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UNIVERSITY OF ALBERTA

APPLICATION OF OXYGEN UPTAKE KINETICS IN EXERCISE PHYSIOLOGY

BY

© STEPHEN R NORRIS

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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DEDICATION

This thesis is dedicated to my parents, Robert James Norris and Joan Grace Norris (formerly Bellinger), for their incredible support of, and commitment to, my continued education. I thank you both for your love, understanding, patience, and financial investment. My one regret concerns the lost time from each other that geographical separation necessitates. I hope that one day I will be able to justify the level of belief in me that you have so clearly demonstrated.

* * * * * * * * * * * * * * * *

ABSTRACT

Three separate studies investigated oxygen uptake kinetics for measurement reliability, monitoring of training adaptation in endurance athletes, and potential performance enhancing effects of Salbutamol.

The reliability study produced a reliability estimate of 0.9 for the time constant measures via a submaximal cycling protocol. This demonstrated an adequate level of reliability and provided the basis for the next two studies. The second study took 16 competitive cyclists through a carefully controlled eight week endurance cycling program. $\dot{V}O_2max$, transient oxygen uptake kinetics, and 40k time trial tests occurred five times (3 times pre-training, once at the midpoint, and once post-training). The transient protocol consisted of three equal ascending submaximal transitions with blood samples drawn at each stage for analysis of lactate concentration. The general trend, as the trained state of the cyclists rose, was for faster oxygen uptake time constants, lower blood lacate concentrations, higher $\dot{V}O_2max$ scores, and faster 40k time trial results. Overall, these results are supported by the literature and suggest that a combination of central and peripheral components are responsible for the time course of oxygen uptake. It was concluded that $\dot{V}O_2$ kinetics are relatively sensitive to endurance training adaptation, although, further investigation is required to clearly describe the underlying mechanism(s).

The third investigation used a submaximal oxygen uptake kinetics task, $\dot{V}O_2max$ cycling, pulmonary function tasks, a 60 second supramaximal sprint test, and a simulated 20k time trial to examine the possible ergogenic effect of Salbutamol on a group of cyclists. Fifteen trained nonasthmatic male cyclists were recuited into a double-blind, randomized cross-over design using a dosage of

Salbutamol twice the normal therapeutic level (400μg). Subjects performed four tests, separated by 48 hours, in each condition (placebo or Salbutamol). No significant differences were observed in any of the dependent variables, leading to the conclusion that Salbutamol has no performance enhancing properties as determined by the protocols adopted in this study.

In summary, this dissertation concludes that oxygen uptake kinetics (gas exchange dynamics) may have the potential to serve as a sensitive overall indicator of cardiorespiratory and muscular adaptation.

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CHAPTER ONE

GENERAL INTRODUCTION

General Introduction

Overview of the problem.

The establishment of valid and reliable non-invasive and, or, minimally intrusive physiological testing procedures has obvious benefits for athletic populations. The growth of exercise physiology as a distinct scientific discipline has led to the development of a myriad of general and sport specific testing protocols. Previous research (Hickson, Bomze, & Holloszy, 1978; Cerretelli, Pendergast, Paganelli, & Rennie, 1979; Cerretelli, Rennie, & Pendergast, 1980; Powers, Dodd, & Beadle, 1985; Burke, Thayer, Belcamino, Crocker, & Porter, 1990; Babcock, Paterson, & Cunningham, 1994) has identified that gas exchange kinetics may have a role to play in the description and quantification of adaptation to certain training stimuli. The monitoring of gas exchange kinetics in high performance athletes may be undertaken more frequently and closer to competition periods than with invasive and strenuous testing methods, since they may be described non-invasively and at submaximal work levels. Oxygen uptake kinetics may also provide a different perspective to training adaptation due to the acute rate component of the kinetic measure. That is, whereas $\dot{V}O_2$ and $\dot{V}O_2max$ reflect the amount of oxygen that can be taken up, the transient oxygen uptake response reflects how quickly that level of $\dot{V}O_2$ can be attained. Therefore, it was the premise for this dissertation that additional accurate and relevant information may be elicited from physiological assessment of oxygen uptake kinetics.

Introduction and review of related literature.

Maximal aerobic power ($\dot{V}O_2max$) has for some time been considered to be the definitive measure of cardiorespiratory efficiency and endurance (Hill & Lupton, 1923; Saltin & Åstrand, 1967; Sutton, 1992), with a number of criteria being cited as having use in the determination of $\dot{V}O_2max$ (Åstrand & Rodahl, 1977; Thomas, Cunningham, Plyley, Boughner, & Cook, 1981; Sutton, 1992). $\dot{V}O_2max$ is often used as a simplified quantitative term to describe the two aspects of oxygen transport (central component) and oxygen utilization (peripheral component) as a single entity. However, these two elements should not be dismissed since they are of extreme importance.

Central and peripheral adaptations to endurance training, generally signified by the increased ability to take up oxygen, have long been recognized. Central adaptations include increased heart efficiency, stroke volume (SV), and blood pressure (BP). Thus, increases in maximum cardiac output ($\dot{Q}$ = HR x SV), SV, and blood volume, and decreases in resting and submaximal exercise HRs are usually seen after endurance training. Peripheral adaptations, in contrast, occur within the trained muscle and are usually described by the traditional expression of oxygen extraction, the arterio-venous oxygen difference. Holloszy (1967) has been credited with the discovery of increased activity of oxidative enzymes in trained muscle, together with increased mitochondrial number and density, and increased skeletal muscle myoglobin content. According to Kiessling, Piehl, and Lundquist (1971), there are at least two advantages of an increased mitochondrial activity level. Initially, the increase in capacity to form adenosine triphosphate (ATP) is the most important. Secondly, the balance between mitochondrial function and lactate level has importance since metabolic changes (brought about due to endurance training) could negate rises in lactate level,

duce the rate of oxygen-independent glycolysis and, us, the formation of pyruvate and extramitochondrial duced nicotinamide adenine dinucleotide (NADH), sulting in reduced lactate levels and the ability to sustain bmaximal work at a higher relative level. Essentially, the :y element is to realize that although endurance-trained hletes may exhibit common 'central' adaptations, their spective 'peripheral' adaptations will reflect the specific ıture of their sports involvement.

These two broad aspects of $\dot{V}O_2max$, have fostered the :velopment of two basic and separate schools of thought, ased towards either central or peripheral limitations utton, 1992). These distinct views have led to much de- ıte between researchers with substantial information ex- ting to support both sides (e.g., Andersen & Saltin, 1985; 'agner, 1988; Connett & Honig, 1989; Stainsby, Brechue, 'Drobinak, & Barclay, 1989; Sutton, 1992). In terms of laptation to endurance training, the model proposed by erretelli and Di Prampero (1987) has received much at- ntion and has led to a development by Wagner (1988 &)91) that reduces the number of overall assumptions and lows for a role by hemoglobin in the peripheral diffusion ocess. The integrative approach by Wagner (1991) dis- nces itself from the traditional format of single limiting ctors to $\dot{V}O_2max$, and emphasizes that for endurance aining, as compared to acute exercise, peripheral changes e major contributors to the increase in $\dot{V}O_2max$, with ıcreased capillarization possibly being the fundamental)mponent. However, the measure of $\dot{V}O_2max$ does not ways demonstrate that training adaptation has actually ken place. It has been shown that $\dot{V}O_2max$ may reach a :iling level after only a few months of systematic

endurance training and yet sport performance can continue to improve (Ekblom, 1969; Saltin, 1969; Bouchard, Boulay, Simoneau, Lortie, & Pérusse, 1988). In fact, although $\dot{V}O_2max$ has been identified as an excellent predictor of endurance performance in athletes of differing maximal aerobic power (Costill, 1967; Foster, Daniels, & Yarborough, 1977), it is a relatively poor predictor in groups of athletes with similar $\dot{V}O_2max$ values (Conley & Krahenbuhl, 1980). Therefore, it appears that factors other than $\dot{V}O_2max$ are of importance for successful endurance performance.

The anaerobic threshold (AT), determined invasively via blood lactate measurment or non-invasively via gas exchange analysis, refers to 'the level of work or O_2 consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur' (Wasserman & McIlroy, 1973). It is often described as either an equivalent power output or a percentage of $\dot{V}O_2max$ ($\%\dot{V}O_2max$), and is widely used by sport scientists as an evaluative tool, since athletes have been found to have ATs occurring at a higher $\%\dot{V}O_2max$ than non-athletes (Wasserman & McIlroy, 1973; MacDougall, 1977; Tanaka & Matsuura, 1984; Londeree, 1986; Wasserman, 1987). The concept has obvious important implications for sport performance and researchers have been quick to adopt this parameter to establish particular training intensities, monitor training adaptation, and predict endurance performance (Whipp & Ward, 1980; Ready & Quinney, 1982; Rieder, Kuller, & Kindermann, 1987; Maffulli, Capasso, & Lancia, 1991). However, the AT continues to be a highly controversial topic with extensive investigations of the postulated underlying mechanisms, accurate detection and interpretation, terminology, and actual existence of this concept (Kindermann, Simon, & Keul, 1979; Skinner & McLellan, 1980; Yeh, Gardner, Adams, Yanowitz, & Crapo,

1983; Green, Hughson, Orr, & Ranney, 1983; Brooks, 1985; Davis, 1985; Hughson, Weisiger, & Swanson, 1987).

It is well established that oxygen consumption increases rapidly and then plateaus towards a steady-state, or maximal value, with the onset of exercise (Henry, 1951; Di Prampero, Davies, Cerretelli, & Magaria, 1970; Whipp & Wasserman, 1972; Whipp & Casaburi, 1982). Cerretelli, Rennie, & Pendergast (1980) have defined this oxygen uptake response at the onset of exercise ($\dot{V}O_2$on) as being an indicator of 'a recovery process' aimed at re-establishing a steady state condition as determined by the stimulus. That is, the rate of increase in $\dot{V}O_2$, as a response to the imposed physical work level, may be an indication of the circulatory capacity to deliver oxygen and for this oxygen to be utilized by the appropriate tissues (de Vries, Wiswell, Romero, Moritani, & Bulbulian, 1982). In keeping with the general concept of AT, Weltman, Katch, Sandy, and Freedson (1978) found that individuals with high ATs (expressed as a %$\dot{V}O_2$max) attained steady state $\dot{V}O_2$ levels significantly faster than those individuals with low ATs. This hints strongly at a tangible link between AT and the oxygen uptake response.

Various models have been put forward to characterize the kinetics of oxygen uptake responses (Swanson & Hughson, 1988; Di Prampero, Mahler, Giezendanner, & Cerretelli, 1989; Barstow, Lamarra, & Whipp, 1990; Whipp & Ward, 1990; Lamarra, 1990), with more complex equations being reported as the understanding of the underlying mechanisms has improved. These include the recognition that the kinetics of oxygen uptake at the onset of a constant work rate exercise follows a three-phase pattern, comprising of an immediate 'cardiodynamic' phase, a continued fast rise, and finally a slower increase as the asymptotic value is approached (Linnarsson, 1974; Whipp, Ward, Lamarra, Davis, & Wasserman, 1982; Barstow &

Molé, 1987; Inman, Hughson, Weisiger, & Swanson 1987; Sietsema, Daly, & Wasserman, 1989). The current consensus suggests that a mono-exponential process utilizing a time delay parameter quantifies the $\dot{V}O_2$on response overall for workloads below the lactate threshold, with oxygen uptake kinetics becoming somewhat more complex at exercise intensities beyond the lactate threshold (Roston, Whipp, Davis, Cunningham, Effros, & Wasserman, 1987). Thus, the $\dot{V}O_2$on response may be evaluated using the time constant τ from a single exponential process given as:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_{2ss} \cdot (1 - e^{-(t-TD)/\tau})$$

where Δ reflects the increment above the previous (rest or exercise) steady state level, and ss represents the steady state or asymptotic value. TD represents the time delay parameter and allows a best fit line (via non-linear least squares) to be calculated such that the time constant (τ) of the response can be established without artificially constraining the regression to pass through the origin. The overall rate of change of the response is then obtained from the sum of τ and TD (known as the Mean Response Time; MRT). The half-time of the $\dot{V}O_2$on response, t1/2$\dot{V}O_2$on, is simply put as the time, in seconds, required to bring about a 50% change in $\dot{V}O_2$ from pre-exercise to steady state exercise levels. More recently the literature has abandoned the use of half-times in favour of direct reporting of the time constant, τ, (Whipp & Ward, 1990).

In cross-sectional studies, the $\dot{V}O_2$max of individuals has been shown to significantly affect the t1/2 $\dot{V}O_2$on in adults. Faster half-times have been seen in subjects with high $\dot{V}O_2$max values as compared to individuals with low $\dot{V}O_2$max scores, for example, Powers, Dodd, and Beadle

(1985) found a correlation of r = -.80 ($p<0.05$) between $\dot{V}O_2max$ and $t1/2\dot{V}O_2on$ for highly trained endurance athletes, and Norris (1987) showed an r value of -.89 ($p<0.05$) for a similar study. Cooper, Berry, Lamarra, and Wasserman (1985) reported that the time constant for $\dot{V}O_2$ 'correlates well' with $\dot{V}O_2max$ in untrained children. However, Lake, Nute, Kerwin, and Williams (1986) did not find any such relationship between $\dot{V}O_2max$ and $t1/2\dot{V}O_2on$ in their study of runners, reporting an r value of .186.

Cerretelli, Pendergast, Paganelli, and Rennie (1979) and Hickson, Bomze, and Holloszy (1978) have shown $t1/2\dot{V}O_2on$ response times to quicken with physical training, and Burke, Thayer, Belcamino, Crocker, and Porter (1990) reported 'strong training effects of O_2 kinetics at the onset of exercise' following interval training. This faster response to the energy demand of increased muscular activity is associated with improvements in the kinetic responses of minute ventilation ($\dot{V}_E$) and heart rate in trained individuals. In addition, Grucza, Nakazono, and Miyamoto (1989) found the 'acceleration' at the onset of exercise for both $\dot{V}_E$ and cardiac output ($\dot{Q}$) to be positively 'connected' with $\dot{V}O_2max$. Further, Grucza et al., (1989) commented that variations in subject physical fitness, as well as genetic characteristics, may explain differences in research findings between various studies in the past. More recently, Babcock, Paterson, and Cunningham (1994) and Babcock, Paterson, Cunningham and Dickinson(1994) have even shown improvements in the oxygen uptake kinetics of elderly men (mean age 72.0, SD±4.4) after 24 weeks of cycle training, as well as an age-related/long-term inactivity decline in oxygen kinetics when compared with younger age groups.

Despite some conflicting information, the level of intensity of exercise is also a factor in the kinetics of oxygen uptake (Di Prampero et al., 1970; Cerretelli et al., 1980).

Indeed, several investigators have commented that if the attainment of steady state is delayed beyond three minutes, then the subject is deemed to be working beyond 'anaerobic threshold' (Whipp & Wasserman, 1972; Wasserman, 1987). From a different viewpoint, Haverty, Kenney, and Hodgson (1988) state that the highest workload at which steady state is not delayed may be equated with the last point at which the subject is in lactate balance and that this work intensity correlated highly with 5k running performance ($r = .87$; $p<0.05$) as shown by their population sample.

Walsh (1992) explained the training-induced faster $\dot{V}O_2$ response by stating that endurance training increases the mitochondrial power within the muscle. Since the glycolytic power is largely unchanged, the enhanced mitochondrial power allows for 'respiration to compete with glycolysis more successfully for substrate'. This translates into a faster oxygen uptake response at the onset of exercise and, therefore, a discernible reduction in the size of the oxygen deficit. In support of this view, Di Prampero, Mahler, Giezendammer, and Cerretelli (1989) found faster oxygen uptake kinetics in subjects with McArdle's syndrome, and also children, with lower glycolytic power than adults, have exhibited similarly faster responses (Armon, Cooper, Flores, Zanconato, & Barstow, 1991).

However, although hypotheses of peripheral regulation of oxygen kinetics would seem to have credence, Hughson (1990) and Walsh (1992) present compelling information to support the implication of an oxygen transport limitation for oxygen uptake kinetics. Several studies have demonstrated that cardiac output and heart rate have faster kinetic responses than oxygen uptake when starting exercise (Davies, Di Prampero, & Cerretelli, 1972; Linnarsson, 1974; Grucza, Miyamoto, & Nakazono, 1990). Perhaps the strongest case for the central limitation of oxygen uptake kinetics has been established by experiments in

which the oxygen delivery system has been altered with the effect that the kinetic response has been modulated in some way. For example, Petersen and co-workers (1983), as well as Hughson (1984), have shown that beta-adrenergic blockade significantly slows the oxygen uptake response, and Linnarsson (1974) demonstrated that oxygen uptake kinetics are also slowed when a reduced inspired oxygen fraction is imposed.

Overall, Walsh (1992) concludes that 'oxygen delivery sets the initial parameters and peripheral mechanisms then regulate oxygen utilization within the bounds initially established by delivery mechanisms'. Also, Gruzca et al., (1989) suggest that the mechanism of faster adjustments of the cardiorespiratory system to exercise in naturally 'fitter' individuals may be comparable to that developed through endurance trai. 'ng. It may be summarized that there appears to be substantial theoretical and allied support for the use of oxygen uptake kinetics, since this parameter may provide information regarding description of a higher trained state.

Rationale for investigative path.

In order to attain a level of expertise in the measurement and evaluation of oxygen uptake responses, it has first been necessary to develop a standard set of investigative protocols and establish an acceptable level of experimental reliability. After initial pilot work, a specifically designed reliability study (Chapter Two) was undertaken to establish the reliability of measurement of this parameter. The information and experience gained from this first study was then incorporated into two further investigations, one examining the responses to specific training (Chapter Three) and one describing the responses to an acute administration of an external agent (Chapter Four).

The reason for undertaking the training study was twofold. First of all, the author wished to pursue the notion that oxygen uptake kinetics could be routinely examined in a large athletic group without undue interference with training and competition schedules. Second, to test the hypothesis that this gas exchange parameter was sensitive to endurance training adaptation, as compared to $\dot{V}O_2max$. The longitudinal design involved a period of systematic aerobic endurance training coupled with a pre, mid, and post-training format of physiological testing which involved the assessment of oxyen uptake kinetics and parallel measures of standard exercise physiology parameters (e.g., $\dot{V}O_2max$, ventilatory threshold, and blood lactate accumulation).

The third study examined the effect of an acute dosage of Salbutamol, a β_2-selective adrenoceptor agonist used legitimately in the day-to-day treatment of asthma, upon oxygen uptake responses and other physiological measures. The rationale for this investigation was primarily driven by the ongoing conjecture, and theoretical support, that this pharmaceutical agent has performance enhancing properties for non-asthmatic athletes and that an indication of this

might be revealed by the examination of oxygen uptake responses.

This investigative route was, therefore, designed to address three fundamental questions:

1) Could oxygen uptake kinetics be measured in a carefully controlled manner, and with an acceptable level of reliability;

2). Does the oxygen uptake response parameter have a role to play in the routine monitoring of individuals undertaking aerobic endurance training; and

3). Does Salbutamol have the potential to enhance physical performance as demonstrated by faster oxygen uptake kinetics?

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CHAPTER TWO

THE RELIABILITY STUDY: RELIABILITY OF MEASUREMENT OF OXYGEN UPTAKE KINETICS DURING CYCLE ERGOMETRY

A version of this chapter was presented at the Canadian Association of Sports Sciences conference in Saskatoon, Saskatchewan, in October 1992.

Introduction

Recently, there has been a growing interest in the theoretical concepts underlying the changes in oxygen uptake ($\dot{V}O_2$) following a change, or changes, in forced power output. The vast majority of the available literature to date has focussed upon the kinetics of $\dot{V}O_2$ after an increase in power output (e.g., Hickson, Bomze, & Holloszy, 1978; Whipp & Casaburi, 1982; Powers, Dodd, & Beadle, 1985; Sietsema, Daly, & Wasserman, 1989; Di Prampero, Mahler, Giezendanner, & Cerretelli, 1989), with an additional emphasis being placed by researchers on the establishment of mathematical models used to describe such dynamic responses (e.g., Swanson & Hughson, 1988; Barstow, Lamarra, & Whipp, 1990; Whipp & Ward, 1990; Lamarra, 1990).

The rapid increase in $\dot{V}O_2$ following the onset of exercise is well established, and has been shown to follow a first order exponential function for step changes in power output at moderate levels of intensity (Cerretelli, Rennie, & Pendergast, 1980; Whipp & Casaburi, 1982; Barstow & Molé, 1987; Whipp & Ward, 1992), with $\dot{V}O_2$ kinetics becoming somewhat more complex at higher exercise intensities as metabolic acidosis is incurred (Roston, Whipp, Davis, Cunningham, Effros, & Wasserman, 1987; Whipp & Ward, 1990; Walsh, 1992). Cerretelli et al., (1980) have defined this $\dot{V}O_2$ transient response as being an indicator of a recovery process aimed at re-establishing a steady state condition as determined by the stimulus. That is, the rate of increase in $\dot{V}O_2$, as a response to the imposed power output, may be an indication of the circulatory capacity to deliver oxygen and for this oxygen to be utilized by the appropriate tissues (de Vries, Wiswell, Ronero, Moritani, & Bulbulian, 1982).

The development of self-contained, open circuit spirometry systems using breath-by-breath sampling methods has expanded the scope of many investigators to include the examination of gas exchange dynamics in humans. Experimental repeatability or consistency is of concern particularly when the dependent variable is associated with an inherent variability. That is, the interbreath variablity found when examining breath-by-breath responses, together with the intersubject variability, may have an impact upon the outcome of the observed parameters. Therefore, the reliability of measurement needs to be addressed before embarking upon further investigation.

The purpose of this investigation was to examine the reliability of measurement of oxygen uptake kinetics, using a SensorMedics 2900z metabolic measurement system, and the efficacy of a specific protocol during submaximal cycle ergometry. Previous pilot work suggested that, as a group, endurance trained individuals exhibit a similar and reduced level of breath-to-breath variation. Therefore, the selection of such subjects became an integral part of this study.

Materials and Methods

Eleven endurance athletes (triathletes and distance runners; eight male and three female: Table 2.1) participated in this project. All interaction with the subjects followed the guidelines for research with human subjects at the University of Alberta, including appropriate ethics approval and written informed consent.

The subjects performed a series of submaximal cycling tasks on a Monark 814E cycle ergometer equipped with a drop basket resistance loading system. During the cycling tasks, the subjects were connected to a previously calibrated SensorMedics 2900z metabolic measurement system, via a Rudolph face mask assembly (series 7920), operating in breath-by-breath mode. This system measured

expired flow levels and gas concentrations for oxygen and carbon dioxide as the basis for the required volume calculations ($\dot{V}O_2STPD$, $\dot{V}CO_2STPD$, and $\dot{V}_EBTPS$). All calculated values were displayed on a computer screen and printed in hard copy in real time, as well as being saved to the computer hard drive. Additionally, heart rate was monitored via the R-R interval of the electrocardiogram (ECG) using a Hewlett-Packard heart rate monitor (model 43200A).

The submaximal cycling tasks consisted of performing three repeated transitions from unloaded to loaded cycling, plus a rest phase, with each complete transition lasting nine minutes. The loaded phase was set at approximately 88 watts (i.e., 1.5 kp at 60 rpm) for all subjects so as to be in the domain of predominantly aerobic metabolism. Each phase (unloaded, loaded, and rest) lasted three minutes. This sequence was repeated by each subject on three separate days with a minimum of 48 hours between each test day. Care was taken to eliminate or reduce distracting elements from the testing environment, such as extraneous noise and unnecessary lab personnel movements.

The data analysis involved time averaging the oxygen uptake values over 10 second periods for each transition. These values were then described via a first order (single exponential) model as shown below:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_2ss \cdot (1 - e^{-(t-TD)/\tau})$$

Where Δ reflects the increment above the previous steady state level (i.e., loaded from unloaded cycling), and ss represents the steady state or asymptotic value. TD represents the time delay parameter and allows a 'best fit' line (via nonlinear least squares) to be calculated such that the time constant (τ) of the response can be established without artificially constraining the regression to pass through the origin.

A mean time constant was then produced from each of the separate trial occasions. These values were then subjected to a one-way ANOVA with repeated measures (α set *a priori* at 0.05). This process established a quantified assessment of reliability stated as an intraclass coefficient.

Results

The mean time constants for the three trials are shown in Table 2.2. The statistical analysis for reliability, via the ANOVA model stated earlier, yielded an intraclass coefficient (reliability estimate) of 0.9 for single treatments. Table 2.3 summarizes the statistical process.

Discussion

This study demonstrated a level of consistency of 0.9 (α = 0.05) for the time constant measures and, therefore, it may be stated that an adequate level of reliability in the assessment of transient oxygen uptake responses was achieved using this particular protocol. In this investigation, both means and variances were of importance and the focus of interest lies with the treatments factor. Thus, the ANOVA model was run as suggested by Winer (1962) and Maguire & Hazlett (1962) since 'the *fundamental* concept of reliability regardless of the discipline in which it is used is *consistency* not correlation' (Maguire & Hazlett, 1962). It would seem, then, that oxygen uptake kinetics may be examined through such methodology. However, there are a number of issues that deserve attention, particularly since they may have varying degrees of impact upon the measurement of gas exchange kinetics, and the quality of the resulting measures.

The recognition that there are differences, both between and within subjects, as regards breath-by-breath measures has been acknowledged for some time now. Priban

(1963) observed that breath-by-breath fluctuations during steady state conditions followed an opposing format That is, low tidal volumes (V_T) were linked with a high breathing frequency (f), and a high V_T with low f levels. The following expression illustrates clearly that an individual's breathing pattern is determined overall by the total minute ventilation ($\dot{V}_E$), which is itself influenced by V_T and f:

$$\dot{V}_E(l \cdot min^{-1}) = V_T(l) \times f(min^{-1})$$

Additionally, the time components to each breath (time for inspiration, T_I; and time for expiration, T_E) impact upon this expression, such that the statement may be expanded to include a breath duration element (T_{tot});

$$\dot{V}_E = V_T \times f = V_T \times 60 / T_{tot}(s)$$

Hence, it can be seen that V_T and f will exhibit a greater degree of variability than $\dot{V}_E$, which, together with alterations in flow patterns within the pulmonary vessels and the end expiratory volume, will result in variations in the level of gas exchange occurring. The possible permutations of the components that constitute a given $\dot{V}_E$ or breath are, therefore, enormous. This author, although at this stage without controlled experimental evidence to support this statement, has found that certain individuals display relatively large variations in interbreath characteristics and that, in general, well-trained and previously-trained endurance athletes exhibit the most regular interbreath responses at steady state levels. This anecdotal observation was the basis for using the group of subjects described earlier for this investigation.

These variations in breathing allow for obvious breath-by-breath fluctuations in the actual gas exchange

taking place in the lung. According to Lamarra et al., (1987), the dynamic response to the onset of exercise may be said to reflect two aspects, 'an underlying physiological response, and noise, whose magnitude proves to be much greater in some subjects than others' (see earlier anecdotal point). Lamarra et al., (1987) have examined the influence of breath-by-breath fluctuations 'on the characterization of their underlying kinetic responses during exercise'. These authors concluded that 'the breath-to-breath fluctuations in $\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ during exercise may be appropriately characterized as uncorrelated Gaussian noise', and that subjects with low noise characteristics would require a fewer number of exercise transitions than would those with high noise levels to achieve a given level of accuracy.

The actual attainment of steady state, both for the initial condition and the subsequent level, should also be determined through the examination of several physiological variables, such as heart rate, $\dot{V}O_2$, $\dot{V}_E$, and $\dot{V}CO_2$, depending upon the outcome measure being evaluated (see Tables 2.4 and 2.5, and Appendix A). This is an important aspect for the effective examination of transient responses derived through step loading protocols, since these steady state levels provide the basis for subsequent evaluation of the response data.

Indirectly associated with the steady state levels and directly with the step loading protocol format, is the ability to impose the required forced power output as instantaneously as possible at the start of the transition phase. In an ideal situation this would be accomplished by using a computer controlled electrically braked ergometer (e.g., Siemans or Mijnhardt cycle ergometers.). Electrically braked cycle ergometers, controlled by computers, are able to impose predetermined power outputs as and when required and, therefore, step loading protocols may be implemented with a high degree of accuracy. The standard Monark mechanically braked cycle ergometer, using a

spring loaded tension applied via a screw mechanism, is inadequate for step loading protocols due to the uncertainty regarding the time element of load application. Where there is an unavailability of electrically braked systems, a compromise may be reached by adopting a drop basket resistance loading mechanism on a mechanically braked cycle ergometer (e.g., Monark 814E). Unlike the highly controlled computerized electrical version, this latter system is somewhat crude, in terms of both accuracy of load timing and step size. However, this mechanism was used in this investigation without any perceived detriment and it is suggested that the use of an electrically braked system would only have enhanced the resulting reliability estimate.

The prevailing test environment is one key area where the researcher does have a high degree of control and when investigating gas exchange dynamics this must be exercised. Obviously, the test conditions must be held constant for all subjects over all test sessions, and should be such that little or no extraneous factors can impinge upon the subject. For example, the number of test personnel present and degree of familiarity with the subject in question should be held constant. That is, a minimum number of test personnel should be involved, and the subject should feel comfortable with these individuals being present during the test phase. Noise disturbances, particularly in the immediate vicinity and, where possible, in the general location of the test site, should be eliminated or minimized, (e.g., incoming telephone calls, opening and closing of doors, and even excessive talking). The concern over noise interference is emphasized when trying to establish steady state criteria. This author has observed that subjects exhibit a noticeable degree of learning with regard to the format of the protocols adopted for transient parameter evaluation and the general expectations of them by the investigative team. Therefore, it is recommended that sufficient time be allowed for subject familiarity with the test conditions before systematic exper-

imentation commences. In summary, the investigation of gas exchange dynamics in applied situations requires careful planning and controlled execution, however, this author believes that with appropriate care such variables may be examined routinely.

Table 2.1. Physical characteristics of the subjects.

Subject	Age yr	Height cm	Weight kg	Sex M/F
1	35	157	55.1	F
2	24	169	76.7	M
3	28	160	51.3	F
4	31	163	63.1	F
5	27	172	80.6	M
6	33	183	75.0	M
7	34	167	72.5	M
8	32	172	68.5	M
9	26	175	75.7	M
10	24	171	76.4	M
11	31	170	75.0	M
MEAN	30	169	70.0	
± SD	4	7	9.5	

Table 2.2. Mean (±SD) individual and group time constants for each day and complete test sequence, plus model statistics.

Subject	Day 1 s	Day 2 s	Day 3 s	MEAN s	±SD s
1	37.2	36.5	37.5	37.1	0.4
2	30.1	30.1	29.2	29.8	0.4
3	30.8	30.8	31.4	31.0	0.3
4	36.1	36.7	36.7	36.5	0.3
5	29.2	29.0	30.6	29.6	0.7
6	34.2	34.5	35.0	34.6	0.3
7	31.5	30.3	31.7	31.2	0.6
8	35.3	34.1	33.9	34.4	0.6
9	35.6	32.0	33.2	33.6	1.5
10	33.7	35.0	32.8	33.8	0.9
11	32.5	32.7	32.3	32.5	0.2
MEAN	33.3	32.9	33.1	33.1	0.2
±SD	2.7	2.7	2.5	2.5	
RSS	0.170	0.159	0.157		
±SD Res	0.097	0.093	0.093		

NB: RSS = residual sum of squares

SD Res = standard deviation of residuals

Table 2.3. One factor ANOVA-repeated measures for reliability of mean time constants.

Source:	df:	SS:	MS:	F-test	P value:
Between subjects	10	190.976	19.098	28.135	.0001
Within subjects	22	14.933	.679		
Treatments	**2**	**.928**	**.464**	**.663**	**.5265**
Residual	20	14.005	.7		
Total	32	205.91			

Single Treatment Reliability Estimate: **0.9**

Table 2.4. Transient oxygen uptake protocol: Mean (±SD) oxygen uptake steady state information (n=11).

Subject	Unloaded $\dot{V}O_2$ SS ml·min^{-1}	±SD	Loaded $\dot{V}O_2$ SS ml·min^{-1}	±SD	$\Delta \dot{V}O_2$ ml·min^{-1}	±SD
1	808	50	1775	34	967	31
2	991	85	2021	58	1031	53
3	706	94	1649	48	943	42
4	879	26	1917	36	1038	21
5	829	70	1743	74	914	164
6	903	55	1913	49	1010	62
7	965	26	1962	28	997	63
8	961	48	1872	75	910	50
9	1013	33	2017	64	1003	56
10	953	62	1878	29	925	41
11	888	92	1854	26	966	21
MEAN	900	58	1873	47	973	55
±SD	91	25	115	18	46	39

NB: No significant differences found for 'within subjects' data ($p>0.05$)

SS = steady state

Δ (delta) = change in O_2 consumption from unloaded to loaded cycling

Table 2.5. Transient oxygen uptake protocol; Mean (±SD) heart rate steady state information (n=11).

Subject	Unloaded HR SS $b \cdot min^{-1}$	±SD	Loaded HR SS $b \cdot min^{-1}$	±SD	ΔHR $b \cdot min^{-1}$	±SD
1	92	1	134	1	43	2
2	90	6	115	2	25	4
3	87	8	133	1	46	7
4	83	7	130	2	47	9
5	80	7	113	1	33	7
6	74	6	110	2	36	3
7	84	3	111	1	27	3
8	91	2	114	1	23	4
9	80	2	105	0	25	2
10	102	6	129	6	27	2
11	79	1	104	3	25	3
MEAN	86	4	118	2	32	4
±SD	8	3	11	1	9	2

NB: SS = steady state

Δ (delta) = change in HR from unloaded to loaded cycling

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CHAPTER THREE

THE TRAINING STUDY: ANALYSIS OF TRANSIENT OXYGEN UPTAKE RESPONSES FOLLOWING AEROBIC TRAINING

An early communication of this chapter appeared as a poster presentation at the American Physiological Society's "Integrative Biology of Exercise" meeting in Colorado Springs, Colorado, in September 1992.

A full version of this chapter was presented at the Canadian Society of Exercise Physiology conference in London, Ontario, in October 1993.

Introduction

It is well established that oxygen consumption increases rapidly and then plateaus towards a steady state, or maximal value, with the onset of a square wave work function (Henry, 1951; Di Prampero, Davies, Cerretelli, & Margaria, 1970; Whipp & Wasserman, 1972; Whipp & Casaburi, 1982). Cerretelli, Rennie, and Pendergast (1980) have defined this '$\dot{V}O_2$on' transient as being an indicator of a recovery process aimed at re-establishing a steady state condition as determined by the stimulus. That is, the rate of increase in $\dot{V}O_2$, as a response to the imposed physical work level, may be an indication of the circulatory capacity to deliver oxygen and for this oxygen to be utilized by the appropriate tissues (de Vries, Wiswell, Romero, Moritani, & Bulbulian, 1982).

Several studies have identified that the time constants for such dynamic responses can be improved with aerobic endurance training (Hickson, Bomze, & Holloszy, 1978, Cerretelli, Pendergast, Paganelli, & Rennie, 1979; Burke, Thayer, Belcamino, Crocker, & Porter, 1990; Babcock, Paterson, & Cunningham, 1994). A strong negative correlation ($r=-.80$, $p<0.05$) has also been reported for the 'half-time' ($t1/2\,\dot{V}O_2$on) of the oxygen uptake response and $\dot{V}O_2$max in trained individuals(Powers, Dodd, & Beadle, 1985; Norris, 1987), although this level of relationship has been refuted by Lake, Nute, Kerwin, and Williams (1986). Grucza, Nakazano, and Miyamoto (1989), in their study of untrained men, reported that 'cardiorespiratory kinetics in response to relative intensity of exercise increased with aerobic capacity', which suggests a similar mechanism being responsible for both inherent cardiorespiratory kinetics and those developed by endurance training. It should be noted that these authors (Grucza et al., 198[illegible] refer to 'aerobic capacity', although they actually measured and evaluated aerobic power. Other investigators have

commented that if the attainment of steady state is delayed beyond three minutes, then the subject is deemed to be working beyond anaerobic threshold (Whipp & Wasserman, 1972), although Haverty, Kenney, and Hodgson (1988) take a different viewpoint and state that the highest workload at which steady state is not delayed may be equated with the last point at which the subject is in 'lactate balance' and that this point correlated highly with 5k running performance ($r=0.87$, $p<0.05$) as shown by their population sample. More recently, Yoshida & Udo (1991), reported a significant relationship between oxygen uptake time constant and lactate threshold during training of endurance athletes ($r=-0.76$).

The use of gas exchange dynamics may offer new information to those monitoring the physiological responses of athletes. Therefore, the purpose of this study was measure and evaluate the changes in oxygen uptake kinetics, in comparison with more traditional physiological parameters, in a select group of cyclists before, during, and after eight weeks of endurance training.

Materials and Methods

Sixteen competitive endurance cyclists (fourteen male and two female; Table 3.1) participated in this project. All interaction with the subjects followed the guidelines for research with human subjects at the University of Alberta, including appropriate ethics approval and written informed consent. The investigation followed a quasi-experimental time-series design (single group) as suggested by Campbell and Stanley (1966), and was made up of three consecutive phases:

1) Pre-training test period to establish reliability of baseline information: this involved an approximate four week time span of three repetitions of the main tests at suitable intervals by each subject;

2) Training period: lasting nine weeks, with four weeks of training, one week of 'midpoint' testing, and another four weeks of training; and,

3) Post-training test period: upon completion of the training phase, all the tests were repeated.

The subjects performed a sequence of tasks on five occasions during the course of this investigation (three pre-training, one after four weeks of training, and one post-training), including of a VT/$\dot{V}O_2$max test, a transient oxygen uptake protocol, and a 40k time trial (Figure 3.1). The VT/$\dot{V}O_2$max test was performed on a cycle ergometer (Monark 818E) using a protocol of 40 watt (W; 0.5kp at 80rpm) power output increments every two minutes until ventilatory threshold (VT) was surpassed, after which time a one minute loading schedule was adopted until $\dot{V}O_2$max was attained. Ventilatory threshold (VT) was determined by visual inspection of the data after each VT/$\dot{V}O_2$max test using the 'Mechanism II' method of Wasserman, Beaver, and Whipp (1990). This method requires a group of responses to occur simultaneously for VT estimation to be made. That is, a systematic increase in the ventilatory equivalent for O_2 (as compared to previously falling or constant values) at a time when the ventilatory equivalent for CO_2 is not rising. A previously calibrated SensorMedics 2900z metabolic measurement system, operating in mixing chamber mode (20 second time averages) and connected to each subject by a Rudolph mouthpiece assembly (Series 2700), was used to collect gas exchange information. This system measured expired flow levels and gas concentrations for oxygen and carbon dioxide as the basis for the required volume calculations ($\dot{V}O_2$STPD, $\dot{V}CO_2$STPD, and $\dot{V}_E$BTPS). Heart rate was monitored via the R-R interval of the electrocardiogram using a Hewlett-Packard heart rate monitor (model 43200A).

The transient oxygen uptake protocol consisted of three equal ascending transitions in power output from unloaded cycling to approximately 78W, 157W, and 235W for the males (Figure 3.2). The two female subjects ascended to 55W, 110W, and 165W in a similar fashion. Henceforth, these three work loads will be referred to as WL1, WL2, and WL3 respectively. The initial transition from unloaded cycling to WL1 was repeated three times. Each transition to WL1 was comprised of three minutes of steady state data unloaded, three minutes of transition time, and three minutes of static rest. At the end of the third WL1 transition a further two minutes (five minutes total) was added and the protocol continued on without further rest to the next two work stages (WL2 and WL3), each lasting five minutes. Gas exchange data was collected using the SensorMedics 2900z system operating in breath-by-breath mode, together with a Rudolph face mask (Series 7920) and a Perma-Pure® small diameter collection tube. Steady state information for the transient oxygen uptake protocol is presented in Appendix B.

As illustrated by Figure 3.2, the final sequence of ascending work rates was extended to allow for appropriate blood collection from each subject at each work level. A teflon catheter, with a heparin lock mechanism, placed in a forearm vein was used to collect the blood samples from each subject for later analysis of blood lactate concentration levels. Immediately after the blood was drawn, 0.5ml of whole blood was transfered to a test tube containing 2ml of cold, 4% perchloric acid. This was then vortexed and allowed to sit for at least five minutes in an ice bath. After this period, the tubes were centrifuged at 2500 rpm for approximately 10 minutes until a clear filtrate was obtained. This filtrate was then transfered to a new plastic test tube and frozen for storage. After being allowed to thaw, 0.05ml of the protein free filtrate was added to 0.7ml

of a reagent mixture containing β-NAD^+, glycine-hydrazine buffer, lactate dehydrogenase suspension, and water. This process was repeated in triplicate. Quantitative analysis of the resulting reaction was then obtained by measurement of the NADH formation via absorption spectrophotometry (Pye Unicam PU8800 UV/VIS spectrophotometer). Finally, these results were compared to standard curve data using a computer-run least squares regression program.

The 40k time trials were performed on a purpose-built computerized cycle ergometer system that allowed the subjects to use their own racing bicycle. A front fork stand was used to optimize stability. The subjects raced the 40k from a stationary start and were given both visual and auditory feedback on distance covered, but were not provided with split or cumulative performance time until completion of the study.

The subjects undertook a progressively overloaded training program requiring supervised training sessions five days per week, for an initial duration of 40 minutes per session. This duration was subsequently raised by five minutes at the end of each two week phase of training, so that at the end of the study the subjects were exercising for 55 minutes per session. The format of training required continuous cycling at an exercise heart rate approximately equivalent to that observed for VT during their VT/ $\dot{V}O_2max$ test. In reality, a five beat heart rate range (heart rate at VT, plus or minus two beats) was implemented. This intensity was performed during four of the five sessions per week, with the fifth session maintained at a lower intensity of effort (i.e., approximately 15 beats per minute lower than for the more demanding sessions). A typical training week would be as follows;

Monday:	40 minutes, HR at ≈	VT
Tuesday:	40 minutes, HR at ≈	VT

Wednesday:	Rest day
Thursday:	40 minutes, HR at ≈ VT
Friday:	40 minutes, HR ≈ 15 below VT
Saturday:	40 minutes, HR at ≈ VT
Sunday:	Rest day

The subjects used their own bicycles and training devices (rollers or wind trainers) and HRs were monitored using Polar Pacer heart rate monitors. In all, the subjects completed eight full weeks of training.

The analysis of the transient oxygen uptake data involved time averaging the oxygen consumption values over 10 second periods for each transition. These values were then described via a first order (single exponential) model as shown below:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_2ss \cdot (1 - e^{-(t-TD)/\tau})$$

Where Δ reflects the increment above the previous steady state level (i.e., loaded from unloaded cycling), and ss represents the steady state or asymptotic value. TD represents the time delay parameter and allows a 'best fit' line (via nonlinear least squares) to be calculated such that the time constant (τ) of the response can be established without artificially constraining the regression to pass through the origin.

The three initial values (pre-training) for each variable were examined for consistency, with no significant differences being identified ($p>0.05$), and then averaged to provide a single and stable pre-training figure (see Appendix B). All dependent variables were then subjected to a one-way ANOVA with repeated measures for the pre, mid, and post-training conditions (α set *a priori* at 0.05). A post hoc multiple comparison test, the Scheffé procedure, was utilized when appropriate. In addition, Pearson Product

Moment correlational analysis was also performed on certain parameters to examine for possible association.

Results

The overview of the results for all the dependent variables clearly illustrates the effect of endurance training on this group of subjects (see Tables 3.1 to 3.4). All the dependent variables, with the exception of maximal heart rate, were significantly different when comparing the pre to post-training values ($p<0.05$). That is, the time constants for oxygen uptake transitions at all three work levels (WL1, WL2, and WL3) were faster, the lactate concentrations were reduced, $\dot{V}O_2max$ increased, VT increased, and 40k time trial performance improved. When comparing the pre to mid-training values, an identical significant response in the dependent variables (excluding maximal heart rate) was also observed ($p<0.05$).

However, with regard to the comparison between the mid and post-training values, the WL1 oxygen kinetics transition decrease, reduction in lactate concentration at WL2 and WL3, and VT improvement were the only observable changes from a statistically significant standpoint ($p<0.05$). In general, however, all dependent variables, with the exception of maximal heart rate and $\dot{V}O_2max$, demonstrated a trend associated with improved performance over the entire course of training.

The steady state heart rate responses at the end of the unloaded cycling phase and each submaximal work load are presented in Table 3.5. Analysis of variance clearly revealed significant differences between the pre and mid-training, and pre and post-training values for all four work conditions ($p<0.05$). In a similar fashion, oxygen uptake steady state values for the four work loads are shown in Table 3.6, with ANOVA revealing significant differences for

the pre vs mid and pre vs post-training WL2, and the pre vs post WL3 condition.

Discussion

The results of this study are in general agreement with the wealth of information regarding the effects of endurance training on humans. That is, an increase in $\dot{V}O_2max$ and VT, a reduction in heart rate and blood lactate accumulation at given submaximal work loads, and an improvement in sports performance (as determined by the 40k time trial) were seen to occur over the course of the training period ($p<0.05$).

A significant improvement in $\dot{V}O_2max$ took place during the first four weeks of training, after which time aerobic power effectively remained constant, whereas the measure of VT (established during the $\dot{V}O_2max$ cycle tests) improved significantly after both training periods. Expressed in terms of power output (watts; W), the mean VTs for the pre, mid, and post-training observations were 188W (SD±40), 219W (SD±41), and 239W (SD±41) respectively. Although the VT is highly controversial in terms of existence, cause, and measurement, it is often used by researchers as a reflection of the 'lactate threshold' (or 'lactate turnpoint'; Noakes, 1991) and, therefore, as a possible indicator of endurance performance (Beaver, Wasserman, & Whipp, 1986; Powers & Howley, 1994). These values illustrate that the highest workload (WL3) was quite rigorous for these subjects and this indicates why the blood lactate values were noticeably elevated throughout the course of the study for WL3.

The blood samples collected during the transient oxygen uptake protocol reveal a trend of reduced lactate for the study as a whole. Blood lactate accumulation level during unloaded cycling was not significantly altered, possibly due

to a lack of sensitivity at such a low work load to determine if any change had actually taken place. This explanation may also apply to the lactate values for WL1 that did show a significant reduction for the pre vs mid and pre vs post periods, but not for the mid vs post condition. The blood lactate concentrations for the two higher work loads (WL2 and WL3) were significantly reduced after both training periods, thereby reflecting the changes in VT and further suggesting some link between the two systems. Overall, these observations support previous investigations reporting increases in anaerobic threshold (lactate and, or, ventilatory) without parallel changes in $\dot{V}O_2max$ (Denis et al, 1982; Henritz et al, 1985; Korht et al, 1989), as well as the documented reduction in blood lactate at the same absolute and relative submaximal work rates after aerobic training (Winder, Hickson, Hagberg, Ehsani, & McLane, 1979; Hagberg, Hickson, Ehsani, & Holloszy, 1980).

The slight differences in steady state $\dot{V}O_2$ shown in Table 3.6 (also Appendix B), although of statistical significance in three cases, are not of particular concern to the author. This is because such small changes (3-4%) may easily be attributed to changes in the subjects' efficiency over the course of the training period, rather than due to some other systematic manifestation.

The oxygen uptake kinetics demonstrated a clear trend of reduction in the respective time constants for each work transition across all conditions (pre vs mid vs post). However, only the WL1 transition exhibited statistically significant differences between the pre, mid, and post-training periods. This occurence may be due to the large degree of subject variance for the higher two work loads, which serves to mask any conclusive findings for these transitions. The WL1 transition results for the mid vs post-training condition, together with the trend of faster time constants for the higher work loads, suggest an

improvement in oxygen uptake kinetics despite a plateauing of $\dot{V}O_2max$. These oxygen uptake kinetics results may well be viewed as an indication of continued adaptation to the endurance training being undertaken in the mid to post-training period. The question that must be addressed concerns the aspect of how and why the time constants continue to decline despite constant aerobic power values. There are a number of plausible explanations for this occurrence.

First of all, it should be realized that the training program itself may not have been of sufficient intensity, particularly during the second half of the training block, to bring about continued and optimal improvement in $\dot{V}O_2max$. That is, the post-training $\dot{V}O_2max$ cannot be viewed as a true genetic 'ceiling' value and, therefore, the plateau seen in $\dot{V}O_2$ between mid and post-training is artificial in the sense of potential physiological adaptation. Second, a number of factors concerned with the cardiovascular and respiratory systems may enhance oxygen transport without impacting upon $\dot{V}O_2max$ necessarily, and these include increases in plasma volume and total hemoglobin (Kanstrup & Ekblom, 1984), and a more effective blood flow distribution to active muscle and an enhanced arteriovenous oxygen difference (Blomqvist, 1983). It is also clearly realized that endurance training brings about marked changes in autonomic fuction such that sinus bradycardia is evident at rest, coupled with reduced heart rate at any absolute level of submaximal exercise (Grucza et al., 1989). This bradycardia is probably due to an increased parasympathetic activity which still exerts a considerable influence during low work levels. At the onset of exercise this parasympathetic activity may then experience rapid inhibition and increasing β-adrenergic stimulation resulting in faster heart rate kinetics and a profound effect upon the acceleration in cardiac

output. Grucza et al., (1989) reported significantly faster kinetics of minute ventilation and cardiac output in subjects with higher $\dot{V}O_2$max scores, although at the present time the mechanism of this response remains unclear. The declining submaximal heart rate responses in this investigation (see Table 3.5 and Appendix B) lend support to this view of central adaptation contributing to enhanced cardiorespiratory kinetics, inclusive of the oxygen uptake responses.

A number of studies have shown that myoglobin, a protein in muscle that significantly aids the diffusion of oxygen from the capillary to the mitochondria, is increased substantially by endurance training (Hickson, 1981). This aspect, coupled with an accelerated minute ventilation and cardiac output, could certainly facilitate faster oxygen uptake kinetics within the time frame of this study.

Holloszy (1967) initially demonstrated the now well-documented finding that endurance training brings about an increase in muscle oxidative enzyme activity, and that this increase would also lead to lower concentrations of metabolic regulators (i.e., adenosine diphosphate, ADP, and inorganic phosphate, Pi) at given submaximal work loads (Holloszy, 1967; Gollnick & Saltin, 1982). Essentially, after endurance training, a smaller change in substrate concentration (ADP) is required to maintain an established flux through the aerobic pathways (Gollnick & Saltin, 1982; Holloszy & Coyle, 1984).

However, although enhanced oxidative enzyme activity may aid the rate of oxygen utilization, Walsh (1992) suggests that it 'may be more appropriate to view faster oxygen kinetics after training as a reduction in diffusion distance' between the blood, the mitochondria, and the myofibrils. The model of Wagner (1991; after Cerretelli and Di Prampero, 1987) regarding $\dot{V}O_2$ would support this notion. Additonally, the well-established concept of increased

capillary density in trained muscle (Hermansen & Wachtlova, 1971; Andersen, 1975) facilitates the oxidative processes by aiding oxygen delivery to the working site, although the extended time course for such adaptation precludes a significant contribution in this instance (Ingjer, 1979). As regards the kinetics of oxygen uptake at the onset of work, the increased sensitivity to ADP concentration results in an earlier activation of oxidative phosphorylation at the expense of glycolysis. According to Walsh (1992), this could mean a 'major reduction' in the size of the oxygen deficit, and, therefore a smaller (faster) $\dot{V}O_2$ tau (τ) as illustrated by the equation:

$$\tau = O_2 \text{ deficit} / \Delta \dot{V}O_2(ss)$$

This concept results in a faster transition of oxygen uptake from the initial level to the new steady state, as well as reduced lactate and hydrogen ion (H^+) formation. Therefore, this description is tentatively supported by the findings of this study, as evidenced by faster τ values, reduced lactate accumulation, and increased VT. In reality, however, since this investigation did not involve itself with highly invasive procedures, these theoretical concepts cannot be substantiated at this point.

The correlation analyses performed upon completion of training are presented in Tables 3.7, 3.8 and 3.9. It can be seen that $\dot{V}O_2max$, as an absolute measure ($l \cdot min^{-1}$), correlated highly with both measures for VT (W and $\dot{V}O_2$), as well as with the 40k time trial parameters (performance time and average $\dot{V}O_2$). In keeping with this trend, the association between the measured VT and 40k markers was also strong. As regards the oxygen uptake response, this investigation did not find the marked negative correlation between the transient response and $\dot{V}O_2max$ previously

reported by Powers et al. (1985) and Norris (1987). However, in this investigation a negative directional association overall for the $\dot{V}O_2$/oxygen uptake response interaction was found.

In summary, the use of submaximal oxygen uptake kinetics, analyzed using appropriate methodology, seems to offer exercise physiologists an additional and relatively sensitive parameter with which to monitor endurance training adaptation, although it should be realized that the time constant of oxygen uptake is a 'whole body measure' evaluated at the mouth. Therefore, in the absence of other invasive procedures designed to examine processes occurring within the exercising athlete, it is inappropriate to assign a specific definition to the parameter at this time. Walsh's (1992) comment concerning an integration between central and peripheral components in the resulting oxygen uptake kinetics encompasses the concept as a whole. This notion allows for plasticity within the system, both in terms of magnitude and time course of adaptation, such that as one facet approaches a physiological ceiling, another component continues the process to some degree.

Finally, it may be stated that further investigation of gas exchange dynamics and adaptation to endurance training is required, particularly in terms of establishing mechanistic links with *in vivo* processes, before a definitive statement can be made concerning a role for oxygen uptake responses in the routine monitoring of athletes.

Table 3.1. Physical characteristics of the subjects.

Subject	Age yr	Height cm	Weight kg	Sex M/F
1	21	182.5	83.7	M
2	21	175.9	72.9	M
3	21	177.2	74.1	M
4	21	190.3	87.1	M
5	25	177.6	64.8	M
6	18	168.7	58.2	M
7	23	154.9	56.2	F
8	23	177.5	64.3	M
9	28	188.5	84.1	M
10	28	176.7	68.9	M
11	24	174.5	71.6	M
12	29	177.1	69.9	M
13	21	165.1	57.4	F
14	18	187.9	75.6	M
15	19	180.1	77.6	M
16	22	179.5	64.1	M
MEAN	23	177.1	70.7	
±SD	3	8.9	9.6	

	TRAINING PERIOD												
	PRE				MID								POST
WEEK	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9
$\dot{V}O_2max.$	•		•	•					•				•
Transient	•		•	•					•				•
40k TT	•		•	•					•				•

• = Test probe/data collection

Design Summary:	01	02	03	X	04	X	05

Figure 3.1. Schematic of testing sequence and design.

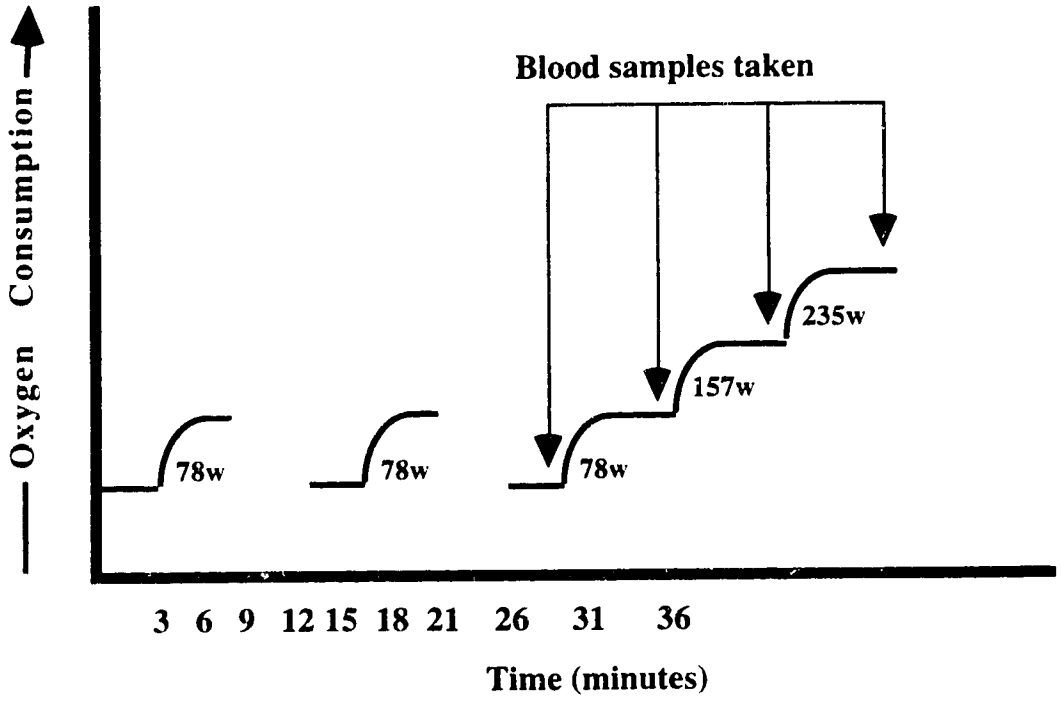

Figure 3.2 . Schematic of transient oxygen uptake protocol for the male subjects.

Table 3.2. Mean (± SD) values of basic descriptive results (Pre/Mid/Post).

	Mean Pre	SD±	Mid	Post
$\dot{V}O_2max$ ($l \cdot min^{-1}$)	4.0_{ab}	0.2	4.2_{a}	4.2_{b}
±SD	0.6	0.2	0.6	0.6
$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	56.8_{ab}	2.3	59.9_{a}	60.8_{b}
±SD	6.6	1.8	7.0	6.9
HRmax ($b \cdot min^{-1}$)	197	3	195	195
±SD	5	1	6	6
VT (W)	188_{ab}	13	219_{ac}	239_{bc}
±SD	40	13	41	41
VT ($l \cdot min^{-1}$)	2.6_{ab}	0.1	3.0_{ac}	3.2_{bc}
±SD	0.5	0.1	0.5	0.5
40k TT (s)	4658.0_{ab}	147.3	4336.2_{a}	4268.0_{b}
±SD	400.3	89.1	351.1	332.1

NB: Paired letters denote significant difference ($p<0.05$)

Table 3.3. Mean (±SD) time constants (τ in seconds Pre/Mid/Post) for the three work loads (WL1, WL2, and WL3).

	WL1 Pre	WL1 Mid	WL1 Post	WL2 Pre	WL2 Mid	WL2 Post	WL3 Pre*	WL3 Mid	WL3 Post
Mean	29.2$_{ab}$	24.4$_{ac}$	21.9$_{bc}$	48.3$_{ab}$	39.5$_{a}$	36.3$_{b}$	76.9$_{ab}$	63.5$_{a}$	56.8$_{b}$
±SD	6.6	5.1	5.5	15.0	9.5	10.0	19.0	11.8	11.8
RSS	0.16	0.18	0.09	1.02	0.51	0.19	2.07	1.24	0.56
SD Res	0.09	0.09	0.07	0.20	0.14	0.10	0.33	0.26	0.16

*NB: Since two subjects did not complete at this level Pre-training, their data was consequently excluded at the Mid and Post-training sampling points: Paired letters denote significant difference ($p<0.05$)

RSS = residual sum of squares

SD Res = standard deviation of residuals

Table 3.4. Mean (±SD) blood lactate accumulation(milliMoles per litre of blood) at each collection level; unloaded cycling, WL1, WL2, and WL3.

	Unl Pre	Unl Mid	Unl Post	WL1 Pre	WL1 Mid	WL1 Post	WL2 Pre	WL2 Mid	WL2 Post	WL3 Pre	WL3 Mid	WL3 Post
Mean	1.10	0.87	0.90	1.68	1.14	1.12	4.00	3.01	2.18	10.71	8.13	6.79
				ab	a	b	ab	ac	bc	ab	ac	bc
±SD	0.33	0.53	0.37	0.70	0.39	0.39	2.05	1.30	1.12	3.45	3.25	2.92

NB: Paired letters denote significant difference ($p<0.05$)

Table 3.5. Mean (±SD) heart rates from transient protocol ($b \cdot min^{-1}$).

		Work Load							
		UNL		WL 1		WL 2		WL 3	
		Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Pre	Mean	101$_{ab}$	5	126$_{ab}$	4	160$_{ab}$	4	185$_{ab}$	4
	±SD	11		14		19		11	
Mid	Mean	91$_{a}$	3	115$_{a}$	4	147$_{a}$		174$_{a}$	
	±SD	9		11		16		12	
Post	Mean	95$_{b}$	4	117$_{b}$	4	147$_{b}$		174$_{b}$	
	±SD	9		12		18		14	

NB: Paired letters denote significant difference ($p<0.05$).

Pre condition had three separate testing occasions.

See Appendix B for individual subject data.

Table 3.6. Mean (±SD) oxygen uptake from transient protocol ($ml \cdot min^{-1}$).

		Work Load							
		UNL		WL 1		WL 2		WL 3	
		Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Pre	Mean	951	38	1747	54	2699$_{ab}$	152	3563$_{a}$	192
	±SD	80		144		266		397	
Mid	Mean	952	49	1711	38	2617$_{a}$		3461	
	±SD	90		118		231		362	
Post	Mean	971	50	1716	45	2582$_{b}$		3406$_{a}$	
	±SD	108		119		247		378	

NB: Paired letters denote significant difference ($p<0.05$).

Pre condition had three separate testing occasions.

See Appendix B for individual subject data.

Table 3.7. Pre-training correlation matrix for selected variables.

	$\dot{V}O_2$ max a	$\dot{V}O_2$ max r	VT PO	VT $\dot{V}O_2$	40k $\dot{V}O_2$	40k s	L WL1	L WL2	L WL3	T WL1	T WL2	T WL3
$\dot{V}O_2$ max a	1											
$\dot{V}O_2$ max r	.48	1										
VT PO	.85	.66	1									
VT $\dot{V}O_2$	.90	.67	.98	1								
40k $\dot{V}O_2$	.94	.45	.92	.94	1							
40k s	-.89	-.71	-.94	-.95	-.85	1						
L WL1	-.31	-.54	-.47	-.46	-.33	.44	1					
L WL2	-.56	-.62	-.64	-.68	-.55	.61	.82	1				
L WL3	-.65	-.37	-.74	-.76	-.74	.68	.55	.74	1			
T WL1	-.27	-.46	-.33	-.32	-.27	.35	.54	.62	.53	1		
T WL2	-.60	-.54	-.58	-.60	-.52	.59	.79	.85	.70	.80	1	
T WL3	-.17	-.26	-.40	-.40	-.31	-.30	.36	.51	.57	.38	.50	1

NB: a = absolute, r = relative, PO = power output (W), L = lactate, T = time constant; Critical r = .497

Table 3.8. Mid-training correlation matrix for selected variables

	$\dot{V}O_2$ max a	$\dot{V}O_2$ max r	VT PO	VT $\dot{V}O_2$	40k $\dot{V}O_2$	40k s	L WL1	L WL2	L WL3	T WL1	T WL2	T WL3
$\dot{V}O_2$ max a	1											
$\dot{V}O_2$ max r	.56	1										
VT PO	.81	.61	1									
VT $\dot{V}O_2$	.89	.58	.92	1								
40k $\dot{V}O_2$	..96	.51	.85	.87	1							
40k s	-.92	-.65	-.91	-.88	-.90	1						
L WL1	-.10	-.67	-.44	-.29	-.10	.34	1					
L WL2	-.66	-.44	-.74	-.69	-.71	.79	.38	1				
L WL3	-.57	-.29	-.66	-.59	-.64	.65	.23	.84	1			
T WL1	-.64	-.72	-.76	-.68	-.63	.77	.51	.79	.79	1		
T WL 2	-.70	-.47	-.72	-.69	-.72	.75	.31	.90	.82	.78	1	
T WL3	-.43	-.34	-.40	-.45	-.49	-.43	.34	.62	.82	.56	.68	1

NB: a = absolute, r = relative, PO = power output (W), L = lactate,T = time constant; Critical r = .497

Table 3.9. Post-training correlation matrix for selected variables.

	$\dot{V}O_2$ max a	$\dot{V}O_2$ max r	VT PO	VT $\dot{V}O_2$	40k $\dot{V}O_2$	40k s	L WL1	L WL2	L WL3	T WL1	T WL2	T WL3
$\dot{V}O_2$ max a	1											
$\dot{V}O_2$ max r	.56	1										
VT PO	.88	.49	1									
VT $\dot{V}O_2$	.94	.59	.93	1								
40k $\dot{V}O_2$	.82	.21	.82	.79	1							
40k s	-.91	-.62	-.93	-.93	-.75	1						
L WL1	-.20	-.39	-.13	-.12	-.02	.26	1					
L WL2	-.43	-.52	-.36	-.44	-.19	.60	.62	1				
L WL3	-.55	-.21	-.52	-.59	-.42	.69	.35	.80	1			
T WL1	-.62	-.78	-.52	-.62	-.35	.74	.48	.86	.69	1		
T WL2	-.5.2	-.59	-.47	-.47	-.31	.61	.56	.83	.57	.86	1	
T WL3	-.33	-.13	-.37	-.45	-.24	-.47	.33	.63	.76	.52	.63	1

NB: a = absolute, r = relative, PO = power output (W), L = lactate,T = time constant; Critical r = .497

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CHAPTER FOUR

THE PHARMACEUTICAL INTERVENTION STUDY:

THE EFFECT OF SALBUTAMOL

ON PERFORMANCE IN

ENDURANCE CYCLISTS

A version of this chapter was presented at the Canadian Society of Exercise Physiology conference in Hamilton, Ontario, in October 1994.

Introduction

The participation of asthmatic individuals in high performance sport has been growing steadily in recent years, and it has been estimated that about 10% of the athletic population are afflicted by exercise-induced asthma (EIA) or exercise-induced bronchospasm (EIB) (Voy, 1984). Additionally, regular exercise is now an accepted part of the management of asthma (Morton & Fitch, 1992). However, because of possible performance enhancing effects, many anti-asthmatic medications are not permitted by the governing bodies of many sport disciplines, in particular the International Olympic Committee (IOC). One of the currently acceptable anti-asthmatic drugs is Salbutamol (Albuterol) which some investigators have reported as having performance enhancing properties (Bedi, Gong, & Horvath, 1988; Signorile, Kaplan, Applegate, & Perry, 1991), while others have refuted this possibility (Meeuwisse, Hopkins, & McKenzie, 1991; Morton, Papalia, & Fitch, 1991; Meeuwisse, McKenzie, Hopkins, & Road, 1992; Morton, Papalia, & Fitch, 1993). This potential to aid performance, plus the known improvements for asthmatic athletes, has led to concern that some non-asthmatic athletes are utilizing Salbutamol prior to competition.

Salbutamol is a β_2-selective adrenoceptor agonist with relatively 'long-acting' characteristics, minimal β_1-receptor effects, and little stimulation of α-adrenoceptors (Price & Clissold, 1989), resulting in bronchodilatory, cardiovascular, uterine, and metabolic effects in humans (Lalos & Joelsson, 1981; Wager, Fredholm, Lunell, & Persson, 1982; Fowler, Timmis, Crick, Vincent, & Chamberlain, 1982; Corea, Bentivoglio, Verdecchia, Motolese, & Sorbini, 1984; Rolf Smith & Kendall, 1984; Mettauer, Rouleau, & Burgess, 1985). However, beyond the pulmonary level, usual therapeutic doses ($\approx$200μg) do not normally produce significant responses in healthy subjects, although dose-related re-

sponses are widely reported particularly when the agent is administered by nebulised spray, orally, or parenterally (Lalos & Joelsson, 1981; Corea et al., 1984; Rolf Smith & Kendall, 1984; Rolf Smith, Ryder, Kendall, & Hodall, 1984; Huupponen & Pihlajamäki, 1986; Price & Clissold, 1989).

In addition, Martin, Soubrie, and Simon (1986) observed a noticeable antidepressant effect, possibly mediated through a serotonergic link, after Salbutamol administration. Variations in brain serotonin concentrations are thought to be linked to behaviour with euphoria, inhibition of the transmission of pain, and circadian rhythm regulation all having been reported (Ganong, 1991).

Theoretically, Salbutamol appears to have a number of possible avenues through which to positively affect human performance. This alone warrants the continued interest in this particular medication. To date, most studies examining ergogenic effects of Salbutamol in humans have focused on normal therapeutic dose levels and somewhat gross measures of performance (e.g., maximal oxygen uptake, power).

The investigation of oxygen uptake kinetics may, however, provide an important additional dimension in the examination of the effects of Salbutamol. Such measures reveal the rate of response, as well as the magnitude, to a given stimuli. The use of a laboratory-based cycle time trial, with previously established reliability (reliability estimate = 0.83), contributes the dimension of examining sport specific performance to the study. Therefore, the purpose of this investigation was to examine the effect of a higher than normal dosage of Salbutamol upon selected physiological tests of aerobic endurance performance and sport specific performance, with special emphasis on submaximal oxygen uptake kinetics, in a group of non-asthmatic endurance trained cyclists.

Materials and Methods

Subjects and research design.

Fifteen previously trained male cyclists (Table 4.1) were selectively recruited for this investigation. The initial screening procedure for this project included a medical examination carried out by a qualified physician and a 'non-asthmatic' diagnosis. All interaction with the subjects followed the guidelines for research with human subjects at the University of Alberta, including appropriate ethics approval and written informed consent. A double-blind, randomized cross-over design was used with Salbutamol (S) or a placebo (P) being administered as required by a predetermined code sequence unknown to the subjects and primary researchers involved.

Habituation, screening, and test sequence.

The subjects were habituated to all the experimental protocols in the week prior to starting the actual investigation. This habituation period included an initial VT/$\dot{V}O_2max$ cycle ergometer test, a submaximal transient oxygen uptake protocol, pulmonary function testing, a 20 kilometre cycle time trial, and a 60 second power test. The initial dosage of Salbutamol was administered under the supervision of a physician and the subjects became familiar with using a Vent-a-haler® spacer device. This device reduces the normal learning effect associated with inhaler use and brings about optimal delivery of the pharmaceutical compound. During the habituation period, the subjects also underwent a medical examination, and performed a Methacholine bronchial provocation test to determine the degree of airway responsiveness and, hence, the absence of asthma (see Appendix B). The results of the bronchial provocation test classified all 15 subjects as having a normal level of airway sensitivity. This was determined by the fact

that FEV_1 values did not fall by 20% (or more) even at the highest methacholine concentration of 16mg·ml^{-1}.

Upon satisfactory completion of the habituation tasks, subjects then performed the four basic tests under each condition (P or S) over a two week period. That is, one test per day, with at least 24 hours between tests, until all eight test sessions were complete. The tests followed the same sequence as in the habituation period, with the experimental condition being randomized for each test. The dosing schedule for each testing session consisted of four puffs (one puff = 100µg) from a previously coded metered-dose inhaler containing either P or S. Initially, two puffs were administered, followed by two more after a five minute latency period. Twenty minutes after the first inhalation the particular test in question was undertaken. This dosing schedule allowed sufficient time for the pharmaceutical agent to take effect.

Experimental protocols.

The $VT/\dot{V}O_2max$ test was performed on a cycle ergometer (Monark 818E) using two minute loading stages with power output increments of 40 watts, until ventilatory threshold (VT) was surpassed, after which one minute stages were applied until $\dot{V}O_2max$ was attained. Ventilatory threshold (VT) was determined by visual inspection of the data after each $VT/\dot{V}O_2max$ test using the 'Mechanism II' method of Wasserman, Beaver, and Whipp (1990). This method requires a group of responses to occur simultaneously for VT estimation to be made. That is, a systematic increase in the ventilatory equivalent for O_2 (as compared to previously falling or constant values) at a time when the ventilatory equivalent for CO_2 is not rising. A previously calibrated SensorMedics 2900z metabolic measurement system, operating in mixing chamber mode (20 second time averages) and connected to each subject by a Rudolph

mouthpiece assembly (Series 2700), was used to collect gas exchange information. This system measured expired flow levels and gas concentrations for oxygen and carbon dioxide as the basis for the required volume calculations ($\dot{V}O_2STPD$, $\dot{V}CO_2STPD$, and $\dot{V}_EBTPS$). All calculated values were displayed on a computer screen and printed in hard copy in real time, as well as being saved to the computer hard drive. Additionally, heart rate was monitored via the R-R interval of the electrocardiogram (ECG) using a Hewlett-Packard heart rate monitor (model 43200A).

At key times during each $\dot{V}O_2max$ testing session, a SensorMedics 2450 pulmonary function laboratory was used to measure the forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). The highest volume was recorded from three trials in the seated position. An initial baseline test was performed as soon as each subject arrived in the laboratory, followed by the inhalation (as previously described) of P or S, and a second test some twenty minutes later, just prior to the $\dot{V}O_2max$ exercise. These pulmonary function tests were then repeated twice more, one five minutes after the completion of the $\dot{V}O_2max$ task, and a final one fifteen minutes later, in a similar manner to Meeuwisse et al., (1990).

The transient oxygen uptake protocol consisted of three equal ascending transitions in power output from unloaded cycling to a workload approximately equivalent to 90% of the subject's ventilatory threshold (VT), based upon the subject's initial $\dot{V}T/\dot{V}O_2max$ test. Each phase (initial steady state, transition, and recovery) lasted for three minutes and was based upon previous experimental experience in this laboratory of the expected time constants for this level of work load. These transitions were performed on a Monark 814E cycle ergometer equipped with a drop basket resistance loading system. Gas exchange data was collected using the SensorMedics 2900z system operating in

breath-by-breath mode and, again, heart rates were monitored using the Hewlett-Packard 43200A.

The 20k time trials were performed on a purpose-built computerized cycle roller system that allowed the subjects to use their own racing bicycle. A front fork stand was used to optimize stability. The subjects 'raced' the 20k from a stationary start and were given both visual and auditory feedback concerning distance covered, but were not provided with precise split or cumulative performance time until completion of the study.

The 60 second supramaximal cycling sprint test was basically an extended Wingate test with the work load set to the subject's body mass multiplied by a constant of 0.075. This test was performed on a highly modified Monark cycle ergometer equipped with a computerized data collection system that calculated absolute and relative values of work done (Joules) and power (Watts) generated through each five second phase.

The analysis of the transient oxygen uptake data involved time averaging the oxygen consumption values over 10 second periods for each transition. These values were then described via a first order (single exponential) model as shown below:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_{2ss} \cdot (1 - e^{-(t-TD)/\tau})$$

Where Δ reflects the increment above the previous steady state level (i.e., unloaded to loaded cycling), and ss represents the steady state or asymptotic value. TD represents the time delay parameter and allows a 'best fit' line (via nonlinear least squares) to be calculated such that the time constant (τ) of the response can be established without artificially constraining the regression to pass through the origin. A mean τ was then produced from each of the separate trial occasions.

All dependent variables were subjected to a one-way ANOVA with repeated measures, or two-way factorial ANOVA for the experimental conditions, (α set *a priori* at 0.05), dependent upon the requirements of the analysis. A post hoc multiple comparison test, the Scheffé procedure, was utilized when appropriate.

Results

Tables 4.2 and 4.3 summarize the overall results of the performance measures (physiological and, or, sport specific) evaluated in this study. No significant differences were observed between the two experimental conditions (P or S) for these measures ($p>0.05$). Figure 4.1 illustrates the grouped average submaximal oxygen uptake kinetics for the P versus S conditions (mean and standard deviation for each data point). Figure 4.2 shows a scatterplot of the 20k time trial results comparing the two experimental conditions.

The pulmonary function data measured during the $\dot{V}O_2max$ tests is shown in Table 4.4. This information reveals that the change in FEV_1 pre- and post-medication/pre-$\dot{V}O_2max$ was significantly lower for the S condition ($p<0.05$), but not for P. The baseline FEV_1 for S was significantly lower from the two post-exercise values, and the post-medication/pre-$\dot{V}O_2max$ figure was also significantly lower than the five minute post-exercise FEV_1 ($p<0.05$). As regards the FVC under the S condition, only the baseline value (5.97 ± 0.85) and the 20 minute post-exercise value (6.13 ± 0.82) differed significantly ($p<0.05$). There were no observable significant differences in either FVC or FEV_1 for the P condition, and overall, there was no difference between the P and S procedures ($p>0.05$).

Discussion

The results of this investigation clearly demonstrate that the acute dosage of Salbutamol administered had no influence on the selected performance variables. In essence, the dependent variables measured ($\dot{V}O_2$max, sub-maximal oxygen uptake kinetics, 20k time trial, and power output during a 60 second supramaximal sprint test) resulted in P versus S values remarkable by their consistency rather than by any prior hypothesized differences. The unique analysis of oxygen uptake kinetics in this investigation further strengthens the argument that Salbutamol does not exhibit any performance enhancing effects at low acute dosages (≤400μg). This stance can be taken, not only because the oxygen uptake time constant is another parameter through which to examine possible performance effects, but because it views the problem from another dimension than purely one of $\dot{V}O_2$. That is, the time constant provides information regarding the rate of change of the organism in response to the given stimulus, and that this response time is due to the coordinated action of both central and peripheral oxygen-focused mechansims. The fact that, in this investigation, no differences were observed between the P and S conditions suggests that these oxygen-focused mechanisms were not altered to any significant degree.

The changes in FEV_1 after Salbutamol inhalation are of similar proportion to those reported in earlier studies (Bedi et al., 1988; Meeuwisse et al., 1991; Morton et al., 1991; Meeuwisse et al., 1992; Morton et al., 1993), and, although of statistical significance, are not in themselves of 'clinical signficance' (Meeuwisse et al., 1992). Previous work has established the variability of FEV_1 measures as ranging from 3-5%, and that a change of 10-15% is required to establish that random test variability is not responsible

(Cochrane, Prieto, & Clarke, 1977; Meeuwisse et al., 1992). Therefore, this study is in agreement with the general findings of Meeuwisse et al., (1991), Morton et al., (1991), Meeuwisse et al., (1992;), and Morton et al., (1993).

Although it would be tempting to speculate that the scatterplot of the 20k time trial results (Figure 4.2) suggests a trend towards performance improvement with Salbutamol, the reality is that no significant differences were observed between the performances ($p>0.05$). However, the theoretical avenues through which Salbutamol has the potential for enhanced athletic performance are not limited to purely respiratory mechanisms, and it should not be forgotten that pharmacological studies clearly illustrate dose related responses (Price & Clissold, 1989). Therefore, despite the support for a nonergogenic argument for Salbutamol, based upon respiratory measures and performance results after relatively low acute dosages, this author cautions against the dismissal of a positive performance effect until further research has conclusively examined the nonrespiratory factors and at suitable levels of administration (i.e., higher dosages and over longer time periods).

Table 4.1. Subject characteristics.

Subject	Age yr	Height cm	Weight kg	$\dot{V}O_2max$ $l \cdot min^{-1}$	$\dot{V}O_2max$ $ml \cdot kg^{-1} \cdot min^{-1}$
1	25	165	58.5	4.5	76.1
2	20	183	76.0	5.3	69.4
3	26	178	64.7	4.1	63.0
4	20	189	72.2	5.1	70.7
5	24	192	72.6	4.1	56.9
6	24	182	64.3	3.9	61.4
7	25	165	68.7	4.3	62.7
8	23	175	72.5	5.3	73.1
9	22	176	65.8	4.1	62.5
10	32	187	77.3	4.6	60.1
11	24	172	89.3	4.9	54.5
12	19	169	70.5	4.8	68.4
13	25	175	72.3	4.2	58.2
14	36	166	75.3	4.2	55.1
15	25	176	73.9	4.3	58.7
MEAN	25	177	71.6	4.5	63.4
±SD	4	9	7.1	0.5	6.7

Table 4.2. Mean (±SD) performance data for placebo and Salbutamol conditions in endurance cyclists (n=15).

Variable	Condition			
	Placebo		Salbutamol	
	Mean	±SD	Mean	±SD
$\dot{V}O_2max$:				
$l \cdot min^{-1}$	4.5	0.4	4.5	0.4
$ml \cdot kg^{-1} \cdot min^{-1}$	63.6	6.7	63.1	6.2
60s Power Test:				
Peak power (W)	798	79	803	70
Mean power (W)	534	41	529	40
Lowest power (W)	379	55	369	49
% Decline	52	9	54	9
20k TT:				
Time (min)	35.02	3.11	34.82	2.86

NB: No significant differences found between P and S ($p>0.05$)

Table 4.3. Mean (±SD) submaximal oxygen uptake protocol results; time constants, time delays, and goodness of fit information (n=15).

Variable	Placebo		Salbutamol	
	Mean	±SD	Mean	±SD
O_2 kinetics:				
Time constant (s)	28.8	1.6	29.0	1.3
Time delay (s)	9.8	0.9	10.6	0.8
F value	5774		8256	
RSS	0.0649		0.0459	
$\dot{V}O_2$ ($l \cdot min^{-1}$):				
SS work	2.869	0.425	2.942	0.369
SS unloaded	1.192	0..12	1.308	0.158
$\Delta \dot{V}O_2$	1.677	0.395	1.634	0.347

NB: No significant differences found between P and S ($p>0.05$)

RSS = residual sum

SS = steady stat

Δ (delta) = ch

ption from unloaded to loaded cycling

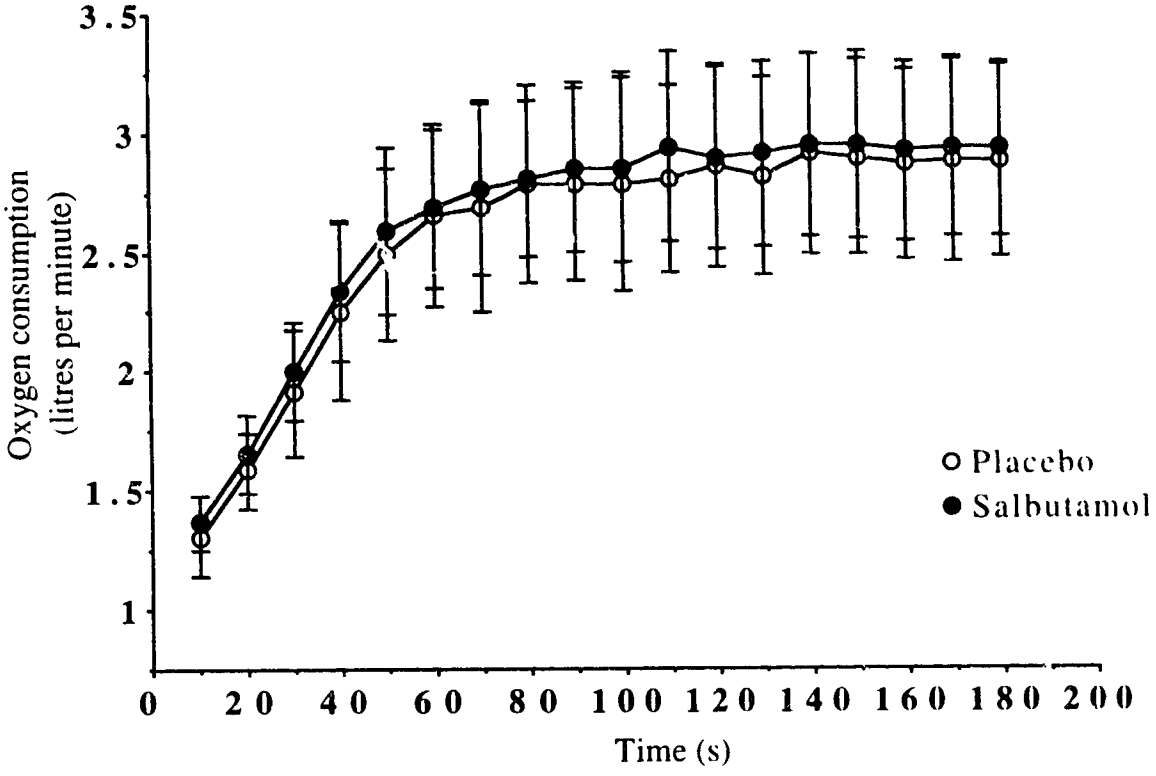

Figure 4.1. Mean (±SD) submaximal oxygen uptake kinetics for placebo and Salbutamol conditions in endurance cyclists (n=15).

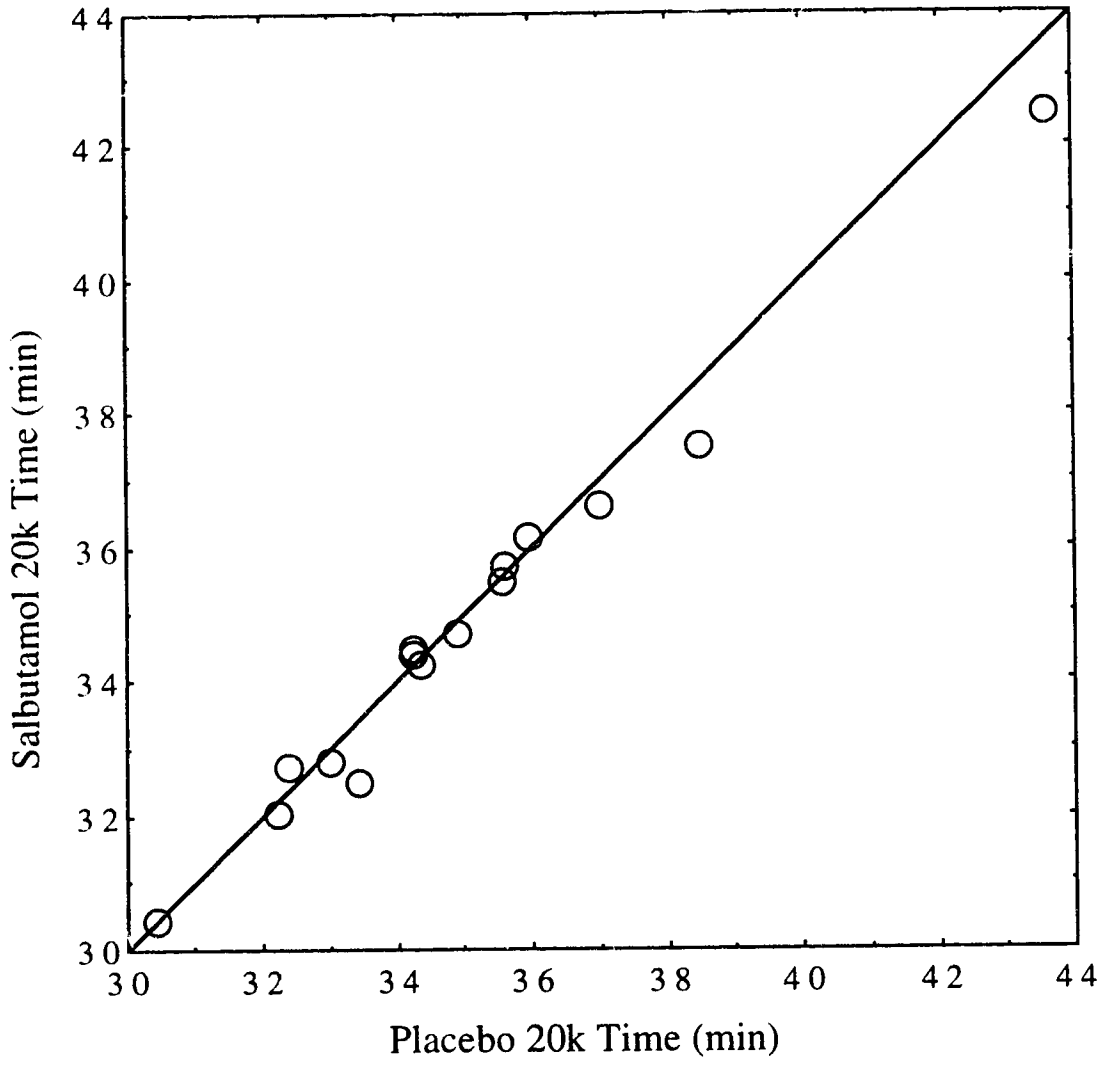

Figure 4.2. Scatterplot of 20k time trial results (seconds) for the P vs S conditions.

Table 4.4. Mean (±SD) pulmonary function data for placebo and Salbutamol conditions before and after $\dot{V}O_2max$ tests for endurance cyclists (n=15).

Variable	Condition			
	Placebo		Salbutamol	
	Mean	±SD	Mean	±SD
FEV_1 (litres)				
Pre-test/pre-med	5.08	0.65	5.06abc	0.73
Pre-test/post-med	5.10	0.67	5.23ad	0.69
5 min post test	5.19	0.69	5.38bd	0.73
20 min post test	5.24	0.73	5.36c	0.72
FVC (litres)				
Pre-test/pre-med	5.98	0.79	5.97a	0.85
Pre-test/post-med	5.99	0.79	6.00	0.81
5 min post test	6.04	0.81	6.04	0.80
20 min post test	6.02	0.79	6.13a	0.82

NB: Small letters denote paired significant difference ($p<0.05$)

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CHAPTER FIVE

GENERAL DISCUSSION

General Discussion

Introduction.

The fundamental impetus of this investigative route has been the belief that gas exchange kinetics may have a possible role to play in the applied scenario of elite human performance and adaptation to specific training influences. Incentive has been provided by the constantly growing research literature examining the underlying theories concerning gas exchange kinetics. This expanding scientific knowledge has provided a great deal to the framework of this thesis, from core concepts to tentative links with other allied mechanisms, and from methodological suggestions through to future research topics. However, the prime motive for pursuing the use of oxygen uptake kinetics has been the thought that this parameter seemingly had the potential to be a sensitive indicator of aerobic endurance training. The underlying reasoning behind this personal hypothesis centres around the fact that the oxygen uptake response has both a quantitative and qualitative aspect. That is, although a specific oxygen uptake response is linked to an increase (or decrease) in oxygen consumption (i.e., a quantitative component), it actually measures in time the efficiency of the system to respond to a given stimulus (i.e., a qualitative component). However, to temper this enthusiasm, it should be realized that investigation of gas exchange kinetics requires expensive, laboratory based equipment, as well as specifically designed protocols centred around standard (and, therfore, limited) ergometers.

These studies have demonstrated three fundamental aspects. First, the oxygen uptake response to a step increase in work load ($\dot{V}O_2$on) may be evaluated reliably using the methodologies adopted. Second, the $\dot{V}O_2$on response improves (quickens) with aerobic endurance training, probably due to a combination of central and peripheral

adaptation. Third, the administration of Salbutamol at the dosage given in the final study does not result in faster $\dot{V}O_2$on responses or significant improvements in $\dot{V}O_2$max, 20k time trial performance, and anaerobic power.

Methodology and reliability.

The initial study concerned the ability to measure oxygen uptake kinetics reliably using the adopted protocols and equipment available. The planning, execution, and review of the reliability study emphasized the need for a sound methodological approach when attempting to measure submaximal gas exchange kinetics. Since there is an inherent variability in human breath-by-breath responses, the number of exercise transitions required to result in reliable data should not be overlooked (Lamarra, Whipp, Ward, & Wasserman, 1987). In the studies presented here, the core exercise transition was always performed three times in succession, with a reasonable level of success (see aforementioned reliablity estimate). However, it is the view of this author that three transitions is the minimum number of repeats required to obtain meaningful data and, where possible, the addition of further transients would only enhance the resulting data. The test environment is one key area where the researcher is able to exert a high level of control and steps should be taken to reduce all forms of distraction for the subject since any disturbance has the potential to influence the outcome of a particular submaximal transient exercise. As well, sufficient time needs to be allowed for subject habituation to the specific tasks required.

The reliability study (Chapter Two) yielded an intra-class coefficient (reliability estimate) of 0.9 (α = 0.05) for the time constant values collated during this preliminary investigation. This demonstrated an adequate level of reli-

ability and provided confidence for the continued investigation of oxygen uptake kinetics.

The investigative design for the training study (Chapter Three) was shaped to a large degree by certain technological limitations of the SensorMedics 2900z metabolic measurement system and the small diameter Perma-Pure® tubing used in the breath-by-breath analysis. Previous experience and pilot work had identified that the window of usable data with the Perma-Pure® tubing was limited and that beyond approximately 35 minutes of continual use the data collected could be suspect. Therefore, the design of the transient protocol for the training study called for three repeat transitions to the first step load (the core transient; WL1), which only left time for one transition each to the second and third work levels (WL2 and WL3), plus blood collection, before the usefulness of the tubing was exhausted. The rationale at the time for adopting this protocol was twofold. First, it was thought that the transitions at this level of intensity would result in breath-by-breath responses driven to a large degree by the underlying physiological mechanisms with a reduced contribution from the noise component. Second, the author had expected a greater degree of adaptation to the higher two work intensities. In hindsight, this was a rather naïve rationale since the noise component essentially remained constant with the underlying signal, probably due to the level of work intensity demanded at the higher two loads, in particular WL3.

The use of absolute loading levels in the training study was an attempt to provide a level of sport performance realism, however, this meant that the subjects experienced different relative work intensities. At the pre-training stage, the two higher exercise intensities were beyond the submaximal, sub-anaerobic threshold capabilities of the group as a whole, although some individuals were able to

cope adequately. This situation improved with training, however, even at the completion of the study the group was unable to cope with WL3 level effectively. Tables 3.3 and 3.4 provide the time constant and goodness of fit data, and blood lactate accumulation values respectively for the training study. This information illustrates that the group was working at an intensity beyond the region initially intended by the author for examination.

This occurence led the author to consider more extensively the impact of absolute vs relative loading protocols in the area of gas exchange kinetics. The loading protocol for the third study (the Salbutamol investigation), a work load approximately equivalent to 90% of VT, was deliberately designed to achieve three criteria. First, it was set at a relative intensity. Second, the intensity was submaximal and sub-anaerobic threshold, and third, it allowed for the near maximization of the change in $\dot{V}O_2$ ($\Delta \dot{V}O_2$) from an unloaded cycling to sub-anaerobic threshold level. This third aspect is more important than it might at first appear, since, by ensuring as large an increase in work intensity as possible, it allows the greatest potential for detecting any differences in kinetic behaviour. An aspect of note is that the author found only one reference concerning the investigation of gas exchange kinetics with regard to absolute vs relative work loads during the literature search stage of this dissertation (Grucza et al., 1989). This would appear to be an oversight by researchers in the area, and the recommendation has to be made that this aspect should be examined more extensively in the near future.

Adaptation to training.

The second question examined the suggestion that $\dot{V}O_2$on responses have a role to play in the routine monitoring of high performance endurance trained athletes. The results from the training study (Chapter

Three) would suggest that $\dot{V}O_2$on data may provide information regarding continued adaptation to training. In addition, this information was gathered submaximally and in a non-invasive, minimally intrusive manner which has obvious attractions for elite athletes in training and, or, near competition. However, this investigation has not clarified any further the definition of the oxygen uptake transient response from a mechanistic standpoint. It is likely that this whole body measure is underscored by the interaction of a myriad of competing and cooperating subsystems, and that the intervention of endurance training over an extended period of time may cause subtle changes in the intercourse of these components. This underlying mesh of complex mechanisms may be an explanation for the differences in correlational analysis between $\dot{V}O_2$on time constants and $\dot{V}O_2$max, particularly when different subject groups have been involved (Powers et al., 1985; Lake et al. 1986; Norris, 1987).

The training study found significant improvements (i.e., changes that would enhance endurance performance) over the first four weeks of training for $\dot{V}O_2$max, VT, blood lactate concentration, 40k time trial, and, of course, the various $\dot{V}O_2$on time constants ($p<0.05$). These changes may all be explained by previously documented work examining physiological adaptation to aerobic endurance training. For example, longitudinal studies reveal the same or slightly decreased heart rates (Ekblom, 1969), as well as increased stroke volumes and $a-\bar{v}O_2$ difference (Saltin, 1969). In addition, both total hemoglobin and plasma volume increase with endurance training which further facilitate the oxygen delivery system (Wilkerson, Gutin, & Horvath, 1977). The increase in $a-\bar{v}O_2$ difference is thought to be mainly due to increased capillary density in the trained muscles (Hermansen & Wachtlova, 1971; Andersen, 1975). This reduces the diffusion distance between the capillaries, mito-

chondria, and myofibrils, thereby aiding the 'diffusive conductance' ability of Wagner's (1991) model of oxygen transport efficiency.

At the subcellular level, the trained muscle exhibits a marked increase in capacity to form ATP aerobically via oxidative phosphorylation, accompanied by increases in mitochondrial size and number, and oxidative enzyme activity (Holloszy, 1967; Kiessling, Piehl, Lundquist, 1971). The overall improvement in mitochondrial aerobic power results in a more efficient work transition with less reliance upon anaerobic glycolysis and a reduction in the size of the oxygen deficit (Walsh, 1992). Therefore, a faster oxygen uptake transition is seen, coupled with a reduced lactate accumulation and, from an applied point of view, a lessened metabolic cost to the athlete. As a summary comment, Walsh (1992) concludes that, with respect to the oxygen uptake response to a square wave work task, oxygen delivery probably sets the overall parameters and subsequently peripheral mechanisms regulate oxygen utilization within the established guidelines.

Obviously, since it was beyond the scope of this investigation to actually record cellular and subcellular adaptation directly, comments regarding adaptation can only be made from the standpoint of conjecture supported by the current literature base. To date, time courses of aspects such as increased capillarization and mitochondrial changes have not been examined in conjunction with $\dot{V}O_2$ kinetics during training. Also, research has been primarily occupied with training adaptation and $\dot{V}O_2$ responses with little attention having been paid to the effect of detraining or to the kinetics of $\dot{V}CO_2$. Indeed, Wasserman (1994) remarks that the simultaneous measurement of dynamic changes in $\dot{V}O_2$ and $\dot{V}CO_2$ could provide information regarding the relative contributions of aerobic and anaerobic metabolism to the bioenergetics of specific exercise tasks. Therefore,

these can be seen to be important areas for future research concerning gas exchange dynamics.

During the second four week period of training, where $\dot{V}O_2max$ was seen to remain constant, the $\dot{V}O_2on$ responses continued to become faster. Admittedly, only the WL1 transition showed significant improvement from the midpoint to the conclusion of training ($p<0.05$), however, comment can be made to the effect that not only was the single exponential model fit good for this level of intensity, but also that the variance in the measure between the subjects was smaller than for the higher two work levels. The subject variance for the time constants of the transitions to WL2 and WL3, together with a lesser degree of model fit (particularly in the case of the WL3 transition), conspired to mask the meaningfulness of the data. However, a trend of faster oxygen uptake kinetics after training was evident, with support for this tendency being provided by the significant reduction in blood lactate accumulation for the WL2 and WL3 intensities and an improvement in VT ($p<0.05$).

The 40k time trial results, although faster for the mid-point as compared to the pre-training level ($p<0.05$), were not significantly improved over the last four weeks of training ($p>0.05$). However, a general reduction in time taken for the event was seen with a mean improvement of approximately 68 seconds after the midpoint in training.

The acute study.

This investigation was designed to build upon the strengths and reduce the weaknesses of previous studies examining Salbutamol and performance enhancement (Bedi et al., 1988; Signorile et al., 1991; Meeuwisse et al., 1991; Morton et al., 1991; Meeuwisse et al., 1992; Morton et al., 1993). The measurement of $\dot{V}O_2$ kinetics at the onset of exercise took the earlier research into a new area of investi-

gation. That is, since the oxygen uptake response had been identified as a relatively sensitive indicator of transient adaptation to a given work task, this parameter had the potential to provide another dimension than purely examining VT/$\dot{V}O_2$max. Furthermore, the use of a sport specific endurance performance test (the 20k time trial), with established reliability, added a valid element which the earlier investigations had failed to acheive.

Salbutamol is reported as having influences on several physiological levels (e.g., pulmonary, cardiovascular, and muscularly) (Price and Clissold, 1989). Although recognized from the outset that the oxygen uptake response would not be able to differentiate between physiological levels, it was thought that if an acute response to Salbutamol was manifest it would be reflected in the $\dot{V}O_2$ time constant. However, the effect of an acute dosage of Salbutamol upon submaximal oxygen uptake kinetics, or the other physiological and performance markers (see Chapter Four), was not revealed to any significant degree between the placebo or Salbutamol conditions ($p>0.05$). Therefore, the third question posed may be answered by stating that since faster oxygen uptake kinetics were not demonstrated to occur after Salbutamol inhalation in this study, this pharmaceutical agent does not have the potential to enhance physical performance with this level of dosage. Despite these findings, the author would still not dismiss the possibility of positive performance enhancing attributes for Salbutamol until further investigations have examined the nonrespiratory factors suggested in the literature and the use of high ingestion levels over extended periods of time.

Future research directions.

The current level of knowledge concerning both the pure and applied aspects of gas exchange dynamics, including the observations described in this dissertation, identifies

the need for further investigative work. The author, therefore, recommends that future investigations in this area should pursue the following:

1) more frequent testing of the gas exchange response times during controlled training periods, in order to allow closer examination of the time course of training adaptation;

2) examination of the interplay between absolute and relative loading protocols (i.e., absolute work loads versus %$\dot{V}O_2$max and, or, %VT), and their effect upon gas exchange kinetics pre and post-training;

3) simultaneous investigation of the $\dot{V}O_2$ and $\dot{V}CO_2$ responses to specific exercise work tasks in order to examine the ability of these measures to assess bioenergetic contribution;

4) comparison of training adaptation in gas exchange kinetics with those occuring at the muscular level (i.e., involving invasive collaboration of the whole body measures); and,

5) the examination of gas exchange dynamics in those athletes engaged in specific intermittent sports where they are required to continually move between sub-anaerobic threshold and supra-anaerobic threshold conditions. This final suggestion is made because i) the vast majority of dynamic gas exchange research has concentrated on aerobic endurance athletes and ii) it would seem appropriate to hypothesize that efficient gas exchange transients would be advantageous for these athletes.

Summary.

This dissertation has demonstrated that oxygen uptake kinetics may be examined routinely in groups of athletes during periods of training. These responses can be monitored noninvasively and at submaximal, sub-anaerobic threshold work intensities if controlled testing procedures

are followed. In addition, gas exchange dynamics may have the potential to serve as a sensitive overall indicator of cardiorespiratory and muscular adaptation in high performance endurance athletes, although this will require further extensive investigation before such analyses become commonplace.

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APPENDIX A

Appendix A, i. Reliability Study; Oxygen uptake steady state data ($ml \cdot min^{-1}$).

	Subject												
Day 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**MEAN**	**±SD**
Unld SS	861	1089	656	909	883	921	995	963	1045	899	948	924	113
Ld SS	1815	2074	1647	1970	1714	2002	1970	1926	2084	1840	1891	1903	140
Δ	954	986	991	1061	831	1081	974	963	1039	940	943	979	68
Day 2													
Unld SS	802	941	814	870	750	947	947	913	1017	939	936	898	79
Ld SS	1747	1959	1730	1900	1853	1921	2015	1777	1956	1895	1904	1878	92
Δ	945	1018	916	1030	1103	975	1068	864	939	956	969	980	69
Day 3													
Unld SS	761	942	649	859	855	842	954	1009	979	1021	782	878	116
Ld SS	1764	2031	1570	1882	1663	1816	1902	1913	2011	1900	1767	1838	140
Δ	1003	1088	921	1022	809	974	948	904	1032	879	985	961	79
MEAN													
Unld SS	808	991	706	879	829	903	965	961	1013	953	888	900	91
Ld SS	1775	2021	1649	1917	1743	1913	1962	1872	2017	1878	1854	1873	115
Δ	967	1031	943	1038	914	1010	997	910	1003	925	966	973	46
±SD Unld	50	85	94	26	70	55	26	48	33	62	92	58	25
±SD Ld	34	58	48	36	74	49	28	75	64	29	26	47	18
±SD Δ	31	53	42	21	164	62	63	50	56	41	21	55	39

Appendix A, ii. Reliability Study; Heart rate steady state data ($b \cdot min^{-1}$).

	Subject												
Day 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**MEAN**	**±SD**
Unld SS	92	97	81	78	72	68	86	91	80	109	80	85	12
Ld SS	132	118	132	132	112	107	110	113	106	135	108	119	12
Δ	40	21	51	55	40	38	24	22	26	26	28	34	12
Day 2													
Unld SS	91	86	96	80	81	72	85	87	79	98	80	85	8
Ld SS	134	114	135	128	114	110	112	115	105	124	102	118	11
Δ	43	28	39	48	33	38	27	28	27	25	22	33	8
Day 3													
Unld SS	92	87	84	91	86	81	82	94	83	100	78	87	7
Ld SS	137	113	133	129	111	113	112	114	105	130	103	118	12
Δ	45	26	49	37	25	33	30	20	22	30	25	31	9
MEAN													
Unld SS	92	90	87	83	80	74	84	91	80	102	79	86	8
Ld SS	134	115	133	130	113	110	111	114	105	129	104	118	11
Δ	43	25	46	47	33	36	27	23	25	27	25	32	9
±SD Unld	1	6	8	7	7	6	2	3	2	6	1	4	3
±SD Ld	1	2	1	2	1	2	1	1	0	6	3	2	1
±SD Δ	2	4	7	9	7	3	3	4	2	2	3	4	2

APPENDIX B

Appendix B, i. Maximal aerobic power, absolute ($l \cdot min^{-1}$).

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	4.675	4.151	4.400	4.409	0.262	4.523	4.910
2	4.787	4.794	4.781	4.787	0.007	5.018	4.966
3	4.424	4.428	3.900	4.251	0.304	4.422	4.519
4	4.324	4.397	4.463	4.395	0.070	4.275	4.386
5	3.494	3.412	3.180	3.362	0.163	3.680	3.688
6	4.033	4.111	3.604	3.916	0.273	4.224	4.259
7	3.178	3.091	2.993	3.087	0.093	3.096	3.197
8	3.706	3.475	4.389	3.857	0.475	3.695	4.070
9	4.516	4.539	4.199	4.418	0.190	4.650	4.663
10	4.082	4.036	3.985	4.034	0.048	4.186	4.023
11	4.715	4.720	4.634	4.690	0.048	4.994	4.946
12	4.137	4.321	4.199	4.219	0.094	4.448	4.390
13	2.894	2.861	2.750	2.835	0.075	3.108	3.098
14	3.328	3.601	3.667	3.532	0.180	3.932	3.668
15	3.958	4.007	4.033	3.999	0.038	4.542	4.396
16	4.424	3.852	4.064	4.115	0.286	4.421	4.180
Mean	**4.042**	**3.988**	**3.953**	**3.994**	**0.163**	**4.201**	**4.210**
±SD	**.578**	**.568**	**.584**	**.551**	**.129**	**.571**	**.571**

Pre-training reliability estimate (intraclass coefficient); **0.873**

Appendix B, ii. Maximal aerobic power, relative ($ml \cdot kg^{-1} \cdot min^{-1}$).

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	54.74	49.59	52.31	52.21	2.58	53.40	58.53
2	65.49	65.76	65.23	65.49	0.27	69.30	70.84
3	58.99	59.33	53.35	[illegible].2	3.36	59.92	62.67
4	49.59	50.66	51.12	50.46	0.79	49.25	51.11
5	52.86	51.70	49.54	51.37	1.68	56.71	57.36
6	68.95	70.40	63.23	67.53	3.79	70.76	72.44
7	55.37	55.19	53.39	54.65	1.09	54.32	56.98
8	58.74	56.59	67.93	61.09	6.02	58.47	63.99
9	54.22	54.36	50.11	52.90	2.41	57.33	58.14
10	59.24	58.33	55.85	57.81	1.75	60.49	59.60
11	65.49	65.92	63.65	65.02	1.21	68.79	68.13
12	59.19	62.53	60.42	60.71	1.69	64.65	63.90
13	50.42	48.57	46.69	48.56	1.87	52.15	51.98
14	45.22	47.70	48.06	46.99	1.55	51.74	49.43
15	51.47	51.57	51.91	51.65	0.23	60.64	59.88
16	72.05	60.56	62.52	65.04	6.15	69.84	67.74
Mean	**57.63**	**56.80**	**55.96**	**56.79**	**2.28**	**59.86**	**60.80**
±SD	**7.41**	**6.86**	**6.80**	**6.64**	**1.77**	**7.02**	**6.85**

Pre-training reliability estimate (intraclass coefficient): **0.836**

Appendix B, iii. Power output at ventilatory threshold (W).

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	196	216	196	203	12	255	275
2	294	235	255	261	30	255	255
3	196	196	196	196	0	255	255
4	157	196	157	170	23	196	235
5	118	118	196	144	45	177	196
6	177	177	177	177	0	196	216
7	137	137	137	137	0	177	177
8	157	157	157	157	0	196	235
9	196	196	216	203	12	216	255
10	216	235	216	222	11	255	275
11	235	235	255	242	12	294	314
12	177	216	216	203	23	235	255
13	117	137	137	130	12	157	157
14	137	137	157	144	12	157	196
15	177	177	177	177	0	235	255
16	235	255	216	235	20	255	274
Mean	**183**	**189**	**191**	**188**	**13**	**219**	**239**
±SD	**47**	**42**	**37**	**40**	**13**	**41**	**41**

Pre-training reliability estimate (intraclass coefficient); **0.822**

Appendix B, iv. Oxygen consumption at ventilatory threshold ($l \cdot min^{-1}$).

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	3.1	2.8	2.8	2.9	0.2	3.5	3.8
2	3.7	3.5	3.6	3.6	0.1	3.8	3.8
3	2.7	2.8	2.6	2.7	0.1	3.3	3.3
4	2.3	2.8	2.7	2.6	0.3	3.0	3.1
5	2.0	2.0	2.3	2.1	0.2	2.7	2.8
6	2.5	2.6	2.4	2.5	0.1	2.9	3.1
7	2.2	2.0	2.1	2.1	0.1	2.4	2.5
8	2.3	2.2	2.7	2.4	0.3	2.5	3.1
9	2.6	2.6	2.8	2.7	0.1	2.9	3.5
10	2.9	3.0	2.9	2.9	0.1	3.4	3.3
11	3.4	3.4	3.4	3.4	0.0	3.7	4.1
12	2.7	2.9	2.9	2.8	0.1	3.4	3.6
13	1.9	1.8	1.8	1.8	0.1	2.3	2.3
14	1.9	2.1	2.2	2.1	0.2	2.5	2.8
15	2.5	2.4	2.6	2.5	0.1	3.2	3.1
16	3.4	3.2	2.8	3.1	0.3	3.2	3.3
Mean	**2.6**	**2.6**	**2.7**	**2.6**	**0.1**	**3.0**	**3.2**
±SD	**0.5**	**0.5**	**0.5**	**0.5**	**0.1**	**0.5**	**0.5**

Pre-training reliability estimate (intraclass coefficient); **0.903**

Appendix B, v. Ventilatory threshold expressed as a % of maximal aerobic power.

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	66.3	67.5	63.6	65.8	2.0	77.4	77.4
2	77.3	73.0	75.3	75.2	2.1	75.7	76.5
3	61.0	63.2	66.7	63.6	2.8	74.6	73.0
4	53.2	63.7	60.5	59.1	5.4	70.2	70.7
5	57.2	58.6	72.3	62.7	8.3	73.4	75.9
6	62.0	63.2	66.6	63.9	2.4	68.7	72.8
7	69.2	64.7	70.2	68.0	2.9	77.5	78.2
8	62.1	63.3	61.5	62.3	0.9	67.7	76.2
9	57.6	57.3	66.7	60.5	5.3	62.4	75.1
10	71.0	74.3	72.8	72.7	1.6	81.2	82.0
11	72.1	72.0	73.4	72.5	0.8	74.1	82.9
12	65.3	67.1	69.1	67.1	1.9	76.4	82.0
13	65.7	62.9	65.5	64.7	1.5	74.0	74.2
14	57.1	58.3	60.0	58.5	1.5	63.6	76.3
15	63.2	59.9	64.5	62.5	2.4	70.5	70.5
16	76.9	82.9	68.9	76.2	7.0	72.4	78.9
Mean	64.8	65.8	67.3	66.0	3.1	72.5	76.4
±SD	7.1	6.9	4.7	5.6	2.2	5.1	3.8

Pre-training reliability estimate (intraclass coefficient); **0.65**

Appendix B, vi. Pre-training time constants for each transition (s).

Subject	WL 1 T1	WL 1 T2	WL 1 T3	WL 2 T1	WL 2 T2	WL 2 T3	WL3 T1	WL3 T2	WL3 T3
1	27.9	29.3	29.5	49.1	48.2	47.9	76.1	75.3	72.1
2	32.3	31.7	31.4	47.5	47.1	46.3	63.2	64.1	61.1
3	23.6	22.9	21.4	31.7	31.0	33.0	94.2	88.2	103.3
4	32.3	33.3	31.2	38.2	39.4	32.2	68.1	74.5	72.8
5	44.4	43.1	43.4	72.8	76.2	74.3	***	***	***
6	23.7	22.9	20.7	37.2	36.9	37.8	60.4	62.5	79.9
7	26.1	24.6	27.1	44.7	49.3	43.1	77.0	79.6	64.2
8	34.2	33.7	32.9	61.2	63.6	63.1	129.1	113.5	126.4
9	24.1	26.1	26.3	38.5	40.1	39.8	98.2	96.7	100.5
10	37.3	38.2	36.5	48.1	48.3	48.7	79.9	75.0	73.8
11	19.7	18.3	18.2	23.3	25.7	22.0	45.0	41.2	38.0
12	25.3	26.1	26.0	39.7	42.5	40.8	74.7	73.6	75.1
13	27.4	28.7	21.7	61.2	64.9	46.0	73.5	70.8	67.7
14	37.8	36.7	39.5	84.5	82.4	76.8	***	***	***
15	30.0	30.7	30.4	57.8	50.8	54.3	95.8	64.1	80.0
16	24.1	25.0	23.9	44.2	41.8	43.2	64.7	68.3	67.5
Mean	**29.4**	**29.5**	**28.8**	**48.7**	**49.3**	**46.8**	**78.6**	**74.8**	**77.3**
±SD	**6.6**	**6.5**	**7.0**	**15.6**	**15.5**	**14.6**	**20.6**	**17.0**	**21.2**

*** denotes failure to complete work load

Pre-training reliability estimates (intraclass coefficients):

Work load 1; **0.962** Work load 2; **0.955** Work load 3; **0.886**

Appendix B, vii. Oxygen uptake time constants (s; Pre, Mid, & Post) for the three transitions.

	WL 1			WL 2			WL 3		
Subject	**Pre**	**Mid**	**Post**	**Pre**	**Mid**	**Post**	**Pre**	**Mid**	**Post**
1	28.9	20.5	21.4	48.4	39.0	41.7	74.5	67.5	68.4
2	31.8	17.5	15.1	47.0	31.6	33.2	62.8	54.1	46.4
3	22.6	22.9	18.4	31.9	31.2	29.6	95.2	77.2	68.2
4	32.3	27.8	22.8	36.6	28.8	24.0	71.8	54.9	41.1
5	43.6	31.9	29.3	74.4	53.2	43.2	***	***	***
6	22.4	20.4	14.7	37.3	35.6	19.9	67.6	62.7	62.3
7	25.9	26.3	22.6	45.7	44.2	38.1	73.6	64.1	59.5
8	33.6	27.5	25.2	62.6	46.4	41.7	123.0	87.5	68.3
9	25.5	22.2	19.6	39.5	34.1	32.3	98.5	62.4	53.2
10	37.3	25.9	23.5	48.4	41.8	37.2	76.2	61.7	55.1
11	18.7	17.6	14.4	23.7	19.9	19.4	41.4	36.6	31.8
12	25.8	25.5	21.3	41.0	39.7	38.8	74.5	68.7	55.3
13	25.9	27.2	25.2	57.4	48.3	44.9	70.7	65.2	63.7
14	38.0	34.9	34.1	81.2	57.3	58.6	***	***	***
15	30.4	25.4	26.3	54.3	43.2	41.5	80.0	70.6	73.2
16	24.3	17.1	16.2	43.1	36.9	37.2	66.8	55.4	49.0
Mean	**29.2**	**24.4**	**21.9**	**48.3**	**39.5**	**36.3**	**76.9**	**63.5**	**56.8**
±SD	**6.6**	**5.1**	**5.5**	**15.0**	**9.5**	**10.0**	**19.0**	**11.8**	**11.8**

*** denotes failure to complete at pre-training stage and subsequent exclusion from overall analysis

Appendix B, viii. Unloaded cycling; Pre-training blood lactate accumulation (mmol·L^{-1}).

Subject	T1	T2	T3	Mean	±SD
1	1.04	1.37	1.33	**1.25**	**0.18**
2	***	0.73	1.36	**1.05**	**0.45**
3	0.33	0.51	0.90	**0.58**	**0.29**
4	0.39	1.17	1.27	**0.94**	**0.48**
5	0.88	1.65	1.45	**1.32**	**0.40**
6	0.83	1.05	0.52	**0.80**	**0.26**
7	1.27	0.89	0.54	**0.90**	**0.37**
8	1.08	1.38	1.43	**1.29**	**0.19**
9	1.34	1.80	0.76	**1.30**	**0.52**
10	0.84	1.23	0.80	**0.96**	**0.23**
11	1.20	1.44	0.84	**1.16**	**0.30**
12	1.33	1.52	1.20	**1.35**	**0.16**
13	0.55	1.62	0.82	**1.00**	**0.56**
14	2.45	1.89	1.30	**1.88**	**0.57**
15	1.17	***	1.38	**1.27**	**0.15**
16	0.70	0.15	0.66	**0.50**	**0.31**
Mean	**1.02**	**1.23**	**1.03**	**1.10**	**0.34**
±SD	**0.51**	**0.49**	**0.33**	**0.33**	**0.14**

Reliability estimate (Intraclass coefficient): **0.367**

Appendix B, ix. Work load 1; Pre-training blood lactate accumulation ($mmol \cdot L^{-1}$).

Subject	T1	T2	T3	Mean	±SD
1	2.53	1.80	2.23	**2.19**	**0.36**
2	***	0.51	1.55	**1.03**	**0.74**
3	0.75	0.94	0.97	**0.89**	**0.12**
4	0.47	1.36	1.70	**1.18**	**0.63**
5	4.01	1.95	2.30	**2.75**	**1.10**
6	1.46	1.72	0.76	**1.31**	**0.50**
7	1.89	0.66	0.89	**1.15**	**0.65**
8	2.75	1.45	1.89	**2.03**	**0.66**
9	2.04	1.51	2.08	**1.87**	**0.32**
10	1.01	1.12	0.76	**0.96**	**0.18**
11	1.31	1.30	1.39	**1.33**	**0.05**
12	1.64	2.18	1.81	**1.88**	**0.28**
13	1.21	2.04	1.44	**1.56**	**0.43**
14	3.76	3.19	3.38	**3.44**	**0.29**
15	2.27	***	1.92	**2.09**	**0.25**
16	1.50	1.52	0.82	**1.28**	**0.40**
Mean	**1.91**	**1.55**	**1.62**	**1.68**	**0.43**
±SD	**1.02**	**0.66**	**0.71**	**0.70**	**0.27**

Reliability estimate (Intraclass coefficient); **0.637**

Appendix B, x. Work load 2; Pre-training blood lactate accumulation ($mmol \cdot L^{-1}$).

Subject	T1	T2	T3	Mean	±SD
1	3.72	3.52	3.25	**3.50**	**0.24**
2	***	2.18	1.74	**1.96**	**0.31**
3	2.20	2.71	2.87	**2.59**	**0.35**
4	2.53	3.08	1.85	**2.49**	**0.62**
5	6.58	9.27	7.32	**7.73**	**1.39**
6	3.46	3.31	2.98	**3.25**	**0.24**
7	2.06	0.55	2.66	**1.75**	**1.09**
8	6.94	4.34	4.98	**5.42**	**1.36**
9	5.00	4.30	3.71	**4.34**	**0.65**
10	2.84	3.68	3.17	**3.23**	**0.42**
11	1.74	1.14	1.38	**1.42**	**0.30**
12	3.12	4.24	3.97	**3.78**	**0.58**
13	6.07	7.22	5.66	**6.31**	**0.81**
14	7.68	7.94	6.76	**7.46**	**0.62**
15	6.68	***	6.08	**6.38**	**0.43**
16	3.03	1.90	2.15	**2.36**	**0.59**
Mean	**4.24**	**3.96**	**3.78**	**4.00**	**0.63**
±SD	**2.04**	**2.47**	**1.85**	**2.05**	**0.37**

Reliability estimate (Intraclass coefficient); **0.873**

Appendix B, xi. Work load 3; Pre-training blood lactate accumulation ($mmol \cdot L^{-1}$).

Subject	T1	T2	T3	Mean	±SD
1	6.69	6.96	6.42	**6.69**	**0.27**
2	***	5.91	5.76	**5.84**	**0.11**
3	7.75	7.26	8.37	**7.79**	**0.56**
4	9.87	8.98	9.69	**9.52**	**0.47**
5	13.55	14.06	15.29	**14.30**	**0.89**
6	11.65	13.69	13.31	**12.88**	**1.08**
7	14.23	10.67	10.89	**11.93**	**1.99**
8	14.68	17.95	14.24	**15.62**	**2.03**
9	10.62	8.27	10.10	**9.66**	**1.23**
10	10.98	12.21	10.83	**11.34**	**0.76**
11	4.97	3.90	3.96	**4.28**	**0.60**
12	11.78	12.65	12.38	**12.27**	**0.45**
13	11.48	12.11	10.79	**11.46**	**0.66**
14	13.33	16.28	15.21	**14.94**	**1.49**
15	16.38	***	12.95	**14.66**	**2.42**
16	8.65	7.62	8.45	**8.24**	**0.55**
Mean	**11.11**	**10.57**	**10.54**	**10.71**	**0.97**
±SD	**3.14**	**4.01**	**3.35**	**3.45**	**0.68**

Reliability estimate (Intraclass coefficient); **0.899**

Appendix B, xii. Summary of blood lactate accumulation ($mmol \cdot L^{-1}$); Pre, Mid, and Post.

	Unl			WL 1			WL 2			WL 3		
Subject	**Pre**	**Mid**	**Post**	**Pre**	**Mid**	**Post**	**Pre**	**Mid**	**Post**	**Pre**	**Mid**	**Post**
1	1.25	1.31	1.23	2.19	1.45	1.60	3.50	2.03	2.21	6.69	5.16	4.78
2	1.05	0.63	0.70	1.03	0.96	0.71	1.96	2.06	0.83	5.84	4.97	3.54
3	0.58	1.42	0.98	0.89	1.19	0.99	2.59	2.28	2.19	7.79	8.11	6.88
4	0.94	0.96	1.42	1.18	1.64	1.23	2.49	1.80	1.68	9.52	5.73	4.93
5	1.32	0.75	1.09	2.75	0.94	0.97	7.73	5.13	2.64	14.30	13.95	10.87
6	0.80	1.20	0.72	1.31	0.86	0.59	3.25	2.44	1.48	12.88	9.77	9.40
7	0.90	2.10	0.82	1.15	0.81	1.08	1.75	3.30	1.43	11.93	8.00	6.49
8	1.29	1.35	0.88	2.03	1.05	1.41	5.42	3.84	3.31	15.62	12.15	9.61
9	1.30	1.19	0.21	1.87	1.48	0.64	4.34	2.23	1.37	9.66	5.72	3.63
10	0.96	0.41	0.70	0.96	0.61	0.98	3.23	2.28	2.29	11.34	8.59	6.86
11	1.16	0.77	0.44	1.33	0.63	0.69	1.42	1.05	0.42	4.28	2.02	1.74
12	1.35	0.77	1.04	1.88	1.26	2.08	3.78	3.51	2.91	12.27	10.61	8.43
13	1.00	0.23	1.50	1.56	1.36	1.32	6.31	4.95	2.47	11.46	8.71	6.81
14	1.88	0.28	0.75	3.44	1.93	1.44	7.46	4.98	5.11	14.94	12.22	11.21
15	1.27	0.15	0.53	2.09	1.43	1.15	6.38	4.39	3.09	14.66	9.70	9.87
16	0.50	0.42	1.36	1.28	0.63	0.97	2.36	1.92	1.45	8.24	4.65	3.52
Mean	**1.10**	**0.87**	**0.90**	**1.68**	**1.14**	**1.12**	**4.00**	**3.01**	**2.18**	**10.71**	**8.13**	**6.79**
±SD	**0.33**	**0.53**	**0.37**	**0.70**	**0.39**	**0.39**	**2.05**	**1.30**	**1.12**	**3.45**	**3.25**	**2.92**

Appendix B, xiii. 40K time trial results (s).

Subject	Pre T1	Pre T2	Pre T3	Mean Pre	±SD	Mid T4	Post T5
1	4802.3	4302.0	4433.4	4512.6	259.4	4103.9	4022.4
2	4027.3	3937.7	3955.5	3973.5	47.4	3876.7	3814.6
3	4648.1	4574.7	4814.9	4679.2	123.1	4149.5	4032.7
4	4672.2	4671.3	4550.6	4631.4	69.9	4419.6	4258.5
5	5004.3	5386.4	5102.9	5164.5	198.4	4704.6	4657.2
6	4771.4	4588.9	4324.4	4561.6	224.8	4272.0	4381.7
7	5389.7	5432.8	5130.0	5317.5	163.8	4813.9	4634.7
8	4583.0	4519.5	4732.0	4611.5	109.1	4436.5	4359.5
9	4414.7	4457.5	4451.1	4441.1	23.1	4126.7	4098.1
10	4310.1	4560.3	4311.4	4393.9	144.1	4095.4	4075.9
11	4088.8	3952.4	3929.2	3990.1	86.2	3747.9	3724.6
12	4599.4	4706.7	4275.7	4527.3	224.4	4420.8	4154.6
13	5186.3	5202.3	5149.9	5179.5	26.9	5011.1	4786.0
14	5283.1	4935.2	5010.6	5076.3	183.0	4671.4	4789.6
15	5205.8	4630.9	4591.9	4809.5	343.7	4201.9	4229.6
16	4185.8	4400.4	4165.2	4250.5	130.3	4070.7	***
Mean	**4698.3**	**4641.2**	**4558.0**	**4632.5**	**147.3**	**4320.2**	**4268.0**
±SD	**429.5**	**431.5**	**401.0**	**399.9**	**89.1**	**345.7**	**332.1**

Pre-training reliability estimates (Intraclass coefficient); **0.837**

Appendix B, xiv. Oxygen uptake steady state data, Pre-training ($ml \cdot min^{-1}$).

Subject	UNL Mean	±SD	WL 1 Mean	±SD	WL 2 Mean	±SD	WL 3 Mean	±SD
1	1050	32	1835	33	3015	239	3957	275
2	1003	36	1846	81	2909	260	3734	59
3	921	53	1689	21	2642	174	3667	230
4	1007	39	1827	63	2697	172	3651	158
5	960	62	1826	61	2738	51	DNC	DNC
6	958	39	1862	52	2878	46	3726	198
7	856	35	1401	45	2091	208	2819	311
8	921	31	1749	22	2743	174	3564	148
9	1016	19	1874	68	2850	268	3889	305
10	887	17	1670	57	2603	152	3464	67
11	944	30	1716	58	2631	202	3650	236
12	875	73	1827	81	2942	275	3855	353
13	783	19	1421	57	2112	43	2549	46
14	926	52	1798	63	2919	39	DNC	DNC
15	1110	67	1824	45	2802	17	3710	109
16	998	10	1788	52	2608	110	3655	200
Mean	**951**	**38**	**1747**	**54**	**2699**	**152**	**3563**	**192**
±SD	**80**	**19**	**144**	**18**	**266**	**90**	**397**	**99**

NB: DNC = Did Not Complete

Appendix B, xv. Oxygen uptake steady state data, Mid and Post-training ($ml \cdot min^{-1}$).

	MID						POST					
	UNL		WL 1		WL 2	WL 3	UNL		WL 1		WL 2	WL 3
Subj	Mean	±SD	Mean	±SD			Mean	±SD	Mean	±SD		
1	1029	55	1799	47	2696	3658	1022	30	1890	16	2837	3807
2	934	50	1723	11	2741	3563	957	70	1781	21	2723	3660
3	968	45	1716	27	2590	3504	1053	21	1777	56	2631	3578
4	1031	63	1799	28	2599	3618	1061	27	1756	36	2617	3485
5	940	39	1764	23	2687	DNC	913	68	1820	69	2600	DNC
6	938	42	1757	58	2783	3625	976	22	1695	77	2682	3583
7	829	77	1426	75	1987	2673	845	51	1456	68	1968	2684
8	1051	80	1786	50	2689	3491	1020	156	1766	23	2765	3501
9	1097	67	1772	37	2675	3572	1155	75	1812	72	2706	3612
10	817	17	1660	59	2557	3454	922	47	1719	81	2467	3562
11	1013	25	1713	29	2645	3623	1068	32	1737	49	2699	3562
12	855	13	1738	10	2833	3766	797	20	1662	62	2630	3193
13	800	30	1441	43	2175	2597	827	25	1472	22	2089	2578
14	1005	81	1797	57	2796	DNC	1061	87	1733	23	2732	DNC
15	1016	51	1827	44	2854	3758	1050	45	1787	11	2798	3764
16	903	55	1664	18	2561	3556	815	29	1594	33	2363	3110
Mean	**952**	**49**	**1711**	**38**	**2617**	**3461**	**971**	**50**	**1716**	**45**	**2582**	**3406**
±SD	**90**	**21**	**118**	**19**	**231**	**362**	**108**	**35**	**119**	**24**	**247**	**378**

NB: DNC = Did Not Complete/Include

Appendix B, xvi. Change in oxygen uptake during transitions ($ml \cdot min^{-1}$).

	Pre-Training			Mid-Training			Post-Training		
Subject	**Δ1**	**Δ2**	**Δ3**	**Δ1**	**Δ2**	**Δ3**	**Δ1**	**Δ2**	**Δ3**
1	785	1179	942	770	897	962	868	947	970
2	843	1063	825	789	1018	822	824	942	937
3	768	952	1025	749	874	914	724	854	947
4	820	870	954	769	800	1019	695	861	868
5	866	912	DNC	824	923	DNC	907	780	DNC
6	904	1016	847	819	1026	842	719	987	901
7	544	690	728	597	561	686	612	512	716
8	828	994	821	735	903	802	746	999	736
9	858	976	1039	674	903	897	658	894	906
10	783	933	861	843	897	897	797	748	1095
11	772	915	1019	701	932	978	669	962	863
12	952	1115	912	883	1095	933	865	968	563
13	639	691	436	641	734	422	644	617	489
14	872	1121	DNC	791	999	DNC	672	999	DNC
15	714	978	908	811	1027	904	737	1011	966
16	791	820	1047	761	897	995	779	769	747
Mean	**796**	**952**	**883**	**760**	**905**	**862**	**745**	**866**	**836**
±SD	**100**	**139**	**160**	**76**	**129**	**154**	**88**	**147**	**167**

NB: DNC = Did Not Complete

Appendix B, xvii. Summary of heart rate steady state data, Pre-training ($b \cdot min^{-1}$).

Subject	UNL Mean	±SD	WL 1 Mean	±SD	WL 2 Mean	±SD	WL 3 Mean	±SD
1	108	5	136	6	178	4	191	1
2	80	7	106	5	139	1	177	4
3	96	7	115	2	141	7	178	8
4	98	6	113	1	134	3	172	8
5	100	4	135	2	179	9	190	0
6	101	3	128	3	162	7	186	2
7	111	7	135	2	170	3	198	2
8	98	3	116	5	162	3	189	4
9	99	5	121	2	148	2	178	1
10	88	3	114	4	146	4	174	6
11	86	5	110	2	134	2	166	2
12	99	5	124	6	162	6	185	8
13	110	3	145	5	172	3	186	4
14	115	5	153	8	200	6	207	2
15	124	4	145	2	178	11	197	6
16	102	5	126	4	153	3	179	3
Mean	**101**	**5**	**126**	**4**	**160**	**4**	**185**	**4**
±SD	**11**	**2**	**14**	**2**	**19**	**3**	**11**	**3**

Appendix B, xviii. Heart rate steady state data, Mid and Post-training ($b \cdot min^{-1}$).

	MID						POST					
	UNL		WL 1		WL 2	WL 3	UNL		WL 1		WL 2	WL 3
Subj	Mean	±SD	Mean	±SD			Mean	±SD	Mean	±SD		
1	81	3	102	4	135	170	86	7	114	2	140	170
2	71	4	93	6	120	155	79	9	96	4	124	162
3	90	5	115	5	139	170	95	1	109	7	135	162
4	86	5	103	3	122	154	96	2	107	11	126	158
5	92	3	123	3	160	190	93	3	125	5	164	191
6	97	5	118	3	160	190	92	4	117	2	150	177
7	100	2	127	8	165	189	109	4	130	1	162	195
8	87	3	117	6	155	180	98	3	120	4	152	173
9	99	1	119	2	132	165	99	2	117	6	144	166
10	84	5	107	3	134	161	95	4	109	2	135	170
11	85	2	107	3	135	165	81	4	103	4	125	160
12	95	3	112	3	148	178	92	6	115	6	144	174
13	94	0	126	3	161	181	96	3	124	1	160	179
14	108	3	136	6	179	186	118	3	148	3	196	210
15	97	1	118	1	150	180	100	3	117	3	153	178
16	97	3	122	3	150	172	92	3	125	2	144	163
Mean	**91**	**3**	**115**	**4**	**147**	**174**	**95**	**4**	**117**	**4**	**147**	**174**
±SD	**9**	**2**	**11**	**2**	**16**	**12**	**9**	**2**	**12**	**3**	**18**	**14**

APPENDIX C

APPENDIX C

Salbutamol; brief review of relevant literature

The participation of asthmatic individuals in high performance sport has been growing steadily in recent years, and estimates of the size of the athletic population who are afflicted by exercise-induced asthma (EIA) or exercise-induced bronchospasm (EIB) fall in the area of 10% (Voy, 1984). Additionally, 'regular exercise is now an accepted part of the management of asthma' (Morton & Fitch, 1992). However, because of possible ergogenic effects, many anti-asthmatic medications are not permitted by the governing bodies of many sport disciplines, in particular the International Olympic Committee (IOC). Of the current acceptable anti-asthmatic drugs, Salbutamol has fallen under the suspicion of having performance enhancing effects (Bedi, Gong, & Horvath, 1988; Signorile, Kaplan, Applegate, & Perry, 1991), although this has been refuted by some researchers (Meeuwisse, Hopkins, McKenzie, 1991; Morton, Papalia, & Fitch, 1992; Meeuwisse, McKenzie, Hopkins, & Road, 1992; Morton, Papalia, & Fitch, 1993). This possible ability to aid performance, plus the known improvements for asthmatic athletes, has led to concern that some non asthmatic athletes are utilizing Salbutamol prior to competition.

Salbutamol (Albuterol) is a β_2-selective adrenoceptor agonist with relatively 'long-acting' characteristics, minimal β_1-receptor effects, and little stimulation of α-adrenoceptors (Price & Clissold, 1989). Salbutamol, a saligenin derivative, mimics the basic catechol structure of norepinephrine and epinephrine, and these characteristics account for its bronchodilatory, cardiovascular, uterine, and metabolic effects in humans. In general, the bronchial effects in healthy individuals are a pronounced dilation of the large airways via a reduction in bronchomotor tone, as demonstrated by standard pulmonary function testing

(forced expired volume in one second; FEV1), and improvements in small airway efficiency (forced expiratory flow between 25% and 75% of vital capacity; FEF25-75%)(Riedel & Van der Hardt, 1986). At the cardiovascular level, usual inhaled therapeutic doses (≈200 mg) do not normally produce significant responses in healthy subjects, however, larger doses, particularly if administered by nebulised spray, orally, or parenterally, do lead to increases in heart rate (positively chronotropic) and systolic blood pressure. Additionally, the velocity of circumferential fibre shortening increases (positively inotropic), although stroke index and ejection fraction improvements are usually small (Corea, Bentivoglio, Verdecchia, Motolese & Sorbini, 1984). Obviously, more significant responses have been demonstrated in unhealthy subjects (i.e., Reversible Obstructive Airways Disease and Cardiovascular Disease)(Mettauer, Rouleau, & Burgess, 1985; Fowler, Timmis, Crick, Vincent, & Chamberlain, 1982). Salbutamol is also routinely given for pain relief from premature labour. This relief is derived from an associated reduction in uterine tonicity (intravenous $10mg \cdot min^{-1}$)(Lalos & Joelsson, 1981), and, to date, no studies have reported any effect of such action upon the resulting child.

Salbutamol also has some marked metabolic effects, and, as with the previously mentioned responses, these seem to be dose-related. Plasma potassium (K^+) is reduced in both healthy and unhealthy individuals, and this has led to the suggestion that Salbutamol be used in treating hyperkalemia in renal failure (Rolf Smith, Ryder, Kendall, & Holder, 1984). The stimulation of β-adrenoceptors directly associated with the membrane-bound enzyme Na^+/K^+-ATPase on skeletal muscle is thought to be the mechanistic route for this action, rather than via the β_2-adrenoceptor-induced insulin release (Rolf Smith & Kendall, 1984). Since the β-receptors are involved in insulin release and

glycogenolysis, it is not surprising that there is evidence that Salbutamol ingestion leads to increases in plasma insulin and glucose levels in all individuals (Rolf Smith & Kendall, 1984). A significant lipolytic activity induced by Salbutamol has also been shown by marked increases in blood levels of non-esterified fatty acid (NEFA) and high density lipoprotein-cholesterol (HDL-cholesterol)(Wager, Fredholm, Lunell, & Persson, 1982).

An interesting response that has been observed in humans is the noticeable antidepressant effect mediated through a possible serotonergic link and increase in activity (Martin, Soubrie, & Simon, 1986). The serotonin-containing neurons may be found throughout the brain and, in particular, around the midline raphe nuclei of the brain stem,the hypothalamus, the limbic system, the neocortex, and the spinal cord (Peroutka, 1988). Variations in brain serotonin concentrations are thought to be linked to behaviour with euphoria, inhibition of the transmission of pain, and circadian rhythm regulation all having been reported.

The mechanism of action for Salbutamol involves it reversibly binding with the β-adrenoceptor, causing a stimulatory G-protein to activate the enzyme adenylate cyclase. When there is a simultaneous binding of adenosine triphosphate (ATP) with adenylate cyclase, ATP is converted to 3',5'-cyclic adenosine monophosphate (cAMP). Thus, cAMP acts as the mediator ("second messenger") through which increased β-adrenoceptor activity results in the 'triggering' of a sequence of intracellular events ending in some physiological response (Price & Clissold, 1989). It should be noted that the nucleotide regulatory proteins (the G-proteins) are critical components in the overall process, since these constructs link the receptor phase to the cyclase loop.

In terms of the pharmacokinetics of Salbutamol and its metabolites, information has been somewhat limited due to the unavailability of valid and reliable measuring methods.

However, the recent development of high performance liquid chromatography (HPLC) assays and the chiral HPLC separation method for optical isomers of Salbutamol have led to more accurate information (Price and Clissold, 1989). In healthy individuals, peak plasma levels are reached one to four hours after oral ingestion, indicating that Salbutamol is readily absorbed. There is, however, extensive presystemic metabolism in the intestinal wall resulting in approximately only 50% 'systemic bioavailability' (Morgan, Paul, & Richmond, 1986). Of note is the finding that for inhaled doses, the majority is swallowed and treated orally, resulting in plasma concentrations being somewhat smaller than oral doses. The reduced amount handled by the lungs ($\approx$10%) appears quickly as the free unmetabolised drug in the circulation, and, in general, at low concentrations (50-200 $mg \cdot L^{-1}$) only 7-8% is bound to plasma proteins, whereas at concentrations of 2 $mg \cdot L^{-1}$ approximately 64% is in the bound form. The drug follows a rapid clearance pattern with only small residues left in the liver and kidneys 24 hours post-oral administration, in fact, 70% of normal oral therapeutic doses is excreted in the urine in 24 hours, with 80-100% being excreted after 72 hours. The main metabolite for Salbutamol is a sulphur conjugate, 4'-*O*-sulphate ester, which is formed in the intestinal wall and liver. The elimination half-life for a single oral dose of 4mg is in the range of 2.7-5.5 hours for a healthy individual.

Unfortunately, adverse side effects are seen, particularly when Salbutamol is administered orally or intravenously and at high dosage levels. The principle effects are tachycardia, palpitation, tremor, peripheral vasodilation, hypokalemia, and a worsening of the asthma condition (in asthmatics) due to increased tolerance (tachyphylaxis).

From a theoretical standpoint Salbutamol appears to have a number of possible avenues through which to positively affect human performance. This alone warrants the

continued interest in this particular medication. To date, most studies examining 'the ergogenic effects' of Salbutamol in humans have focused on somewhat gross measures (e.g., $\dot{V}O_2max$) and therapeutic dose levels despite the evidence suggesting enhancement may not be reflected in increased $\dot{V}O_2max$ and that larger doses are required to elicit these effects.

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APPENDIX D

APPENDIX D

Methacholine Bronchial Provocation Test

This particular test is one of several stimuli that may be used to 'challenge' the bronchial system and provoke some degree of airway change. Essentially, there are four reasons for performing such a test, and these are as follows;

1). in the diagnosis of asthma
2). to confirm the diagnosis of asthma
3). to document the severity of airway hyperresponsiveness, and
4). to follow any changes in such hyperresponsiveness.

Overall, the results of tests using methacholine have been shown to have a high degree of reproducibility, and it is [illegible] able differentiate between asthmatics and normal subjects and does not have the level of adverse side effects that are associated with other agents used in such challenges (e.g., histamine).

The methacholine test requires the subject to undergo a procedure whereby an increasing concentration of the challenge agent is systematically administered via a nebulised spray. The agent is allowed to take effect and then the subject repeats the pulmonary function tests after each dosage. Since the subjects used in this investigation had reported no previous history of asthma, and had undergone a routine medical examination, they started the provocation test at a higher concentration of methacholine ($2mg \cdot ml^{-1}$) than would have been the norm. The test was continued until either the highest concentration was inhaled, or the FEV_1 had fallen by 20%. A 20% fall in FEV_1 is taken as being meaningful and, where appropriate, a linear interpolation of the results can yield the dose that brought about this response. For purposes of diagnosis, this concentration value

may then be used to describe the degree of airway sensitivity that a patient may have, i.e.,

$PC_{20}FEV_1$ (mg·ml^{-1})*	*Severity*
0.03-0.124	Severe
0.125-1.99	Moderate
2.00-7.99	Mild
Above 8.00	Normal

*Provocation concentration for 20% decline in FEV_1

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