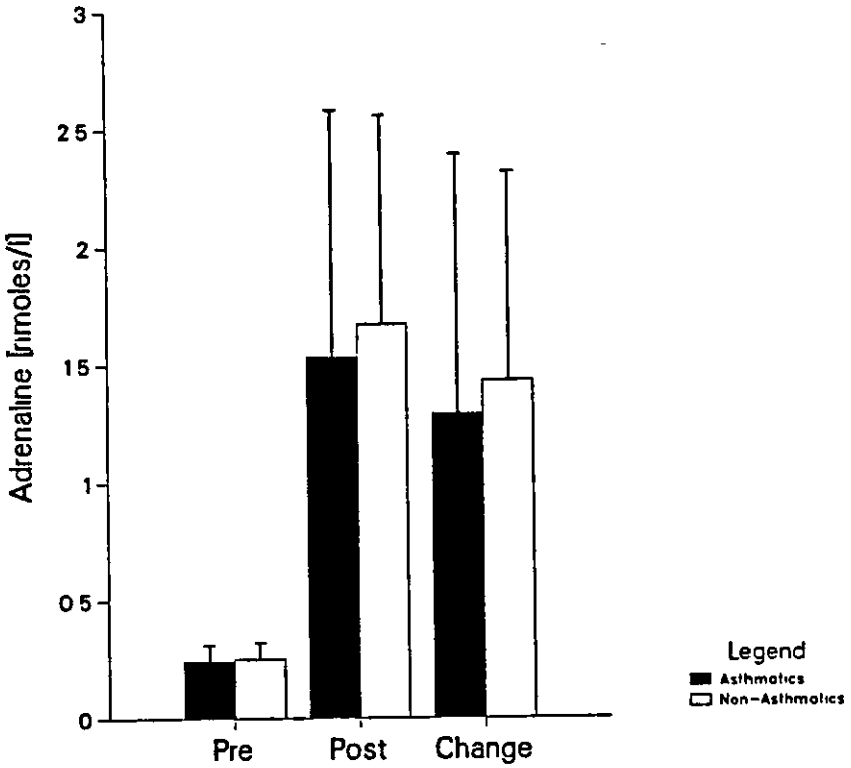
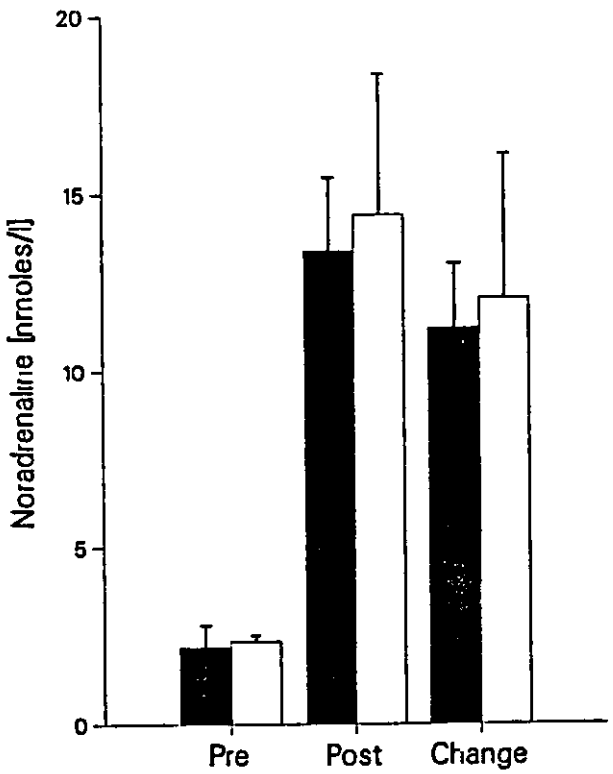


Figure 7.4b



Figures 7.4a and 7.4b. The adrenaline (7.4a) and noradrenaline (7.4b) concentrations before and after the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Figure 7.5a

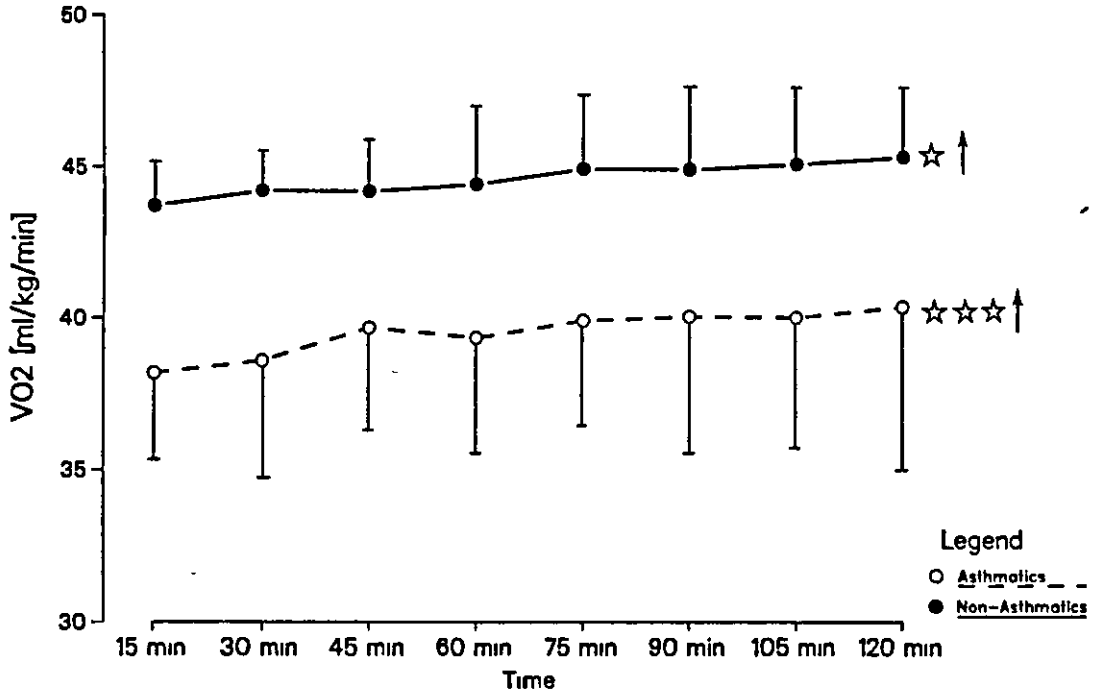
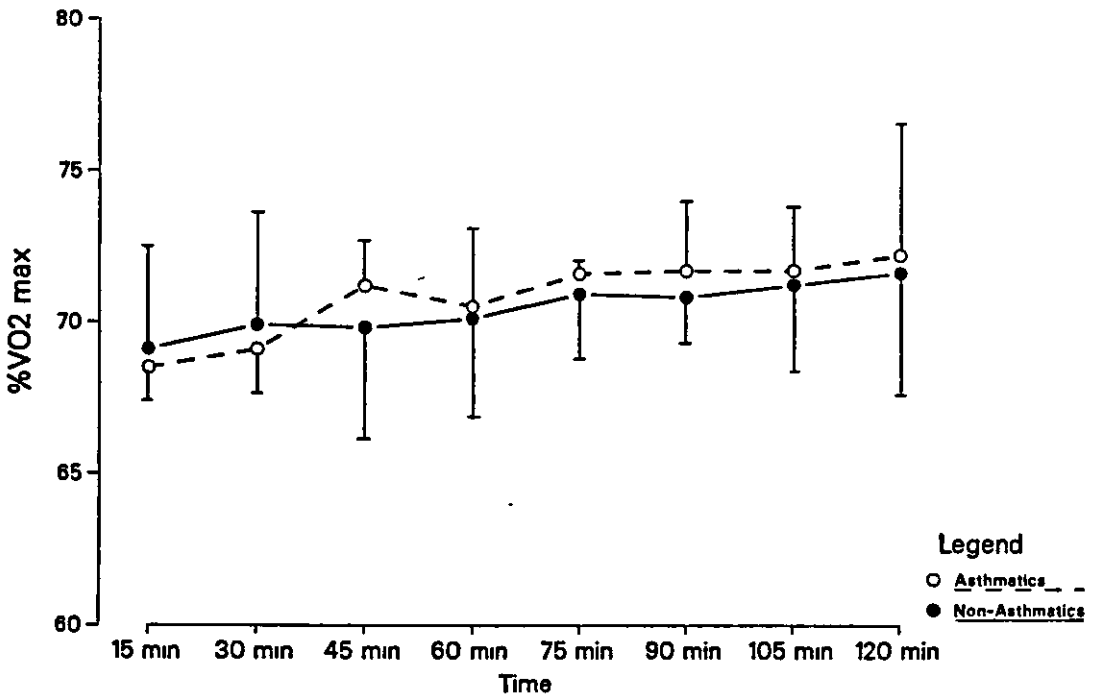


Figure 7.5b



Figures 7.5a and 7.5b. The oxygen uptake expressed in absolute terms (7.5a) and as a $\%VO_2$ max (7.5b) during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆☆ $p<0.001$

Figure 7.6a

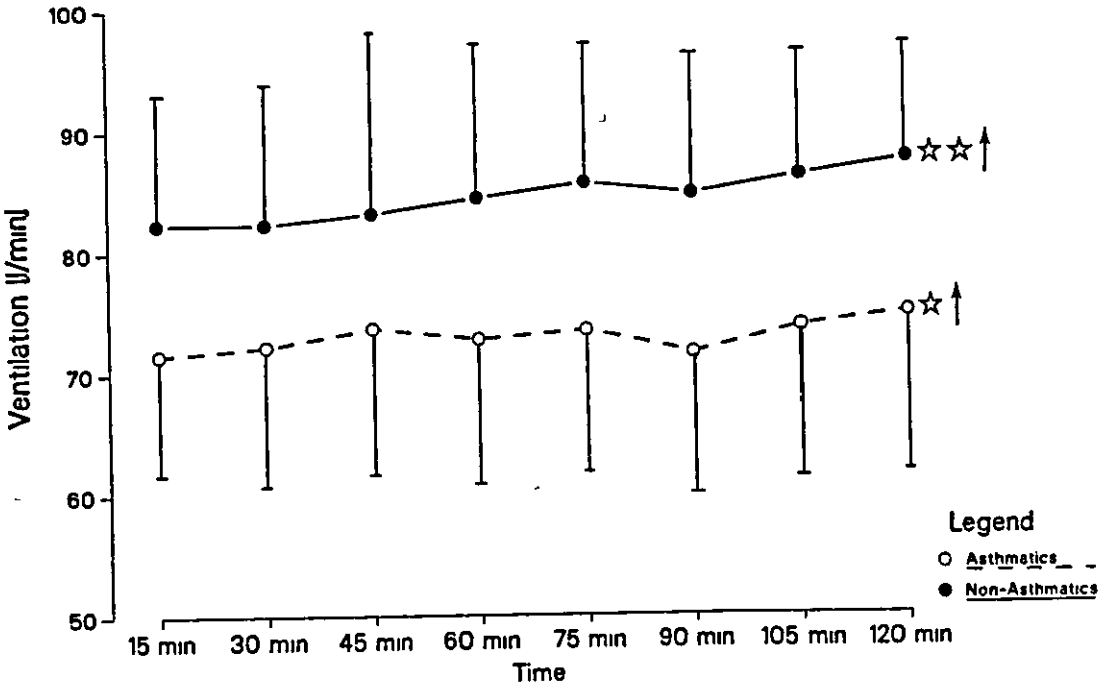
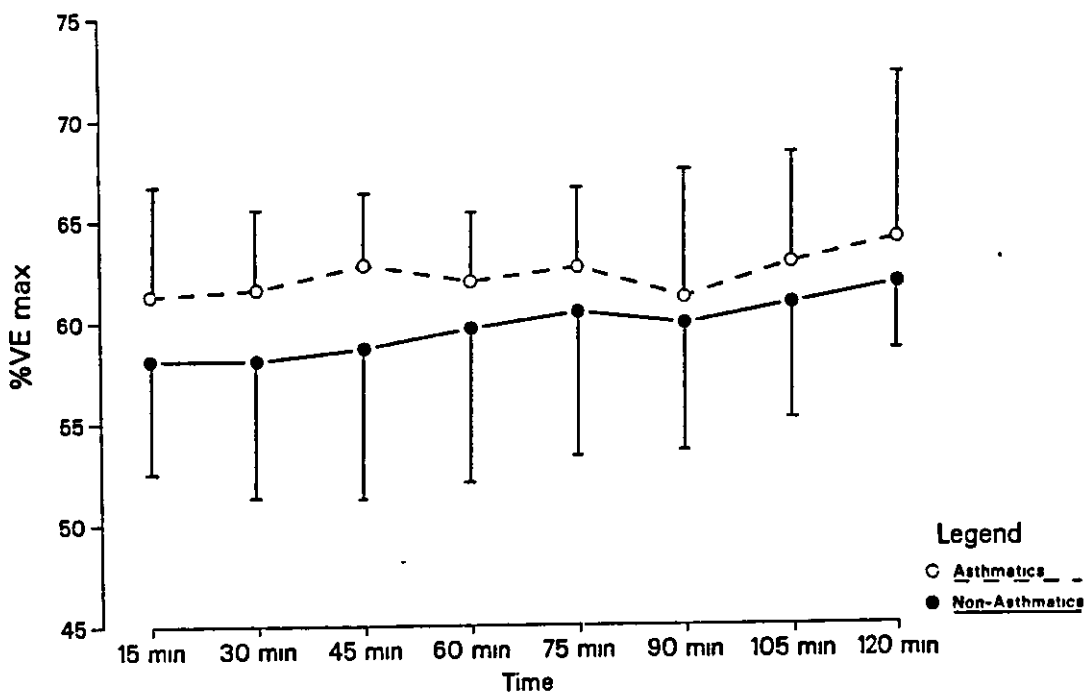


Figure 7.6b



Figures 7.6a and 7.6b. The ventilation rate expressed in absolute terms (7.6a) and as a percentage of the maximum ventilation (7.6b) during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆ $p<0.01$

Figure 7.7a

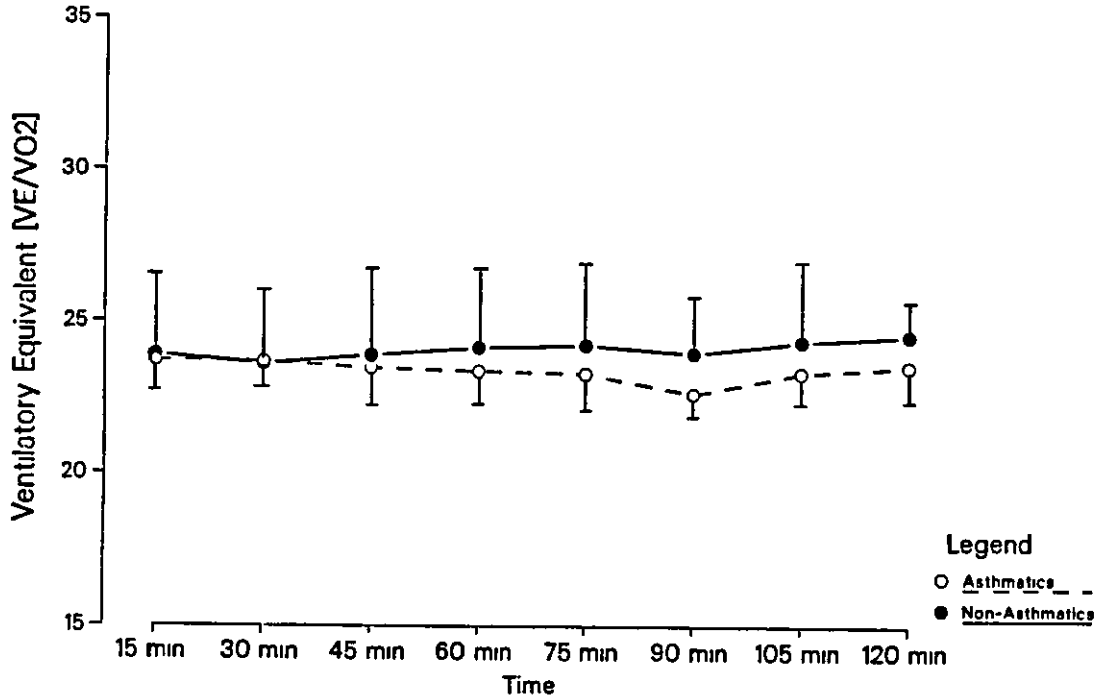
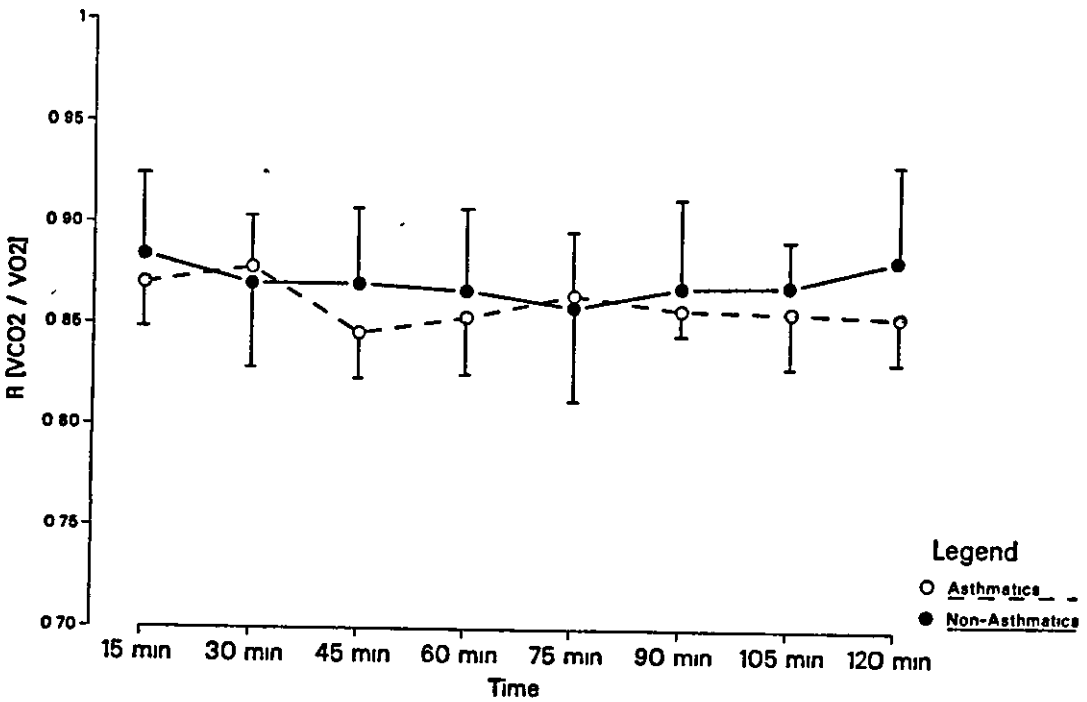


Figure 7.7b



Figures 7.7a and 7.7b. The ventilatory equivalent (7.7a) and the respiratory exchange ratio (7.7b) during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Figure 7.8a

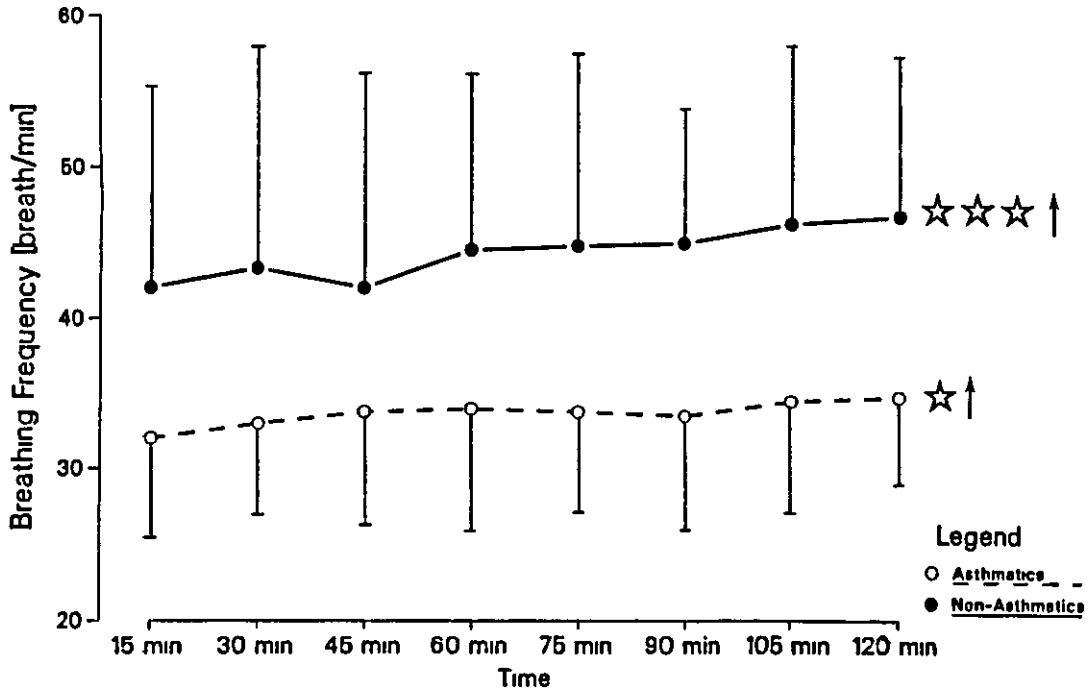
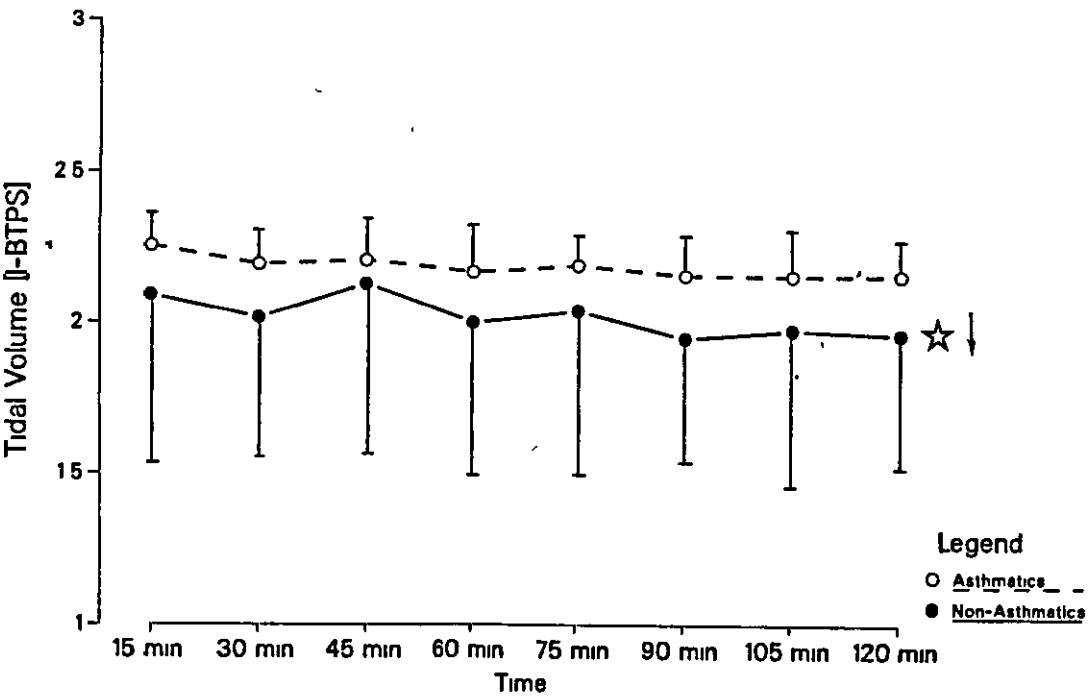


Figure 7.8b



Figures 7.8a and 7.8b. The breathing frequency (7.8a) and tidal volume (7.8b) during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Denotes significant change over time: ☆ $p<0.05$; ☆☆☆ $p<0.001$

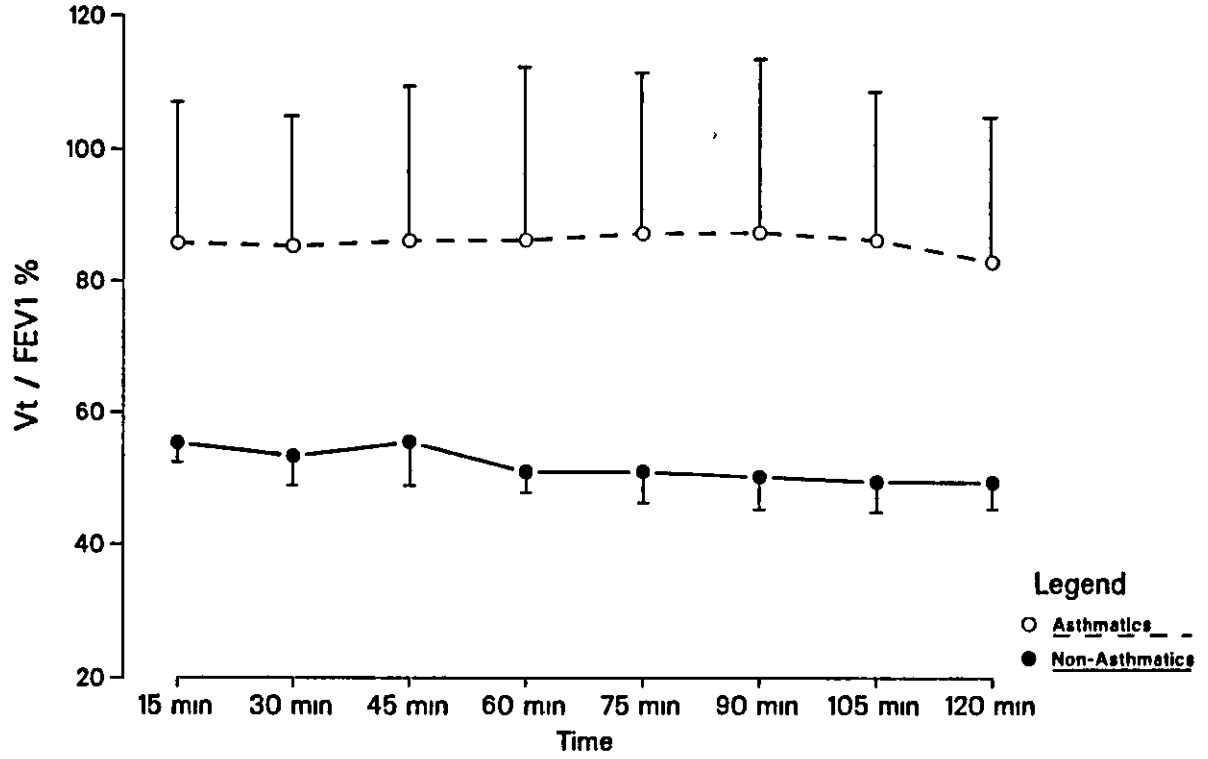


Figure 7.9. The tidal volume expressed as a percentage of the FEV_1 during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Figure 7.10a

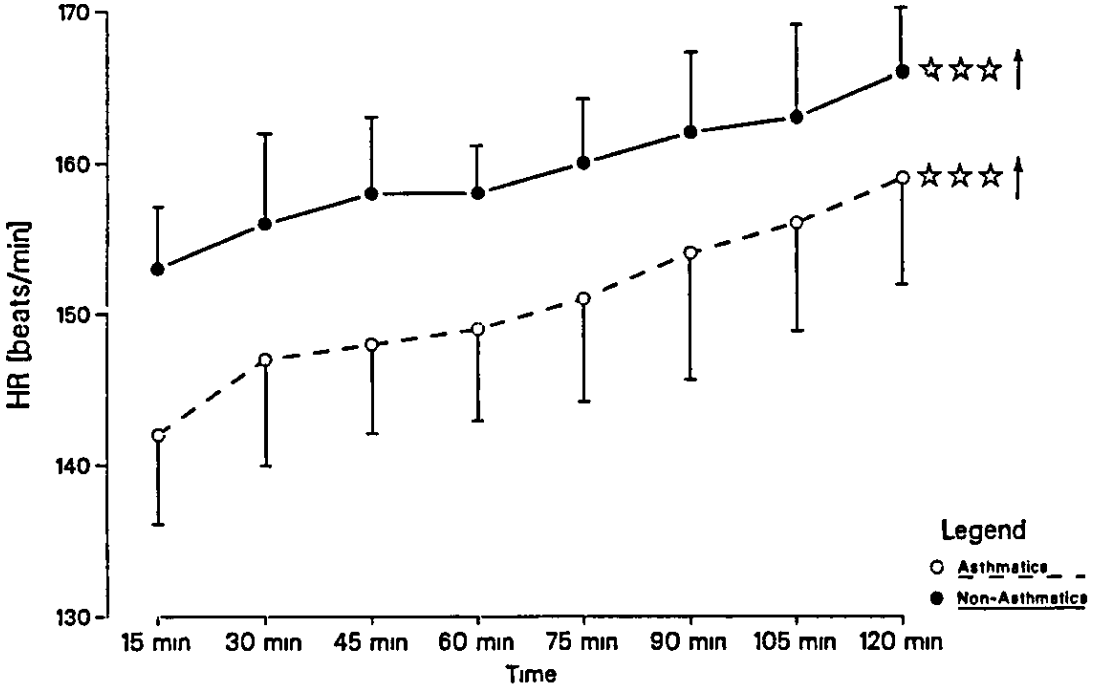
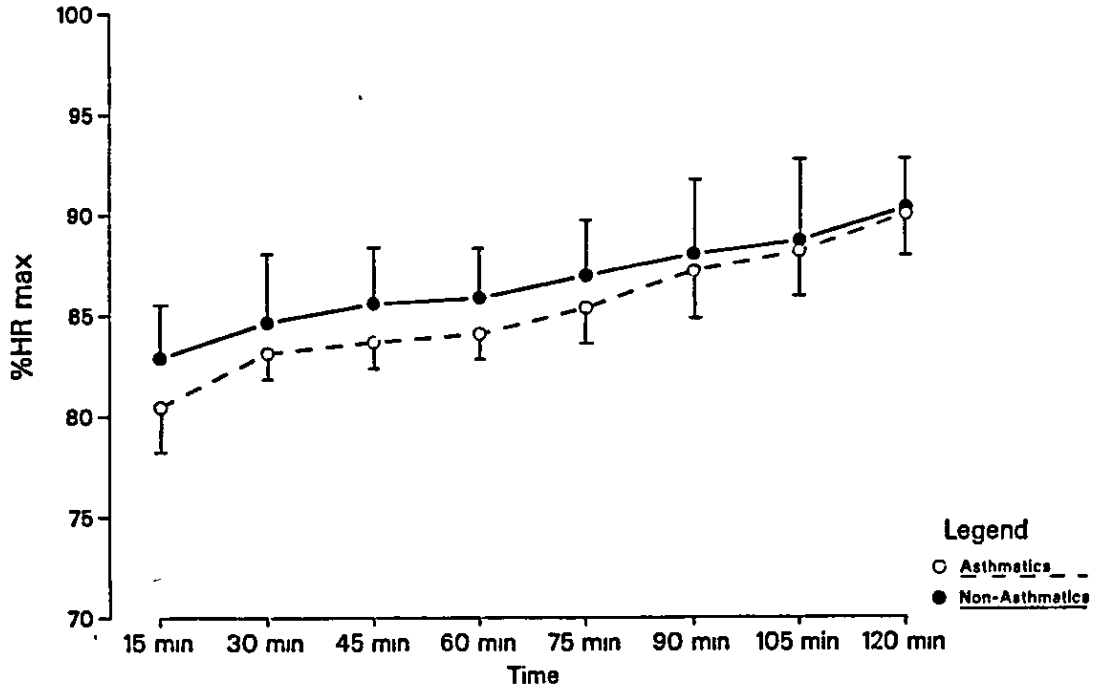


Figure 7.10b



Figures 7.10a and 7.10b. The heart rate expressed in absolute terms (7.10a) and as a percentage of the maximum heart rate (7.10b) during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Denotes significant change over time: ☆☆☆ $p<0.001$

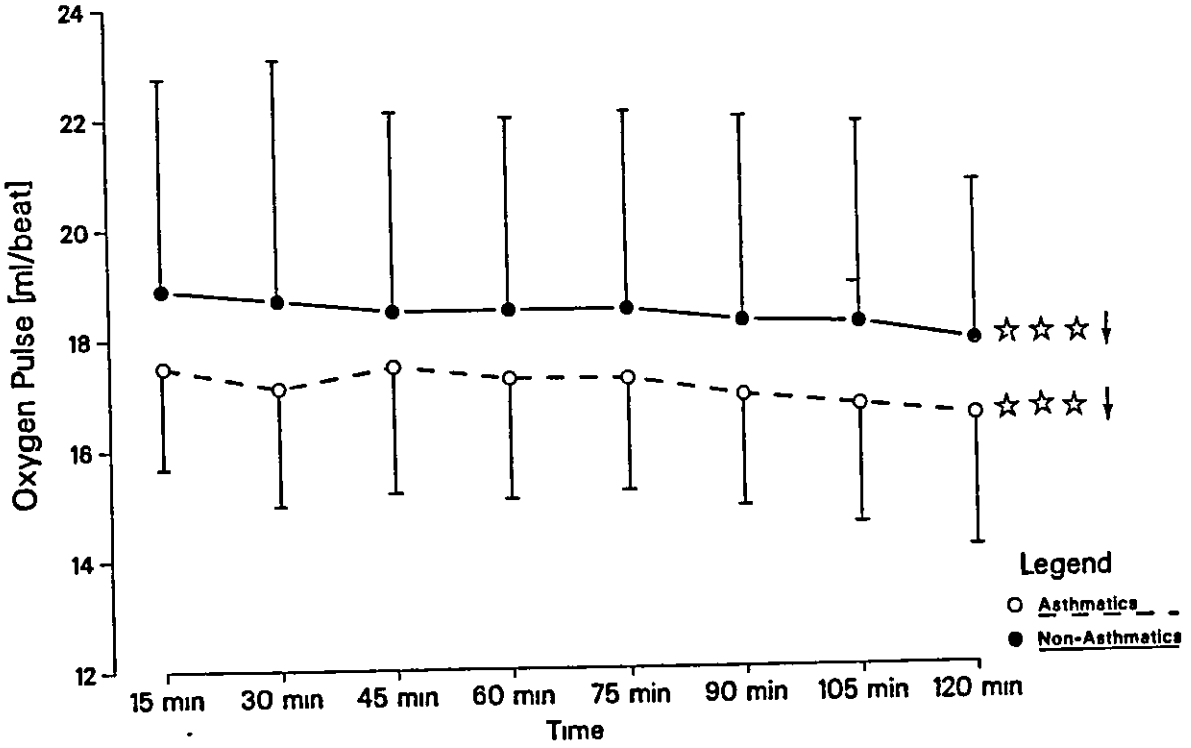


Figure 7.11. The oxygen pulse during the 2 hour run at 70% VO_2 max, for the asthmatic and non-asthmatic groups.

Denotes significant change over time: ☆☆☆ $p<0.001$

7.4 Discussion.

The cardio-respiratory and metabolic responses to the two hour treadmill run at 70% VO_2 max were similar, both absolutely and over time, for the asthmatics taking pre-exercise medication and the non-asthmatics. However, there were subtle differences in the pattern of breathing between the two groups which may be associated with airflow obstruction. The response of the lung function to the prolonged run was also different for the asthmatic and non-asthmatic groups.

7.4.1 Cardio-Respiratory Responses to the 2 Hour Run.

The selection of the running speed to elicit 70% VO_2 max was successfully obtained for both groups. The oxygen uptake, however, showed significant increases over time for both the asthmatic (7.1%) and non-asthmatic (3.6%) groups. This increase in the oxygen demands as running is prolonged is consistent with the results from other investigators (Saltin and Stenberg 1964, Martin et al 1981, MacDougall et al 1974). A variety of reasons have been put forward to explain this apparent decrease in mechanical efficiency during prolonged exercise. Firstly, if there is an increased utilisation of fat to meet the energy demands as exercise is prolonged, an increased amount of oxygen would be required for its metabolism and energy release (Hartley 1977). However, the respiratory exchange ratio did not show a downward trend for either group, indicating that an increase in fat metabolism over time is not a likely explanation for the increase in oxygen uptake. Secondly, an increased energy need for peripheral circulation and sweat gland activity for thermoregulatory control as exercise is prolonged may lead to a higher oxygen uptake (MacDougall 1974). However, it is impossible to assess the oxygen cost for these activities. Thirdly, a loss of mechanical coordination with fatigue as exercise is prolonged, will lead to the recruitment of less efficient muscle fibres (Rowell 1969). Fourthly, increased energy demands of the respiratory muscles to supply a greater ventilation as exercise is prolonged, may increase the oxygen uptake. The increased airway obstruction during the 2 hour run for the asthmatic group, as implied by the lowering of the FEV_1, may lead to a higher oxygen uptake of the respiratory muscles, which could explain why the asthmatics

experienced a slightly greater increase in oxygen uptake, than the non-asthmatic group.

The absolute ventilation rate, while running at 70% VO_2 max, was lower for the asthmatic group compared to the non-asthmatic group. However, there was no difference between the groups when the ventilation rate was expressed as a percentage of maximum ventilation. The asthmatic and non-asthmatic groups both showed 'ventilatory drift' over the 2 hour run, as illustrated by the trend for significant increases in ventilation rate over time. The 'ventilatory drift' was not as pronounced as that observed by one investigation (Hanson et al 1982), although two studies have not observed any change during prolonged steady state running (Sawka et al 1980, Gass et al 1983). Martin et al (1981) suggested that such increased ventilation led to more 'wasteful breathing' for a given gas exchange. However, both the asthmatic and non-asthmatic groups showed not only an increased ventilation, but also an increased oxygen uptake, so that the ventilatory equivalent was essentially unaltered over the 2 hour period. This agrees with the work of Martin et al (1981) who suggested that an increase in ventilation rate with time may be attributed to the increased metabolic demands of the muscle, and that the increase in ventilation is a consequence of the increased oxygen uptake.

The 'ventilatory drift' over the 2 hour run was not as marked for the asthmatics (4.6%) compared to the non-asthmatics (6.9%). The increased ventilation in the non-asthmatic group was associated with a significant increase in breathing frequency, whilst tidal volume was significantly reduced over time. This is consistent with the ventilatory pattern described by Hanson et al (1982) for non-asthmatics during prolonged running. The smaller, but significant increase in the ventilation rate over time for the asthmatic group, was associated with a significant increase in breathing frequency with no change in tidal volume. It is postulated that the asthmatic group have to maintain more 'control' over their breathing patterns because, due to airway obstruction, asthmatics find it more difficult to increase breathing frequency if ventilation is to be 'effective'.

The asthmatic and non-asthmatic groups have similar absolute tidal volumes, although the frequency of breathing is slower for the asthmatic group. Indeed, the tidal volume expressed as a percentage of the FEV_1 was higher for the asthmatics compared to the non-asthmatics, and thus to attain the same tidal volume to allow efficient gas

exchange, breathing frequency is slower. The ventilatory equivalent was similar for both groups, thus indicating that the pattern of breathing developed by the asthmatics is as efficient at gas exchange as that of the non-asthmatics. This slower pattern of breathing 'developed' by the asthmatic is in all probability an adaptation to overcome their airway obstruction.

The asthmatic group had a lower heart rate during the 2 hour run compared to the non-asthmatics. However, when expressed as a percentage of the maximum heart rate there were no differences between the groups. In addition, both groups showed 'cardio-vascular drift' as indicated by a highly significant increase in heart rate of 17 and 13 beats per minute over the 2 hours for the asthmatic and non-asthmatic groups, respectively. These increases in heart rate were similar to that observed by Sawka et al (1979) for well trained runners. This increase in heart rate is thought not to be due to increased exercise intensity, but due to the shunting of blood to the subcutaneous vessels for thermoregulation (Rowell 1974).

To offset the loss of fluid associated with the thermoregulatory process of sweating the intake of fluid is encouraged during exercise. However, in the light of the recommendation by Sinclair et al (1983) to drink 1 litre per hour of endurance exercise, the asthmatics and non-asthmatics drank very little water during the 2 hour run. Inspite of this low fluid intake, dehydration, defined as a reduction in body weight of 4% (Astrand and Saltin 1964), was not experienced by any athlete, asthmatic or non-asthmatic. However, it is the reduction in plasma volume as a result of the fluid loss that may have profound physiological consequence. Although Myhre et al (1984) stated that plasma volume will be maintained as long as the water deficit is limited to approximately 4% of body weight, both groups did experience a reduction in plasma volume. The observed changes in the plasma volume were of a similar magnitude to those previously reported by Sawka et al (1980) for trained athletes after similar exercise. A fall in plasma volume leads to a reduction in the ventricular filling pressure, which in turn will reduce the venous return and the stroke volume. Thus in order to maintain the cardiac output, a compensatory rise in heart rate has been observed during the 2 hour run for both groups.

The similar cardio-respiratory responses, both absolutely and over time, to the 2 hour constant paced run at 70% VO_2 max would suggest

that well trained asthmatics are not at an inherent disadvantage in endurance running compared to non-asthmatics. The slower breathing frequency during running at the same $\%VO_2$ max may be an adaptive response to the airflow obstruction of the asthmatic.

7.4.2 Metabolic Responses to the 2 Hour Run.

The asthmatics and non-asthmatics have, in addition, shown similar metabolic responses both absolutely and over time.

With increased duration of exercise, as glycogen stores are reduced, a shift towards the metabolism of fat may occur. Over the 2 hour run, however, there was no significant reduction in the respiratory exchange ratio (R) for either group, indicating that the glycogen stores were not markedly reduced with the 2 hour run at 70% VO_2 max. In addition, there was no difference in the response of the R value between the groups. Thus the similar respiratory exchange ratio between the groups, reflects a similar ability to metabolise carbohydrate and free fatty acids of the asthmatic and non-asthmatic athletes. The results of the present study do not support the work of Barboriak et al (1973) which suggested that asthmatics have an impaired ability to metabolise free fatty acids.

There was no apparent difference in the response of blood glucose during the 2 hour run for the asthmatic and non-asthmatic groups. In addition there was no evidence of hypoglycaemia at the end of exercise as defined by a blood glucose concentration of less than 2.5mM (Felig et al 1982), for any of these athletes. This agrees with the work of Hall et al (1983) and Costill (1970a) who have not observed hypoglycaemia during prolonged running. Indeed, it has been suggested that trained athletes have a better glucose tolerance than untrained individuals owing to a greater sensitivity of the cell membranes to insulin, enabling a better regulation of blood glucose.

Blood lactate concentrations were similar for the well-trained asthmatic and non-asthmatic athletes running at the same relative work load. This finding supports the suggestions of McFadden (1984a), that any differences in the blood lactate concentration observed between asthmatic and non-asthmatic groups, are more likely to be due to differences in fitness rather than the asthma per se. The blood lactate concentrations were low for the entire 2 hour run, with no significant increase or decrease over time for either group,

indicating that blood lactate is not necessarily associated with fatigue in endurance running under these conditions.

There were no differences in the response of the catecholamines, for the asthmatic and non-asthmatic groups. Both groups showed a five fold increases from resting values for adrenaline and noradrenaline over the 2 hour run. Thus, although previous investigators have suggested that asthmatics have impaired adrenal response to exercise (Barnes 1981b, Reinhardt et al 1980), the results of this study suggest that the response of the asthmatic taking pre-exercise medication, is not different from non-asthmatics exercising at the same relative exercise intensity.

The similar responses to the 2 hour run at the same relative exercise intensity documented above, again give support to the argument that the asthmatic is not metabolically disadvantaged when participating in prolonged running.

7.4.3 The Response of the Lung Function to the 2 Hour Run.

Although there were no major differences in the cardio-respiratory and metabolic responses to the 2 hour run, there were differences in the response of the lung function between the asthmatic and non-asthmatic groups.

Despite pre-exercise medication, two of the asthmatics experienced a large fall in the FEV_1 after the 2 hour run. The fall in the FEV_1 was similar to that experienced following short term (8 minutes) exercise when non-medicated. The suggestion of Silverman and Anderson (1972) that EIA may decline with increasing duration of exercise, thus cannot be supported. Therefore, for these two asthmatics the medication taken prior to the 2 hour run was not adequate for the severity of their asthma. This could be due to a function of either the dosage or the duration of action of the medication. Neither athlete experienced the asthma during the run, and thus it was not possible to examine the effect of bronchoconstriction on the physiological responses during exercise.

7.5 Summary.

The asthmatic and non-asthmatic groups showed similar cardiac, ventilatory and metabolic responses to a prolonged run at 70% VO_2 max. The asthmatics, however, had slower breathing frequencies than the non-asthmatics. This is likely to be an adaptation to the airway obstruction which helps the asthmatic to participate alongside the non-asthmatic in endurance running. The physiological responses during prolonged constant speed running do not suggest any reason why the performance of the asthmatic should be impaired. However, the fall in the FEV_1 after exercise of two of the asthmatics, despite taking pre-exercise medication, implies that the asthmatic is at some risk when participating in endurance running.

CHAPTER 8

THE EFFECT OF ENDURANCE RUNNING TRAINING ON ASTHMATIC ADULTS.

8.1 Introduction.

Asthmatics may have an impaired maximal response to exercise as indicated by the comparison between the untrained asthmatic and non-asthmatic groups in Chapter 4. A fear of provoking exercise-induced asthma may also lead to inactivity, which as for non-asthmatics, would impair the cardio-respiratory response to maximal exercise (McFadden 1984a). However, the results of Chapter 5 would suggest that asthma does not preclude the development of good endurance fitness with the appropriate training. Indeed, physical training, with the use of pre-exercise asthmatic medication, is now recommended in the management of asthma to improve the cardio-respiratory fitness (Holgate 1983).

Studies on the effect of physical training on the asthmatic adult have illustrated the safety and improvement in physical fitness after training comprising general sports and calisthenics (Itkin and Nacman 1966); circuit training (Hirt 1964); and high intensity, intermittent exercise (Afzelius-Frisk et al 1977). However, such activities are more likely to lead to gains in strength and muscular coordination rather than in cardio-respiratory fitness, compared to activity of a continuous nature. Although the beneficial effects of continuous activities, such as endurance swimming (Fitch et al 1976) and endurance running (Nickerson et al 1983), have been documented for asthmatic children, the benefit and safety of continuous exercise have not been examined for previously sedentary asthmatic adults.

Inspite of the participation of a number of asthmatics in endurance running, it is the least preferred sport for several reasons. Activity of a continuous nature, such as distance running, is more likely to provoke EIA than activity of an intermittent nature (Morton et al 1982). In addition, the incidence and severity of EIA is greater after running when compared to other forms of exercise such as swimming and cycling (Bar-Yishay et al 1982). However, there is no difference in the severity of EIA for running and swimming when these activities are compared using pre-exercise medication (Schnall and Landau 1982).

The training intensity required to improve the cardio-respiratory

fitness may provoke EIA in the untreated asthmatic. Therefore, effective training intensities may be hindered by the EIA they provoke (Svenonius et al 1983). To prevent training being limited by EIA, the asthmatics should therefore be encouraged to take appropriate medication prior to training sessions (Oseid and Haaland 1978).

The rise in both the rate and depth of ventilation with physical activity is a major cause of exercise-induced asthma in asthmatic individuals. Physical training may reduce the ventilation rate at submaximal running speeds in the non-asthmatic (Astrand and Rodahl 1977). If asthmatics show such adaptations to physical training, a beneficial effect on the condition of EIA is possible, although previous investigations have yielded conflicting results. Some reports have suggested a reduction in the severity of EIA (Oseid and Haaland 1978, Henriksen et al 1981b) whilst others have reported no change (Nickerson et al 1983, Bundgaard et al 1982b).

The present study examined the effect of short-term endurance running training, with pre-exercise medication, on the cardio-respiratory fitness and the degree of EIA in asthmatic adults. Their responses were compared to a group of non-asthmatic adults performing similar training. The duration of the training was selected as only 5 weeks because the major physiological changes are shown to take place in the first few weeks of training.

8.2 Methods.

8.2.1 Subjects.

Sixteen asthmatic adults, 18 to 38 years (mean age $\pm$ SD, 24.9 $\pm$ 7.4 years) comprising 9 males and 7 females volunteered for the study to investigate the effect of endurance running training on the untrained asthmatic. Six healthy, but relatively untrained students with no previous history of asthma, served as the control group. None of the subjects, asthmatic or non-asthmatic, were currently engaged in endurance running training, although several of the subjects from each group took part in some form of activity.

8.2.2 Pre- and Post-Training Laboratory Testing.

To document the physiological changes associated with endurance running training, the three treadmill tests described in the General Methods (Chapter 3), were performed by each subject before and after the five week period of treadmill running training. These tests were the maximum oxygen uptake test, the 'speed-lactate' test at a series of submaximal speeds and the test for EIA. The test without medication was performed at the same absolute running speed pre- and post-training.

A fourth treadmill test was a two mile (3.2Km) treadmill time trial, performed before and after the period of running training. For this test, the speed of the treadmill was controlled by the subject using a hand held switch. Details of the running speed, distance covered and time elapsed were visible on the screen of a microcomputer. Expired air collections and heart rate recordings were made every half mile (0.8Km). From the oxygen uptake data, an average $\%VO_2$ max utilised throughout the run was calculated.

8.2.3 Endurance Running Training.

The endurance running training was performed three times per week on the treadmill for a 5 week period. The speed of the treadmill could be altered using a hand held switch, so that individuals trained at 'self selected' speeds. Subjects were encouraged to run at a continuous pace aiming to improve their 'endurance', as represented by distance covered or training time. For each training session the distance run, time elapsed and the running speed were available on the screen of a microcomputer, as used for the two-mile time trial. The use of pre-exercise asthmatic medication prior to each training session was encouraged.

For each training session, the lung function was recorded pre-exercise (with and without medication) and at 7-10 minutes post exercise. The severity of the asthma was calculated as the percentage fall of FEV_1 from the baseline readings recorded without asthmatic medication.

Subjects were encouraged not to alter their habitual level of activity, and to perform the running training in addition to other activities in which they normally participated. Furthermore, subjects were asked not to alter their prophylactic asthmatic treatment for the duration of the study.

8.2.4 Diary Cards.

Daily diary cards recording morning and evening peak flows before their medication, the severity of asthma that day, and th use of asthmatic medication were completed by a number of asthmatics during the training study.

8.2.5 Statistics.

A paired 't' test was used to examine the significance of any changes after training for the asthmatic and non-asthmatic groups. The Pearson product moment correlation was employed to examine any relationships between the training-induced changes.

8.3 Results.

8.3.1 Subject Withdrawals.

Sixteen asthmatic adults (9 males, 7 females) started the running training study, whereas only nine (3 males, 6 females) completed the entire programme. The nine who completed the study were not significantly different from the group of seven who did not, in terms of maximum oxygen uptake or severity of asthma. The VO_2 max for the group completing the study was 40.9 $\pm$ 8.2 $ml.kg.^{-1}min^{-1}$, which was slightly lower than the value observed for those not completing the study (45.3 $\pm$ 7.3 $ml.kg.^{-1}min^{-1}$). The severity of EIA, after the running test without medication, was however less severe for those completing the study compared to those not completing the study, although the difference was not significant (26.4 $\pm$ 11.7 vs 38.3 $\pm$ 17.9 % fall FEV_1). Although one subject had to cease endurance running training due to an exacerbation of his asthma caused by infection, factors other than asthma accounted for the subject withdrawals. Lack of time (2), minor injuries (2) and poor motivation (2) were the major reasons for the reduction in subject numbers.

8.3.2 Physical Characteristics of the Subjects.

The physical characteristics for the nine asthmatic and six non-asthmatic subjects who completed the study are shown in Table 8.1. The FEV_1 for the asthmatic group was 87.6% of the predicted normal values. In accord with the categorisation of the severity of asthma by Cropp and Tanakawa (1977), the abnormalities in the resting pulmonary

function were categorised as 'normal' in 6, 'mild' in 2 and 'moderate' in 1. The non-asthmatics had 'normal' lung function in accord with the above categorisation.

Table 8.2 shows the duration of asthma, current medication, and the severity of EIA for the 9 asthmatics who completed the training study. Each subject demonstrated EIA as defined as greater than 10% fall in the post-exercise FEV_1 (Anderson et al 1983), with the group mean showing a 26.4% fall in the FEV_1. Seven out of the nine asthmatics were taking regular maintenance and pre-exercise asthmatic medication, although the other two did not take any regular or pre-exercise medication for their asthma.

8.3.3 Endurance Running Training - Quantity and Quality.

Details of the quantity and quality of training for each subject are shown in Table 8.3. The total distance run during the 5 week training period for the asthmatic group (35.4 $\pm$ 15.9 miles or 57.0 $\pm$ 25.6 km) was not significantly different from that of the non-asthmatic group (38.3 $\pm$ 7.0 miles or 61.6 $\pm$ 11.3). In addition, the average training intensity, expressed as a percentage of the pre-training VO_2 max, was not significantly different for the two groups. As a result of this training various physiological changes were recorded:

8.3.4 Physiological Changes after Endurance Running Training.

(a) Maximal Test. Table 8.4 shows the results from the maximum oxygen uptake test. Run time (mins) to 'exhaustion' increased significantly for both the asthmatic and non-asthmatic groups. Maximum oxygen uptake, increased significantly ($p<0.05$) by approximately 7 percent for both groups, although there was a large range of improvement from no change up to 24% as a result of the training. There were no statistically significant changes in maximum ventilation and maximum heart rate.

(b) Submaximal Test. Blood lactate concentration was reduced at a range of submaximal running speeds for the asthmatic group (Figure 8.1a), but only at the fastest running speed for the non-asthmatic group (Figure 8.1b). However, the blood lactate concentrations expressed in relation to the new VO_2 max, were not different for

either group (Figures 8.2a and 8.2b). To analyse these changes further, the running speed, oxygen uptake, and $\%VO_2$ max at a reference blood lactate concentration of 2mM were calculated, before and after training for each subject (Table 8.5). The running speed at which 2mM blood lactate accumulated had increased significantly after training for the asthmatics ($p<0.01$). This compares very favourably with the smaller and non-significant increase of the non-asthmatic group. However, the $\%VO_2$ max at which 2mM blood lactate accumulates was not significantly different for either the asthmatics or non-asthmatics after training.

In addition the asthmatic group showed a significant ($p<0.01$) decrease in heart rate at submaximal running speeds after training, whereas the non-asthmatic group only showed a significant change at the highest running speed (Figures 8.3a and 8.3b). The ventilation rates were slightly reduced over the range of submaximal speeds, although the differences were not significant for either the asthmatics or non-asthmatics (Figures 8.4a and 8.4b). In addition, the oxygen uptake at a range of submaximal running speeds were identical before and after training for both groups (Figures 8.5a and 8.5b). Subjectively, as rated by the Borg (1973) scale, the submaximal speeds were perceived as significantly easier by the asthmatic group after training, whereas no difference was recorded by the non-asthmatic group.

(c) 3.2 Km (2 miles) Performance Test. The results from the 3.2Km performance test are shown in Table 8.6. The asthmatic and non-asthmatic groups significantly ($p<0.01$) reduced their 3.2Km treadmill performance time. In addition to being able to run the 2 miles faster (Figure 8.6a), both groups were able to sustain a significantly higher $\%VO_2$ max after training (Figure 8.6b).

(d) Exercise-Induced Asthma. Table 8.7 shows the physiological demands of the running test performed without asthmatic medication by the asthmatic group. The test was performed at the same absolute speed before and after training. However, the test demanded a significantly lower $\%VO_2$ max, ventilation and heart rate after training, thus reflecting the improved fitness of the asthmatic group. However, the degree of EIA experienced after running was not significantly changed (Table 8.8), the greatest percent fall in the FEV_1 being 26.4 $\pm$ 11.6

% pre-training, compared to 23.0 ± 17.5 % post-training (Figure 8.7). An examination of the individual data revealed that 7 out of the 9 asthmatics showed a reduction in the degree of EIA. However, the other 2 asthmatics showed large increases in the severity of EIA which may have been due to the adverse affect of a period of cold weather, or more probably due to modifications in the asthmatic treatment of these two individuals. One of the asthmatics (6), under the supervision of her general practitioner, stopped taking beclomethasone-dipropionate (Becotide) for two weeks in the middle of the training period. Although she restarted the Becotide prior to the post-training tests, the interuption of treatment seemed to adversely affect her asthma. The other asthmatic subject experiencing an increase in the severity of EIA (4) voluntarily reduced the daily and pre-exercise use of sodium cromoglycate. Instead she prefered to use salbutamol, as this gave more immediate relief. The alteration in the treatment regimes of these two asthmatics may explain their greater severity of EIA when running without medication.

The changes in the degree of EIA after training could not be explained by changes in VO_2 max ($r=0.184$), by changes in the ventilation rate required to complete the non-medicated running test ($r=-0.300$), or by changes in blood lactate accumulation at submaximal running speeds ($r=-0.278$).

(e) Lung Function. Table 8.9 shows lung function parameters of VC, FEV_1, $FEV_1/FVC\%$ and PEFR, of the asthmatic and non-asthmatic groups before and after training. There was no significant difference in any of these parameters after training for either the asthmatic or non-asthmatic groups.

8.3.5 Responses of the Lung Function to Endurance Running Training Sessions.

Table 8.10 shows the pre-exercise medication taken before each training session. In addition, the mean FEV_1 recorded before (with and without pre-exercise medication) and after each training session is shown for each asthmatic. The two asthmatics not taking pre-exercise medication, showed a significant degree of EIA. In addition, three asthmatics on pre-exercise medication showed significant decreases in FEV_1 after training sessions, although the severity of EIA was not as great as when running without medication. Therefore, it is evident

that the pre-exercise medication taken by these two subjects did not totally inhibit an asthmatic response.

The changes in the FEV_1 values after each training session for the asthmatics are illustrated as a histogram in Figure 8.8, showing a 'normal' type distribution. On a few occasions the fall in the FEV_1 after training was marked. The EIA provoked was always successfully reversed by the use of salbutamol taken from an inhaler or from a 'spacer' device.

One subject (3) performed half of his training sessions on the treadmill and half of his training sessions outside, all without pre-exercise asthmatic medication. The severity of EIA was greater when training outdoors compared to when training indoors (20.9 $\pm$ 10.2 compared to 8.4 $\pm$ 4.8 % fall in FEV_1).

8.3.6 Diary Cards

Unfortunately only a few subjects completed their daily diary cards for the duration of the study. However, one subject (5) completed her diary cards not only for the duration of the training study, but for several weeks afterwards during which she continued to train. The morning and evening PEFR recordings are shown (Figure 8.9a), along with the asthmatic medication used (Figure 8.9b). It is evident that as time progressed, the absolute PEFR increased along with a reduction in the diurnal variation, which was accompanied by a reduction in the medication taken. This may or may not be attributed to the programme of running training.

Table 8.1. The age, height, weight and the FEV_1 of the asthmatic and non-asthmatic subjects, who completed the training study.

Subject	Age (yrs)	Height (m)	Weight (kg)	FEV_1 (l BTPS)	FEV_1 % Predicted
Asthmatics					
Males					
1	22	1.71	58.3	3.45	75.5
2	18	1.81	62.6	4.28	81.2
3	18	1.61	61.1	3.95	98.5
Females					
4	37	1.75	77.4	2.92	89.8
5	24	1.72	62.3	3.57	102.9
6	24	1.66	51.1	2.95	89.9
7	19	1.66	54.7	3.64	108.3
8	34	1.74	74.0	2.38	74.4
9	35	1.65	52.7	2.00	67.6
mean	25.7	1.70	61.6	3.24	87.6
±SD	7.6	0.08	9.0	0.74	13.9
Non-Asthmatics					
Males					
1	18	1.80	62.6	4.4	87.6
Females					
2	20	1.62	65.5	3.65	113.7
3	21	1.65	60.1	3.40	103.3
4	20	1.57	55.2	2.65	86.6
5	20	1.60	58.0	3.20	101.6
6	19	1.65	65.9	4.02	120.7
mean	19.7	1.65	61.0	3.52	102.3
±SD	1.0	0.06	4.0	0.60	13.7

Table 8.2. The duration of asthma, daily medication and the severity of EIA for the asthmatics who completed the training study.

Subject	Years of Asthma	Asthmatic Medication	EIA % Fall FEV_1
Males			
1	21	Intal Co.	20.3
2	9	None	18.2
3	9	None	19.0
Females			
4	30	DSCG, Salbutamol	39.7
5	23	Intal Co., Salbutamol	30.0
6	9	Beclomethasone dipropionate Salbutamol	10.2
7	1	Salbutamol	43.7
8	30	Intal Co.	19.3
9	30	Intal Co., Salbutamol	37.5
mean	18.0		26.4
±SD	11.2		11.6

DSCG is Disodium cromoglycate [Intal].
Intal Co. is DSCG with isoprenalin sulphate.

Table 8.3. The distance, duration and intensity of endurance running in the training study, for the asthmatic and non-asthmatic subjects.

Subject	No. of Sessions	Total Dist. Run (miles)	Total Time Run (min)	Speed ($m.s^{-1}$)	Intensity $\%VO_2$ max
Asthmatics					
Males					
1	13	53.7	459	3.13	97.0
2	13	36.2	340	2.86	95.6
3	13	58.5	391	4.01	75.2
Females					
4	13	23.3	264	2.36	92.1
5	13	48.9	480	2.74	86.0
6	13	20.8	219	2.54	90.9
7	9	26.8	225	3.19	76.2
8	13	37.8	403	2.52	86.8
9	10	12.5	167	2.00	64.4
mean	12.2	35.4	328	2.82	83.8
±SD	1.6	15.9	113	0.58	10.1
Non-Asthmatics					
Males					
1	13	42.5	306	3.73	76.9
Females					
2	13	45.1	428	2.82	75.1
3	13	31.4	357	2.36	91.9
4	13	46.2	445	2.78	80.7
5	13	33.2	324	2.75	74.7
6	11	31.7	281	3.03	83.2
mean	12.7	38.3	357	2.91	80.4
±SD	0.8	7.0	67	0.46	6.5

Table 8.4. The physiological responses obtained with the maximum oxygen uptake test, pre and post training for the asthmatic and non-asthmatic subjects.

Subject	Run Time (min)		VO_2 max ($ml.kg.^{-1}min^{-1}$)		V_E max ($l.min^{-1}$)		HR max ($b.min^{-1}$)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Asthmatics								
Males								
1	7.50	11.17	44.0	54.5	106.3	109.8	193	180
2	8.00	10.83	43.6	46.8	83.5	77.8	180	177
3	10.17	11.00	57.4	60.6	107.8	125.7	173	171
Females								
4	5.00	7.50	30.5	35.2	79.1	82.0	178	173
5	8.83	10.75	40.7	41.4	90.3	92.4	190	188
6	7.50	7.50	37.9	39.4	69.3	72.8	189	187
7	8.00	8.42	46.4	43.6	76.5	77.4	180	185
8	8.00	10.25	33.2	36.7	55.3	66.8	172	176
9	7.58	8.75	34.8	36.0	57.6	60.4	190	191
mean	7.93	9.57**	41.0	43.8*	81.5	85.0	184	181
±SD	1.40	1.53	8.2	8.8	19.4	21.0	8	7
Non-Asthmatics								
Males								
1	11.75	14.08	57.8	63.8	126.7	140.7	198	195
Females								
2	7.50	7.83	44.8	45.6	91.3	89.6	188	190
3	8.00	10.17	33.9	38.7	66.0	66.7	192	189
4	7.83	8.75	38.8	42.0	69.2	79.2	189	188
5	7.00	7.83	39.7	42.6	85.8	89.3	198	194
6	7.83	7.83	42.9	44.2	111.2	108.9	189	192
mean	8.32	9.42*	43.0	46.0*	93.1	95.7	192	191
±SD	1.72	2.46	8.2	9.1	22.3	26.0	6	3

Significant difference pre and post training: * $p<0.05$, ** $p<0.01$

Table 8.5. The running speed, oxygen uptake, and $\%VO_2$ max at a blood lactate concentration of 2mM, pre and post training, for the asthmatic and non-asthmatic subjects.

Subject	Speed ($m.s^{-1}$)		VO_2 ($ml.kg.^{-1}min^{-1}$)		$\%VO_2$ max	
	Pre	Post	Pre	Post	Pre	Post
Asthmatics						
Males						
1	1.90	2.40	28.5	31.8	64.8	58.4
2	2.21	2.87	31.2	39.6	71.7	84.8
3	3.60	3.59	37.8	40.6	65.8	67.1
Females						
4	1.66	1.86	17.3	20.2	56.6	57.2
5	2.19	2.35	30.0	31.2	73.8	75.4
6	1.93	1.95	24.8	23.1	65.5	58.7
7	2.69	2.87	29.4	33.3	63.4	76.3
8	2.53	2.70	28.9	30.6	87.2	83.5
9	1.90	2.24	20.1	26.4	57.9	73.2
mean	2.29	2.54**	27.6	30.8*	67.4	70.5
±SD	0.59	0.54	6.1	6.8	9.3	10.7
Non-Asthmatics						
Males						
1	3.15	3.62	36.9	40.6	63.8	63.5
Females						
2	2.36	2.59	28.5	32.4	63.5	71.0
3	2.08	2.23	28.1	29.3	82.7	75.7
4	2.30	2.34	25.0	27.3	64.5	64.8
5	2.63	2.65	28.0	31.4	70.5	73.7
6	2.28	2.35	27.6	29.4	64.4	66.4
mean	2.47	2.63	29.0	31.7*	68.3	69.2
±SD	0.38	0.51	4.1	4.8	7.6	5.0

Significant difference pre and post training: * $p<0.05$, ** $p<0.01$

Table 8.6. Two mile time, the average oxygen cost and % VO_2 max utilised, pre and post training, for the asthmatic and non-asthmatic subjects.

2 Mile Time Trial

Subject	Run Time (min)		Speed ($m.s^{-1}$)		VO_2 ($ml.kg.^{-1}min^{-1}$)		% VO_2 Used	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Asthmatics								
Males								
1	19.08	14.83	2.81	3.62	39.4	48.4	88.9	88.8
2	17.43	16.02	3.08	3.35	42.8	43.1	93.2	92.2
3	13.07	11.85	4.10	4.53	47.1	56.5	82.0	93.3
Females								
4	26.00	21.18	2.07	2.53	27.6	33.3	90.5	94.6
5	18.75	18.50	2.86	2.90	35.2	37.7	86.6	91.4
6	21.25	19.50	2.52	2.75	30.8	34.2	81.3	86.9
7	17.02	15.67	3.15	3.42	39.6	39.5	85.3	90.6
8	22.08	19.17	2.43	2.80	26.7	32.4	80.6	88.2
9	28.00	26.68	1.91	2.01	24.5	26.7	70.5	74.0
mean	20.30	18.16**	2.77	3.10**	34.9	39.1**	84.9	88.9*
±SD	4.62	4.28	0.65	0.73	7.9	9.1	7.7	6.1
Non-Asthmatics								
Males								
1	14.13	12.02	3.80	4.46	45.6	55.3	78.8	86.6
Females								
2	18.67	16.67	2.87	3.22	37.7	41.4	84.1	90.8
3	22.25	20.18	2.41	2.66	31.6	37.5	93.2	96.9
4	18.92	16.33	2.84	3.29	33.1	39.2	85.4	95.2
5	20.18	18.83	2.66	2.85	32.1	36.1	80.8	84.8
6	16.68	15.67	3.21	3.42	37.1	39.3	86.6	88.8
mean	18.47	16.62*	2.97	3.32*	36.2	41.5**	84.8	90.5**
±SD	2.81	2.82	0.49	0.63	5.3	7.0	5.0	4.8

Significant difference pre and post training: ** $p<0.01$; * $p<0.05$

Table 8.7. The physiological demands of the test for EIA without asthmatic medication, pre and post training for the asthmatic group.

Subject	VO_2 ($ml.kg.^{-1}min^{-1}$)		$\%VO_2$ max		V_E ($l.min^{-1}$ BTPS)		HR ($b.min^{-1}$)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Asthmatics								
Males								
1	42.5	39.3	95.9	72.1	96.1	69.5	168	145
2	42.1	43.3	96.6	92.5	87.6	71.3	183	171
3	53.0	51.4	92.3	84.9	122.1	120.7	165	162
Females								
4	29.7	30.9	94.5	87.6	99.2	70.2	184	158
5	36.8	29.8	90.4	72.0	103.0	66.7	188	178
6	35.3	32.7	93.1	82.9	61.6	53.5	195	160
7	42.3	41.1	91.2	94.3	74.1	76.6	189	177
8	31.2	36.2	93.9	98.7	62.8	57.9	169	156
9	29.9	27.1	86.0	75.3	55.8	48.0	186	170
mean	38.1	36.9	92.7	84.5*	84.7	70.5*	181	164**
±SD	7.7	7.7	3.2	9.8	22.5	21.0	11	11

Significant difference pre and post training: * $p<0.05$, ** $p<0.01$

Table 8.8. The FEV_1 after the non-medicated running test, pre and post training, for the asthmatic group.

Subject	Pre-Ex FEV_1		Lowest Post-Ex FEV_1		% Fall in FEV_1	
	Pre	Post	Pre	Post	Pre	Post
Asthmatics						
Males						
1	3.45	3.52	2.75	3.12	20.3	11.4
2	4.28	4.63	3.50	4.29	18.2	7.3
3	3.95	3.58	3.20	3.41	19.0	4.8
Females						
4	2.92	2.86	1.76	1.04	39.7	63.6
5	3.57	3.47	2.50	2.70	30.0	22.2
6	2.95	2.90	2.65	2.17	10.2	25.2
7	3.64	3.45	2.05	2.70	43.7	27.8
8	2.38	2.14	1.92	1.77	19.3	17.3
9	2.00	1.86	1.25	1.35	37.5	27.4
mean	3.24	3.16	2.40	2.51	26.4	23.0
±SD	0.74	0.83	0.72	1.04	11.6	17.5

Table 8.9. The baseline pulmonary function from a dry spirometer [Vitalograph] and a peak flow meter, pre and post training, for the asthmatic and non-asthmatic groups.

Subject	VC (l BTPS)		FEV_1 (l BTPS)		$\%FEV_1$		PEFR ($l.min^{-1}$)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Asthmatics								
Males								
1	4.64	4.90	3.45	3.52	74.4	71.8	455	470
2	5.07	5.51	4.28	4.63	84.4	84.0	515	575
3	4.55	4.22	3.95	3.58	86.8	84.8	505	500
Females								
4	3.90	3.81	2.92	2.86	74.9	75.1	470	465
5	4.15	3.86	3.57	3.47	86.0	89.9	470	435
6	3.18	3.55	2.95	2.90	92.8	81.7	415	390
7	3.95	3.89	3.64	3.45	92.2	88.7	520	490
8	3.75	3.42	2.38	2.14	63.5	62.6	365	315
9	3.15	3.33	2.00	1.86	63.5	55.9	320	305
mean	4.04	4.05	3.24	3.16	79.8	77.2	448	438
±SD	0.65	0.72	0.74	0.83	11.3	11.8	69	88
Non-Asthmatics								
Males								
1	5.12	4.94	4.40	4.50	85.9	91.1	545	515
Females								
2	3.98	4.03	3.65	3.65	91.7	90.6	455	490
3	3.62	3.79	3.40	3.55	93.9	93.7	435	420
4	2.88	3.28	2.65	2.98	92.0	90.9	350	355
5	3.47	3.42	3.20	3.14	92.2	91.8	430	410
6	4.75	4.35	4.02	3.74	84.6	86.0	560	465
mean	4.00	3.97	3.55	3.59	90.1	90.7	463	443
±SD	0.67	0.62	0.62	0.53	3.8	2.6	79	59

Table 8.10. Pre-exercise medication and the incidence and severity of EIA after training sessions for the asthmatic group.

	Pre-exercise Medication	Mean FEV_1 for Training Pre-Ex	With Med.	Post Ex	EIA (% fall FEV_1)
Asthmatics					
Males					
1	DSCG	3.64	3.60	2.98***	-18.1%
2	-	4.58	-	4.14***	-9.6%
3	-	3.70	-	3.18***	-14.1%
Females					
4	DSCG & Salbutamol	2.78	2.89	2.71	-2.5%
5	Intal Co.	3.40	3.83	3.29	-3.2%
6	Salbutamol	3.69	3.73	3.46*	-6.2%
7	Salbutamol	2.92	3.15	2.99	+2.4%
8	Intal Co.	2.08	2.45	2.10	+1.0%
9	Salbutamol	2.02	2.29	1.64**	-18.8%

Significant difference between pre-exercise FEV_1 (without medication) and post-exercise FEV_1: *** $p<0.001$, ** $p<0.01$, * $p<0.05$.

Figure 8.1a

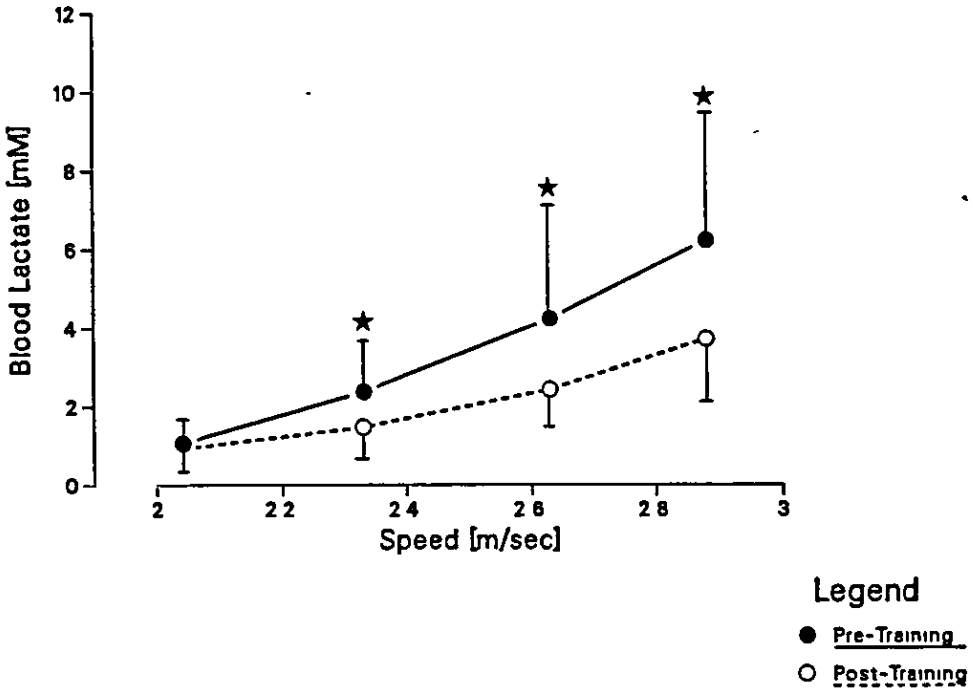
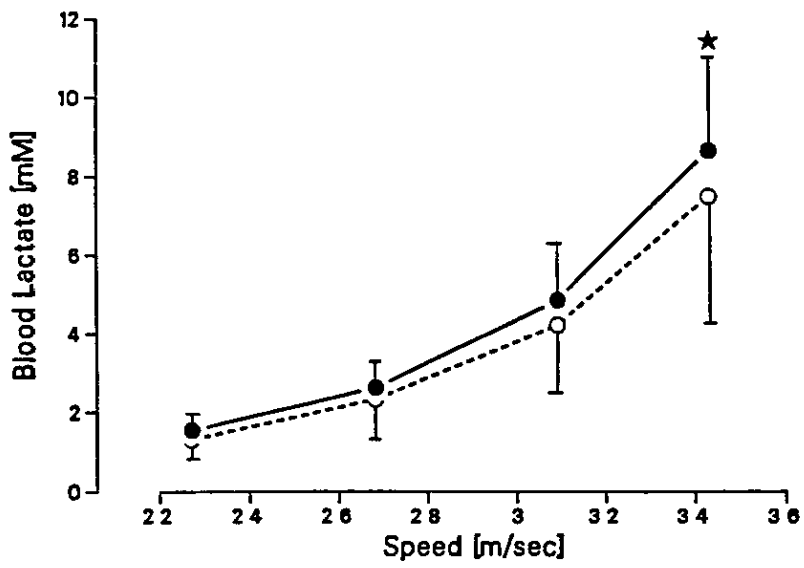


Figure 8.1b



Figures 8.1a and 8.1b. The blood lactate concentration at a range of submaximal running speeds, pre- and post-training, for the asthmatic (8.1a) and non-asthmatic groups (8.1b).

Significant difference pre- and post-training: ★ $p<0.05$

Figure 8.2a

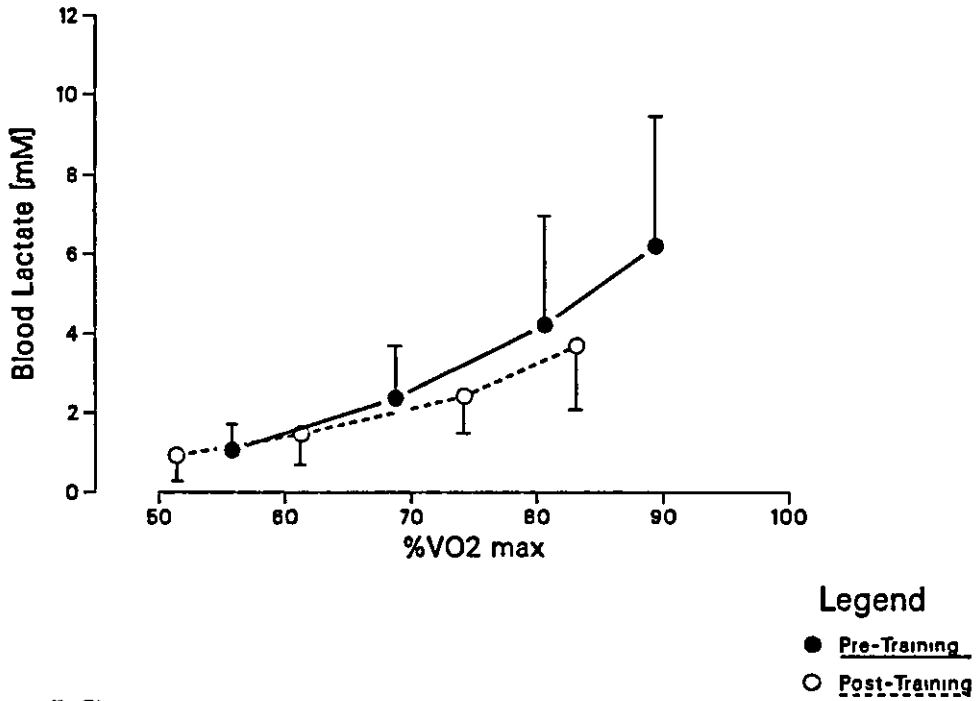
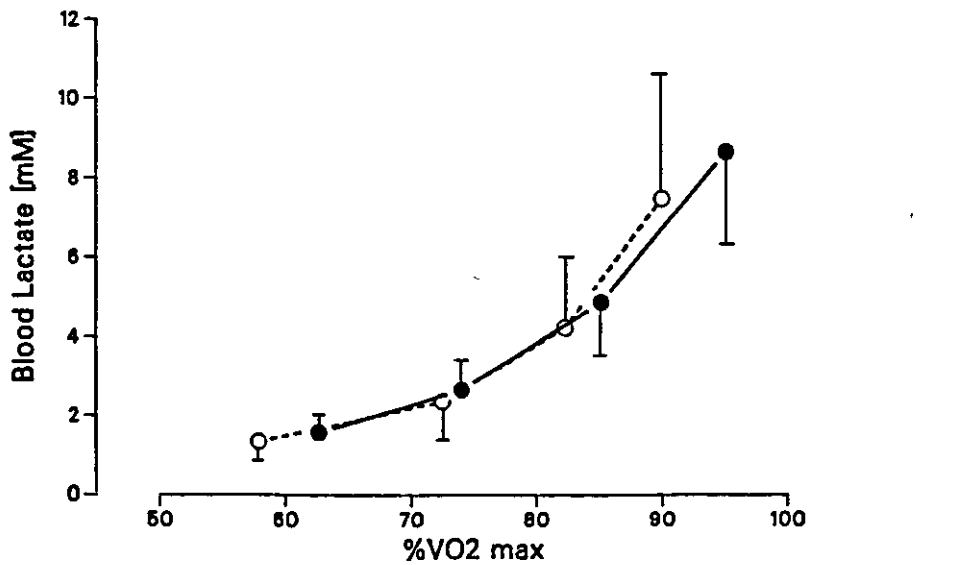


Figure 8.2b



Figures 8.2a and 8.2b. The blood lactate concentration at a range of submaximal running speeds expressed as a $\%VO_2$ max, pre- and post-training, for the asthmatic (8.2a) and non-asthmatic groups (8.2b).

Figure 8.3a

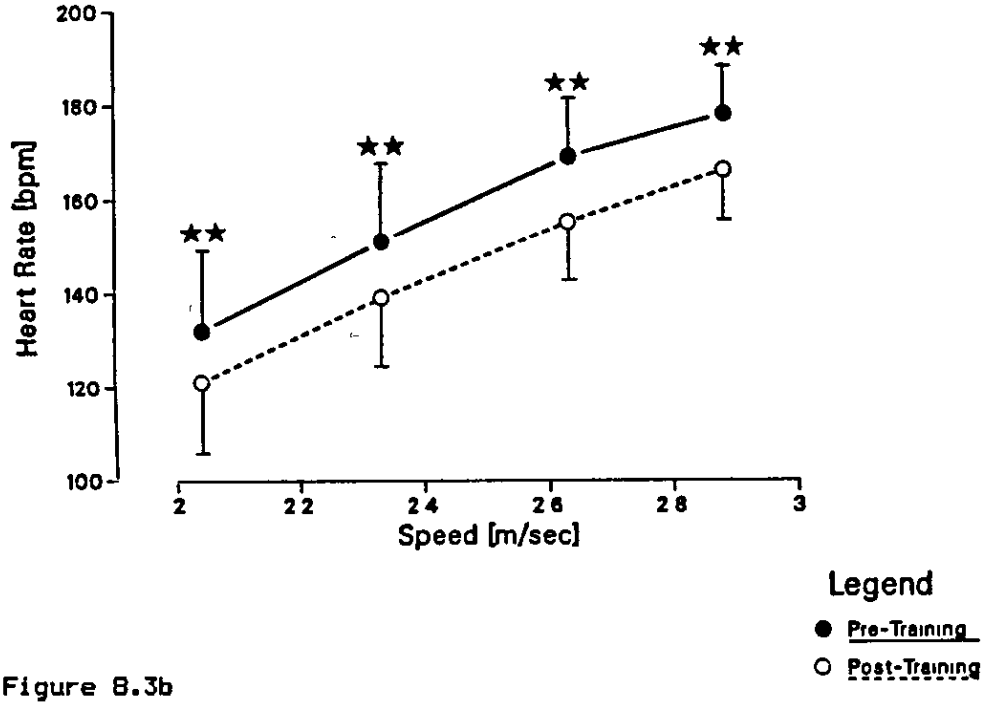
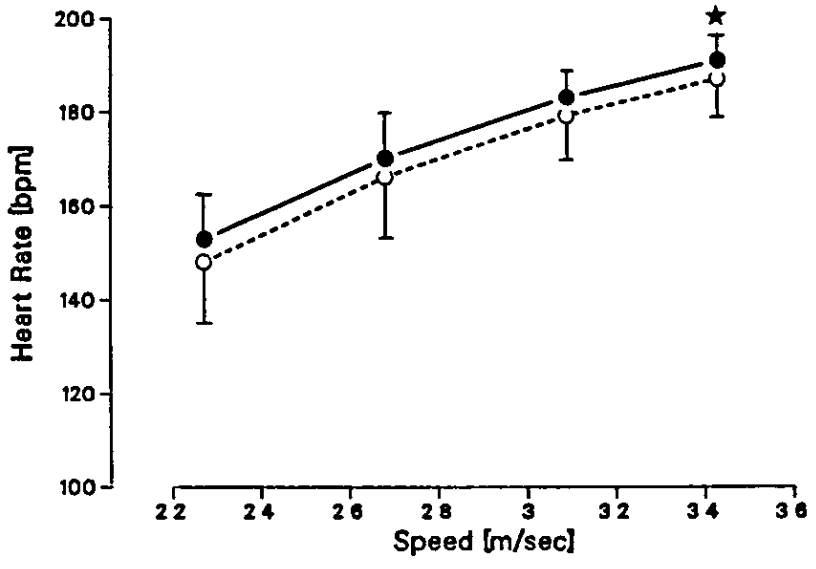


Figure 8.3b



Figures 8.3a and 8.3b. The heart rate at a range of submaximal running speeds, pre- and post-training, for the asthmatic (8.3a) and non-asthmatic groups (8.3b).

Significant difference pre- and post-training: ★ $p<0.05$; ★★ $p<0.01$

Figure 8.4a

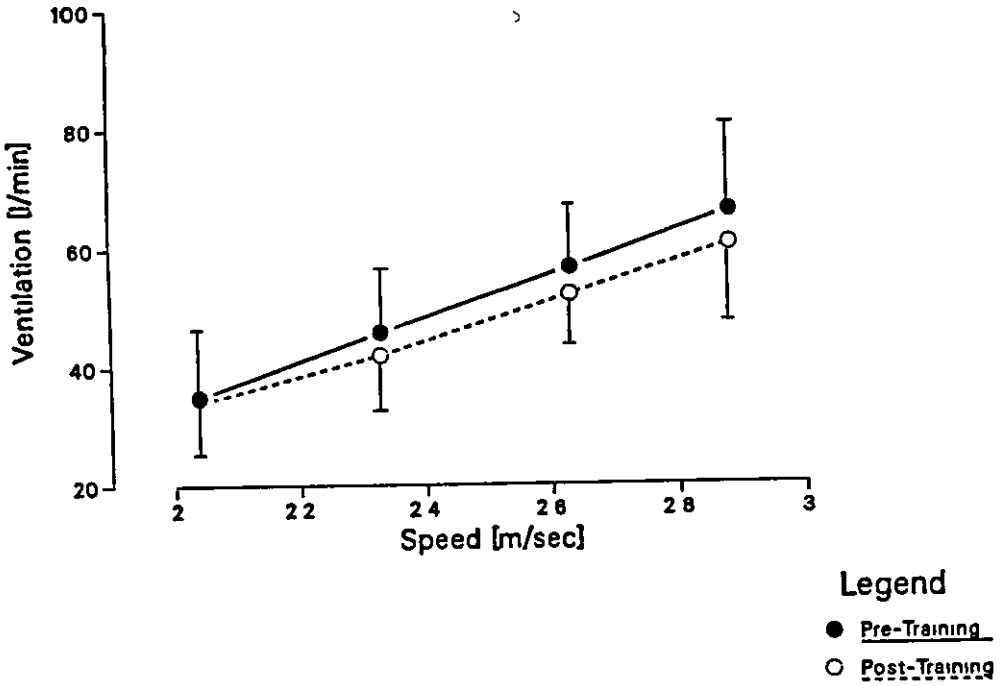
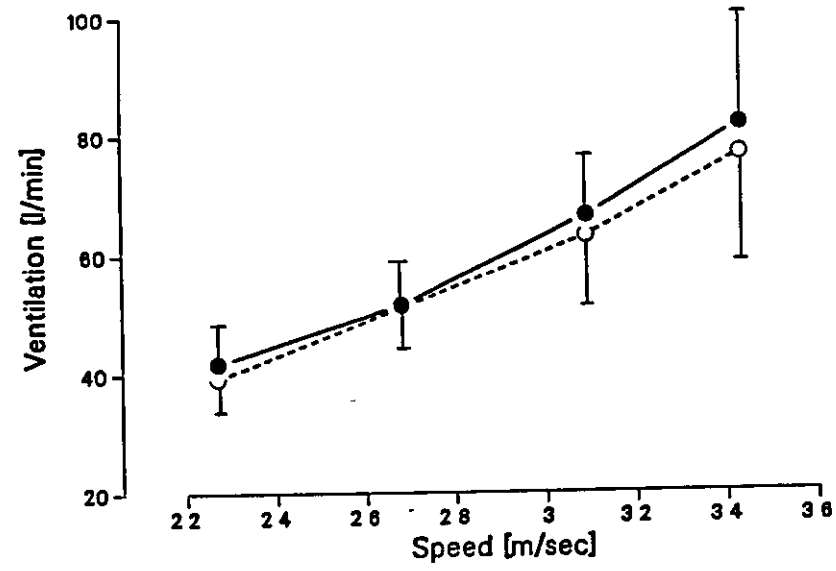


Figure 8.4b



Figures 8.4a and 8.4b. The ventilation rate at a range of submaximal running speeds, pre- and post-training, for the asthmatic (8.4a) and non-asthmatic groups (8.4b).

Figure 8.5a

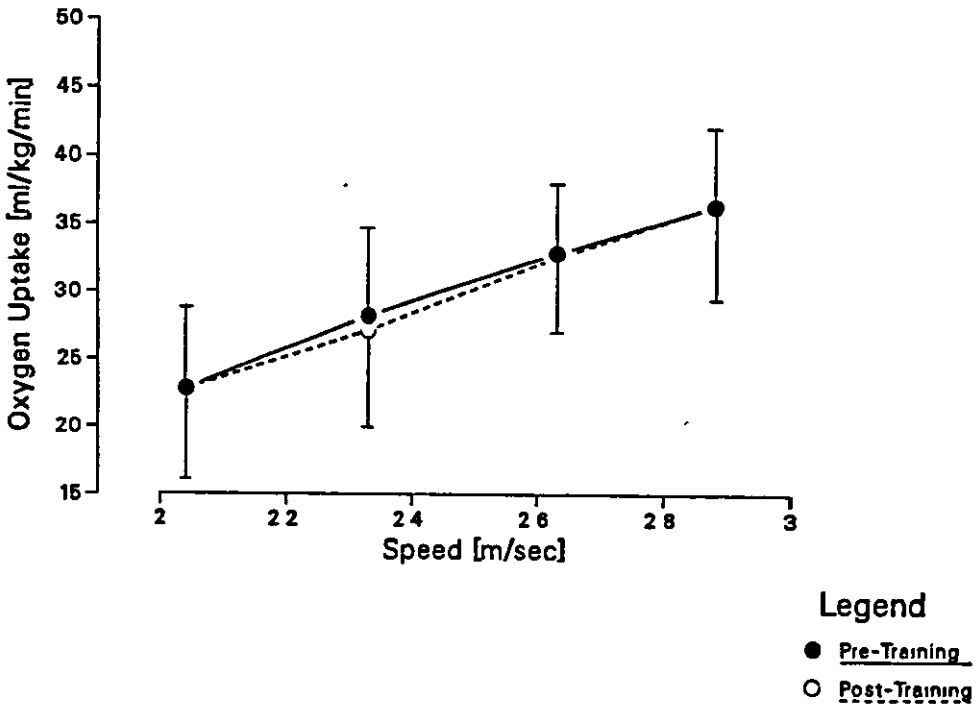
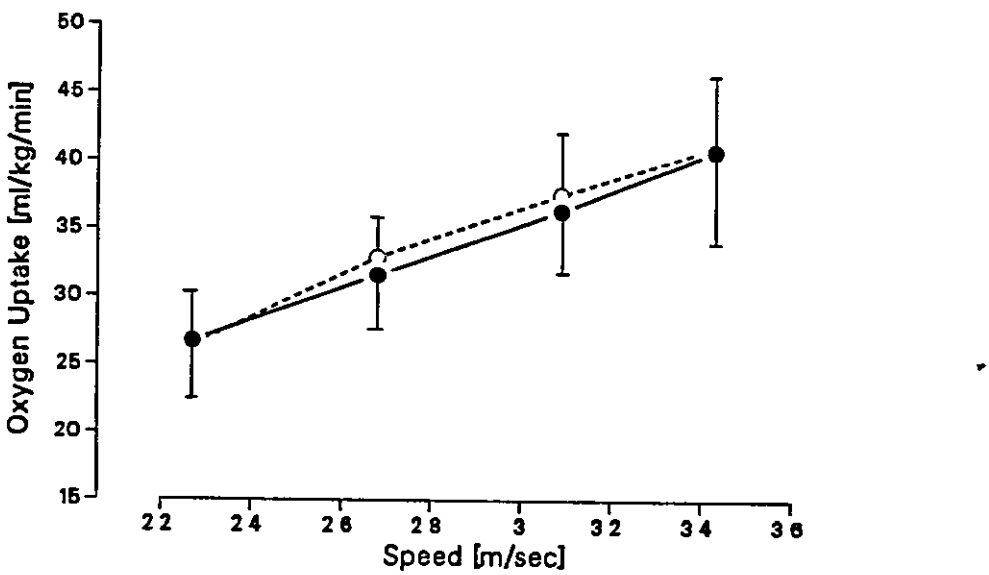


Figure 8.5b



Figures 8.5a and 8.5b. The oxygen uptake at a range of submaximal running speeds, pre- and post-training, for the asthmatic (8.5a) and non-asthmatic groups (8.5b).

Figure 8.6a

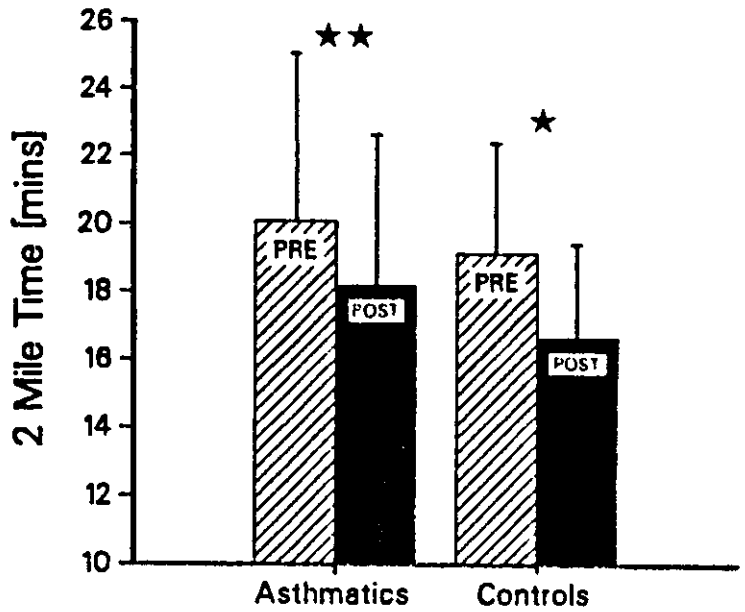
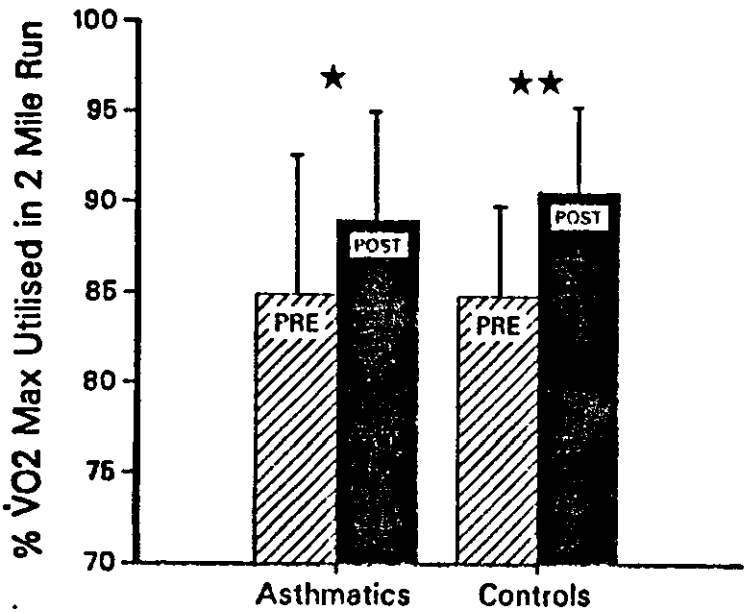


Figure 8.6b



Figures 8.6a and 8.6b. The 2 mile time (8.6a) and $\%\dot{V}O_2$ max utilised (8.6b), pre- and post-training, for the asthmatic and non-asthmatic groups.

Significant difference pre- and post-training: ★ $p<0.05$; ★★ $p<0.01$

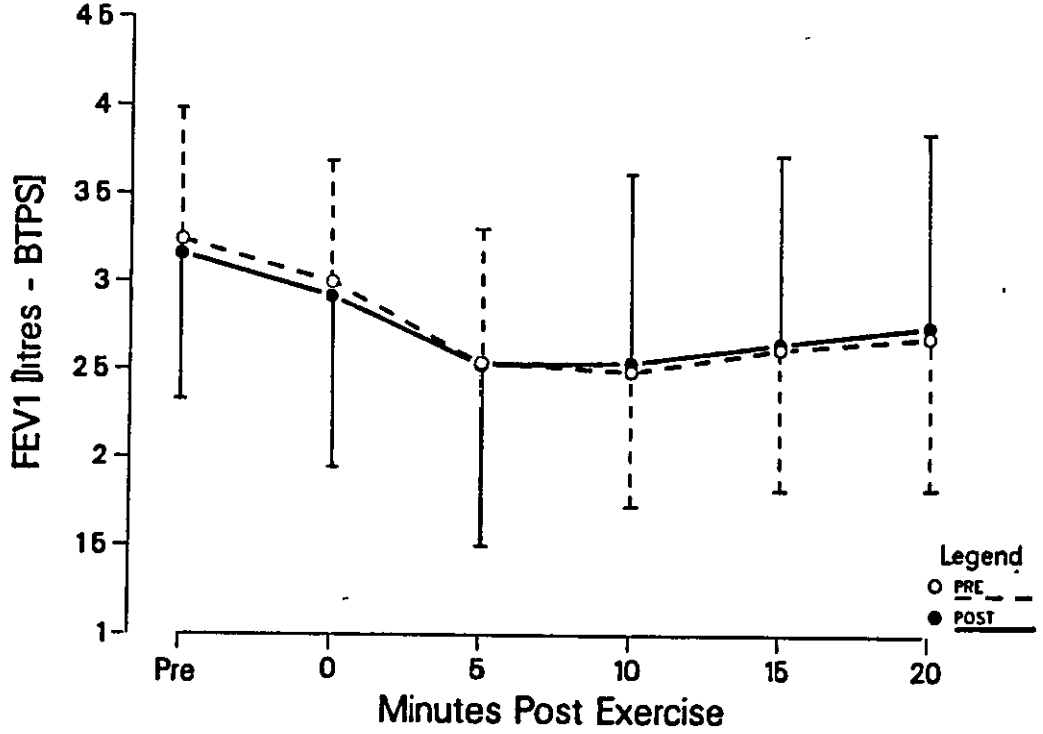


Figure 8.7. The severity of exercise-induced asthma from the non-medicated running test, pre- and post-training for the asthmatic group.

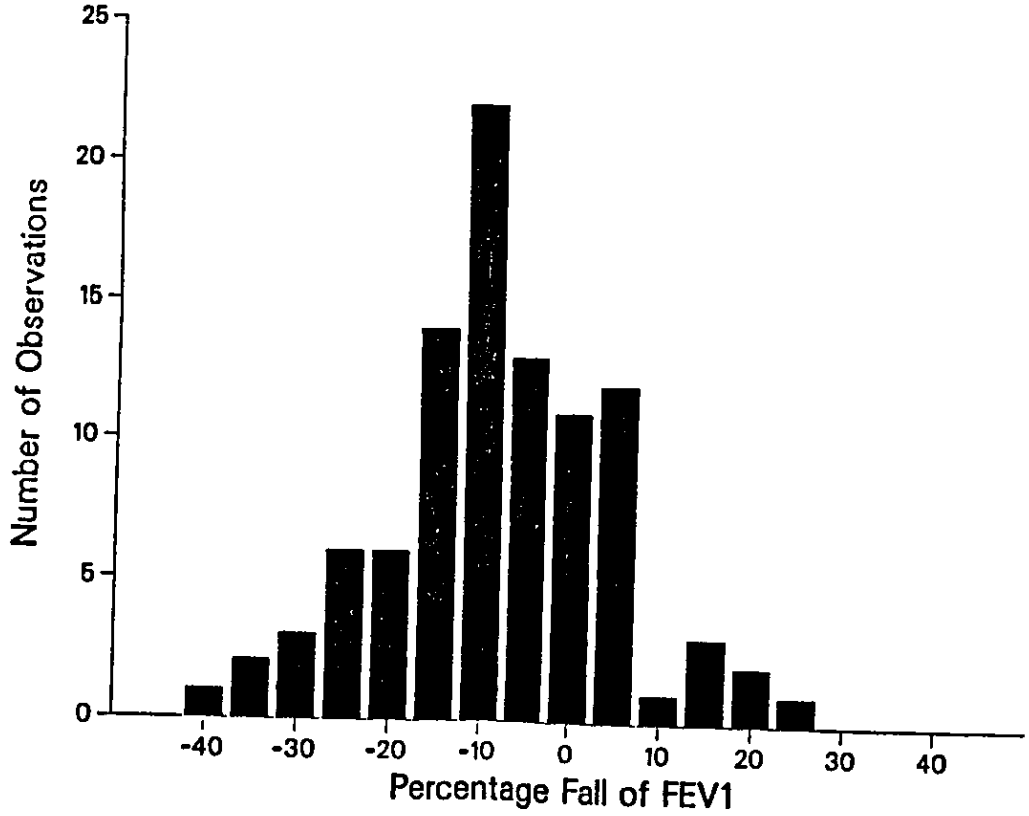


Figure 8.8. The distribution of the change in the FEV_1 after training sessions for the asthmatic group.

Figure 8.9a

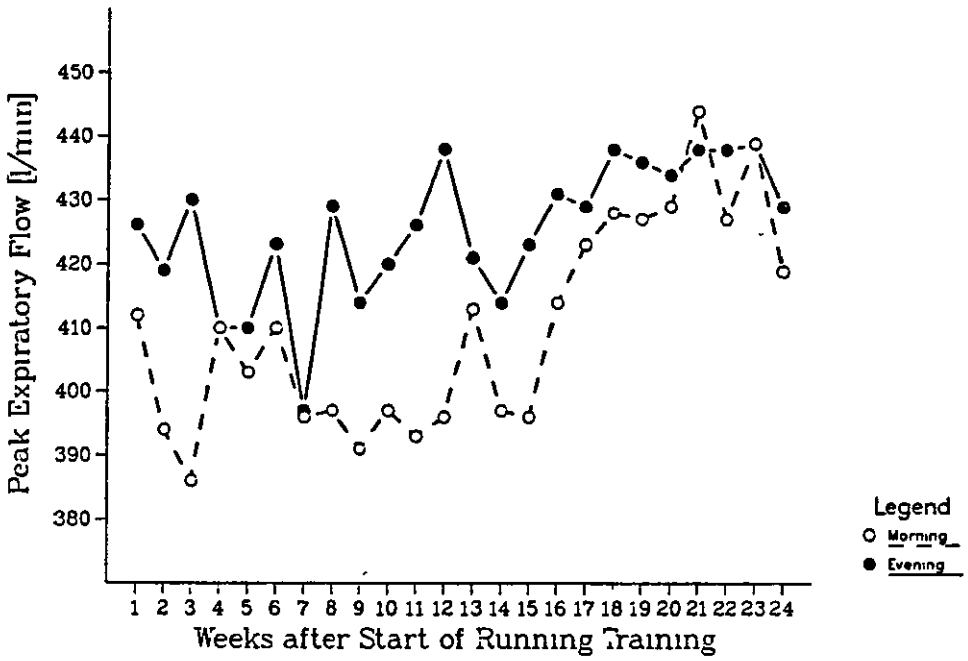
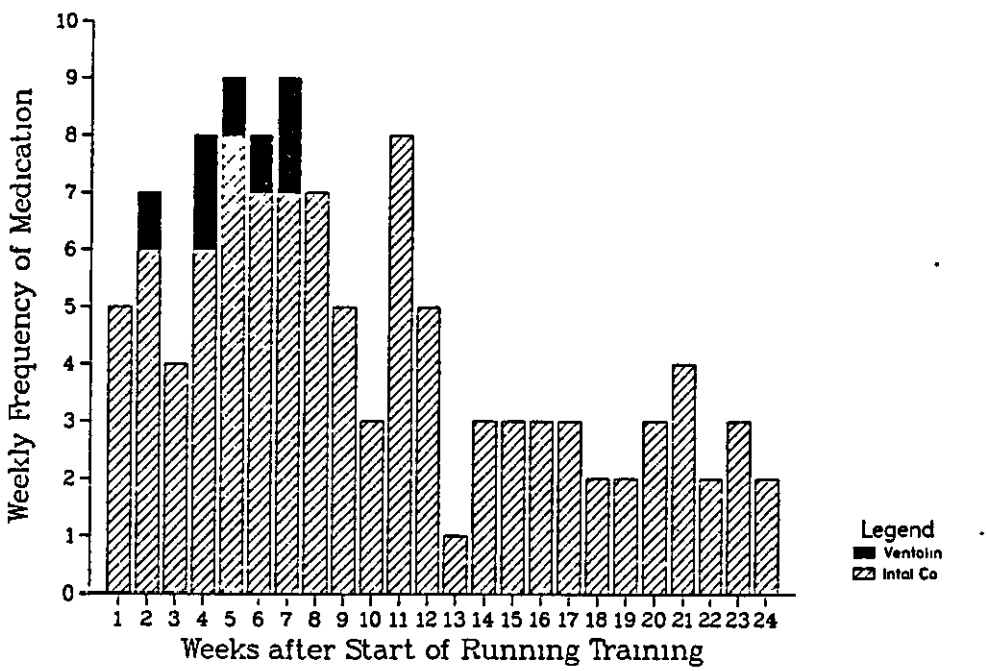


Figure 8.9b



Figures 8.9a and 8.9b. The peak flow records (8.9a) and the asthmatic medication (8.9b) from the daily diary cards, for an asthmatic who continued endurance running after the end of the 5 week training programme.

8.4 Discussion.

Although physical training has been recommended for the management of asthma (Holgate 1983), the prescription of the type of exercise is not well defined. Keens (1979) suggested that asthmatics should be allowed to participate in all activities, including those that are likely to provoke EIA. However, the safety of training employing activities that are likely to provoke EIA such as distance running, has not previously been examined for the asthmatic adult. This study observed the physiological effect of 5 weeks of endurance running training on the asthmatic adult, and compared their responses to a non-asthmatic group. The training was performed at "self-selected" running speeds on the treadmill, akin to that which would be undertaken at the start of an endurance running training programme performed out of doors.

A reduction in numbers of the asthmatics from 16 to 9 in the training study, could be explained by a variety of reasons. One asthmatic was forced to stop training due to a worsening of his asthma caused by infection, and not necessarily due to the training. Minor injuries prevented two asthmatics completing the training period. The other two asthmatics did not have sufficient time to perform the training, and thus were forced to leave the study. A similar reduction in numbers has been observed by Bundgaard et al (1982b) when training asthmatic adults. The major findings from the asthmatic and non-asthmatics who completed the endurance running training study are discussed below.

8.4.1 The Effect of Endurance Running Training on the Cardio-Respiratory Fitness.

The five week period of endurance running training performed on the treadmill at self-selected training speeds, resulted in a similar improvement in VO_2 max for the asthmatic and non-asthmatic groups. The increment in VO_2 max of 7% for both the asthmatic and non-asthmatic groups, agrees with other investigators examining the effect of short term training in previously untrained non-asthmatic subjects (Holloszy 1973). An increase in VO_2 max is due to both an increase in the cardiac output and an increased arterio-venous oxygen difference suggestive of an increased extraction of oxygen by the muscle (Rowell

1974).

It is recognised that short term endurance running training reduces the accumulation of blood lactate at the same absolute exercise work load (Davies et al 1979), reflecting an increased contribution of energy from aerobic metabolism consequent on the increased oxidative capacity of the mitochodria (Henrikssen 1977). The asthmatic group showed a significant reduction in blood lactate after the 5 weeks of training, whereas the non-asthmatic group showed no change. This lack of change for the non-asthmatic group may be attributed to the greater level of conditioning of the non-asthmatic group prior to the start of the training. Blood lactate concentrations were not different, however, when the running speeds were expressed at the same relative exercise intensity (% VO_2 max). Previous studies however, on non-asthmatics have suggested that a longer period of training is required to reduce blood lactate at the same relative work load (Ekblom 1968, Skinner and McClellan 1979).

The significantly reduced heart-rate at submaximal running speeds, with no significant decrease in the maximum heart-rate, for the asthmatic group are consistent with the findings of other studies of physical training in non-asthmatics (Flint et al 1974, Smith and Stansky 1975). The greater reductions in heart-rate after exercise at submaximal running speeds for the asthmatic group would also suggest greater physiological benefit from the training, when compared to the non-asthmatic group. This reduced heart-rate is thought to be due to an increase in stroke volume and a decrease in peripheral resitance (Eckblom 1969).

In addition to the improvements in the physiological parameters measured, an improvement in the running performance over the 3.2Km (2 miles) was also demonstrated. Previously an improvement in running performance was simply associated with increases in VO_2 max. However, observations by Daniels et al (1978) suggested that other factors not involved in the test of VO_2 max, contribute to the improvements in running performance. After training, the asthmatic and non-asthmatic groups were able to sustain a higher %VO_2 max during the two mile run. The absence of a reduction in blood lactate at the same relative work load after training, suggests that the subjects could tolerate a higher level of blood lactate over the 2 mile performance trial, enabling them to sustain a higher %VO_2 max post-training compared to pre-training. Thus endurance fitness, as reflected in the ability to

sustain a large fraction of VO_2 max (Costill 1971), has been significantly improved for both the asthmatic and non-asthmatic groups as a result of short-term endurance running training.

As a word of caution, it has been suggested by Sjodin (1982) that the use of a timed distance, as a measure of endurance capacity, is a method of low precision and validity. Whether the increased familiarity with the treadmill has allowed a better selection of running pace in the post-training tests is a possibility, allowing subjects to sustain a higher $\%VO_2$ max. Therefore, the results suggesting an ability to sustain a higher $\%VO_2$ max in an endurance running time-trial after short-term training, is questionable and indeed controversial.

This increase in aerobic capacity after endurance running training for the asthmatic adult, is consistent with the observations of Nickerson et al (1983) for asthmatic children. This suggests that endurance running training will lead to the physiological changes associated with an increased exercise tolerance in untrained asthmatic adults. In addition, the physiological changes were similar if not more pronounced, for the asthmatic group when compared to the non-asthmatic group, which implies that asthma does not impair the ability to improve the aerobic capacity. As a consequence, daily activities could be performed more easily.

8.4.2 The Effect of the Improved Cardio-Respiratory Fitness on Exercise-Induced Asthma.

It has been suggested that the reduction in EIA, is the most important effect of an improvement in physical fitness (Oseid and Haaland 1978). In the present study, the effect of an improved aerobic capacity on the severity of EIA at the same absolute work load pre- and post-training has been examined, and has been shown not to be significantly different. However, the individual results show that 7 out of the 9 asthmatics experienced a reduction in EIA after training. Other studies have suggested that at a given work load the severity of the EIA is reduced after training, either due to a reduced ventilatory demand (Oseid and Haaland 1978, Henriksen et al 1981b), or as a result of a reduction in the basic hyperreactivity of the airways (Arborelius and Svenonius 1984). However, the changes in EIA for the asthmatics in the present study were not associated with the changes in the ventilation rate required to perform the test. Other factors,

including the underlying state of the airway inflammation and the climatological factors, are also known to affect the severity of EIA. Unfortunately, the laboratory conditions of humidity and temperature were not controlled precisely, and therefore changes in the test environment may have accounted for the differences in the severity of the EIA.

Other studies employing continuous activity have not shown any change in the severity of EIA after training. However, these studies also fall short in their methodology. Fitch and Godfrey (1976) trained their asthmatic children in the swimming pool, whereas they tested for EIA on a cycle ergometer. They did not adhere to the principle of the specificity of training, in which the tests should be the same as the training mode. Nickerson et al (1983), did examine the effect of running training on the severity of EIA experienced whilst running, and showed no change after training. However, the work load was not constant before and after training, because the investigators used an uncontrolled free running test to assess the severity of EIA.

Future studies to assess the effect of an improved fitness on the severity of EIA, must be able to control the test environment, employ the same mode of exercise for the EIA test as used in the training, and examine the severity of EIA at the same absolute work load before and after training.

8.4.3 The Effectiveness of Pre-Exercise Medication for Training Sessions.

The use of pre-exercise medication to prevent EIA, ensures that full benefit can be gained from the training programme (Oseid and Haaland 1978). Indeed, Svenonius et al (1983) has stated that effective training work loads will be limited by the EIA they provoke. Seven out of the nine asthmatics took pre-exercise medication, thus reducing the EIA. However, EIA experienced during and after running training, was not totally abolished for three of the asthmatics, although it was always reversed by bronchodilators. The effectiveness of various drugs to inhibit EIA has been evaluated with short term exercise (6-8 minutes), but not with more prolonged exercise. Thus, further work on the optimisation of pre-exercise asthmatic medication for more prolonged exercise, is necessary, as has been previously mentioned for very prolonged endurance running in asthmatic athletes.

In the present study the running training was performed indoors on

a treadmill, however, one asthmatic did, by choice, perform half of his training out of doors and did not take pre-exercise medication prior to any training session. The outdoor training sessions provoked more severe EIA than similar indoor training. This observation is consistent with the findings of Anderson et al (1971), Eggleston et al (1979), and Shapiro et al (1979), who demonstrated that free range running provokes more severe asthma than treadmill running. The frequent clinical complaint that EIA is more severe when exercising in cold conditions is supported quantitatively by Strauss et al (1977). A further study to evaluate the risk of outdoor running training on the asthmatic is required. Indeed, when training in cold conditions out of doors, it may be necessary for the asthmatic to use face masks to warm and humidify the inspired air (Bake et al 1986).

8.5 Summary.

The major findings of this study suggest that asthmatic adults taking pre-exercise medication, show similar and even enhanced improvements in their cardio-respiratory fitness after short term endurance running training, when compared to non-asthmatics. The severity of exercise-induced asthma when running without medication, was however unchanged by this improvement in physical fitness. Exercise-induced asthma was experienced by a number of asthmatics after the running training sessions, despite taking pre-exercise asthmatic medication.

CHAPTER 9

GENERAL DISCUSSION

There were three major aims of this study. Firstly, to evaluate the cardio-respiratory and metabolic responses of untrained and endurance trained asthmatics to maximal and submaximal exercise. Secondly, to compare the physiological effect of prolonged endurance running on well trained asthmatics and non-asthmatics and determine any detrimental effect on the performance of the asthmatic. Thirdly, to study the beneficial or detrimental effect of endurance running training on previously sedentary asthmatic adults.

9.1 Cardio-Respiratory Response to Exercise and Asthma.

Asthma has the potential to restrict the maximum response to exercise in two ways. Firstly, Fitch (1975b) has stated that a proportion of severe asthmatics compete at a disadvantage, due to the limitation on the maximum ventilation by the airflow obstruction associated with the asthma. Secondly, McFadden (1984a) has stated that the fear of developing EIA may lead to inactivity, which will impair the maximum response to exercise, rather than the asthma per se. In an attempt to identify the roles of inactivity and asthma, the physiological responses to maximal and submaximal exercise of similar groups of untrained asthmatics and non-asthmatics, and a group of endurance running trained asthmatics were compared.

The maximum oxygen uptake attained during exercise in untrained non-astmatics, is determined by the "weaker links" in the chain for oxygen transport such as stroke volume, cardiac output and the oxidative capacity of the skeletal muscle, and not by the capacity for gas exchange of the pulmonary system (Dempsey 1986). However, in pulmonary diseases where the capacity for the utilisation of oxygen by the working muscles may be beyond that of the gas exchange capacity of the lungs, the limitation of the maximum oxygen uptake may now be at the ventilatory level. Indeed the VO_2 max of the untrained asthmatics was significantly lower than that for the untrained non-asthmatic group.

The wide variation in the VO_2 max values of the untrained asthmatic

group from 35 to 57 ml.kg.$^{-1}$min^{-1} was not random but was positively correlated to the percent predicted FEV_1 ($r=0.502$, $p<0.05$) and to the maximum ventilation ($r=0.598$, $p<0.05$). Furthermore, the percent predicted FEV_1 was also postively correlated to the maximum ventilation ($r=0.701$, $p<0.01$). Airway obstruction is therefore associated with a lowering of the maximum ventilation attainable during exercise, which in turn may limit the maximal oxygen uptake. Thus in untrained asthmatics with severe airway obstruction, the impairment of maximum ventilation may be the rate limiting factor to determine VO_2 max.

In addition, highly trained non-asthmatic individuals may also have a capacity for oxygen utilisation that is beyond the gas exchange capacity of the lungs. This is because the limiting factor in maximum exercise changes with an improved level of endurance fitness. Such re-ordering of the limiting factors occurs because training increases the capacity of the cardio-vascular system and greatly increases the oxidative capacity of the skeletal muscle, so that the lung assumes a more critical rate limiting step in determining VO_2 max (Dempsey 1986). Thus, it is likely that for well trained asthmatic athletes, maximum ventilation may impose a greater limitation on the VO_2 max than for asthmatics who are untrained.

Despite the possible limitations of the airway obstruction on the VO_2 max, a large number of asthmatics do participate in endurance running training and racing. The mean VO_2 max of the asthmatic endurance athletes was 61.8 ml.kg.$^{-1}$min^{-1}, this being much higher than that obtained for the untrained asthmatics. The higher VO_2 max of the asthmatic athletes may have been due to a naturally high maximal oxygen uptake thus encouraging selection of endurance running as their preferred activity, or alternatively the physiological responses to training has allowed an improvement in the maximal oxygen uptake. It is impossible to aportion the effects of hereditary or training on the VO_2 max, although it is likely that both factors will have played a part in the higher VO_2 max compared to the untrained asthmatics.

As for the untrained asthmatics, the wide range of VO_2 max values for the trained group from 50 to 71 ml.kg.$^{-1}$min^{-1} was correlated with maximum ventilation ($r=0.779$, $p<0.01$). This correlation was higher than that obtained for the untrained asthmatics for maximum oxygen uptake and maximum ventilation ($r=0.595$, $p<0.05$). This suggests that as asthmatics progress up the fitness continuum, maximum ventilation

attainable on exercise is indeed more critical in determining VO_2 max.

It is not known whether the pulmonary system adapts to minimise the limitation of maximum ventilation on maximum oxygen uptake in the highly trained asthmatic. In non-asthmatics, the pulmonary system remains largely unchanged with training. During maximal exercise highly trained athletes may have a lowering of the arterial oxygen saturation. This is due to the inability to hyperventilate which is associated with either mechanical limitation as the maximum flow rate is reached or respiratory muscle fatigue (Dempsey 1986). However, although normal physical training does not usually result in true structural adaptation of the respiratory muscles, the response to chronic overload has been shown to be marked. For example, studies of rats with artificially induced airway obstruction have shown an increased oxidative capacity of the diaphragm (Keens et al 1978). Furthermore, specific breathing exercises in humans increase the strength and endurance of respiratory muscles (Leith and Bradley 1976). Therefore, it is possible that the asthmatic with airway obstruction may show similar adaptations with endurance running training, enabling them to compensate in some way for the ventilatory limitations.

The physiological responses of the untrained asthmatics and non-asthmatics were also compared during submaximal running. As indicated by the poorer ventilatory equivalent, the untrained asthmatic group exercises under less efficient ventilatory conditions both at the same absolute and relative exercise intensities, compared to the non-asthmatic group. This finding agrees with the work of Cropp and Tanakawa (1977) on asthmatic adults. In addition, blood lactate was significantly higher for the asthmatics compared to the non-asthmatics at the same absolute running speed, which agrees with the work of Seaton et al (1969) and Silverman et al (1972). McFadden (1984a) postulated that this higher lactate may be due to a general lack of fitness. Indeed, the higher blood lactate concentrations were purely a function of the lower VO_2 max of the asthmatic group, because when the untrained asthmatic and non-asthmatic groups were compared at the same relative exercise intensity there were no differences. Furthermore, a comparison of the responses of trained and untrained asthmatics to submaximal exercise, revealed that endurance training results in lower blood lactates both at a given running speed and at

the same relative exercise intensity. This is as would be expected for non-asthmatic athletes engaged in endurance running training, and therefore reflects a normal adaptive response of the asthmatics to endurance running training.

Thus, asthma does not grossly impair the VO_2 max in a group of mild to moderate asthmatics, nor does it seem to severely restrict the levels of VO_2 max that can be attained by trained asthmatics. However, with increasing severity of airway obstruction it is likely that for untrained and trained asthmatics alike, the inevitable reduction in maximum ventilation may be the rate limiting factor in determining VO_2 max. During submaximal exercise the higher blood lactate of untrained asthmatics compared to similar non-asthmatics is due to their lower VO_2 max. However, the poorer ventilatory equivalent both at the same absolute and relative exercise intensities of the untrained asthmatics compared to the non-asthmatics, would seem to be a function of the asthma per se. Therefore, the suggestion by McFadden (1984a) that an impaired cardio-respiratory response to exercise is more likely to be due to inactivity rather than the asthma per-se, cannot be supported by the results of the present study.

9.2 Endurance Running Performance and Asthma.

Although the high VO_2 max and a low blood lactate concentration at submaximal exercise intensities of the asthmatic athletes are associated with a high degree of aerobic fitness, more recent definitions of fitness have concentrated on the ability to sustain a high $\%VO_2$ max over prolonged periods of time. Outdoor performance times over the half-marathon distance were available for eleven of the sixteen asthmatic athletes. This provided an opportunity to evaluate the effect of asthma on both competitive endurance running performance and on the endurance fitness as defined by the ability to sustain a high $\%VO_2$ max. Extrapolations from the treadmill data revealed that the asthmatic athletes were able to sustain an average of 81.9% VO_2 max during the half-marathon, which is very similar to that quoted for non-asthmatic recreational runners (Williams and Nute 1983). This would indicate that asthma has not impaired the development of a high degree of endurance fitness, allowing asthmatics who have undergone appropriate training to compete alongside non-asthmatics in endurance running events.

The determinants of half-marathon running performance obtained from the treadmill tests were similar to investigations of non-asthmatics (Williams and Nute 1983, Farrell et al 1979). Half-marathon running spped for the asthmatic group was highly correlated to VO_2 max (r=0.881), but more so to the running speed at which blood lactate accumulates (V2mM) (r=0.971), accounting for 94% of the variation in the half-marathon times within the group of asthmatic athletes.

The estimated $\%VO_2$ max utilsed over the half-marathon was most strongly correlated with the $\%VO_2$ max at a blood lactate concentration of 2mM (r=0.817, $p<0.01$). Thus the $\%VO_2$ max utilised during the half-marathon is largely dependent on the capacity of the working muscles to cover their energy needs by aerobic metabolism, supporting the observations of Williams and Nute (1983). The estimated $\%VO_2$ max sustained over the half-marathon was also correlated with the percent predicted FEV_1 (r=-0.800). As previously illustrated, the VO_2 max of the asthmatic athlete may be limited by poor lung function. To adapt to this possible impairment in VO_2 max training has allowed the asthmatic with poor lung function to sustain a higher $\%VO_2$ max than those with better lung function. This observation is similar, although not as extreme, to the adaptation which allows cardiac patients to work very close to their VO_2 max with minimal blood lactate accumulation following endurance training (Coyle et al 1983).

A closer examination of the physiological responses of asthmatic athletes to endurance running, has been obtained from laboratory assessment on the treadmill. Similar cardio-respiratory, metabolic and adrenergic responses were observed for groups of asthmatics taking pre-exercise medication and non-asthmatics during both prolonged running (2 hours) at a constant speed at the same relative exercise intensity (70% VO_2 max), and during race conditions over the half-marathon distance. However, observations of lower breathing frequencies of the asthmatics compared to the non-asthmatics would suggest that the pattern of breathing during exercise is different for asthmatics. This finding is supported by recent work during short term exercise comparing asthmatic and non-asthmatic children (Ramonatxo et al 1986). Further assessment of the breathing patterns of asthmatics during prolonged exercise would appear to be worthwhile.

The effect of the pre-exercise medication may, however, be masking any differences between the physiological responses to prolonged

running of asthmatic and non-asthmatic subjects. The majority of asthmatics used 'selective' $Beta_2$ agonists in conventional inhaled dosages, both before and during the prolonged runs. Although these drugs have been shown to have only minimal effects on the physiological parameters at rest (Neville et al 1977), their effect on exercise have not been determined. The large differences in the physiological responses during two half-marathons performed by one asthmatic, with and without aminophylline, underlined the need to examine and quantify the effects of the asthmatic drugs on the physiological responses to exercise.

The similar cardiovascular, metabolic and adrenergic responses to prolonged running for asthmatics and non-asthmatics, would suggest no reason why the asthmatic should be at a disadvantage in endurance running. However, the control of EIA is necessary if the asthmatic is to participate in endurance running safely and without respiratory disadvatage (Fitch 1986). Pre-exercise medication was successful in inhibiting EIA for four of the six asthmatic half-marathon runners, and for two of the four asthmatics who performed the 2 hour run at 70% VO_2 max. However, two asthmatics experienced marked bronchoconstriction after the 2 hour run showing a similar response as would be expected for a short running test without medication. Under the race conditions of the half-marathon two asthmatic athletes experienced a large fall in the FEV_1 both during and after exercise. The fall in the FEV_1 during the run could not be reversed even with and reduction in the running speed and inhaled bronchodilators. These results cannot support the notions that it is possible to 'run-through' the asthma (Fitch and Godfrey 1973) or that EIA will be reduced if exercise is prolonged (Silverman and Anderson 1972).

In addition to the inability to reverse the EIA whilst running, the bronchoconstriction observed after the prolonged runs did not seem to be immediately reversible with standard dosages of inhaled bronchodilators. It is postulated that the type of airway obstruction experienced after very prolonged running, may be more akin to the late asthmatic bronchoconstrictor response documented after inhalational challenges. The 'late response', characterised histologically by oedema and inflammatory cell infiltrates, often involves a greater fall in the FEV_1 and bronchodilator treatment is frequently only partially effective (Dolovich et al 1983). Further studies are required to examine the reversibility of EIA experienced after

prolonged running.

A reduction in the running speed and hence impaired performance time is an inevitable consequence of a fall in the FEV_1. However, the possible risks for the asthmatic have not been evaluated in this study. Previous investigations have shown that EIA leads to inequalities in the ventilation-perfusion relationships with resulting arterial hypoxemia (McFadden et al 1977, Young et al 1982) and possibly carbon dioxide retention (Cropp and Tanakawa 1977, Anderson et al 1972). The asthmatic should be warned of the potential dangers of endurance running, and should be encouraged to stop running if EIA develops. It is imperative that pre-exercise medication is optimised to prevent or reduce EIA, to ensure the safety of the asthmatic in endurance running.

Although Sly (1984) has suggested that the $Beta_2$ agonist, salbutamol, will provide protection from EIA for 4 hours, it did not give full protection from EIA in prolonged running for this length of time. In addition, the suggestion that EIA will be minimised or inhibited in the majority of asthmatics by pre-exercise $Beta_2$ agonist supplemented, if necessary, by sodium cromoglycate and theophylline (Fitch 1986) cannot be supported when exercise is prolonged. It may be worthwhile to assess the effect of a more prolonged acting $Beta_2$ agonist, such as fenoterol or terbutaline, in asthmatics for whom conventional pre-exercise medication does not inhibit EIA with endurance running. It has been recommended that each asthmatic should discover the best therapy to control their exercise-induced asthma (Cummings and Strunk 1984). Self-monitoring of peak expiratory flow rate before and after training sessions and races would be an aid to assess the most effective pre-exercise treatment. This form of assessment has has been recommended by a Drug and Therapeutics Bulletin (1982) to assess the effectiveness of asthma treatment, though not specifically for EIA.

The asthmatics for whom EIA has been observed during and after prolonged running usually had more severe pre-exercise airway obstruction and hence a greater baseline reactivity. In addition to pre-exercise medication, treatment should be taken prophylactically, in order to reduce the overall hyperreactivity of the airways. Indeed, obtaining overall control of the asthmatic condition seems to be a prerequisite to control EIA (Fitch 1986).

It must be stressed that the prolonged runs were on the treadmill,

in the relatively warm environment of the laboratory. Endurance running often takes place in cold air, conditions which are known to provoke EIA (Strauss et al 1977). Therefore prolonged running out of doors may impose even more severe EIA than observed treadmill running.

The cardio-respiratory, adrenergic and metabolic responses to prolonged endurance running and racing were similar for the asthmatics and the non-asthmatics. Thus, if pre-exercise medication is adequate there is no reason why the asthmatic is at a disadvantage in endurance running. However, if pre-exercise medication does not protect the asthmatic from EIA, the resulting bronchospasm will cause a reduction in the running speed leading to an impaired performance and more importantly may place the asthmatic at risk.

9.3 Endurance Running Training and Asthma.

Although exercise may provoke asthma, physical training is recommended in the management of the disease to improve the cardio-respiratory fitness and, as a consequence to reduce the severity of EIA. Although, endurance running has been shown to improve the cardio-respiratory 'fitness' of non-asthmatic groups, the effect of endurance running training has not been previously evaluated for the asthmatic adult. For the asthmatic group the 5 weeks of endurance running training on the treadmill resulted in an increase in VO_2 max and lower blood lactate at submaximal running speeds, suggestive of an improvement in the aerobic capacity. The reduction in the time taken to run 2 miles and a significant increase in the $\%VO_2$ max sustained over the 2 miles underlined these changes. The improvements of the asthmatic group were of a similar magnitude to those observed in a non-asthmatic group performing the same training. Clearly, asthma does not impair the ability to obtain the physiological benefits associated with endurance running training, supporting the observations with asthmatic children (Nickerson et al 1983). Endurance running is therefore a good activity for the asthmatic when an improvement in the cardio-respiratory fitness is sought.

It is important, however, to be cautious when recommending distance running for the asthmatic, for three reasons. Firstly, pre-exercise medication did not totally block the EIA experienced after training sessions for three of the nine asthmatics in the training study, although the bronchospasm was always immediately reversed by the

inhalation of salbutamol. Secondly, one asthmatic performed half of his training outdoors and experienced more severe EIA than after the training sessions on the treadmill. Thirdly, whether endurance running is the most suitable sport for the beginning exerciser, asthmatic or non-asthmatic, must be questioned due to the risk of minor injuries with this weight bearing activity (Pollock 1977b).

The improvement in aerobic fitness was not accompanied by any significant changes in the severity of EIA, although 7 out of the 9 asthmatics did experience a reduction in EIA post-training. This lowering of EIA may be attributed either to either the lower ventilatory demands of a given activity after training or to a lowering of the basic hyperreactivity of the airways as suggested by Svenonius et al (1983). The former possibility is more likely because the asthmatic athletes with a high degree of endurance fitness showed a similar severity of EIA compared to the previously untrained asthmatics (23.6 $\pm$ 12.7 vs 26.4 $\pm$ 11.6 percent fall in FEV_1). This indicates that the EIA is a persistent feature of the hyperresponsiveness of the airways of the asthmatic, which is not necessarily reduced by a high degree of endurance fitness. However, this is not the definitive study and as McFadden (1984a) has stated no study has controlled all the relevant variables when assessing EIA before and after training, and until this is done the effect of an improved fitness on the severity of EIA remains unanswered.

In summary, endurance running training on previously untrained asthmatics resulted in improvements in the cardio-respiratory fitness. Although the severity of EIA was unchanged by the improved aerobic fitness, seven out of nine of the asthmatics showed a reduction in the severity of EIA after training. Pre-exercise medication did not always prevent EIA after the training sessions on every occasion. Endurance running is, however, an excellent activity to improve the cardio-respiratory fitness of the asthmatic.

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APPENDIX 1.

Daily Diary Card to Record PEFR, Severity of Symptoms and Medication.

INSTRUCTIONS

Fill in your diary card every morning and evening using the following guides

Grade OVERALL ASTHMA SEVERITY
BREATHLESSNESS ON EXERTION and COUGH

on a 0 10 scale of increasing
severity as shown below

MILD → SEVERE →

0 1 2 3 4 5 6 7 8 9 10

NONE MODERATE VERY SEVERE

SLEEP DIFFICULTY DUE TO ASTHMA

0 = None
1 = Awoke up to one hour
2 = Awoke 2-4 hours
3 = Awoke most of the night

PEAK FLOW RECORDINGS

Record each morning and evening the BEST of three blows before bronchodilator use (hold the instrument horizontally)

COMMENCING DATE ____ DAY	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Overall asthma severity							
Breathlessness on exertion							
Cough							
Sleep difficulty due to asthma							
Peak Flow (Morning)							
Peak Flow (Night)							
Other treatment for asthma* Name of drug(s) Please record No of doses taken in 24 hrs in daily boxes — 1							
2							
3							
4							
Comments							

APPENDIX 2.

Expired Air Analysis.

(1) The expired air was mixed in the Douglas bag.

(2) One and two minute samples of expired air were passed through the oxygen and carbon dioxide analysers respectively, and the percentages of these gases were noted. The flow rate into the gas analysers, was measured by a gap flow meter and used to determine the volume of expired air lost through sampling.

(3) The expired air in the Douglas bag was then evacuated using a vacuum pump with the air passing through a dry gas meter, to obtain the volume. The temperature of the expired air was noted. The volume of expired air was added to the volume of air lost through sampling, to give the total volume of expired air in litres per minute. To correct this volume of expired air to standard temperature and pressure of a dry gas (STPD), the following formula was used:

$$V_E\ (STPD) = V_E \times \frac{273}{273 + t^{\circ}c} \times \frac{BP - SWVPt^{\circ}c}{760}$$

where V_E is the volume of expired air ($l.min^{-1}$).

$t^{\circ}c$ is the temperature of expired air.

BP is the barometric pressure (mm Hg).

and SWVPt°c is the saturated water vapour pressure at t°c.

$$(SWVPt^{\circ}c = (t^{\circ}c \times 1.1001) - 4.1878)$$

(4) To calculate oxygen uptake and carbon dioxide production, the Haldane correction method was employed. This converts expired air volumes to inspired air volumes, using the differences in the fraction of nitrogen in expired and inspired air:

$$V_I = \frac{F_E\ N_2\%}{F_I\ N_2\%} \times V_E\ (STPD)\ l.min^{-1}$$

where V_I is inspired air,

$F_E\ N_2\%$ is the fraction of nitrogen in expired air (100-(% O_2 and

% CO_2)),

and $F_I N_2$% is the fraction of nitrogen in inspired air (79.04%).

(5) Oxygen uptake ($l.min^{-1}$) was then calculated:

VO_2 = VO_2 Inspired (I) - VO_2 Expired (E)

where VO_2 I = V_I (STPD) x $\frac{F_E O_2\%}{100}$ and VO_2 E = V_E (STPD) x $\frac{F_I O_2\%}{100}$

$F_E O_2$%. and $F_I O_2$% represent the fraction of oxygen in expired and inspired (20.93%) air respectively.

(6) Carbon dioxide ($l.min^{-1}$) was then similarly calculated:

VCO_2 = VCO_2 Expired (E) - VCO_2 Inspired (I)

where VCO_2 E = V_E (STPD) x $\frac{F_E CO_2\%}{100}$ and VCO_2 I = V_I (STPD) x $\frac{F_I CO_2\%}{100}$

$F_E CO_2$% and $F_I CO_2$% represent the fraction of oxygen in expired and inspired (0.03%) air respectively.

(7) The values for oxygen uptake and carbon dioxide production ($l.min^{-1}$) were divided throughout by body weight (kg) to obtain VO_2 and VCO_2 in millilitres per kilogram of body weight per minute ($ml.kg.^{-1}min^{-1}$).

APPENDIX 3.

Methods for Calculating the Respiratory Exchange Ratio, Ventilatory Equivalent and Oxygen Pulse.

(1) Respiratory exchange ratio (R)

Respiratory exchange ratio (R) was calculated as follows:

$$R = \frac{VCO_2}{VO_2}$$

(2) Ventilatory Equivalent.

Ventilatory equivalent (the minute ventilation required to obtain 1 litre of oxygen) can be calculated as follows:

$$\text{Ventilatory equivalent} = \frac{V_E \ (l.min^{-1} - STPD)}{VO_2 \ (l.min^{-1})}$$

(3) Oxygen Pulse.

Oxygen Pulse (the millilitres of oxygen per heart beat) can also be calculated:

$$O_2 \text{ Pulse} = \frac{VO_2 \ (ml.min^{-1})}{HR \ (beats.min^{-1})}$$

APPENDIX 4.

Lactic Acid Assay.

The method employed was an adaptation of that described by Olsen (1971). It is dependent on the release of NADH by the following reaction, which is measured by its native fluorescence:

Lactate + NAD + ^{LDH} Pyruvate + NADH

Deproteinization.

A 25 ul of blood was deproteinized by adding it to 250ul of perchloric acid (2.5%). It was then mixed thoroughly, centrifuged at 12000 rpm for 3-4 minutes (Eppendorf microcentrifuge, model 5414) and then stored at -20°C before analysis.

Solutions.

Perchloric Acid: 2.5% w/v

Hydrazine buffer (1.1 M, pH 9.0): 1.3g hydrazine sulphate, 5.0g hydrazine hydrate and 0.2g disodium ethylenediaminetetraacetic acid (EDTA) in 100ml distilled water.

Reaction Mixture: Prepared immediately prior to use: 2mg NAD^+ and 10ul LDH per ml of hydrazine buffer.

Standards were made from 1.0 M Sodium L-lactate stock solution.

Procedure.

(1) Samples were removed from the freezer and allowed to thaw at room temperature.

(2) Samples were then mixed thoroughly and centrifuged.

(3) 25ul of either the supernatant or standard was then transferred to a clean test tube, whereupon 250ul of reaction mixture was added.

(4) Tubes were mixed and allowed to incubate for 30 minutes.

(5) 1 ml of diluent was then added to the tubes. The samples were then read against the standards and the blank with a Perkin-Elmer (1000) Fluorimeter.

(6) The blank was subtracted from the sample and standard readings, and the lactate concentration of each sample was calculated from the sample curve.

APPENDIX 5.

Glucose Assay.

A colourimetric method was used, based on the following principles:

$Glucose + O_2 + H_2O_2 \xrightarrow{GOD} Gluconate + H_2O$

$H_2O + ABTS \xrightarrow{POD} Coloured\ complex + H_2O$

Solutions*:

Phosphate buffer: 100 $mmol.l^{-1}$, pH 7.0

POD: > 0.8 $U.ml^{-1}$

GOD: > 10.0 $U.ml^{-1}$

ABTS: 1.0 $mg.ml^{-1}$

A 0.505 $mmol.l^{-1}$ standard was used.

* A Boehringer Mannheim diagnostic kit was used for the solutions and standards of this assay.

Deproteinization:

Blood was deproteinized in the same manner as that used in the lactate assay.

Procedure:

(1) The samples, standards and reaction mixture were removed from the freezer and allowed to warm at room temperature for at least one hour.

(2) The samples were then mixed thoroughly and centrifuged.

(3) 20ul of standard and supernatant (Reaction mixture for blank) was placed in a test tube with 1 ml of reaction mixture and mixed well.

(4) The tubes were then allowed to incubate for 20 minutes.

(5) An Eppendorf photometer (model 1101M)was then used to measure the absorbance of the standards and samples at a filter wavelength of Hg 436 nm in a cuvette of 1cm light path.

(6) The glucose concentration ($mmol.l^{-1}$) in the samples were calculated in the following way:

$$c = 5.5 \times \frac{A\ sample}{A\ standard}$$

APPENDIX 6

Haemoglobin Assay.

A cyanmethaemoglobin method was used (Van Kanipen, 1961). This is a colourimetric method based on the following principle:

Haemoglobin + cyanide + ferricyanide --- cyanmethaemoglobin.

Solutions:

* Drabkins Reagent:

1.63 mmol.l^{-1} phosphate buffer.
0.75 mmol.l^{-1} potassium cyanide.
0.60 mmol.l^{-1} potassium ferricyanide.
5% detergent.

All dissolved in 1000ml of redistilled water.

* A Boehringer Manheim diagnostic kit was used to produce the reaction mixture for this assay.

Procedure:

(1) 20ul of blood was added to 5000ul of Drabkins reagent and mixed well to avoid clumping of the erythrocytes.

(2) The solution was allowed to incubate at room temperature for at least 3 minutes, but not longer than 24 hours.

(3) The absorbance (A) of the samples was measured with an Eppendorf photometer at a filter wavelength of Hg 546 nm in a cuvette with a 1cm light path against a blank of drabkins reagent.

(4) Haemoglobin concentration (c) of the samples was calculated using the following equation:

$$c = 36.77 \times A \quad (g.100ml^{-1})$$

APPENDIX 7.

Plasma Catecholamine Analysis.

The analytical procedure employed for the determination of plasma adrenaline and noradrenaline by HPLC with electrochemical detection used a modification of the methods described by Davies, Kissinger and Shoup (1981). This relies on a liquid-solid extraction of the catecholamines onto the alumina, followed by their elution with dilute acid. The alumina is selective for catecholamines and allows for their preconcentration prior to liquid chromotography. The method employed an internal standard. Each plasma sample was analysed in duplicate.

Assay Method:

(1) Thaw the stored plasma samples at room temperature.

(2) Mix the following together:

50mg activated alumina powder

1ml Tris buffer (pH 8.6)

3.0ml plasma (approximately)

96ul internal standard (pre-exercise sample)

or 192ul internal standard (post-exercise sample)

(3) Shake for 10 minutes.

(4) Allow alumina to settle and then aspirate supernatant and discard.

(5) Wash alumina twice with 3ml double distilled water, aspirating near to dryness each time.

(6) Add approximately 1ml double distilled water to the alumina, and then transfer alumina slurry with a disposable pipette to a microfilter (0.2um cellulose membrane). Place microfilter in centrifuge and spin until dry (3-4 minutes).

(7) Discard the filtrate, and put new recovery tube on microfilter. Add 120ul of 0.1M perchloric acid to the alumina. Shake thoroughly.

(8) Centrifuge sample until dry (3-4 minutes).

(9) The acidotic filtrate in the recovery tube contains the catecholamines ready for injection to the HPLC column. The filtrate was stored in the dark until aliquots of 50ul of post-exercise sample or 100ul of pre-exercise sample were applied using a 100ul glass syringe (Hamilton).

(10) Output was recorded on two flat bed chart recorders.

(11) Measurements of peak heights using a standard ruler graduated in millimeters.

Calculation of adrenaline and noradrenaline concentrations was made using the following formula:

$$\text{Amine content } (\text{pmoles.ml}^{-1}) = \frac{\text{Pk.X(mm)} \times \text{Amount IS(pM.ml}^{-1}) \times \text{RMR}}{\text{Pk.IS(mm)} \times \text{Plasma vol (ml)}}$$

where:

Pk.X(mm): Peak height of amine on trace.
Pk.IS(mm): Peak height of internal standard on trace.
Amount IS: Amount of internal standard initially added (16pmoles).
RMR: Relative molar response previously determined in a preliminary experiment.

Determination of Variance of the HPLC Method:
A preliminary experiment was conducted in order to establish the variance introduced by the analytical procedure.

The coefficients of variation for the recovery of each amine and the peak height response per picomole were calculated for the standards and recovery samples.

$$\text{Percentage recovery} = \frac{\text{Response per picomole (plasma sample)}}{\text{Response per picomole (standard)}}$$

The relative molar response was then calculated for the samples and standard.

$$\text{Relative molar reponse} = \frac{\text{Response per mole X}}{\text{Response per mole IS}}$$

where, X and IS are the responses for the amines and internal standard respectively determined on recovery samples.

Apparatus:

A Gilson pump (model 302) with a 10ml self-centering head, set to a flow rate of 1.5 $ml.min^{-1}$, was fitted with a Gilson pressure module (model 308c) which was pressure damped. The pressure developed was in the region of 2.8kpsi. An Anachem Spherisorb HPLC column was packed with a Spherisorp C18 (ODS 2) and was prefixed by a guard column containing Hypersil ODS 2 (particle size 5um).

Additions into the column were made using a 100ul glass syringe (Hamilton) into a Rheodine 712s injector connected to a 200ul injector loop to ensure complete passage of the sample.

Electrochemical detection was made using a LC-3A amperometric detector (BAS) with an applied range of 1nA full scale deflection. The potential accross the oxidising electrode was +0.65V. The output was recorded upon two flat bed recorders (Bryans 2800; Rikadenki DVE 3, Mitusui Electronics). Each was set to a chart speed of 0.5 mm/min and a sensitivity of 0.5V.

The mobile phase was prepared as described below and was degased under vacuum after 3 days use. The ion-pairing agent was 0.4mM sodium octane sulfonic acid.

Solution Preparation:

All solutions were made up in HPLC grade water (Fisons), and standards were made using ANALAR grade chemicals.

(1) Mobile Phase. 41 0.8M monochloroacetic acid
2mM ethylenediaminetetraacetic acid
disodium salt adjusted to pH 3.0
0.4mM sodium octane sulfonic acid

The above solution was filtered through a 0.2um ultipore membrane filter (Pall) and degased under vacuum prior to use.

(ii) Concentrated internal standard solution.

100ul of 1mM internal standard (3,4-dihydrobenzylamine; Sigma Chemicals Co.) was diluted to 10ml with 0.1M perchloric acid.

(iii) Noradrenaline standard solution.

100ul of 1mM noradrenaline bitartate (Sigma Chemicals Co.) was diluted to 10ml with 0.1M perchloric acid.

(iv) Adrenaline standard solution.

100ul of 0.4mM adrenaline bitartate (Sigma Chemicals C.) was diluted to 10ml with 0.1M perchloric acid.

(v) Tris buffer (pH 8.6).

45g of Tris and 5g of EDTA were dissolved in 250ml of distilled water. Using a previously calibrated pH meter the solution was adjusted to pH 8.6 using concentrated HCl.

(vi) Phosphate buffer.

1.0833g disodium hydrogenphosphate

0.236g potassium dihydrogenphosphate

2.0g EDTA

made up to 100ml with distilled water.

(vii) Acid Washed Aluminium Oxide.

20mg of acid washed aluminium oxide (Bioanalytic System) was required for each sample.

APPENDIX 8

Free Fatty Acid Assay.

FFA were analysed by a modification of a photometric, colourimetric assay (Chromy et al 1977).

Solutions:

Extraction solvent (CHM): 280ml chlorofrom
210ml n-heptane
10ml methanol

Stable copper reagent: 1.878g sodium citrate
16.775g triethanolamine
8.125g copper nitrate
62.5g sodium chloride

Made up to 250ml with distilled water.

TAC: 10mg 2-thiozolylazo-p-cresol in 100ml ethanol.

Standards:

From a 4mM stock solution and CHM of palmitic acid, 0.2mM, 0.4mM, 0.8mM and 1.0mM standards were made. These were kept refrigerated in glass bottles with plastic screw caps stable to CHM, until required.

Procedure:

(1) 100ul of standard or plasma (CHM for blank) was added to 3ml CHM in acid washed screw capped glass tubes.
(2) 1ml of stable copper reagent was added.
(3) The tubes were shaken vigorously for 6 minutes and centrifuged at 6000 rpm in a Koolspin centrifuge for 5 minutes.
(4) 1ml of the upper phase was transferred to a tube containing 0.25ml of TAC and the resulting solution was mixed well.
(5) Standards and samples were read in an Eppendorf photometer in a cuvette of 1cm light path at Hg 578 nm.

The concentraion of FFA in the samples was determined from the standard curve.

APPENDIX 9

Glycerol Assay

A fluorimetric assay was used, modified from that described by Laurell and Tibling (1966). This was based on the following reactions:

Glycerol + ATP $\xrightarrow{GK}$ Glycerol-1-Phosphate + ADP

Glycerol-1-Phosphate + NAD^+ $\xrightarrow{GDH}$ Dihydroxyacetone Phosphate + NADH

The dihydroxyacetone phosphate produced is trapped by hydrazine, and the amount of NADH formed is determined by measurement of its native fluorescence.

Solutions:

Zinc Sulphate: 0.087M

Barion Hydroxide: 0.083M

Hydrazine HCl buffer: 1M reagent grade with 1.5mM $MgCl_2$ adjusted to pH 9.4 with HCl.

Diluent: 0.01M NaOH with 1mM EDTA.

Glycerokinase: 1 $mg.ml^{-1}$ (Boehringer Biochemical).

Reaction Mixture: Per 5ml reaction mixture: 3.5ml Hydrazine HCl buffer, 1.5ml distilled water, 6 mg ATP, 10 mg NAD, 12.1mg cysteine, 5ul glycerokinase and 25ul of glycerin 3 phosphate dehydrogenase.

Standards:

From a 0.4mM stock solution, 20%, 40%, 60%, 80% and 100% standards were made using distilled water.

Deproteinization:

A 0.1ml of plasma or standard (distilled water as blank) was transferred to a small centrifuge tube containing 0.5ml of zinc sulphate. The resulting solution was then mixed and chilled. Next 0.5ml of barium hydroxide was added and the solutions allowed to stand for 5 minutes. They were centrifuged at 12000 rpm for 2 minutes.

Procedure:

(1) 0.1ml of reaction mixture and 0.2ml of supernatent were transferred to a test tube annd mixed.

(2) The tubes were capped and left to stand for 60 minutes.

(3) 1ml of diluent was added and the samples and standards were read in a Lochart fluorimeter. After subtracting the blank from the readings of the standards and samples, the concentration of glycerol in the samples was calculated from the standard curve.

APPENDIX 10.

Peak Expiratory Flow Rate and Medication, of an Asthmatic Athlete Changing Treatment.