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Juha Peltonen

Effects of Oxygen Fraction in Inspired Air on Cardiorespiratory Responses and Exercise Performance

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Academic Dissertation

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Department of Biology of Physical Activity,
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Effects of Oxygen Fraction in Inspired Air on Cardiorespiratory Responses and Exercise Performance

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Vasta paineessa
syntyy aineessa
kuohuvan uutta
vallattomuutta.

Mika Waltari

ABSTRACT

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The present series of studies were conducted to investigate the relationship between exercise performance and oxygen uptake ($\dot{V}O_2$) by altering the fraction of oxygen in inspired air (F_IO_2) in an attempt to elucidate the mechanisms that regulate and limit physical work capacity. A total of 29 endurance athletes were examined in hyperoxia (F_IO_2 0.293 – 0.622), normoxia (F_IO_2 0.209) and hypoxia (F_IO_2 0.150-0.166). Hypoxia impaired (mean 14.7%) and hyperoxia improved (12.2%) maximal oxygen uptake ($\dot{V}O_{2max}$) in comparison with normoxia. Impaired $\dot{V}O_{2max}$ was accompanied by a decrement in exercise performance (P_{max}) in hypoxia (7.3%). Also, P_{max} tended to be higher in hyperoxia (3.6%) than in normoxia. Thus, in both hypoxia and hyperoxia, the change in $\dot{V}O_{2max}$ exceeded the change in P_{max}. Maximal cardiac output ($\dot{Q}_{max}$) was reduced (8.8%) in acute hypoxia when compared with normoxia. The reduction in $\dot{V}O_{2max}$ in acute hypoxia is therefore explained both by the narrowing of the arterio-venous O_2 difference and reduced $\dot{Q}_{max}$. The reduced $\dot{Q}_{max}$ in hypoxia and the finding that hypoxia had a tendency to diminish the sum of integrated electromyography signals during maximal exercise in comparison with normoxia and hyperoxia both suggest that the central nervous system (CNS) is among those factors that limit exercise performance and $\dot{V}O_{2max}$ in acute hypoxia. Therefore, reduced $\dot{Q}_{max}$ and $\dot{V}O_{2max}$ in acute hypoxia may be the result rather than the cause of reduced P_{max} and skeletal muscle recruitment, which can be interpreted to support the “central governor” hypothesis. However, further studies are needed to indicate the existence and mode of action of the proposed “central governor”. This study indicates that some of those responses that previously were expected to occur only in chronic hypoxia can also be seen in acute phase, at least in highly trained endurance athletes. This study also indicates that exercise performance and $\dot{V}O_{2max}$ may not be dependent only on the O_2 delivery and utilization, but also on other factors including factors possibly linked to CNS function.

Key words: hyperoxia, hypoxia, normoxia, oxygen uptake, arterial O_2 saturation, cardiac output, integrated electromyography

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Hämeenlinna, January 2002
Juha Peltonen

CONTENTS

LIST OF ORIGINAL ARTICLES

This dissertation is based on the following publications, which will be referred to in the text by their Roman numerals:

I Peltonen JE, Leppävuori AP, Kyrö K-P, Mäkelä P, and Rusko HK (1999) Arterial haemoglobin oxygen saturation is affected by F_IO_2 at submaximal running velocities in elite athletes. Scand J Med Sci Sports 9: 265-271.

II Peltonen JE, Rantamäki J, Niittymäki SPT, Sweins K, Viitasalo JT, and Rusko HK (1995) Effects of oxygen fraction in inspired air on rowing performance. Med Sci Sports Exerc 27: 573-579.

III Peltonen JE, Rusko HK, Rantamäki J, Niittymäki SPT, Sweins K, and Viitasalo JT (1997) Effects of oxygen fraction in inspired air on force production and electromyogram activity during ergometer rowing. Eur J Appl Physiol 76: 495-503.

IV Peltonen JE, Tikkanen HO, Ritola JJ, Ahotupa M, and Rusko HK (2001) Oxygen uptake response during maximal cycling in hyperoxia, normoxia and hypoxia. Aviat Space Environ Med 72: 904-911.

V Peltonen JE, Tikkanen HO, and Rusko HK (2001) Cardiorespiratory responses to exercise in acute hypoxia, hyperoxia and normoxia. Eur J Appl Physiol 85: 82-88.

ABBREVIATIONS

α_b	blood Bunsen solubility coefficient for acetylene
α_t	lung tissue Bunsen solubility coefficient for acetylene
β_s	slope of the disappearance curve for acetylene (C_2H_2)
τ	time constant, time for the occurrence of 0-63% of the response, s
τ_1	time constant of response in Phase 1, s
τ_2	time constant of response in Phase 2, s
τ_3	time constant of response in Phase 3, s
$(a\text{-}v)O_2$	arterio-venous oxygen difference, $ml \cdot dl^{-1}$
A_0	$\dot{V}O_2$ at rest, $l \cdot min^{-1}$
A_1	amplitude of $\dot{V}O_2$ in Phase 1, l
A_2	amplitude of $\dot{V}O_2$ in Phase 2, l
A_3	amplitude of $\dot{V}O_2$ in Phase 3, l
aa_3	cytochrome oxidase
AMS	acute mountain sickness
ATP	adenosinetriphosphate
C_2H_2	acetylene
Ca^{2+}	calcium ion
C_aO_2	arterial oxygen content, $ml \cdot l^{-1}$ blood
CNS	central nervous system
CO_2	carbon dioxide
C_vO_2	venous oxygen content, $ml \cdot l^{-1}$ blood
dF/dt	peak force production rate, $N \cdot s^{-1}$
DO_2	muscle O_2 diffusing capacity
ECG	electrocardiogram
EDP	end-diastolic pressure, mmHg
EDV	end-diastolic volume, ml
EIAH	exercise-induced arterial hypoxemia
EMG	electromyogram
F_IO_2	fraction of oxygen in inspired air
F_{max}	maximal force
FT	fast twitch fiber
H^+	hydrogen ion
HACE	high altitude cerebral edema
HAPE	high altitude pulmonary edema
Hb	hemoglobin
[Hb]	hemoglobin concentration, $g \cdot l^{-1}$ blood
HR	heart rate, $beats \cdot min^{-1}$
HR_{max}	maximal heart rate, $beats \cdot min^{-1}$
I	impulse, $N \cdot s$
IEMG	integrated electromyogram

LAT	lactic acidosis threshold
MRT	mean response time, 0 – 63% of the response, s
N	newton
NME	neuromuscular efficiency (= impulse / sum-IEMG)
O_2	oxygen
P_AO_2	oxygen partial pressure in alveolar air, mmHg
P_aO_2	oxygen partial pressure in arterial blood, mmHg
P_B	barometric pressure, mmHg
$P_{cap}O_2$	mean oxygen partial pressure in muscle capillary, mmHg
PCO_2	carbon dioxide partial pressure, mmHg
PCr	phosphocreatine
PCWP	pulmonary capillary wedge pressure, mmHg
pH	activity of hydrogen ions
P_IO_2	oxygen partial pressure in inspired air, mmHg
P_{max}	maximal power, W
$P_{mito}O_2$	mitochondrial oxygen partial pressure, mmHg
PO_2	oxygen partial pressure, mmHg
$\dot{Q}$	cardiac output, $l \cdot min^{-1}$
$\dot{Q}_{max}$	maximal cardiac output, $l \cdot min^{-1}$
RPE	rate of perceived exertion
S_aO_2%	arterial hemoglobin oxygen saturation (measured with blood gas analysis)
SD	standard deviation
SpO_2%	arterial hemoglobin oxygen saturation (measured with pulse oximeter)
Sum-IEMG	sum of integrated electromyogram signals
SV	stroke volume, ml
SV_{max}	maximal stroke volume, ml
TD	time delay before the appearance of the response at the mouth, s
TD_1	time delay before the appearance of the response at the mouth in Phase 1, s
TD_2	time delay before the appearance of the response at the mouth in Phase 2, s
TD_3	time delay before the appearance of the response at the mouth in Phase 3, s
V_A	alveolar ventilation, $l \cdot min^{-1}$
$V_A / \dot{Q}$	ventilation / perfusion ratio
$\dot{V}O_2$ (t)	response of O_2 uptake ($\dot{V}O_2$) as a function of time (t)
$\dot{V}O_2$	oxygen uptake, $l \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$
$\dot{V}O_{2max}$	maximal oxygen uptake, $l \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$
V_S	initial, combined lung and rebreathing bag volume, l
V_t	lung tissue volume, ml

1 INTRODUCTION

Maximum oxygen uptake ($\dot{V}O_{2max}$) is an indicator of the highest rate at which oxygen (O_2) can be taken up and utilized by the body during severe exercise. It is frequently used to indicate combined cardiorespiratory, circulatory and muscular fitness. A strong correlation exists between $\dot{V}O_{2max}$ and maximal endurance exercise performance (Costill et al. 1973; Bassett and Howley 2000). Numerous studies have shown that $\dot{V}O_{2max}$ can be modified rapidly by influencing one or several of the parameters determining this property. These rapid changes exclude structural changes that normally take several weeks to occur. Examples of $\dot{V}O_{2max}$ modification are its increase along with rising partial pressure of inspired oxygen (P_IO_2) and its impairment with decreasing P_IO_2 (Consolazio et al. 1966; Dill et al. 1966; Klausen et al. 1966; Faulkner et al. 1968; Hughes et al. 1968; Saltin et al. 1968b; Davies and Sargeant 1974; Welch et al. 1974; Ekblom et al. 1975; Squires and Buskirk 1982; Terrados et al. 1985; Fulco et al. 1988; Cymerman et al. 1989). Accordingly, $\dot{V}O_{2max}$ rises as a consequence of red cell transfusion (Gledhill 1982; Gledhill 1985; Spriet et al. 1986; Gledhill et al. 1999) and decreases with sympathetic blockade (Hughson and MacFarlane 1981; Tesch 1985; Hughson and Kowalchuk 1991). In addition to humans, adaptation of $\dot{V}O_{2max}$ has also been studied in animals (Hogan et al. 1988). In a longer time frame, $\dot{V}O_{2max}$ increases with endurance training and decreases with detraining (Saltin et al. 1968a) and a longer exposure to high altitude (Cymerman et al. 1989; di Prampero and Ferretti 1990; Ferretti et al. 1990; Green et al. 2000). Thus, structural changes are involved in addition to functional changes in these conditions.

Interest in the factors limiting $\dot{V}O_{2max}$ predominantly focus on the delivery of O_2 to the mitochondria and the use of O_2 in the mitochondria, and a lively debate over the definition and nature of $\dot{V}O_{2max}$ has enriched the recent literature (Bassett and Howley 1997; Noakes 1997; Noakes 1998; Noakes 2000; Wagner 2000a).

The classical theory supports the view that exercise is limited once oxygen delivery to the exercising skeletal muscle becomes inadequate (Bassett and Howley 1997). In addition, theories combining O_2 delivery and utilization have gained attention (Roca et al. 1989; di Prampero and Ferretti 1990; Wagner 1991; Wagner 1992; Wagner 1995; Wagner 1996; Wagner 2000a). An alternative theory favors the view that a "central governor" regulates skeletal muscle function in an attempt to protect the heart from developing myocardial ischemia during maximal exercise (Noakes 1998; Noakes 2000). The most recent theories favor the idea that instead of trying to find *the* limiting factor of $\dot{V}O_{2max}$, interest should be focused on identifying the possible factors that contribute to the limitation of O_2 supply or utilization under specific conditions (Wagner 2000a; Noakes et al. 2001).

Among attempts to clarify the effect of O_2 delivery on $\dot{V}O_{2max}$, the use of hypoxia (i.e. decreased P_IO_2) and hyperoxia (i.e. increased P_IO_2) have enormously increased knowledge on this issue. Hypoxia is the major accompaniment of ascent to high altitude, and is the basic stimulus to a variety of adaptations and maladaptations that occur in that environment. In addition to the theoretical model of $\dot{V}O_2$ limitation, the effects of P_IO_2 on exercise capacity and physiological responses have a practical application in athletic training (Levine et al. 1991b; Chick et al. 1993; Rusko 1996; Levine and Stray-Gundersen 1997), recreational exercise, and in the treatment of some chronic pulmonary diseases (Rooyackers et al. 1997; Calverley 2000; Garrod et al. 2000). Training at moderate altitude is widely used among competitive endurance athletes. It has become clear that if competitions are held at high altitude, the preparatory period must take place in similar conditions. However, if competitions take place at sea level, there is controversy about the benefits of pre-competition high altitude training. It has therefore become tempting to combine the benefits of high altitude training while avoiding its hazardous effects. This "living high - training low" (Levine et al. 1991b; Rusko 1996; Levine and Stray-Gundersen 1997; Stray-Gundersen et al. 2001) combination offers one approach to finding the best sides of each, although more information about it is needed (Friedmann and Bartsch 1997). Taken together, it is becoming increasingly important to gain knowledge of the acute effects of P_IO_2.

The present study was undertaken with an attempt to gather new information about the relationship between $\dot{V}O_{2max}$ and exercise performance by using moderate hypoxia and hyperoxia as a modified stimulus during exercise. The focus was on the physiological responses linked to $\dot{V}O_2$ during an acute change in the fraction of oxygen in inspired air (F_IO_2). Special attention was directed to the factors affecting O_2 delivery to the working muscles in order to determine whether changes in F_IO_2 and the concomitant physiological responses would induce comparable changes in performance and hence point to a central cardiopulmonary limitation on exercise performance.

2 REVIEW OF THE LITERATURE

2.1 Maximal aerobic capacity, exercise performance and F_IO_2

The ability to sustain muscular exercise is dependent in large part on the body's ability to transport O_2 from the atmosphere for use as the terminal oxidant in the mitochondrial electron transport chain. Those with the highest aerobic capacity will in general be able to perform best, although, of course, additional factors are involved (Green 1989). Although resting oxygen uptake is very similar in trained and untrained individuals, there is at least a twofold higher $\dot{V}O_{2max}$ in the trained vs. the untrained individual (Ekblom and Hermansen 1968; Ekblom 1969; Rowell 1974; Clausen 1977; Rowell 1986). The pathway for O_2 from the atmosphere for use in the tissues is well established and includes pulmonary gas exchange and the transport of O_2 within hemoglobin (Hb) to the peripheral tissues and its release and diffusion into the mitochondria. Each of these phases consists of several phases. Thus, pulmonary gas exchange is dependent on alveolar ventilation (V_A), the amount of ventilation/perfusion mismatch ($V_A/\dot{Q}$) and O_2 diffusion from the alveoli to the blood. Consequently, O_2 transport in the blood is dependent on cardiac output ($\dot{Q}$), muscular blood flow and blood oxygen carrying capacity. Peripheral diffusion includes the dissociation of O_2 from hemoglobin, O_2 diffusion from red blood cells to the plasma, through the capillary wall and interstitial space into the muscle cell where it is facilitated with myoglobin into the mitochondria. Dissociation of O_2 from hemoglobin and diffusion is affected by muscle blood flow and capillary density as well as by the partial pressure of carbon dioxide (PCO_2), pH and temperature. Muscle metabolism, substrate delivery, muscle mass, fiber type, size and number, energy stores as well as the amount of myoglobin and mitochondria and the activity of oxidative enzymes all affect the oxygen consumed during exercise (see e.g. Saltin and Strange 1992; Sutton 1992).

As research in this field has been ongoing for almost a century, it might be

expected that a consensus had been reached on the most critical issue: what limits $\dot{V}O_{2max}$? This is, however, not the case, and two separate schools of thought have emerged: one favoring a central limitation and the other favoring a peripheral limitation. Central oxygen delivery depends on maximal cardiac output ($\dot{Q}_{max}$) and maximal arterial oxygen content (C_aO_2): $\dot{Q} \times C_aO_2$. The peripheral extraction of the delivered oxygen is expressed as the arterial-venous O_2 difference ($(a\text{-}v)O_2$). Combining these, we have the circulatory ability to deliver and extract oxygen. Thus, $\dot{V}O_{2max}$ is expressed as the Fick equation $\dot{V}O_{2max} = \dot{Q}_{max} \times (a\text{-}v)O_{2max}$. In the past, the beliefs about the primary factors limiting $\dot{V}O_{2max}$ have alternated between the central and the peripheral. The theories supporting the central factors are based on the assumption that $\dot{V}O_{2max}$ is limited by the O_2 delivery to the mitochondria in the working muscles. Correspondingly, the ability of the mitochondria to use the delivered O_2 is pivotal in the theories favoring the peripheral factors as the primary limit for $\dot{V}O_{2max}$. According to the latter model, $\dot{V}O_{2max}$ does not increase by an increase in O_2 delivery, as the partial pressure of oxygen (PO_2) in the mitochondria does not limit the flux for adenosinetriphosphate (ATP) production in the citric acid cycle and electron transport chain. This hypothesis is supported by Stainsby et al. (1989), who indicated using a near-infrared spectrophotometric method that mitochondrial cytochrome oxidase (cytochrome aa_3) was properly oxidized during contractions of dog gastrocnemius muscle in situ. They concluded that these findings should put to rest any arguments that inadequate O_2 is a determinant of $\dot{V}O_{2max}$ during repetitive contractions with free blood flow in self-perfused muscles in normoxia. The well known observation that venous blood from maximally working muscles contains a considerable amount of O_2 (Pirnay et al. 1972; Horstman et al. 1976) could be taken as a support for this view, on the argument that if the muscles could use more O_2, they would extract more from the blood.

Nevertheless, many studies have ended in contradictory explanations in terms to establish the connection between O_2 delivery and $\dot{V}O_{2max}$. The essential effect of the amount of working muscles was nicely presented by Andersen and Saltin (1985) when they indicated that the $\dot{V}O_{2max}$ of human quadriceps muscle was significantly higher when the muscle was working alone than when the muscle was doing work together with other muscles. In addition, studies in an isolated muscle preparation indicated that oxygen delivery rather than oxygen consumption of the muscle normally limits $\dot{V}O_{2max}$ (Horstman et al. 1976). Similarly, a strong interaction has been found between $\dot{V}O_{2max}$ and arterial O_2 delivery, whether the change in O_2 delivery was due to changes in blood flow (Brechue et al. 1995; Stainsby et al. 1995), hemoglobin concentration (Ekblom et al. 1972; Gledhill 1985) or changes in P_IO_2, indicating that $\dot{V}O_{2max}$ is reduced in hypoxia and increased in hyperoxia (Consolazio et al. 1966; Dill et al. 1966; Klausen et al. 1966; Faulkner et al. 1968; Hughes et al. 1968; Saltin et al. 1968b; Davies and Sargeant 1974; Welch et al. 1974; Ekblom et al. 1975; Squires and Buskirk 1982; Terrados et al. 1985; Fulco et al. 1988;

Cymerman et al. 1989). As this study focuses on the effects of O_2 delivery on $\dot{V}O_{2max}$ the following sections present a more detailed review of the different links between O_2 delivery from the atmosphere and the working muscles.

2.1.1 Pulmonary ventilation and gas exchange

It is generally accepted that the pulmonary system of normal healthy individuals is capable of meeting increased ventilatory demands during exercise at sea level (Dempsey et al. 1980; West 1990). This is evident in that the partial pressure of oxygen in arterial blood (P_aO_2) and arterial hemoglobin O_2 saturation (S_aO_2%) are maintained near resting level during light, moderate and heavy exercise (Asmussen and Nielsen 1960; Hesser and Matell 1965).

However, there is strong evidence that highly trained endurance athletes may develop exercise-induced arterial hypoxemia (EIAH) during maximal (Dempsey et al. 1984) or near maximal (Williams et al. 1986) exercise. In athletes, such incomplete pulmonary gas exchange approximates to a 1-2% decrement in $\dot{V}O_{2max}$ for each 1% decrement in S_aO_2% below the 95% level (Williams et al. 1986; Powers et al. 1989b; Dempsey and Wagner 1999). Moreover, the level of arterial desaturation has been indicated to be inversely related to $\dot{V}O_{2max}$, i.e. those with the highest $\dot{V}O_{2max}$ show the largest decrease in S_aO_2% (Williams et al. 1986). Recently, Rice et al. (1999) demonstrated exercise-induced hypoxemia in highly trained cyclists at 40% of peak $\dot{V}O_2$ as well as at peak $\dot{V}O_2$. In addition, Dempsey et al. (1984) reported that some subjects showed hypoxemia during constant load exercise that required 50% of the $\dot{V}O_{2max}$.

Both an excessive alveolar-to-arterial PO_2 difference ($(A\text{-}a)O_2$) (>25-30 mmHg) and inadequate compensatory hyperventilation (arterial PCO_2 >35 mmHg) commonly contribute to EIAH, as do acid- and temperature-induced shifts in O_2 dissociation at any given arterial PO_2. In turn, limitation on expiratory flow presents a significant mechanical constraint on exercise hyperpnea, whereas ventilation-perfusion ratio ($\dot{V}_A / \dot{Q}$) maldistribution and limitation on pulmonary diffusion contribute about equally to the excessive $(A\text{-}a)O_2$. It is important to keep in mind that S_aO_2% may be reduced in heavy exercise, not only because of reductions in P_aO_2 but also (and often to an equal extent) by a pH- and temperature-induced rightward shift of the HbO_2 dissociation curve (Dempsey and Wagner 1999). The effect of the venoarterial shunt on EIAH is of minor importance in healthy subjects (Powers et al. 1993). The existence of hypoventilation may be more common among women than men as tidal volume and ventilation are mechanically constrained in many fit women because the demand for high expiratory flow rates encroaches on the maximum flow-volume envelope of the airways (McClaran et al. 1998).

Compensation for the impairments in $\dot{V}O_{2max}$ and exercise performance due to arterial desaturation can be achieved if athletes breathe mildly hyperoxic air to restore their S_aO_2% close to resting level (Dempsey et al. 1984). In

hypoxia, the decreased P_IO_2 limits pulmonary oxygen diffusion, and causes more pronounced arterial desaturation during severe exercise (Hughes et al. 1968; West 1990). The lowest altitude reported to decrease $\dot{V}O_{2max}$ in comparison to sea level value due to arterial desaturation is only 580 m above sea level (Gore et al. 1996).

2.1.2 Cardiac output

The relationship between heart size and $\dot{V}O_{2max}$ has been verified with heart weight measurements (Grande and Taylor 1965), x-ray pictures (Rost and Hollmann 1983), ultrasound techniques (Simon et al. 1978; Keul et al. 1981) and magnetic resonance imaging (Milliken et al. 1988). Atrial and ventricular volumes are known to be enlarged in endurance-trained athletes, and longitudinal studies have revealed adaptive alterations with both physical activity and inactivity (Saltin et al. 1968a).

The product of heart rate (HR), stroke volume (SV) and C_aO_2 during a relatively short-term exhaustive exercise to elicit a subject's $\dot{V}O_{2max}$ indicates the value of arterially transported oxygen. The majority of this O_2 is directed to the contracting muscles (Rowell 1993). Consequently, the relation between O_2 delivery and $\dot{V}O_{2max}$ is very close. This fact is used to indicate that the variation in O_2 delivery is a function of the stroke volume, as maximal heart rate and arterial oxygen content are both unaffected by training (Rowell 1986). Thus, the pump capacity is expected to be decisive for maximal arterial O_2 delivery. Consequently, $\dot{Q}$ rises nearly linearly with $\dot{V}O_2$ with a slope of approximately 6 $l \cdot min^{-1}$ of cardiac output per 1 $l \cdot min^{-1}$ in oxygen uptake in normally active subjects and endurance athletes (Faulkner et al. 1977; Rowell 1986; Leyk et al. 1994; Proctor et al. 1998).

Although the pivotal role of the cardiovascular system in limiting exercise performance is well established, the underlying mechanisms that are responsible for the changes in varying P_IO_2 conditions are not completely understood. Altering C_aO_2 by breathing gas mixtures with various oxygen concentrations (F_IO_2) or by affecting ambient air pressure by ascend to altitude or modifying air pressure by a barometric chamber have all been reported to affect maximal exercise performance and $\dot{V}O_{2max}$ concomitantly (Welch et al. 1974; Ekblom et al. 1975; Squires and Buskirk 1982). However, a more detailed analysis of the $\dot{V}O_2$ and $\dot{Q}$ in altered P_IO_2 situations reveals variation in these physiological responses. In acute hypoxia, the only generally accepted finding is that $\dot{V}O_{2max}$ is diminished but $\dot{V}O_2$ is unaffected at light and moderate workloads (Stenberg et al. 1966; Hughes et al. 1968; Hartley et al. 1973; Ekblom et al. 1975; Fulco et al. 1988). In hyperoxia, some studies indicate a significant increase in $\dot{V}O_{2max}$ when compared with normoxia (Welch et al. 1974; Ekblom et al. 1975; Welch 1982) while in other studies such an increase has not been seen (Hughes et al. 1968; Adams and Welch 1980). The same controversy is seen at submaximal workloads as some studies indicate a similar $\dot{V}O_2$ in hyperoxia

as in normoxia (Asmussen and Nielsen 1955; Hughes et al. 1968), while the study of Ekblom et al. (1975) indicated a significantly higher $\dot{V}O_2$ in hyperoxia at a workload corresponding to 30% of normoxic $\dot{V}O_{2max}$, but a similar $\dot{V}O_2$ at 70% workload when compared with normoxia.

There is a general agreement that $\dot{Q}_{max}$ diminishes during chronic exposure to high altitude due to reduced maximal heart rate (HR_{max}) and maximal stroke volume (SV_{max}) (Saltin et al. 1968b; Vogel et al. 1974; MacDougall et al. 1976; Richalet et al. 1992; Sutton et al. 1992; Kayser et al. 1994; Savard et al. 1995). In addition, the fall in $\dot{Q}$ is not limited to maximal exercise, but it also has been reported to occur during submaximal work after acclimatization to chronic hypoxia (Wolfel et al. 1991).

Until now, only two studies have been published (Hughes et al. 1968; Ekblom et al. 1975) where $\dot{Q}$ has been measured from the same subjects exercising until exhaustion in both acute hypoxia, hyperoxia and normoxia, and several other studies where either hypoxia or hyperoxia has been used in addition to normoxia. Hughes et al. (1968) reported an increased $\dot{Q}$ at submaximal workload in hypoxia (F_IO_2 0.11 and 0.16), but a similar $\dot{Q}$ in hyperoxia (F_IO_2 0.33) when compared with normoxia. Maximal cardiac output was similar at all F_IO_2. On the contrary, Ekblom et al. (1975) reported maintained submaximal $\dot{Q}$, but decreased $\dot{Q}_{max}$ during carbon monoxide induced hypoxia (C_aO_2 was on average 5.1% lower than in normoxia, $P<0.05$), mainly due to decreased SV. In hyperoxia (F_IO_2 0.50), $\dot{Q}_{max}$ was unchanged but significantly lower than in normoxia at 70% workload. According to studies comparing only normoxia and acute hypoxia, the prevailing hypothesis is that $\dot{Q}_{max}$ is identical (Stenberg et al. 1966; Hartley et al. 1973; Rowell and Blackmon 1987).

During submaximal exercise, Asmussen and Nielsen (1955) found $\dot{Q}$ to increase in hypoxia (F_IO_2 0.12), but to be similar in normoxia and hyperoxia (F_IO_2 1.00). Similarly, Davies and Sargeant (1974) reported $\dot{Q}$ to be rather similar at submaximal workloads in normoxia and hyperoxia. More recently, Nakazono and Miyamoto (1987) reported a decrease ($P<0.05$) in $\dot{Q}$ in hyperoxia (F_IO_2 0.42) with no change in hypoxia (F_IO_2 0.14) in comparison with normoxia during a steady state exercise at 70 W. Heart rate is higher in hypoxia during submaximal exercise (Dill et al. 1966; Stenberg et al. 1966; Hartley et al. 1973) and lower in hyperoxia (Ekblom et al. 1975; Welch et al. 1977) than in normoxia.

2.1.3 Hemoglobin concentration and blood volume

Hemoglobin concentration ([Hb]), and especially total hemoglobin, are significant variables affecting exercise performance and $\dot{V}O_{2max}$ in normal subjects. When [Hb] is reduced, there is a roughly proportional reduction in $\dot{V}O_{2max}$ and exercise capacity (Woodson et al. 1978). Consequently, an increased capacity to transport oxygen in blood is reflected in an increase in work

capacity and $\dot{V}O_{2max}$ (Kanstrup and Ekblom 1984; Gledhill 1985; Spriet et al. 1986).

2.1.4 Blood flow and peripheral diffusion of oxygen

By measuring the blood flow and oxygen uptake of exercising muscles when only a small fraction of the total muscle mass is engaged in exercise, it has been demonstrated that the skeletal muscle of man could accommodate a blood flow of at least 200 ml/100 g min, and consume 300 ml O_2/100 g min at exhaustive exercise. Such high blood flows are achieved when only part of the muscle mass is recruited during exercise (Andersen and Saltin 1985; Saltin 1985; Saltin 1988).

With two or more limbs exercising, the pump capacity of the heart will limit the blood flow available to the muscles (Secher et al. 1977; Rowell 1993). During whole-body exercise, the norepinephrine spillover becomes elevated, but the functional significance is not apparent until the oxygen uptake reaches more than 80% of the maximal level. At these high work rates the sympathetic discharge overrides the local vasodilator factors and causes vasoconstriction. Thus, blood pressure can be maintained (Saltin 1988; Rowell 1993). It has also been observed that at a high muscle perfusion rate the arteriovenous O_2 difference is small (14 to 15 vol%), and that the low extraction of oxygen is related to the mean transit time of the red blood cells passing through the capillaries. It has been concluded that the primary importance of enlargement of the capillary bed with endurance training is not to accommodate flow but to maintain or elongate mean transit time (Saltin 1985; Saltin et al. 1986; Rowell 1993). It has also been concluded that, in whole body exercise, the capacity of the muscles to receive a flow exceeds by a factor of 2 to 3 the capacity of the heart to supply that flow. Thus, the vasoconstrictor tone must also be present in the arteries that supply exercising muscles (Andersen and Saltin 1985; Saltin 1985; Rowell 1993). One of the landmarks in this area was the study by Secher et al. (1977). They indicated that when a large muscle group is heavily engaged (leg exercise), additional engagement of another muscle group (leg plus arm exercise) led to a fall in blood flow and oxygen uptake of the active legs. That is, the heart could not supply both the legs and the arms with blood because the combined demand exceeded the pumping capacity of the heart. Therefore, blood pressure had to be maintained by vasoconstriction in active muscle (Secher et al. 1977).

The evidence that $\dot{V}O_{2max}$ is limited by the supply of O_2 is substantial. However, there are several steps in O_2 delivery from arterial blood to muscle mitochondria that affect $\dot{V}O_2$ including blood flow distribution, perfusion pressure and O_2 diffusion from Hb to mitochondria. Blood flow and its distribution during contractions near $\dot{V}O_{2max}$ is affected by inhomogenously distributed vascular compression via pressure in the muscle, which is related to tension in the muscle during and between contractions (Brechue et al. 1995; Stainsby et al. 1995) and by metabolic rate (Wagner 1992). However, the results of several studies (Hogan et al. 1988; Hogan et al. 1989; Roca et al. 1989; Wagner

1992) show that $\dot{V}O_{2max}$ is not uniquely dependent on O_2 delivery and support the hypothesis that $\dot{V}O_{2max}$ can be limited by peripheral tissue O_2 diffusion. The basis for this lies in the fact that a combination of "low flow - high C_aO_2" produces a higher $\dot{V}O_2$ than a "high flow - low C_aO_2" treatment, despite similar O_2 delivery. Therefore, the pressure gradient for O_2 and mean red cell transit time in capillaries are essential determinants of $\dot{V}O_{2max}$ at the tissue level. This complex entity of factors affecting $\dot{V}O_2$ has been succintly presented by Roca et al. (1989) and Wagner (1995) when they suggested that for any given level of O_2 delivery it is the O_2 diffusional transport capacity of the tissues that sets $\dot{V}O_2$.

2.1.5 Interaction of O_2 delivery and peripheral diffusion

Increasing interest has been shown toward theories that combine the individual links in the O_2 delivery and utilization chain, suggesting that the connections between various links are so close that no one specific variable can be identified as being more critical than another. In their studies di Prampero and Ferretti (1990) concluded that blood O_2 transport is responsible for ~ 70% of the overall limits on $\dot{V}O_{2max}$, the rest depending on the various peripheral factors (O_2 transfer from the capillaries to the mitochondria and O_2 utilization in the mitochondria). They also concluded that in addition to untrained subjects at sea level, this ratio is also valid after structural and functional readjustments in the respiratory system following either endurance training or exposure to chronic hypoxia. In his theory Wagner (1992) combines two interrelated hypotheses: 1) $\dot{V}O_{2max}$ is not limited by any single component of the O_2 transport pathway. Rather, each step contributes in an integrated manner to setting $\dot{V}O_{2max}$. 2) The limitation on the diffusion of O_2 between hemoglobin within the red cells and of the muscle capillary and muscle mitochondria is a key component of this theory such that for a given level of O_2 delivery, it is the muscle diffusing capacity that limits the rate at which O_2 molecules can flow from the capillary to the mitochondria.

In this integrative theory (Wagner 1992) both circulatory convective and muscle diffusive aspects of the O_2 pathway are simultaneously considered. The circulatory convective O_2 pathway is described by the Fick principle:

$$\dot{V}O_2 = \dot{Q} \cdot (C_aO_2 - C_vO_2) \quad (2)$$

where $\dot{V}O_2$ is oxygen uptake, $\dot{Q}$ is muscle blood flow, and C_aO_2 and C_vO_2 are arterial and muscle venous O_2 concentrations. Fick's law of diffusion then describes muscle diffusion:

$$\dot{V}O_2 = DO_2 \cdot (P_{cap}O_2 - P_{mito}O_2) \quad (3)$$

where DO_2 is muscle O_2 diffusing capacity, $P_{cap}O_2$ is mean muscle capillary PO_2 and $P_{mito}O_2$ is mitochondrial PO_2.

Mitochondrial PO_2 of cytochrome aa_3 approaches zero at $\dot{V}O_{2max}$ and can be omitted from the equation (Severinghaus 1994) as mean $P_{cap}O_2$ is of the

order of 30 - 40 mmHg (Wagner 1992). Mean capillary PO_2 is not itself measurable, but is proportional to the measurable muscle venous PO_2 (P_vO_2):

$$P_{cap}O_2 = K \cdot P_vO_2 \quad (4)$$

where K is a constant. Combining equations 3 and 4 gives:

$$\dot{V}O_2 = DO_2 \cdot K \cdot P_vO_2 \quad (5)$$

If $\dot{V}O_2$ is plotted for equation 2 against P_vO_2, then, for given values of $\dot{Q}$ and C_aO_2, there is a curvilinear relationship reflecting the Hb O_2 dissociation curve. If P_vO_2 is zero, $\dot{V}O_2$ from this equation is the product of blood flow and arterial O_2 concentration, namely convective O_2 delivery. When $\dot{V}O_2$ is plotted against P_vO_2 for equation 5 in the same diagram, a straight line is produced passing through the point of origin. The basis of this theory (Wagner 1992) is that $\dot{V}O_{2max}$ is indicated by the intersection of the two relationships. Thus, mass balance must always hold so that for equation 2 a point somewhere on the curve represents $\dot{V}O_{2max}$. In addition, since diffusional transport is constrained by the diffusing capacity, $\dot{V}O_{2max}$ must also reflect equation 5. Thus, $\dot{V}O_{2max}$ is given by the highest value from equation 5 that also satisfies mass balance (Hogan et al. 1989; Roca et al. 1989; Wagner 1992).

2.2 Oxygen uptake on-response during exercise

Fast and slow phases in the response of pulmonary $\dot{V}O_2$ during the transition from rest to heavy or severe exercise are described by several authors (Whipp et al. 1982; Barstow and Molè 1987; Hughson et al. 1988). Most often, three phases are separated, where Phases 1 and 2 together form the fast component while the slow component consists of phase 3. In Phase 1 (ranging from ~0-15 s), increases in $\dot{V}O_2$ have been attributed principally to augmented $\dot{Q}$ and thus pulmonary blood flow (Wasserman et al. 1974), with smaller contributions arising from changes in lung gas stores (Barstow and Molè 1987) and mixed venous O_2 content (Casaburi et al. 1989; Cochrane and Hughson 1992). Phase 2 (average range 15 s - 3 min during heavy exercise or 15 s - ~ 100 s during severe exercise) is initiated by the arrival of venous blood in the lungs from the exercising muscle, and increased $\dot{V}O_2$ in this phase represents augmented O_2 extraction and a continued increase in pulmonary blood flow (Whipp et al. 1982). In Phase 3, the steady-state $\dot{V}O_2$ response increases as a linear function of the work rate below the lactic acidosis threshold (LAT) (Whipp and Wasserman 1972) or at work rates above LAT, a steady state may not be achieved but $\dot{V}O_2$ increases slowly up to the maximum (Whipp et al. 1982; Barstow and Molè 1991).

Alternative mechanisms could affect the rate of increase in $\dot{V}O_2$ at the onset of exercise: a limitation on the transport of O_2 to the working muscles, a limitation in the ability of the muscles to use O_2 or possibly an interaction of these two (Tschakovsky and Hughson 1999). Some studies suggest that O_2

delivery is sufficient to meet the metabolic requirement of active muscle during, at least, submaximal exercise and $\dot{V}O_2$ kinetics at the onset of exercise reflect the kinetics of muscle phosphocreatine (PCr) and thus the rate of muscle O_2 utilization (Barstow et al. 1994). On the other hand, O_2 transport is dependent on $\dot{Q}$ and C_aO_2, and the latter can be affected by the F_IO_2 (Dempsey et al. 1984). The importance of F_IO_2 and transported O_2 for the kinetics of $\dot{V}O_2$ is supported by the results of MacDonald et al. (1997), who indicated faster on-transient responses in $\dot{V}O_2$ with hyperoxia (F_IO_2 0.70) when compared with normoxia at work loads above the ventilatory threshold. Accordingly, Engelen et al. (1996) reported a significant slowing of the time constant (τ) during Phase 2 in hypoxia (F_IO_2 0.12) when compared with normoxia at a constant work load between LAT and $\dot{V}O_{2max}$.

2.3 Neuromuscular function and exercise performance

Motor units are recruited according to their recruitment thresholds and firing rates (“size principle”), which results in a continuum of voluntary force in the agonist muscle. Thus, with most muscles containing a range of motor units (with both Type I and Type II fibers), force production can span from very low levels of force production to maximal force production. Maximal force production requires not only the recruitment of all motor units, but also that these motor units are recruited at a high enough firing rate to produce maximal force. (Kraemer et al., 1996). Within a studied individual, muscle force and integrated electromyogram signal (IEMG) are both roughly proportional to the number and diameter of active muscle fibers (recruitment) and to activation frequency within a scale from light to maximal contractions (Bigland-Ritchie 1981; Häkkinen 1993; Häkkinen 1994; Häkkinen et al. 1997; Häkkinen et al. 1998).

A decline in power output and force production (i.e., fatigue) is a common phenomenon during maximal exercise. The reasons for fatigue vary according to the task involved (Simonson 1971; Karlsson 1979) and the probability that a single reason for impaired exercise performance could be identified seems minute. However, the implications of fatigue are clear; decreased maximal force and a slowed rate of force production and relaxation (Komi and Rusko 1974; Viitasalo and Komi 1977; Bigland-Ritchie 1981) as well as decreased IEMG during short maximal exercises are well documented (Grimby et al. 1981). During prolonged submaximal exercise IEMG increases until exhaustion (Edwards 1981). These seemingly contradictory changes in IEMG are due to differences in motor unit firing rate and recruitment pattern (Naeije and Zorn 1982; De Luca and Knaflitz 1990). Moreover, such factors as decreased pH due to lactate production, loss of potassium ions from the muscle cell and intramuscular temperature may affect the EMG signal (Gamet et al. 1993). During 60 maximal consecutive knee extensions, hyperoxia increased exercise

performance but only a slight decrease was observed in hypoxia when compared with normoxia (Eiken and Tesch 1984; Eiken et al. 1987). Throughout that exercise bout, electromyographic activity of the quadriceps femoris muscle remained relatively unaltered in hyperoxia whereas a slight increase occurred in normoxia (Eiken et al. 1987). The authors concluded that it was unlikely that the faster rate of decline in muscle force in normoxia would be due to diminishing neuromuscular drive. Thus, in hyperoxia, the improved performance found in exercise bouts of both shorter and longer duration may have metabolic causes, as with exercise performance an increase in oxygen consumption is normally found but neural drive is not linearly changed. In hypoxia, performance and $\dot{V}O_{2max}$ deteriorate during prolonged exercise but are unaffected during exhausting exercise of short duration when the demands on the oxygen supply are not critical.

3 PURPOSE OF THE STUDY

The present series of studies were conducted to investigate the relationship between exercise performance and oxygen uptake by altering the fraction of oxygen in inspired air in an attempt to elucidate the mechanisms that regulate and limit exercise performance. Changes in F_IO_2 were used to modify arterial hemoglobin O_2 saturation, which has a fundamental effect on O_2 delivery and thus on maximal oxygen uptake.

Special attention was paid to seeking answers to the following questions:

1. Does arterial desaturation occur at submaximal workloads in endurance athletes and is saturation affected by mild and moderate changes in F_IO_2? The question was also raised as to whether the expected changes in arterial O_2 saturation would affect respiratory variables, heart rate, blood lactate concentration and perceived exertion at submaximal workloads.

2. Is the effect of F_IO_2 on $\dot{V}O_{2max}$ and exercise performance similar, i.e. does the expected impairment of $\dot{V}O_{2max}$ in hypoxia and improvement in hyperoxia have an equal effect on the change in exercise performance?

3. Is $\dot{Q}_{max}$ independent of F_IO_2, suggesting that all of the expected change in $\dot{V}O_{2max}$ in hyperoxia and hypoxia is due to the change in $(a\text{-}v)O_2$?

4. Is the $\dot{V}O_2$ on-response altered during maximal exercise as a function of F_IO_2? If O_2 delivery during maximal exercise were changed according to the amount of hemoglobin O_2 saturation, then $\dot{V}O_2$ kinetics would be accelerated in hyperoxia and decelerated in hypoxia in comparison with normoxia.

5. Are the effects of hypoxia and hyperoxia on force production similar to those they are suggested to have on $\dot{V}O_{2max}$, i.e. impairment and improvement, respectively? Are the expected changes in force production accompanied by similar changes in electromyography?

4 MATERIAL AND METHODS

4.1 Subjects

As some of the physiological responses to severe exercise may differ among sedentary individuals, normally active individuals and highly trained endurance athletes, the subjects studied in this research project consisted of a relatively homogenous group of endurance athletes. A total of 24 men and 5 women volunteered to participate in the present study (Table 1). All of the women were international-level cross-country skiers, and the men's group included six national/international level rowers, eight national-level cyclists, seven national-level triathletes, two national-level orienteers and one international-level cross-country skier. All the athletes had been in daily training for several years, and all were healthy at the time of the tests.

TABLE 1 Subject characteristics

Study	n	Gender	Age	Height	Body mass
			years	cm	kg
I	6	5 women +1 man	25 (4)	170.5 (8.7)	62.0 (9.4)
II, III	6	men	23 (3)	187.1 (2.3)	80.3 (3.9)
IV	11	men	29 (5)	179.3 (5.3)	72.7 (6.9)
V	6	men	24 (5)	181.0 (3.4)	73.6 (2.1)

Values are means (SD).

4.2 Experimental design

4.2.1 Exercise protocol

In all the studies, all the subjects were tested in conditions of normobaric hyperoxia, normoxia and hypoxia in a randomized single blind fashion. The F_IO_2 used are presented in table 2. The hypoxic conditions equaled altitudes of 1900 m (IV) 2300 m (II-III), 2500 m (I) and 2700 m (V), which are commonly used in athletic training and competitions as well as recreational activities. In studies II-III a relatively high F_IO_2 was used during hyperoxia. In studies I, IV and V, a F_IO_2 was chosen that was high enough to prevent exercise-induced arterial hypoxemia (Dempsey et al. 1984; Williams et al. 1986; Powers et al. 1989b) but low enough to prevent an overwhelming increase in P_aO_2.

To ascertain that the method used to alter F_IO_2 would be valid and lead to results comparable with those of previous studies, the subjects were examined in a test that closely simulated their own sports discipline. In study I, the subjects ran 4 × 4 min on a motor-driven treadmill. The running velocities corresponded to 50%, 60%, 70% and 80% of their previously determined normoxic $\dot{V}O_{2max}$. The measurements were done within a week and at least one day of normal training separated two consecutive tests for each subject.

In studies II-III, the subjects performed maximal 2500 m rowing ergometer (Concept II, Inc., Morrisville, VT, USA) tests. Performance was evaluated by the final time taken to complete the test and by the lap times in 500-m intervals. Interval times (s) were converted to power (watts, W) by a coefficient provided by the manufacturer of the ergometer. The measurements were carried out during one week. Each test day was preceded by a day of physically less strenuous exercise.

In study IV, the experimental protocol consisted of three 7-minute maximal exercise tests on an electrically braked cycle ergometer (Tunturi E980, Tunturipyörä Oy, Piispanristi, Finland) with two to five days between each test.

In study V, the experimental protocol required each subject to visit the laboratory three times. On each visit they performed two identical (peak power the same, difference in duration of tests within ± 30 s) progressive tests on an electrically braked cycle ergometer (Ergoline 800 S, Mijnhardt, Bunnik, the Netherlands) with a one-hour interval between tests. Breath-by-breath respiratory data was obtained in the first test while the other test focused on cardiac output. First, the subjects sat at rest for 5 minutes. After that they started cycling at 0 W and the power was increased by 100 W at 5-minute intervals until exhaustion. If a subject was able to continue cycling after completing 400 W, then, power was increased by 50 W instead of 100 W as this was known to be more within the limits of his exercise capacity. Each subject completed the three two-test protocols with three to six days between each visit to the laboratory. The subjects were encouraged during the tests but they were not informed about F_IO_2 or any physiological data.

TABLE 2 Fraction of oxygen in inspired air (F_IO_2) during exercise in studies I – V.

Study	Hypoxia (F_IO_2)	Hyperoxia (F_IO_2)	Normoxia (F_IO_2)
I	0.155	0.293	0.209
II - III	0.158	0.622	0.209
IV	0.166	0.325	0.209
V	0.150	0.320	0.209

4.2.2 Methods used to modify F_IO_2

All measurements were done at sea level (II-III, V) or at the altitude of 150 m above sea level (I, IV). In normoxic conditions the subjects breathed room air. A hypoxic environment was accomplished either by conducting the preferred gas mixture from gas bottles (Oy AGA Ab, Espoo, Finland) to the respiratory mask (II-III, V) or in a so-called altitude house (I, IV) (Rusko 1996), where the fraction of nitrogen and oxygen in the inspired air can be regulated. Hyperoxic conditions were accomplished either by conducting the preferred gas mixture from gas bottles to the respiratory mask (I-III), or with two oxygen concentrators (NewLife, AirSep, Buffalo, NY, USA) by conducting O_2 to two plastic containers (each 200 l) connected with a hose to a face mask and a flow meter (IV, V).

In detail, the procedure of administering the gas mixtures was as follows: The gas mixture was conducted into the inspiratory side of the respiratory valve (Hans Rudolph Inc., Kansas City, MO, USA, Adult 7921 Series) and/or volume turbine and face mask (Hans Rudolph Inc., Kansas City, MO, USA, Adult 7930 Series) from a gas bottle (Oy AGA Ab, Espoo, Finland) through a flow meter (Kytölä, Muurame, Finland) and a buffer bag. The buffer bag was composed of two elastic meteorological balloons (100 l, lying one inside the other) and was used to adjust the total pressure of the inspired gas mixture to the ambient level. To avoid irritation of the respiratory pathways, the inner bag contained 500 ml water to moisturize the inspired air. In normoxia, the instrumentation was similar to the two other trials except that the tube connecting the inspiratory side of the respiratory valve and the buffer bag was only connected to the respiratory valve while the other end remained free and subjects breathed room air. As the buffer bag and all other instrumentation were situated behind the athletes' back and out of their sight, they were not aware of whether they were breathing room air or other gas mixture.

4.3 Measured variables

4.3.1 Cardiorespiratory parameters

Two different systems for measuring $\dot{V}O_2$ and related parameters were used: a mixing chamber systems for expired air (I-III) and a breath-by-breath gas exchange and ventilation analysis system (IV-V).

In studies I-III, respiratory gases were measured with a mixing chamber system (M-919 Ergospirometer, Medikro Oy, Kuopio, Finland, I; Mijnhardt Oxycon-4, Odijk, Holland, II-III) and the mean values of every 30 seconds were recorded. In studies IV-V, breath-by-breath gas exchange and ventilation were obtained with a respiratory mass spectrometer (AMIS 2000, Innovision A/S, Odense, Denmark) and a digital volume turbine (Interface Associates, Aliso Viejo, CA, USA, IV; Triple V, Jaeger Mijnhardt, Bunnik, The Netherlands, V). Breath-by-breath respiratory data were collected in raw data mode and calculated afterwards. This method allowed calculation of individual delay times (Fowler 1948; Heller et al. 1999) for each test because of the effect of gas density on the flow rate in the sampling catheter. A moving average of the individual test data was calculated (Beaver et al. 1981) over 5 s periods to reduce some of the inherent breath-by-breath variability and interpolated to give values second by second. $\dot{V}O_{2max}$ was obtained as the highest value maintained for one minute. Both a progressive test to exhaustion (V) and shorter "all-out" tests (II, IV) were considered suitable to obtain real $\dot{V}O_{2max}$ values, as these two test types have been shown to elicit similar results (Mahler et al. 1984).

$\dot{V}O_2$ *kinetic parameters* were analyzed in study IV. The individual data were fitted to a curve by using a three-exponential model (Eq. 6), where each of the exponentials was set to zero before the corresponding delay time.

$$\dot{V}O_2(t) = A_0 + A_1[1 - e^{-(t - TD_1)/\tau_1}] + A_2[1 - e^{-(t - TD_2)/\tau_2}] + A_3[1 - e^{-(t - TD_3)/\tau_3}] \quad \text{(Eq.6)},$$

see Figure 1 for explanations. The curve-fitting procedure was iterated with a LabVIEW program (National Instruments Corporation, Austin, TX, USA) until no further improvement in the least square error between the fit model and the raw data was seen. Phases 1 and 2 together formed the fast component while the slow component consisted of Phase 3. To obtain a parameter that was independent of dividing the response into three phases, mean response time (MRT) was obtained from the fit curve as the time to 63% of the total change in $\dot{V}O_{2max}$.

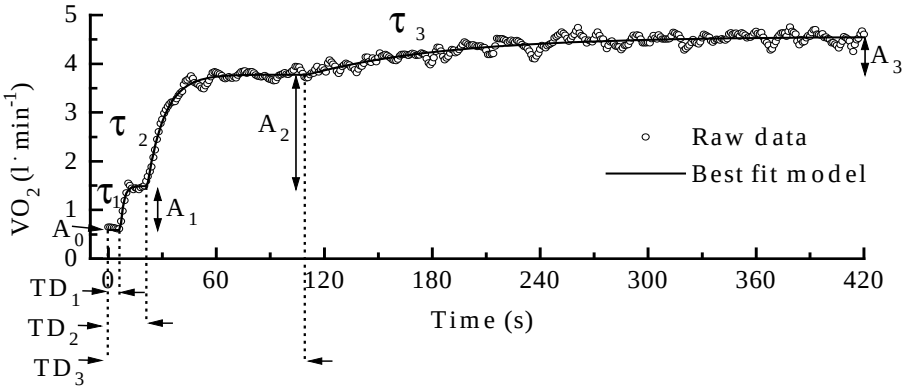


FIGURE 1 An example of $\dot{V}O_2$ raw data and the corresponding three-exponential fit model. $\dot{V}O_2$ (t) = response of O_2 uptake as a function of time (t); A_0 = $\dot{V}O_2$ at rest; A_1, A_2, A_3: $\dot{V}O_2$ amplitude for the particular phase; τ_1, τ_2, τ_3 = time constants of response; TD_1, TD_2, TD_3 = time delays for the appearance of the response at the mouth.

Heart rate was measured with a Sport Tester PE-3000 heart rate monitor (Polar Electro, Kempele, Finland) in studies I-III. In studies IV-V heart rate was measured with electrocardiogram (ECG) (S&W Diascope 2, S&W Mediko Teknik A/S, Albertslund, Denmark) and recorded in 1-s intervals in the same file with respiratory data.

Cardiac output (V) was measured at rest and at each workload during the last 30 s by an acetylene (C_2H_2) rebreathing method (Sackner et al. 1975; Triebwasser et al. 1977; Liu et al. 1997) (Eq. 7, Fig. 2). The rebreathing gas consisted of 0.30% acetylene, 5.00% helium and 35.00% oxygen in nitrogen. The volume of the rebreathing bag was adjusted to 40% of the measured forced vital capacity (FVC). The rebreathing time was 15 s from rest up to 200 W and 10 s at 300 W and upwards. The rebreathing frequency varied between 30-60 breaths per minute according to the workload. At rest and at the lowest workloads the subjects were instructed to increase their breathing frequency to obtain a fast mixing of gases between the rebreathing bag and alveolar air. At higher workloads a voluntary breathing frequency was allowed. Stroke volume was calculated by dividing cardiac output by heart rate.

$$\dot{Q} = -\beta_s \cdot \frac{V_S\,(STPD) \cdot 760 / (P_B - 47) + V_t \cdot \alpha_t}{\alpha_b}, \qquad \text{(Eq. 7)}$$

where β_s = slope of the disappearance curve for acetylene (C_2H_2) in a semilogarithmic plot ($d(\ln(F_{C2H2}))/dt$ determined by a least square fit through expiratory data points. V_S = initial, combined lung and rebreathing bag volume. P_B = Barometric pressure in mmHg. V_t = lung tissue volume. α_t = lung tissue Bunsen solubility coefficient for acetylene, given as ml (STPD) of soluble gas per ml of tissue per atmosphere of partial pressure, determined at 37 °C. α_b = blood Bunsen solubility coefficient for acetylene, given as ml (STPD) of soluble gas per ml of blood per atmosphere of partial pressure, determined at 37 °C.

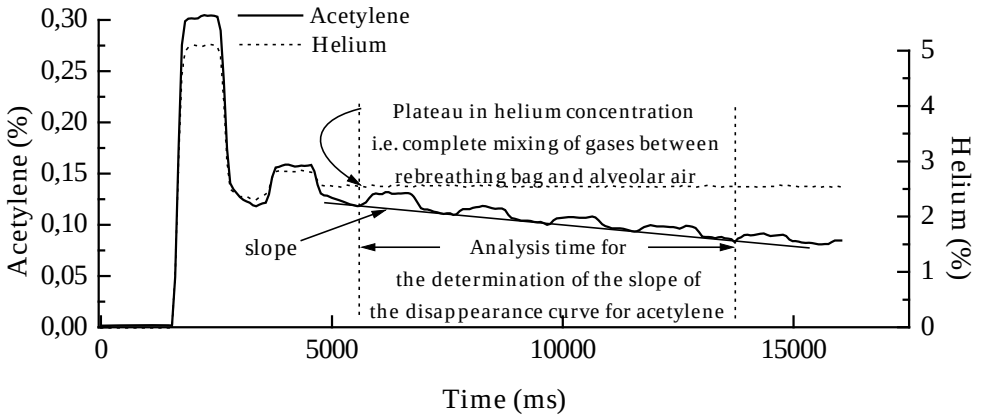


FIGURE 2 An example of the determination of the slope of the acetylene disappearance curve from the rebreathing data for the calculation of cardiac output.

Arterio-venous oxygen difference, (a-v)O_2, was calculated by dividing $\dot{V}O_2$ by $\dot{Q}$ (V).

Arterial hemoglobin O_2 *saturation* (SpO_2%) was monitored with a pulse oximeter and a finger probe. Two different models were used (Oxypleth, Novametrix Medical Systems Inc., Wallingford, CT, USA (IV-V) and Nellcor N-20, Nellcor Inc., Hayward, CA, USA (I)).

4.3.2 Capillary blood lactate concentration

In study I, 20 µl of blood was taken from the fingertip at rest and after each workload to determine lactate concentration (Eppendorf EBIO plus, Eppendorf-Netheler-Hinz Gmbh, Hamburg, Germany). In study IV, capillary blood samples (20 µl) for lactate (Eppendorf EBIO6666, Eppendorf-Netheler-Hinz Gmbh, Hamburg, Germany) were taken from the fingertip at rest and at minutes two, five and seven during cycling as well as after one, three, five and seven minutes of recovery. In study II, a capillary blood sample (25 µl) was obtained from the fingertip two minutes prior to the test, immediately after the end of the exercise and one, three, five and ten minutes later and analyzed immediately (YSI 23L Lactate Analyzer, YSI Scientific, Yellow Springs, OH, USA).

4.3.3 Neuromuscular function

In study III, *force production* during a rowing stroke was measured by a strain-gauge transducer (Digitest, Muurame, Finland) attached between the handle and the chain of the ergometer. A similar method is widely used in ergometer rowing (e.g. Wilson et al. 1988). The range of movement of the knee joint was monitored by an electrical goniometer attached to the medial side of the right knee. The purpose of the goniometer was to ascertain that the expected changes in the force and EMG parameters would have a physiological basis and not arise from the changes in the range of movement. The force and angle signals were amplified and recorded (Racal Recorder V-Store, Racal Recorder Ltd.,

Southampton, England) on a magnetic tape, digitized at 250 Hz frequency and low-pass filtered (20 Hz). Maximal force (F_{max}, N), impulse (I, N·s) and peak force production rate (dF / dt, $N \cdot s^{-1}$) were analyzed from the force-time signal (Codas, Dataq Instruments, Inc. Akron, OH, USA, and RowForce, Reflex Sport, Inc., Jyväskylä, Finland, programs). A moving average value (smoothing factor 8) was applied to the force-time signal before calculation of the first derivative, the maximal value of which served as the dF / dt value. The duration of a stroke phase and the stroke rate were ascertained from the force-time signal as well. Due to a minor fluctuation of the force level during the recovery phase, a threshold value of 50 N was used for the determination of the beginning and the end of a stroke. This corresponded to approximately 5% calculated from the maximal force values.

Electromyographic (EMG) signals of seven muscles (m. gastrocnemius, m. vastus lateralis, m. rectus femoris, m. biceps femoris, m. gluteus maximus, m. erector spinae and m. biceps brachii) were recorded from the right side of the body using Beckman miniature size surface electrodes (interelectrode distance 10 mm). In the limbs, the electrodes were placed on the muscle bellies between the motor point area and the distal tendon in such a position that they did not disturb the full rowing movement. A reference electrode was placed over the left scapula. The EMG signals were amplified (60 dB), transmitted telemetrically (Glonner Biomes 2000, Glonner Electronic Gmbh, Martinsried, Germany) and recorded (Racal Recorder V-Store, Racal Recorder Ltd., Southampton, England) on a magnetic tape at 1 kHz frequency simultaneously with the force and goniometer signals. Integrated electromyography (IEMG) was chosen to represent the electrical activity pattern of these muscles. For the calculation of IEMG, the signals were digitized at 500 Hz, high-pass filtered (Butterworth, 20 Hz) and full-wave rectified. Instead of using the IEMG results for individual muscles, the EMG integrals of each muscle were added together and a new sum-IEMG parameter was used to represent the general behavior of muscular electrical activity during a stroke phase (Figure 3). Sum-IEMG has previously (Viitasalo 1984; Clarys and Cabri 1991) been used to represent overall muscular electrical activity in a situation where the behavior of individual muscles is of less importance than their overall activity pattern. Most of the electrical activity of the measured muscles occurred during the stroke phase but leg muscles in particular were also active during the recovery phase, especially in the catch position (Figure 2). However, the EMG and force signals were analyzed from the stroke phase as the force production and power output on an ergometer are effective only during the pulling phase. This is contrary to the rowing on boats where the velocity of the boat is also affected by the movements of the body's mass during the recovery phase (Sanderson and Martindale 1986).

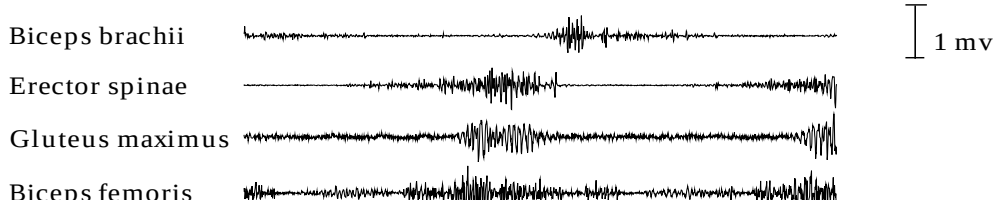


FIGURE 3 Electromyogram (EMG) signals from seven muscles were integrated and added together to form a sum-IEMG. Force and knee angles are also shown.

After a standardized warm-up (30 min, similar to preparation for a competition) the subjects performed five maximal strokes to obtain their maximal force and EMG levels. The two best strokes with the highest F_{max} values were averaged and the average was used to represent the subject's maximum (100%) level of the force and EMG parameters. To monitor the change in the maximal force output and maximal electrical activity of the muscles during the rowing ergometer test, the subjects performed two maximal strokes at each 500-m mark among their normal strokes. These two strokes were averaged and the force and EMG parameters were compared with the respective maximum pre-exercise levels. Five strokes between 5 to 15 seconds after the start were averaged to represent the force and EMG parameters at the beginning of the test. Ten to twenty seconds before each 500-m mark five strokes were averaged to represent the corresponding rowing distance. The averaged value of the last five strokes represented the end of the test. Neuromuscular efficiency (NME) was analyzed as the ratio of force impulse and sum-IEMG (NME = Impulse / Sum-IEMG).

All the force and EMG parameters were normalized on the basis of the pre-test maximum level (100%). By doing this, it was possible to compare the changes within each test as well as the differences between the conditions of normoxia, hypoxia and hyperoxia. Normalization is used widely when the effects of fatigue on force production and EMG activity are studied (Bigland-Ritchie 1981). In addition to the analysis of the data at 500-m intervals, cumulative analyses were done for sum-IEMG, F_{max} and impulse. Therefore, the start data was analyzed as it was, 500-m data was start + 500 m, 1000-m data was start + 500 m + 1000 m etc. The purpose of the cumulative analysis was to study whether it would add information about the effects of F_IO_2 on the variables being studied. This analysis can be compared with a competition or

the present final time where the differences between participants are counted up throughout the duration of a race, not just in a single lap. Finally, a mean value for the whole 2500-m test was calculated for sum-IEMG, F_{max} and impulse.

The rate of perceived exertion (*RPE*, 6-20**)** was evaluated with a Borg scale after each workload in study I. (Borg 1970; Borg 1982).

4.4 Safety precautions

All the subjects were familiar with regular training and competitions as well as laboratory exercise testing. The details of the experiments were explained to each subject, and a consent form approved by the local ethical committee was signed. All the measurements were in accordance with the regulations regarding the use of human subjects. The subjects were instructed to stop exercising immediately if unusual symptoms developed.

The normality of flow-volume spirometry was controlled before the first test in three studies (I, IV, V) (Pony Spirometer 3.4, Cosmed S.r.l., Rome, Italy (I); Medikro 904 Spirometer, Medikro, Kuopio, Finland (IV, V)). A standard 12-lead ECG was obtained before the first test in study V.

When healthy individuals are exposed to sustained hypoxia, a number of clinical syndromes may develop, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE). During prolonged exposure to high altitude, headache, nausea, vomiting, insomnia and peripheral edema are the most important symptoms of AMS, which occur within 6 to 12 hours after exposure to altitudes of more than 2500 m above sea level. Usually, these symptoms resolve spontaneously; however, they may progress to life threatening HACE and/or HAPE. The frequency and severity of these illnesses depend on altitude, rate of ascent and degree of individual susceptibility (Bärtsch 1993; Steinacker et al. 1998; Dublain et al. 1999; Levine 2000). In addition, pulmonary dysfunction has been reported to occur after severe prolonged hyperoxia (Hendricks et al. 1977; Jackson 1985; Beckett and Wong 1988). Such severe symptoms were not expected to occur as only moderate hypoxic and hyperoxic conditions were used for a short period of time.

4.5 Statistical methods

Analysis of variance for repeated measures (ANOVA) was performed to analyze the effect of F_IO_2 on the measured parameters. If a significant main effect was found, a Tukey honest significant difference test was used *post hoc* to analyze the differences between hyperoxia, normoxia and hypoxia. When a change within a test was observed in SpO_2% or a neuromuscular parameter, the

values at the point of interest were compared with the situation at rest or at the beginning of the test by using analysis of variance for repeated measures. The effect of F_IO_2 on $\dot{Q}$ and HR at a given $\dot{V}O_2$ was analyzed with a linear regression fit. Thus, for each subject individually, two linear regressions ($y = a + b \cdot x$) were performed: one on the values of $\dot{Q}$ versus $\dot{V}O_2$, and one on the values of HR versus $\dot{V}O_2$. The values of the y-axis intercept (a) and slope (b) were chosen for further analysis with ANOVA. The Pearson and Spearman rank order correlation tests were used for the correlation analyses. A significant level of $P<0.05$ was maintained for all comparisons.

Statistical analyses were accomplished by the SAS/STAT (SAS Institute Inc. Cary, NC, USA) and Statistica 5.0 (StatSoft, Tulsa, OK, USA) programs. Data are presented as mean and standard deviation (SD).

5 RESULTS

5.1 Arterial hemoglobin O_2 saturation, ventilation and blood lactate concentration

The chosen F_IO_2 levels were effective in modifying arterial hemoglobin O_2 saturation (I, IV, V). The SpO_2% pattern is presented in Figure 4 and the resting and the lowest exercise values observed in the various studies in Table 3.

TABLE 3 Arterial hemoglobin O_2 saturation measured by pulse oximetry (SpO_2%) at rest and the lowest values during exercise in three different F_IO_2 conditions.

	Hyperoxia		Normoxia		Hypoxia	
Study	Rest	Exercise	Rest	Exercise	Rest	Exercise
I	99.5	94.0 ¤	98.0	91.0 ¤	94.7	72.8 §*¤
	(0.5)	(3.8)	(1.4)	(3.6)	(2.0)	(10.2)
IV	98.6	94.3 ¤	97.5	90.7 ¤	96.0	79.1 §*¤
	(0.7)	(3.8)	(1.0)	(5.5)	(0.9)	(5.1)
V	98.9	97.1 ¤	97.5	95.1 ¤	95.3	84.1 §*¤
	(0.9)	(1.4)	(0.5)	(1.1)	(0.8)	(3.1)

Values are mean (SD). * Significantly different from normoxia ($P<0.05$); §Significantly different from hyperoxia ($P<0.05$); ¤ Significantly different from rest ($P<0.05$). Type of exercise, F_IO_2 and oximeter differed between the three studies.

In hypoxia, SpO_2% indicated a rapid decline both during submaximal and maximal exercise. A moderate decline in SpO_2% was seen in normoxia and hyperoxia, but the absolute level remained closest to the resting level in hyperoxia. In all three studies, the lowest values measured during exercise were significantly different from rest values, and the effect of F_IO_2 became more evident with increasing intensity of exercise.

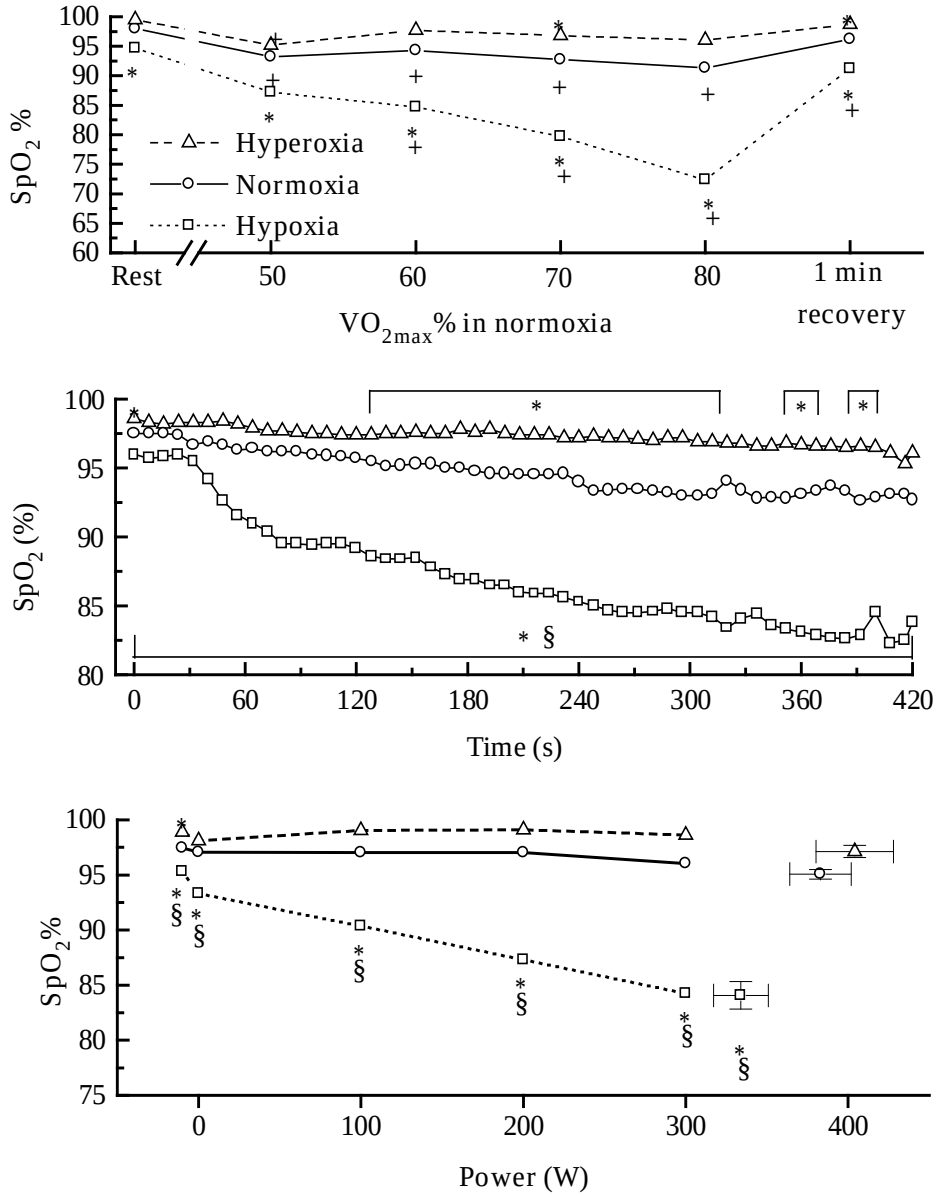


FIGURE 4 Effect of F_IO_2 on arterial O_2 saturation (SpO_2%) during submaximal treadmill running (above) (I), maximal cycling (middle) (IV) and progressive cycling (bottom) (V). Note that the x-axis is different in each figure. * Different from normoxia ($P<0.05$), § different from hyperoxia ($P<0.05$), $^+$ different from rest ($P<0.05$).

Pulmonary ventilation. When compared with normoxia and hyperoxia, ventilation was elevated in hypoxia at submaximal workloads. However, maximal ventilation values did not differ between hyperoxia, normoxia and hypoxia in any study.

Blood lactate concentration. The mean maximal blood lactate concentration after exhaustive exercise was highest in hypoxia and lowest in hyperoxia, although a significant difference between hypoxia and hyperoxia was only seen in study IV (Table 4).

TABLE 4 Maximal blood lactate concentration after maximal exercise in hyperoxia, normoxia and hypoxia.

Study	Hyperoxia	Normoxia	Hypoxia
	mmol · l^{-1}	mmol · l^{-1}	mmol · l^{-1}
II-III	13.2 (3.7)	13.7 (5.4)	16.4 (5.3)
IV	12.7 (2.9)	14.9 (2.2)	16.0 (3.6) §

Values are mean (SD) § Significantly different from hyperoxia (P<0.05).

In addition, an elevated blood lactate concentration was seen in hypoxia also during submaximal exercise (Fig. 5). Similarly, blood lactate concentration was higher (P<0.05) in hypoxia during maximal cycling in study IV at minutes 2, 5 and 7 when compared with hyperoxia.

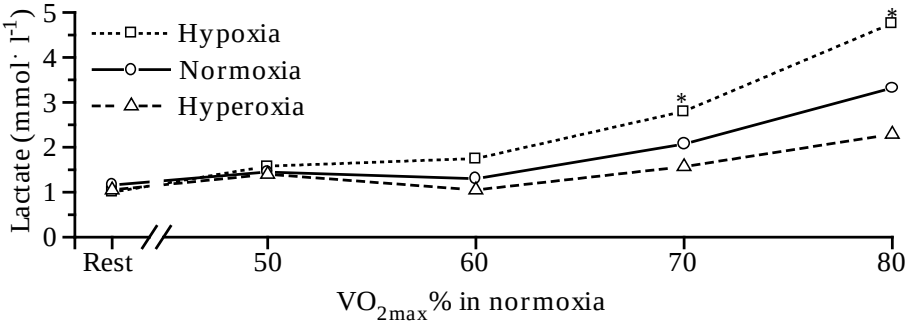


FIGURE 5 Blood lactate concentration during submaximal running in hypoxia, normoxia and hyperoxia (I). * Different from normoxia (P<0.05).

5.2 Oxygen uptake and exercise performance

The effect of F_IO_2 on $\dot{V}O_2$ during submaximal cycling (V) was evident as $\dot{V}O_2$ was elevated in hyperoxia. During submaximal running on the contrary, no such difference was seen (I). During severe exercise, the differences were clearly visible as not only were the $\dot{V}O_{2max}$ values different in hyperoxia, normoxia and hypoxia (Table 5), but the ability to maintain a high $\dot{V}O_2$ was also affected (Fig 6).

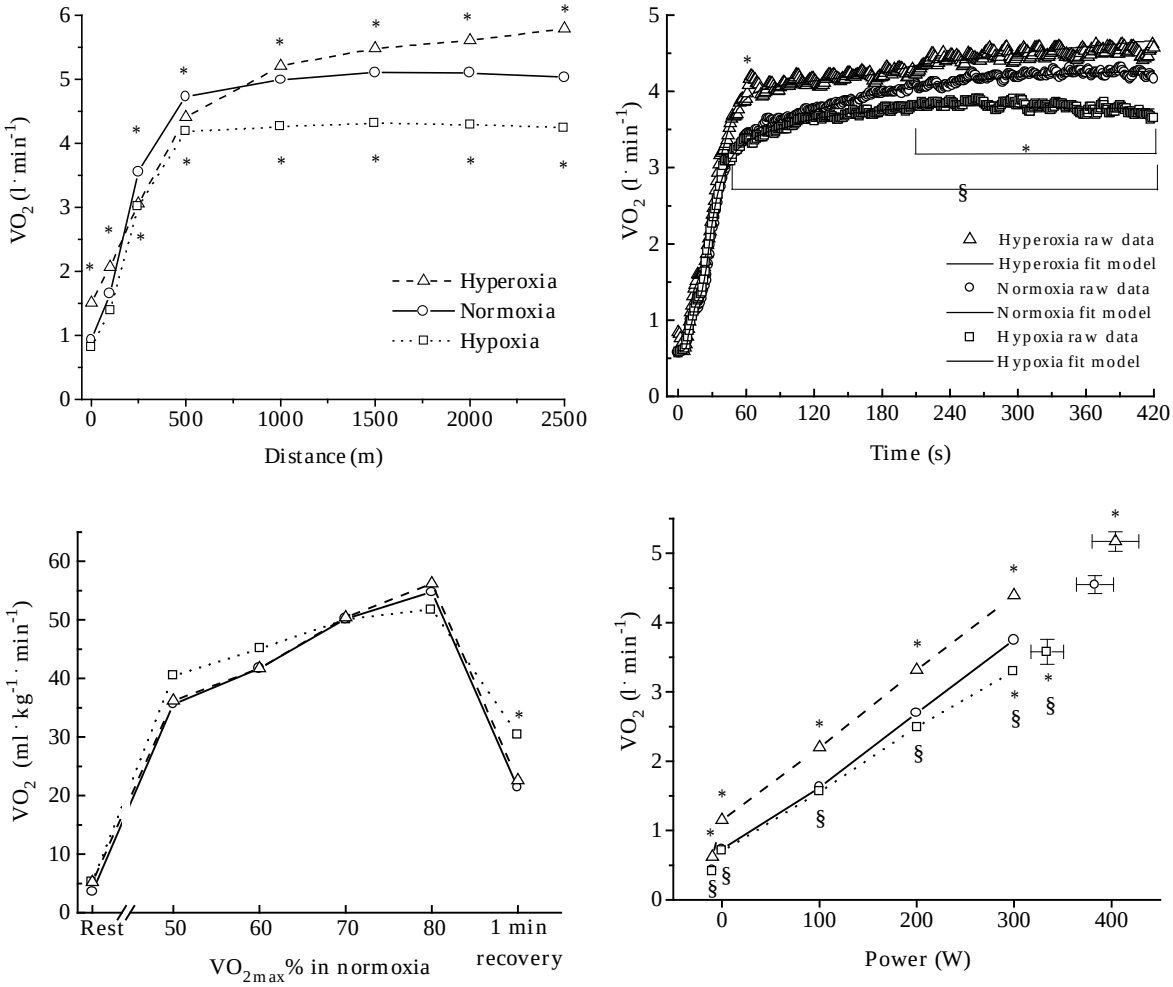


FIGURE 6 Oxygen uptake ($\dot{V}O_2$) during maximal rowing (above left, II), maximal cycling (above right, IV), submaximal running (below left, I) and progressive cycling (below right, V) in hyperoxia, normoxia and hypoxia. Note that the x-axis is different in each figure. * Different from normoxia ($P<0.05$), § different from hyperoxia ($P<0.05$).

TABLE 5 The effect of F_IO_2 on $\dot{V}O_{2max}$ during maximal rowing (II, III) and cycle ergometer exercise (IV, V).

Study	Hyperoxia $l \cdot min^{-1}$	Hyperoxia $ml \cdot kg^{-1} \cdot min^{-1}$	Normoxia $l \cdot min^{-1}$	Normoxia $ml \cdot kg^{-1} \cdot min^{-1}$	Hypoxia $l \cdot min^{-1}$	Hypoxia $ml \cdot kg^{-1} \cdot min^{-1}$
II, III	5.83	72.6	5.25	65.4	4.43	55.2
	(0.50)*	(6.7)*	(0.37)	(4.3)	(0.23)*	(4.9)*
IV	4.80	66.2	4.36	59.8	4.03	55.1
	(0.48)*	(7.2)*	(0.44)	(4.5)	(0.46)*	(4.8)*
V	5.23	71.3	4.54	61.8	3.59	49.0
	(0.42)*	(7.5)*	(0.32)	(4.0)	(0.42)*	(7.2)*

Values are means (SD). F_IO_2: fraction of oxygen in inspired air; $\dot{V}O_{2max}$: maximal oxygen uptake. * Significantly different from normoxia ($P<0.05$).

An increasing fraction of oxygen in inspired air was beneficial in terms of exercise performance as the mean (II-III, IV) or peak (V) power (P_{max}) was highest in hyperoxia and lowest in hypoxia in each study, indicating that F_IO_2 had a significant main effect on exercise performance. *Post hoc* analysis revealed that the difference between normoxia and hypoxia was significant in each study. However, a significant difference in power between normoxia and hyperoxia was only found in study II - III (Table 6).

TABLE 6 The effect of F_IO_2 on mean (II, III, IV) and maximal (V) power during exercise

Study	Hyperoxia W	Normoxia W	Hypoxia W
II, III	375 (22)*	352 (26)	304 (20)*§
IV	372 (30)	361 (33)	347 (364) *§
V	404 (58)	383 (46)	334 (41)*§

Values are mean (SD). * Significantly different from normoxia ($P<0.05$); § Significantly different from hyperoxia ($P<0.05$).

A more detailed analysis indicated that power output was very similar between the maximal tests (II-III, IV) during the first minutes. Thereafter, power output was highest in hyperoxia and lowest in hypoxia, showing an increasing difference towards the end of the tests (Fig. 7). When the percentage change in the mean or peak power and $\dot{V}O_{2max}$ from normoxia to hyperoxia and hypoxia was evaluated, the following results were obtained (Table 7):

TABLE 7 The average percentage change in final time (II, III), mean (IV) or peak (V) power and $\dot{V}O_{2max}$ during exercise in hyperoxia and hypoxia compared to normoxic values.

Study	Power Hyperoxia	Power Hypoxia	$\dot{V}O_{2max}$ Hyperoxia	$\dot{V}O_{2max}$ Hypoxia
II, III	2.3% ↑ *	5.3% ↓ *	11.2% ↑ *	15.5% ↓ *
IV	3.0% ↑	3.9% ↓ *	10.1% ↑ *	7.6% ↓ *
V	5.5% ↑	12.8% ↓ *	15.2% ↑ *	20.9% ↓ *
MEAN (II – V)	3.6% ↑	7.3% ↓	12.2% ↑	14.7% ↓

↑ = increase; ↓ = decrease; * Significantly different from normoxia (P<0.05).

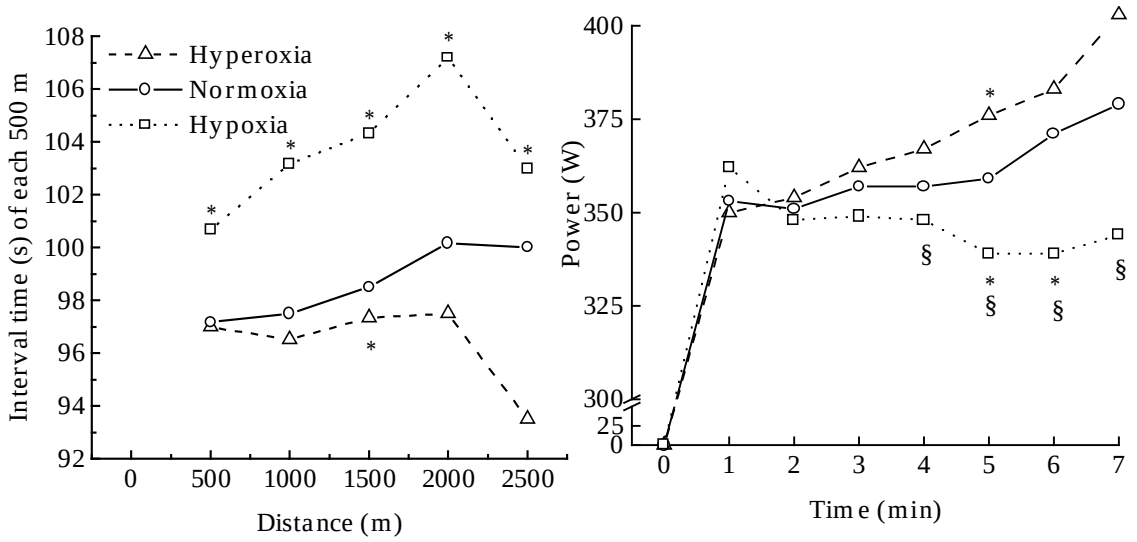


FIGURE 7 Interval times (s) of each 500 meter during maximal 2500-meter rowing (left, II, III) and power output during maximal 7-minute cycling (right, IV) in hyperoxia, normoxia and hypoxia. * Different from normoxia (P<0.05).

5.3 Heart rate, stroke volume and cardiac output

During submaximal exercise, heart rate was elevated in hypoxia in comparison to normoxia and hyperoxia at the same absolute workload (I, V) (Fig. 8).

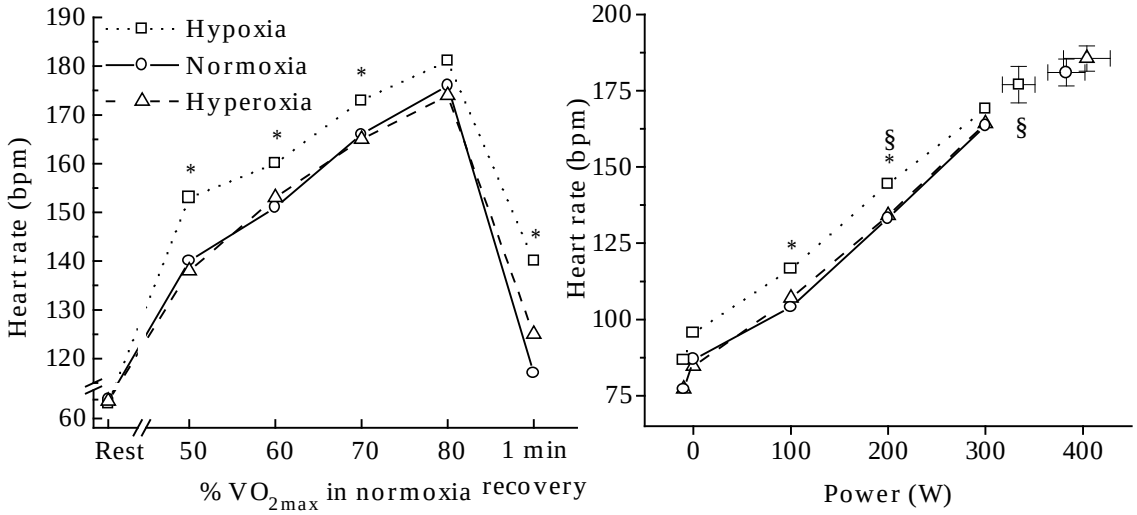


FIGURE 8 Heart rate during submaximal running (left, III) and progressive cycling until exhaustion (right, V) in hyperoxia, normoxia and hypoxia. Note that the x-axes are different. In study V, there were individual differences in maximal power. Therefore, SD is presented both for the y- and x-axis. * Different from normoxia ($P<0.05$), § different ($P<0.05$) from hyperoxia.

Maximal heart rate tended to be highest in hyperoxia and lowest in hypoxia (II-III, IV, V), but a significant difference was only seen after progressive exercise until exhaustion (V) (Table 8).

TABLE 8 Maximal heart rates in hyperoxia, normoxia and hypoxia.

Study	Hyperoxia bpm	Normoxia bpm	Hypoxia bpm
II-III	189 (9)	182 (9)	178 (10)
IV	183 (10)	182 (10)	181 (7)
V	186 (10)	181 (11)	177 (15) §

Values are mean (SD) § Significantly different from hyperoxia ($P<0.05$).

Cardiac output (V) increased almost linearly with increasing workloads and was slightly elevated in hypoxia at a given workload in comparison with normoxia and hyperoxia. However, $\dot{Q}_{max}$ was on average 8.8% smaller ($P<0.05$) in hypoxia and 5.7% higher in hyperoxia when compared with normoxia. In hypoxia, SV leveled off to the level attained at 100 W, while the highest values in normoxia and hyperoxia were seen at exhaustion. At P_{max}, SV was on

average 3.2% higher in hyperoxia and 7.0% lower in hypoxia ($P<0.05$ to hyperoxia) than in normoxia. Hypoxia tended to elevate HR at submaximal workloads. In addition, HR_{max} differed significantly, the highest value occurring in hyperoxia and the lowest in hypoxia. When compared with normoxia, HR_{max} was on average 5 bpm higher in hyperoxia and 4 bpm smaller in hypoxia ($P<0.05$ to hyperoxia) (V) (Table 9). Table 10 presents the correlation coefficients between P_{max}, $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ (V).

TABLE 9 Maximal cardiac output and the corresponding stroke volume and heart rate at the end of a progressive cycle ergometer exercise in hyperoxia, normoxia and hypoxia (V)

F_IO_2	$\dot{Q}_{max}$	SV_{max}	HR_{max}
	$l \cdot min^{-1}$	ml	bpm
Hyperoxia	30.13 (2.06)	163 (16)	186 (10)
Normoxia	28.51 (2.36)	158 (13)	181 (11)
Hypoxia	25.99 (3.37) *§	147 (19)§	177 (15)§

Values are means (SD); n = 6 subjects. F_IO_2: fraction of oxygen in inspired air; $\dot{Q}_{max}$: maximal cardiac output; SV_{max}: maximal stroke volume; HR_{max}: maximal heart rate. *Significantly different from normoxia ($P<0.05$); § significantly different from hyperoxia ($P<0.05$).

TABLE 10 Spearman rank order correlation coefficients between P_{max}, $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ (V).

F_IO_2	$\dot{V}O_{2max}$ v.s. P_{max}	$\dot{V}O_{2max}$ v.s. $\dot{Q}_{max}$	P_{max} v.s. $\dot{Q}_{max}$
0.32	0.66	0.83*	0.83*
0.21	0.83*	0.78	0.83*
0.15	0.88*	0.88*	0.94*

F_IO_2: fraction of oxygen in inspired air; $\dot{V}O_{2max}$: maximal oxygen uptake; $\dot{Q}_{max}$: maximal cardiac output; P_{max}: maximal power. * $P<0.05$.

A noteworthy effect of F_IO_2 on HR, $\dot{Q}$, $(a\text{-}v)O_2$ and O_2 pulse was demonstrated when plotted against $\dot{V}O_2$. Stroke volume was similar in normoxia and hypoxia at a given $\dot{V}O_2$, but lower in hyperoxia at low $\dot{V}O_2$ values (Figure 9). The regressions of $\dot{Q}$ versus $\dot{V}O_2$ yielded a mean intercept of 8.82 ± 0.87 in hypoxia ($P<0.05$ to normoxia and hyperoxia), 7.24 ± 0.66 in normoxia and 4.48 ± 0.74 in hyperoxia ($P<0.05$ to normoxia and hypoxia). The regression slopes were almost identical at each F_IO_2 being 4.70 ± 0.17, 4.52 ± 0.20 and 4.81 ± 0.31 in hyperoxia, normoxia and hypoxia, respectively. The regressions of HR versus $\dot{V}O_2$ yielded

a mean intercept of 58 ± 7 in hyperoxia, 66 ± 10 in normoxia and 74 ± 10 in hypoxia ($P<0.05$ to hyperoxia). The regression slopes were 23.97 ± 1.26, 25.47 ± 1.60 and 28.72 ± 2.17 in hyperoxia, normoxia and hypoxia, respectively. The HR slope was steeper ($P<0.05$) in hypoxia than in hyperoxia.

The calculated $(a\text{-}v)O_2$ was lower in hypoxia than in normoxia through the test, but higher in hyperoxia up to the 300-W workload. At P_{max}, the calculated $(a\text{-}v)O_2$ was on average 13.7% smaller in hypoxia and 7.1% greater in hyperoxia when compared with normoxia.

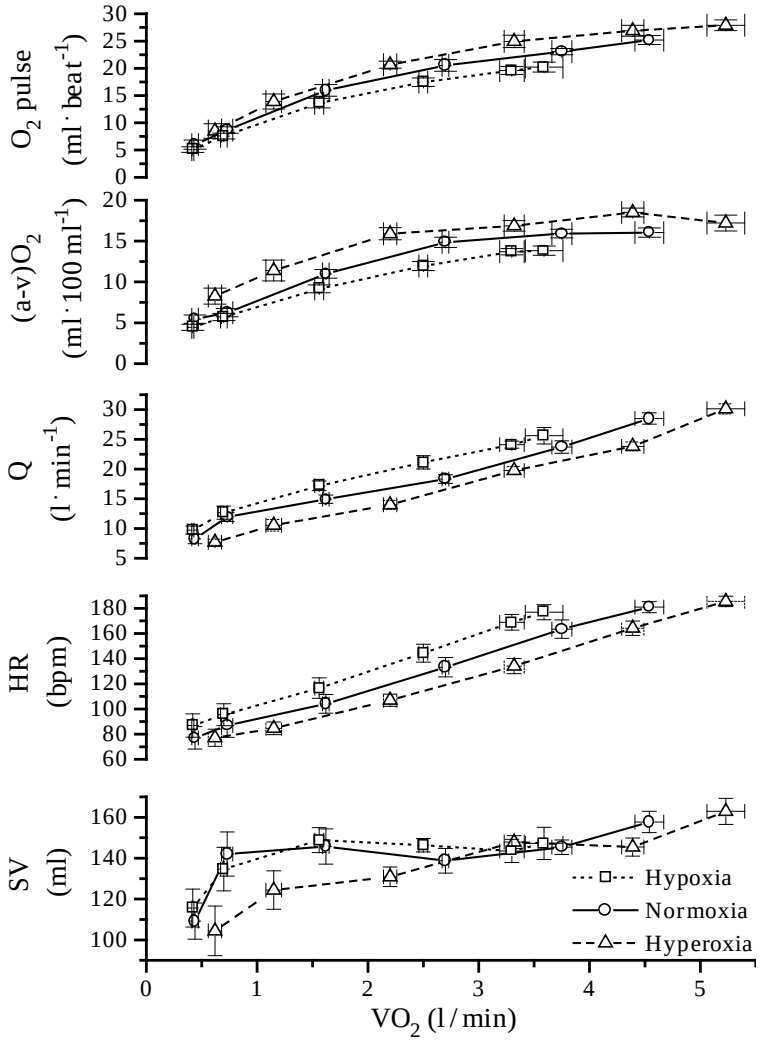


FIGURE 9 Effect of fraction of oxygen in inspired air (F_IO_2) on stroke volume (SV), heart rate (HR), cardiac output ($\dot{Q}$), arterio-venous oxygen difference ($(a\text{-}v)O_2$) and oxygen pulse (O_2 pulse) at a given oxygen uptake ($\dot{V}O_2$). See text for results of the regression analysis.

5.4 Oxygen uptake on-response

$\dot{V}O_2$ indicated a rapid increase at the beginning of maximal cycling in all three trials (IV). As work proceeded, $\dot{V}O_2$ continued to increase in hyperoxia and normoxia towards the end of the test, but an early plateau was seen in hypoxia (Fig. 6). Three $\dot{V}O_2$ kinetic parameters were affected by F_IO_2: 1) the $\dot{V}O_2$ amplitude (A_2) during Phase 2 was lower in hypoxia when compared with hyperoxia; 2) the time constant of $\dot{V}O_2$ slow component (τ_3) was shorter in hypoxia when compared with hyperoxia; and 3) MRT (O-63%) was shorter in hypoxia when compared with normoxia and hyperoxia (Table 11). The magnitude of the slow component term as percentage of the total net increase in $\dot{V}O_2$ above the pre-exercise baseline was on average 19.5%, 19.1% and 8.8% in hyperoxia, normoxia and hypoxia, respectively, but the differences were not statistically significant. A strong correlation was observed between A_3 and τ_3 in hyperoxia ($r = 0.81$, $P<0.05$) and normoxia ($r = 0.77$, $P<0.05$) but not in hypoxia.

5.5 Force production and electromyography

Force output. A decrease in the force parameters during maximal rowing was seen both in maximal and normal strokes in each F_IO_2-trial (III). The impairment of F_{max} was smaller in hyperoxia and greater in hypoxia as compared with normoxia (Figure 10). The mean F_{max} of normal strokes was 80.5 ± 2.9% in hyperoxia, 76.7 ± 2.6% in normoxia and 70.3 ± 3.4% in hypoxia ($P<0.05$ as compared with both normoxia and hyperoxia). Impulse was also impaired less in hyperoxia than in normoxia (Figure 11), but the differences between the mean values (87.7 ± 1.5%, 85.5 ± 1.1% and 80.8 ± 3.4% in hyperoxia, normoxia and hypoxia, respectively) were not statistically different. Stroke rate, duration of stroke phase or dF/dt were not significantly different between the three tests.

Electromyography. The sum-IEMG of maximal strokes decreased in each F_IO_2 situation. In the case of normal strokes, sum-IEMG remained stable or increased slightly in normoxia and hyperoxia. In hypoxia, sum-IEMG decreased from the 500-m mark to the 2000-m mark but then increased at the end of the exercise. As shown in figure 12, sum-IEMG was lower in hypoxia than in normoxia. In hyperoxia, sum-IEMG was very similar to that in normoxia. When compared with the pre-exercise maximum (100%) level, the mean sum-IEMG of normal strokes was 71.1 ± 83%, 73.7 ± 4.7%, and 62.3 ± 8.3% ($P<0.05$ as compared with pre-exercise maximal value) in hyperoxia, normoxia and hypoxia, respectively.

The correlation between force production and muscular electrical activity varied within and between the tests. In normal strokes, the correlation between F_{max} and sum-IEMG was statistically significant in normoxia at the start ($r=0.84$) and at the end of the exercise ($r=0.86$); in hyperoxia at the start ($r=0.88$) and at

the 1000 m mark (r=0.82). No significant correlation was found for hypoxia. Impulse and sum-IEMG correlated statistically significantly only at the end of normoxic exercise (r=0.81). No significant difference was found in NME between normoxia and the other trials.

TABLE 11 Parameter estimates for VO_2 response during maximal 7-minute ergometer cycling in hyperoxia, normoxia and hypoxia.

	A_0	A_1	TD_1	τ_1	A_2	TD_2	τ_2	A_3	TD_3	τ_3	MRT
	l/min	l/min	s	s	l/min	s	s	l/min	s	s	s
Hyperoxia	0.66	0.88	7.9	3.1	2.55	25.0	13.1	0.83	156.7	187.5	41.7
	(0.21)	(0.36)	(2.2)	(2.1)	(0.59)	(5.7)	(3.8)	(0.69)	(70.3)	(160.0)	(5.7)
Normoxia	0.56	0.72	6.7	5.3	2.33	23.4	15.0	0.72	100.3	109.0	39.7
	(0.07)	(0.24)	(2.9)	(5.0)	(0.52)	(2.1)	(4.8)	(0.42)	(26.2)	(55.2)	(7.8)
Hypoxia	0.60	0.90	7.8	6.7	2.01[§]	22.7	12.1	0.28	118.7	74.6[§]	35.0*[§]
	(0.13)	(0.47)	(3.1)	(7.0)	(0.58)	(3.3)	(6.6)	(0.45)	(64.0)	(53.0)	(6.5)
	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=	F(2,20)=
ANOVA	1.17	0.48	0.51	0.68	4.47	2.50	0.99	2.34	1.94	4.30	5.49
F_IO_2 main effect	n.s.	n.s.	n.s.	n.s.	P=0.0287	n.s.	n.s.	n.s.	n.s.	P=0.0350	P=0.0153

Values are means (SD); n = 11 subjects. A_0, VO_2 at rest; A_1, A_2, A_3: amplitudes of response; TD_1, TD_2, TD_3: time delays; τ_1, τ_2, τ_3: time constants; MRT: mean response time 0-63 % of VO_{2max}. * Significantly different from normoxia (P<0.05); [§] Significantly different from hyperoxia (P<0.05); n.s., non-significant.

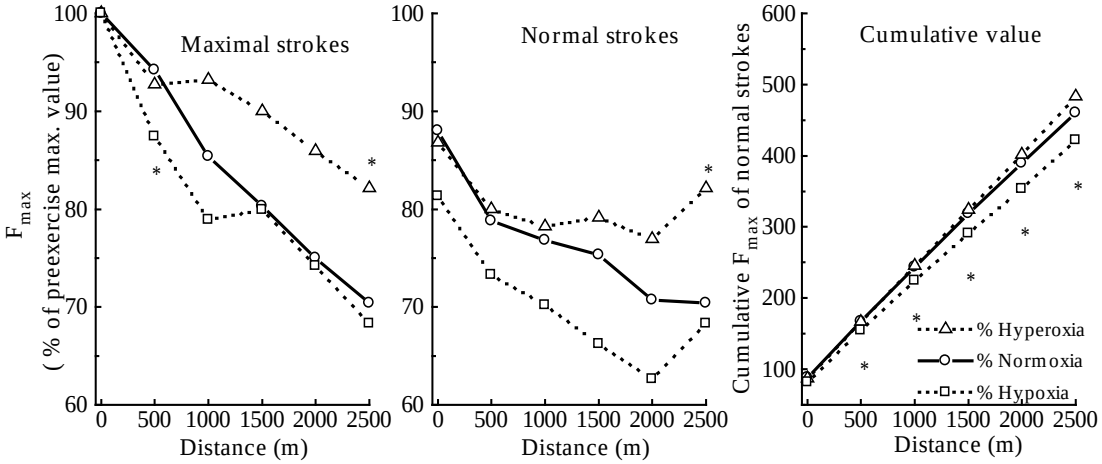


FIGURE 10 Maximum force (F_{max}) in maximal (left) and normal (middle) strokes during 2500-meter rowing. F_{max} is also expressed as a cumulative value (right) (III). * Different from normoxia (P<0.05).

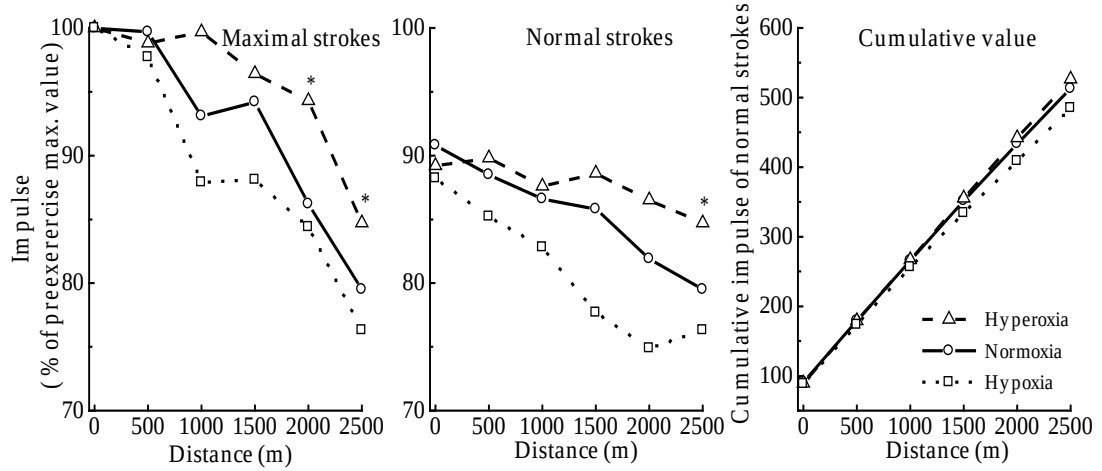


FIGURE 11 Force impulse in maximal (left) and normal (middle) strokes during 2500-meter rowing. Impulse is also expressed as a cumulative value (right) (III). * Different from normoxia (P<0.05).

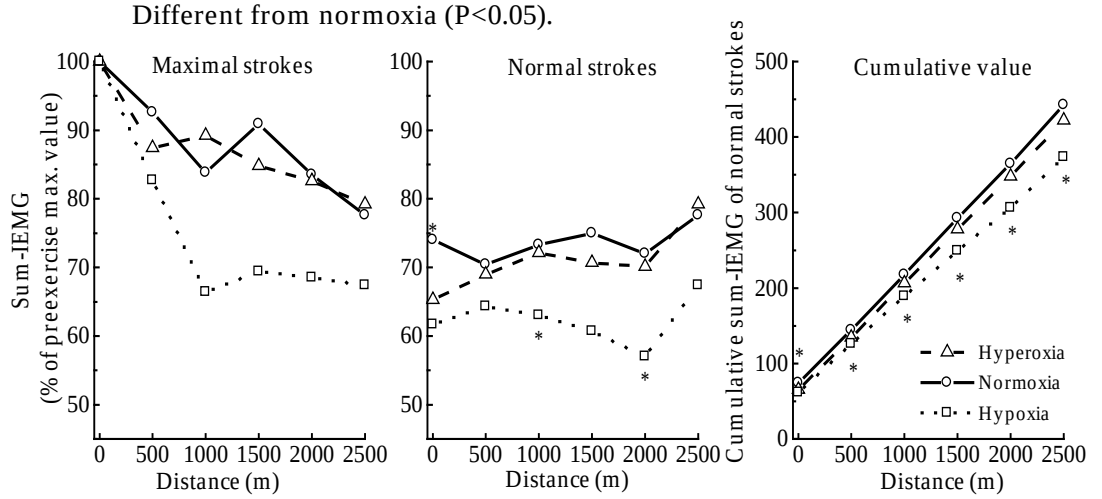


FIGURE 12 Sum of integrated electromyogram signal from seven muscles (sum-IEMG) in maximal (left) and normal (middle) strokes during 2500-m rowing. Sum-IEMG is also expressed as a cumulative value (right) (III). * Different from normoxia (P<.0.05).

6 DISCUSSION

The present series of studies compared the effects of hypoxia, normoxia and hyperoxia on various aspects of exercise performance and oxygen uptake in different types of exercise. In addition to the previously known impairment in $\dot{V}O_{2max}$ and exercise performance in hypoxia and their improvement in hyperoxia, several new findings were seen. The results indicate that arterial O_2 saturation is effected by F_IO_2 not only during severe exercise, but also during tasks of moderate intensity. The results also indicate that exercise performance is not solely dependent on oxygen uptake as the change in VO_{2max} exceeds the change in exercise performance. Furthermore, the reduced electromyogram activity and maximal cardiac output observed in hypoxia confirm this conclusion, indicating that some of the responses that previously have been seen only during chronic hypoxia can also be seen in acute hypoxia in endurance athletes. In addition to the pivotal role of the central circulatory functions, the present results, like those obtained previously, suggest that factors that are related to the functioning of the central nervous system (CNS) may be important for exercise performance and O_2 delivery.

6.1 Arterial O_2 saturation and blood lactate concentration

The methods used to modify F_IO_2 were effective in altering arterial O_2 saturation and causing changes in physiological responses between the conditions of hyperoxia, hypoxia and normoxia. The results also indicate that, in hypoxia, similar results are obtained both by using inspiratory gases of the preferred mixture from gas bottles and by using normobaric hypoxic room air (i.e. the “altitude house”) to adjust F_IO_2. Both methods gave comparable responses to those obtained during exposure to moderate altitude. The results of the present study are in agreement with previous studies (Dempsey et al. 1984; Rice et al. 1999) and provide evidence that arterial desaturation is not

limited only to severe exercise, but may occur during light or moderate workloads in trained athletes, both in men and women. In addition, F_IO_2 affects the exercise intensity where desaturation occurs. During severe exercise, the observed lowest values of SpO_2% were in close agreement with those of previous studies (Dempsey et al. 1984; Williams et al. 1986; Miyachi and Tabata 1992; Gore et al. 1996) and support the observations (Dempsey et al. 1984; Williams et al. 1986; Powers et al. 1993; Gore et al. 1996) that athletes with the highest aerobic capacity are the most vulnerable to exercise-induced hypoxemia. The lack of interaction between SpO_2% and $\dot{V}O_{2max}$ in hypoxia differs from the results of Cymerman et al. (1989) who found a strong positive correlation between these variables at extreme altitude. The lack of correlation between SpO_2% and $\dot{V}O_2$ in hyperoxia is difficult to interpret as some studies (Welch et al. 1977) indicate reduced leg blood flow and similar $\dot{V}O_2$ in hyperoxia when compared with normoxic controls, while other studies (Knight et al. 1993) report maintained blood flow and increased $\dot{V}O_{2max}$. In the present study, SpO_2% remained so high in hyperoxia in all subjects that the differences in $\dot{V}O_{2max}$ could only be determined by other factors.

Exercise-induced hypoxemia has previously been attributed to a widened alveolar-arterial PO_2 difference, which may reflect either a $V_A/\dot{Q}$ mismatch, an alveolar end-capillary diffusion limitation, inadequate hyperventilation and/or temperature, PCO_2 and pH-induced rightward shift of the HbO_2 dissociation curve (Dempsey et al. 1984; Wagner et al. 1986; Powers et al. 1993; Gore et al. 1996; Dempsey and Wagner 1999). The sudden initiation of moderate or heavy exercise commonly causes transient hypoxemia secondary to a ventilatory response that lags behind a rising $\dot{V}O_2$ (Barr et al. 1964). In addition, a strong correlation between arterial (P_aO_2) and alveolar oxygen partial pressure (P_AO_2) suggests that inadequate hyperventilation is a major contributor to exercise-induced hypoxemia (Rice et al. 1999). Thus, a plausible explanation for the initial drop in SpO_2% at light workloads in this study during hyperoxia and normoxia is inadequate hyperventilation. In hypoxia, O_2 diffusion limitation due to lowered P_AO_2 is the most likely explanation for the very fast drop in SpO_2%. In all F_IO_2 situations, the very rapid red blood cell transit time in the pulmonary capillary bed of the trained athlete possessing a high cardiac output is expected to be a major contributor to the arterial hypoxemia and desaturation that occurs during heavy and severe exercise (Dempsey et al. 1984; Williams et al. 1986; Powers et al. 1993; Dempsey and Wagner 1999). Moreover, in study I, five of the six subjects were women and thus the sex of the subjects may have affected the results as tidal volume and ventilation are mechanically constrained in many fit women because the demand for high expiratory flow rates encroaches on the maximum flow-volume envelope of the airways (McClaran et al. 1998). The flow-volume loops were not measured during exercise, but some of the subjects approached their estimated (Hansen et al. 1984) maximal voluntary ventilation (MVV) in hypoxia. Despite the disadvantages of the MVV method compared to flow-volume loop method in

the evaluation of flow limitation (Johnson et al. 1999), it may nevertheless be concluded that it was not the low P_IO_2 alone but also the limitation on mechanical ventilatory flow that caused the decreased SpO_2% in hypoxia. Obviously, flow limitation was not present in normoxia and hyperoxia, as there was a large reserve between estimated MVV and the measured peak ventilation.

Despite similar $\dot{V}O_2$ values, *blood lactate* concentration was affected by F_IO_2 at the 70% and 80% workloads of normoxic $\dot{V}O_{2max}$ (I). This result is supported by the finding of Linnarsson et al. (1974) who indicated that lactate accumulation varied inversely with inspired P_IO_2 during submaximal but not during maximal exercise. In addition, Green et al. (1992) reported higher muscle lactate concentrations during exercise in acute hypoxia when compared with normoxia. Blood lactate concentration was highest in hypoxia both during and after maximal exercise, but the results showed variation as the difference from normoxia and hyperoxia was significant only after maximal cycling (IV) but not after maximal rowing (II). The lactate appearance rate is strongly correlated with, and may be influenced by, the amount of β-adrenergic stimulation, which in turn may partly be determined by the degree of arterial oxygenation (Reeves et al. 1992). In addition, hypoxia-induced increase in circulating catecholamine levels (Cunningham et al. 1965; Escourrou et al. 1984; Strobel et al. 1996) may affect the response. It is also known that β-blocked subjects, exercising at the same relative workload as controls, demonstrate significantly lower lactate levels during acute high-altitude exposure compared with controls (Mazzeo et al. 1994). Thus, part but not all of the lactate accumulation during exercise under acute hypoxia is mediated through epinephrine action on β-adrenergic receptors, because β-blocking does not completely prevent the rise in blood lactate (Mazzeo et al. 1994). Thus, the present results showing higher blood lactate concentrations in hypoxia and lower concentrations in hyperoxia when compared with normoxia may reflect differences in β-adrenergic stimulation (Reeves et al. 1992) and are supported by the conclusion that lactate production during submaximal exercise is O_2-dependent (Katz and Sahlin 1988).

6.2 Relationships between exercise performance, neuromuscular function and oxygen uptake

6.2.1 Submaximal exercise

The similarity of $\dot{V}O_2$ at light and moderate workloads in normoxia and hypoxia (I, V) is supported by previous studies (Stenberg et al. 1966; Hughes et al. 1968; Hartley et al. 1973; Ekblom et al. 1975; Adams and Welch 1980; Fulco et al. 1988). In hypoxia, higher heart rate and ventilation compensated for the reduced SpO_2% to maintain an adequate level of $\dot{V}O_2$. However, the result that $\dot{V}O_2$ was higher in hyperoxia than normoxia and hypoxia during submaximal

cycling (V) was contrary to the hypothesis, especially as such an elevation was not seen during submaximal running (I). The previous studies also show variation in this respect, as some studies indicate a similar $\dot{V}O_2$ in hyperoxia as in normoxia (Asmussen and Nielsen 1955; Hughes et al. 1968; Davies and Sargeant 1974; Adams and Welch 1980) while others (Welch et al. 1974; Ekblom et al. 1975) indicate elevated $\dot{V}O_2$ at light workloads in hyperoxia. This result is difficult to interpret as there is conflicting evidence in the previous studies as to whether blood flow to the working muscles is altered in hyperoxia or not (Welch et al. 1977; Knight et al. 1993). Because blood flow to the working muscles or other tissues was not measured in the present study, the issue remains open. However, there are several possibilities that could explain this finding, including a smaller need for glycolytic energy production in hyperoxia (Linnarsson et al. 1974), enhanced metabolic rate in "non-exercising" tissue, especially in the splanchnic region (Nielsen et al. 1998), O_2 storage in the body during inhalation of O_2-enriched air and that some O_2 might be utilized in other reactions besides those in the respiratory chain (Welch et al. 1974). In addition, the possible differences between running and cycling in muscular recruitment patterns and the contraction-relaxation cycle might affect blood flow to the working muscles and thus explain the observed differences.

6.2.2 Maximal exercise

The methods used to modify F_IO_2 were effective in altering SpO_2% and causing changes in $\dot{V}O_{2max}$ and exercise capacity as hypothesized. The magnitude of impairment in $\dot{V}O_{2max}$ in hypoxia is analogous with the results of previous studies that have indicated the dependency of $\dot{V}O_{2max}$ on P_IO_2 (Ekblom et al. 1975; Squires and Buskirk 1982; Houston et al. 1987; Reeves et al. 1987a; Sutton et al. 1988; Cymerman et al. 1989). Accordingly, the result that $\dot{V}O_{2max}$ was significantly higher in hyperoxia than in normoxia is in agreement with some studies (Welch et al. 1974; Ekblom et al. 1975; Welch 1982) but contrary to others (Hughes et al. 1968; Adams and Welch 1980) where a similar increase in $\dot{V}O_{2max}$ was not seen.

Some of the differences between the present study of competitive athletes and previous studies examining less athletic subjects in the effects of F_IO_2 on the physiological responses and exercise performance could be explained by the principle of symmorphosis. Weibel and Taylor (1981) defined symmorphosis as "a state of structural design commensurate to functional needs resulting from regulated morphogenesis." In their scheme as well as in more recent articles (Hoppeler and Weibel 1998) every part of the respiratory system (i.e. lungs, cardiovascular system, and muscle mitochondria) is closely matched functionally to every other part so that there are no specific weak links in the chain of oxygen delivery and utilization. The concept of symmorphosis argues that for any system, such as the respiratory chain for oxygen transport, the maximal capacity of each parameter is adjusted quantitatively to match the structural and functional limits of the demands placed on the system as a

whole. Thus, for the “elite athletes” of the animal kingdom, each step along the oxygen pathway from the atmosphere to the mitochondria has evolved toward optimal function and maximal aerobic power, allowing little room for further adaptive improvement, and making athletes particularly susceptible to small perturbations in one component, such as the concentration of inspired oxygen. For example, foxes, dogs, and horses have a mass-specific rate of O_2 consumption approximately 2.5 times that of sedentary species of the same size, such as the agouti, goat, or steer. For such animals, the mechanism of this large adaptive range of O_2 consumption appears due to several factors: a large mitochondrial volume, matched by a large muscle capillary volume and vascular conductance in skeletal muscle; a higher hemoglobin concentration; and a large maximal stroke volume. It is evident that in the “athletic species” the capacity of the cardiovascular system to transport O_2 is not matched to their metabolic capacity (Rowell 1993). Thus, trained humans also have a great excess of mitochondria and mitochondrial oxidative capacity compared to their capacity for systemic oxygen transport, emphasizing the importance of convective O_2 transport, rather than O_2 utilization as the factor limiting $\dot{V}O_{2max}$. Furthermore, the symmorphosis hypothesis does not hold for the pulmonary systems in animals adapted to high metabolic rates (Weibel and Kayar 1988; Hoppeler and Weibel 1998). The hypothesis is clearly inapplicable to the human pulmonary system because of its failure to improve its function along with cardiovascular function during physical conditioning (Dempsey 1986; Wagner 2000a).

The physiological basis for the change in $\dot{V}O_{2max}$ in hyperoxia and hypoxia is assumed to rely on modified O_2 delivery and/or O_2 utilization. The results indicated that both factors of the Fick equation were effective as $\dot{Q}_{max}$ and the calculated (a-v)O_2 at $\dot{V}O_{2max}$ on average were 5.7% and 7.1% higher in hyperoxia but 8.8% and 13.7% lower in hypoxia than in normoxia (V). Both O_2 delivery and O_2 utilization consist of several phases. As a part of O_2 delivery, SpO_2% was decreased in hypoxia (I, IV, V). According to the Fick's law of diffusion (West 1990) P_IO_2 has a major effect on O_2 flow from alveoli to pulmonary capillary blood, and the effect of P_IO_2 is accentuated in endurance athletes with a reduced red blood cell pulmonary transit time during exercise (Powers et al. 1993). One possible factor responsible for the increase of $\dot{V}O_{2max}$ in hyperoxia is improved pulmonary oxygen diffusion at higher F_IO_2 (Dempsey et al. 1984). In addition, the amount of oxygen dissolved in plasma increases when the PO_2 in the alveoli exceeds 100 mmHg (Guyton 1981). $\dot{V}O_{2max}$ is also effected by the peripheral diffusion of oxygen (Roca et al. 1989; Wagner 1992). Therefore, the increased F_IO_2 raises the oxygen partial pressure in blood and the O_2 diffusion constant (see eq. 3 – 5). Thus, $\dot{V}O_{2max}$ changes more than might be expected only from the increase in oxygen delivery. Unfortunately, the present study offers no direct data on blood flow, (a-v)O_2, peripheral O_2 diffusion or O_2 utilization in the working muscles. Therefore, it is impossible to calculate the effect of the various parameters as only some of them were measured. Even had

they been measured, their detailed calculation is difficult as the various determinants of aerobic capacity are assumed to be interdependent (Roca et al. 1989; Wagner 1995; Tschakovsky and Hughson 1999).

The metabolic explanatory models for changes in $\dot{V}O_{2max}$ were beyond the scope of the present study and they are not treated in depth. However, as an explanation for an unexpectedly great increase in $\dot{V}O_{2max}$ in relation to P_{max}, Welch et al., (1974) suggested a decrease in anaerobic metabolism, O_2 storage in the body, and the possibility that some O_2 might be utilized in other reactions besides those in the respiratory chain. In this respect, calcium (Ca^{2+}) metabolism, at least, should be regarded as a possible factor that may influence the ratio between $\dot{V}O_2$ and exercise performance. It is suggested (Carafoli and Lehringer 1971) that Ca^{2+} released during excitation-contraction coupling increases $\dot{V}O_2$ in two ways. First, mitochondria have an affinity to accumulate Ca^{2+} ions. This process requires energy and increases $\dot{V}O_2$ without concomitant ATP production. Secondly, an increased intramitochondrial [Ca^{2+}] enhances the coupling of oxidation and phosphorylation leading to an increase in $\dot{V}O_2$. However, the highest P_{max} in hyperoxia (II, IV, V) indicates that increased $\dot{V}O_{2max}$ was mainly due to the elevated O_2 consumption in the working muscles.

The change in $\dot{V}O_{2max}$ clearly exceeded the change in P_{max} both in hyperoxia and hypoxia. Taken together, the mean improvement (II-V) in work capacity was 3.6% in hyperoxia and mean impairment in hypoxia 7.3% in comparison with normoxia. Correspondingly, on average $\dot{V}O_{2max}$ was 12.2% higher in hyperoxia but 14.7% lower in hypoxia than in normoxia. A fundamental question in exercise physiology has been the ratio between $\dot{V}O_{2max}$ and exercise performance. Two ways of thinking have existed: one favouring the view that $\dot{V}O_{2max}$ sets the upper limit for endurance performance (Bassett and Howley 2000) and another where $\dot{V}O_{2max}$ is considered more an effect than a cause of maximal workload (Noakes 2000). If $\dot{V}O_{2max}$ determined exercise performance strictly, then, there should be an equal change from normoxic values in both $\dot{V}O_{2max}$ and exercise performance in conditions of acute hypoxia and hyperoxia. However, this is not the case as both previous studies (Saltin et al. 1968b; Drinkwater et al. 1979; Maresh et al. 1983; Fulco et al. 1988; Roca et al. 1989; Knight et al. 1993; Gore et al. 1997; Nielsen et al. 1998) and the present one indicate a greater change in $\dot{V}O_{2max}$ than in maximal workload in both hypoxia and hyperoxia. A nonlinear increase in $\dot{V}O_{2max}$ against power output is expected in rowing (Secher 1983) and always in $\dot{V}O_2$ slow component area (Barstow and Molè 1991). However, these are not potent explanations for the observed changes between the various F_IO_2 conditions, and alternative mechanisms should be looked for. Interestingly, increased efficiency has been observed after acclimatization in chronic hypoxia that could not solely be explained by an increase in carbohydrate utilization but rather appeared to represent an actual increase in efficiency in the excitation-contraction processes involved in contraction (Green 2000; Green et al. 2000). There is no data to

indicate that this could happen in acute hypoxia, or possibly the contrary in acute hyperoxia, and thus explain the finding that $\dot{V}O_{2max}$ changed more than exercise capacity in the present study. Nevertheless, it emphasizes the complexity of adaptation processes and the need for further studies.

It is well documented that several factors affect exercise performance and cause fatigue during intense exercise (Simonson 1971; Karlsson 1979; Green 1989; Paavolainen et al. 1999a) and athletes with a similar $\dot{V}O_{2max}$ may exhibit significantly different levels of exercise performance (Paavolainen et al. 1999b). The present results indicate that the subjects were not able to take full advantage of the increase in $\dot{V}O_{2max}$ in terms of exercise performance in hyperoxia. It is not known whether this indicates CNS and/or neuromuscular limitation or is a sign of teleoanticipation (Ulmer 1996), i.e. that the subjects were accustomed to exercise at their "normal" maximum level and did not utilize their whole potential until at the end of the hyperoxic exertion. The same phenomenon can be seen in a study (Martin et al. 2000) where physically active but not cycle-trained subjects improved their cycling performance when tested several times on consecutive days, whereas a similar improvement was not seen among trained cyclists. Part of the improvement may be due to training effects but part is expected to be due to the fact that after a few trials, the subjects learn to use their whole capacity. Therefore, it is possible that the athletes in the present study might have been able to increase their power output in hyperoxia if they had had the possibility to train a few times in hyperoxic conditions. As the $\dot{V}O_2$ measurements did not explain all the changes in exercise performance, the neuromuscular factors were included.

6.2.3 Neuromuscular functions

The findings of the present study indicated that maximum force and impulse were impaired less in hyperoxia and more in hypoxia when compared with normoxia during maximal ergometer rowing. Moreover, hypoxia had a tendency to lower sum-IEMG from the normoxic level whereas hyperoxia had no effect on it. A strong correlation between F_{max} and $\dot{V}O_2$ in normoxia supports the view that oxygen consumption affects exercise performance whereas the absence of a significant similar correlation in hypoxic and hyperoxic conditions may suggest a partial uncoupling of these processes and the existence of other limiting factors in addition to $\dot{V}O_2$.

In part the differences in cumulative force output can be explained by the cumulative sum-IEMG as this was significantly lower in hypoxia than in normoxia throughout the test, indicating a lower level of neural activity in hypoxia. If the similarity between normoxia and hyperoxia in the sum-IEMG is regarded as a sign of similar neural input, then, the results may suggest that there are factors in normoxia as against hyperoxia that hinder the attainment of an equal level of exercise performance. These factors are most probably related to the availability of oxygen. In hyperoxia, this may indicate an inability to exercise as hard as the increased F_IO_2 would have permitted (teleoanticipation) or a neural limitation, i.e., full motor unit recruitment, action potential

conduction and/or CNS activity are achieved in normoxia, and therefore the extra oxygen made available in hyperoxia is of no particular benefit to these mechanisms. This would be in accordance with Noakes's (1988) theory that when no plateau in $\dot{V}O_2$ is observed during an exhaustive exercise (as in hyperoxia in the present study), the factors limiting maximal exercise performance might be explained in terms of failure of muscle contractility, which may be independent of tissue oxygen deficiency. However, this remains as a hypothesis in the absence of data to confirm this. In addition to the availability of oxygen, force production is subject to the influence of several other factors, such as intra- and extracellular pH and neural input. As the majority of hydrogen-ion (H^+) accumulation comes from lactic acid formation (Jones 1980), it is possible that lactate concentration and pH during rowing were affected by F_IO_2 (as they were during cycling in study IV), although the post-exercise peak values were not significantly different in study II.

Sum-IEMG did not follow the changes in force production linearly, as only few statistically significant correlation coefficients were found between sum-IEMG and the force parameters. Several factors may explain this finding. In a dynamic contraction, various mechanical, physiological, anatomical, and electrical modifications occur throughout the contraction that affect the relationship between signal amplitude and muscle force. For example, the force-length relationship of the muscle fibers varies nonlinearly, and the shapes of the motor unit action potentials that construct the EMG signal are altered because the relative position of the electrode fixed on the skin surface changes with respect to the contracting muscle fibers (De Luca 1997). During fatiguing exercise, factors including conduction velocity, motor unit recruitment, synchronization of motor unit activity, and lowering of motor unit firing frequencies are expected to affect the EMG signal (Krogh-Lund and Jorgensen 1991). Recruitment and fatigue act in opposition to muscle fiber conduction velocity. Recruitment boosts average conduction velocity, whereas fatigue provokes a slowing in conduction velocity (Arendt-Nielsen et al., 1989). In addition, the relation between force and IEMG may show a curvilinear rather than linear shape, as is the case with the biceps brachii (Bigland-Ritchie 1981). Similarly, the IEMG-work intensity relationship for the rectus femoris muscle has been shown to have a tendency to be curvilinear, indicating significant increases in IEMG at post-lactate/ammonia threshold work intensities and thus reflecting increases in fatigue and type II motor unit recruitment (Taylor et al., 1997). The lowest correlation between sum-IEMG and force found in hypoxia may partly be explained by a postexercise lactate concentration that was highest after hypoxic exercise. Although the difference was not statistically significant, such factors as lactate production, change in pH, loss of potassium ions from the muscle cell, and intramuscular temperature may affect the EMG-signal (Gamet et al. 1993) and its correlation with force parameters. Finally, the seven muscles monitored were not solely responsible for force production during rowing. It is therefore possible that an increase in force is produced by the contraction of muscles not being monitored. The muscles measured are,

however, reported to be among the most essential in rowing (Ballè et al. 1983; Wilson et al. 1988).

It has been well documented that IEMG and $\dot{V}O_2$ act linearly during submaximal exercise in normoxia (Bigland-Ritchie and Woods 1974). In the present study, the exercise was maximal and sum-IEMG and $\dot{V}O_2$ did not correlate significantly in any F_IO_2 situation. The lower power output and $\dot{V}O_2$ in acute hypoxia per se may contribute to a smaller neural input and/or IEMG activity, as chronic hypoxia has been indicated to withdraw the common increase in IEMG during exhaustive exercise (Kayser et al. 1994). The reason for the low correlation between $\dot{V}O_2$, force production and sum-IEMG in hyperoxia may be that the subjects underestimated their capacity in hyperoxia, as they were able to increase their power during the last 500 m more than at the end of the two other tests.

The lower sum-IEMG in hypoxia in comparison with normoxia and hyperoxia is in accordance with other findings of the present study, indicating that some of the physiological responses that have previously been thought to happen only in chronic hypoxia may also be seen in acute hypoxia, at least in trained athletes. The inability to raise sum-IEMG, HR_{max} and $\dot{Q}_{max}$ to the same level as in normoxia might suggest a common origin, a potent candidate being CNS limitation. In absence of such a limitation, higher sum-IEMG, HR_{max} and $\dot{Q}_{max}$ levels than those observed would have been anticipated, as sympathetic nervous activity increases in a highly predictable manner in relation to the intensity of dynamic exercise (Rowell 1974; Rowell 1986; Rowell and Blackmon 1987) and as hypoxia per se is known to increase sympathetic stimulation (Suarez et al. 1987; Levine 2000). Of particular importance is the finding that both force production and sum-IEMG decreased in maximal strokes (two strokes performed at 500-m intervals among normal strokes) during ergometer rowing at all F_IO_2, indicating not only that muscular contractility was impaired but also that neural innervation was reduced. Whether the reduction in sum-IEMG and force production indicate central fatigue (reduction in efferent motor command to active muscles) and/or peripheral fatigue (decrease in force generating capacity of the skeletal muscle owing to altered crossbridge cycle activity, excitation-contraction coupling failure and/or impaired action potential propagation) is not known.

6.3 Cardiac output, stroke volume, heart rate and (a-v)O_2

This study confirmed the previous results (Wagner et al. 1986; Wagner 2000b) that acute hypoxia increases $\dot{Q}$ and HR at a given submaximal $\dot{V}O_2$ and workload. During maximal exercise the group mean of HR_{max} was always highest in hyperoxia and lowest in hypoxia although the differences were not always significant. The main new finding was that $\dot{Q}_{max}$ was significantly

smaller in hypoxia than in hyperoxia and normoxia at exhaustion in progressive cycling (V). This is the first study to indicate a reduction in $\dot{Q}_{max}$ during acute hypoxia under physiological conditions (arterial desaturation caused by decreased F_IO_2, not by carbon monoxide).

An attempt should be made to discuss why some studies indicate a reduction in cardiac parameters during acute hypoxia and others do not. A possible explanation could be the fitness of the subjects, as O_2 delivery and F_IO_2 may be more important in fit subjects than in their less fit counterparts because the circulatory and oxidative capacity in their trained muscles exceeds what the heart can supply them (Hoppeler and Weibel 1998; Wagner 2000a). Thus, among subjects whose $\dot{V}O_{2max}$ in normoxic conditions is relatively high (58 ml · kg^{-1} · min^{-1} (Ekblom et al. 1975) or 62 ml · kg^{-1} · min^{-1} (V)), $\dot{Q}_{max}$ is more likely to decrease in acute hypoxia than in subjects with lower values (53 ml · kg^{-1} · min^{-1} (Stenberg et al. 1966) and 36 ml · kg^{-1} · min^{-1} (Hughes et al. 1968)).

The present reduction of $\dot{Q}_{max}$ in acute hypoxia is in accordance with the previous theories (Ferretti and di Prampero 1995; Wagner 2000a) that without parallel upward adjustment in both pulmonary and muscle O_2 diffusive transport conductance a very high cardiac output would cause substantial arterial desaturation and also impair muscle O_2 extraction. While high cardiac output is necessary for elite performance, it must be matched with high pulmonary and muscle diffusing capacity for its benefits to be realized. Although the reduction in $\dot{Q}_{max}$ in acute hypoxia would be physiologically beneficial, the question to be answered is: what are the mechanisms that block an increase in $\dot{Q}$, SV and HR during severe exercise in acute hypoxia? The reduced $\dot{Q}_{max}$ in acute hypoxia is a novel finding, and the present study does not have data to offer on the possible regulatory mechanisms that lead to the reduced pumping capacity of the heart. Therefore, it is only possible to speculate whether those mechanisms that are thought to be responsible for reduced $\dot{Q}_{max}$, SV_{max} and HR_{max} in chronic hypoxia may in fact also apply in acute hypoxia among trained athletes, or whether some other mechanisms are responsible. The detrimental effects of chronic hypoxia on $\dot{Q}_{max}$ include increased blood viscosity from erythrocytosis and increased hematocrit, reduced cardiac filling pressures from reduced plasma volume, autonomic changes such as increased parasympathetic or reduced sympathetic activity, hypoxic myocardial dysfunction, and the possibility that since skeletal muscle O_2 availability is impaired by ambient hypoxia, exercise capacity is reduced and the requirement for $\dot{Q}$ is thus correspondingly reduced (Wagner 2000b). In acute hypoxia, however, there is no time for changes in erythrocytosis and viscosity. Therefore, this explanation can be rejected. In the following paragraphs, the possible mechanisms for reduced $\dot{Q}_{max}$ are sought in cardiovascular and CNS limitations.

6.3.1 Central nervous system limitation

The autonomic nervous system is the key adaptive pathway through which humans respond to normobaric or hypobaric hypoxia. Various components of the autonomic nervous system are affected by acute hypoxia. Peripheral chemoreceptors located in the carotid body and the arch of aorta are stimulated, and via afferent signals to the cardiovascular center in the rostral ventorolateral medulla lead to an increase in both efferent sympathetic and vagal nerve traffic. The resultant increase in ventilation also stimulates pulmonary afferents, which leads to a counterbalancing vagal withdrawal. Increases in ventilation also lead to increased blood pressure variability due to respiratory mechanical alterations in intrathoracic pressure and cardiac filling, which provide input to arterial baroreceptors, and which lead to synchronization of sympathetic nervous activity to respiration. Acute hypoxia also has a direct effect on peripheral resistance vessels, leading to the release of active vasodilators and "functional sympatholysis" whereby sympathetic activation is overridden by local vasodilation. The ultimate outcome of this integrated response to acute hypoxia is an increase in heart rate and cardiac output, a decrease in peripheral vascular resistance, and a decrease in blood pressure (Levine 2000).

In the present study, the elevated $\dot{Q}$ and HR in hypoxia at given levels of $\dot{V}O_2$ are in accordance with augmented sympathetic activity (Suarez et al. 1987; Levine 2000) and with increased circulating catecholamine levels (Cunningham et al. 1965; Escourrou et al. 1984). The close relationship between norepinephrine, heart rate and percentage $\dot{V}O_{2max}$ are essentially unaffected by hypoxemia; that is, they are all changed in the same relative proportions (Rowell 1986). Therefore, it is interesting that $\dot{Q}_{max}$, HR_{max}, SV_{max} and P_{max} were lowest in hypoxia, in precisely a situation where maximal sympathetic stimulation is expected. One feasible explanation for the reduced cardiac and overall performance is that limitations originate centrally during heavy exercise in acute hypoxia. The notion that the level of sympathetic activity at a given heart rate is the same under normoxic and hypoxic conditions (Rowell 1986) suggests that the tendency to a decrement in HR_{max} in hypoxia (II, IV, V) might indicate either lesser sympathetic stimulation or disturbances in cardiac innervation.

The reduction of HR_{max} in acute hypoxia has not received much attention previously. However, results in agreement with those of the present study have also been obtained in some other recent studies. An important finding is that the decrement in HR_{max} in acute hypoxia follows a dose-response principle, i.e. the size of the reduction increases along with the increase in hypoxia, whereas maximal plasma norepinephrine and lactate concentration do not change under hypoxic conditions as compared to sea level (Lundby et al. 2001). Moreover, the breathing of oxygen in acute hypoxia completely reverses HR_{max} to values not different from those at sea level (Lundby and Olsen 2001). This result is supported by studies on chronic hypoxia (Kayser et al. 1994; Savard et al. 1995) where the breathing of oxygen increased peak heart rate at exhaustion,

although values similar to those found in normoxia were not attained. As an explanation for their finding, Lundby and Olsen (2001) suggested that postganglionergic desensitization was responsible for the early decrease in HR_{max} during maximal hypoxic exercise. Support for the idea that the CNS may play an important role explaining the physiological responses and alterations in performance to acute changes in P_IO_2 can be obtained from several other studies. Firstly, the typical signs of neuromuscular fatigue (i.e. an increase in the integrated electromyogram signal, IEMG) are absent during chronic hypoxia (Kayser et al. 1994) and the response is attenuated in acute hypoxia (III). Secondly, the blunting of afferent signals from the working muscles does not diminish the hypoxia-induced enhancement of cardiovascular adaptation suggesting that the limitations on exercise performance are of central origin (Kjaer et al. 1999). Thirdly, vasomotor depression is induced by central hypoxia in non-acclimatized subjects (Koller et al. 1991). Fourthly, the animal experiments (Jones et al. 1981) have shown that, as C_aO_2 falls, there is a reciprocal increase in cerebral blood flow such that cerebral O_2 delivery remains constant. This indicates that the brain has the ability to sense acute hypoxia and to increase blood flow in response. The finding that the extent of the cerebral microvasculature increases with chronic exposure to hypoxia (Harik et al. 1996) further indicates the capacity of the CNS to sense, and to respond, to hypoxia. Finally, hypoxia has a tendency to increase both overall and respiratory perceptions at a given absolute oxygen consumption (Shephard et al. 1992).

These explanations together with the present results are supported by the recent hypothesis by Noakes (1998; 2000) that a "central governor" regulates skeletal muscle recruitment during severe exercise. According to this hypothesis, reduced $\dot{Q}_{max}$ and $\dot{V}O_{2max}$ in acute hypoxia might be the result rather than the cause of reduced skeletal muscle recruitment. Interestingly, the changes in P_{max} (representing skeletal muscle recruitment) and $\dot{Q}_{max}$ were very similar and had a strong positive correlation (V), supporting the possible existence of a central governor. Noakes' suggestion is that oxygen tension in the coronary vascular bed is the variable that should be the monitored in order to prevent the development of progressive myocardial ischemia. Hill, Long and Lupton originally introduced the central governor hypothesis in the 1920s. Their hypothesis was that the heart is able to regulate its output, to some extent, in accordance with the degree of saturation of the arterial blood. They suggested that there is a mechanism in the body (either in the heart muscle itself or in the nervous system), which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and vice versa. This mechanism would tend, to some degree, to act as a "governor," maintaining a reasonably high degree of saturation of the blood: the breathing of a gas mixture rich in oxygen would produce a greater degree of saturation of the blood and so allow output to increase until the "governor" stopped it again. (Hill et al. 1925). Although both Hill's and Noakes's hypothesis are interesting, further studies are needed to demonstrate the existence and mode of action of the proposed central governor. Present knowledge of hypoxia-induced changes in CNS

function and the maintenance of myocardial contractility indicates that the "governor" is more likely to be found in the CNS than in the heart itself.

6.3.2 Cardiovascular limitation

Stroke volume is determined by preload, afterload and myocardial contractility. Although myocardial hypoxemia would be a tempting explanation for reduced HR_{max}, SV_{max} and $\dot{Q}_{max}$ found in hypoxia, the previous papers (Blomqvist and Stenberg 1965; Ekblom et al. 1975) in which a detailed ECG analysis was performed did not reveal signs of myocardial ischemia. In addition, the studies from Operation Everest II (Groves et al. 1987; Reeves et al. 1987) and Operation Everest III (Boussuges et al. 2000) indicated that although SV_{max} decreased at altitude, the decrement was equal to the decrease in filling pressure, suggesting myocardial contractility was preserved. Reeves et al. (1987b) concluded that reduced ventricular filling resulting from tachycardia and/or a reduction in blood volume was one possible cause of the reduced SV. These mechanisms, however, cannot explain the findings of the present study as HR_{max} was not higher but lower in hypoxia than in the other trials and the time required for the decrease in plasma volume seen in chronic hypoxia was most probably too short. As the importance of the muscle pump on venous return is pivotal (Rowell 1993), one possible explanation for the decreased SV in hypoxia might be a decrement in venous return due to an impaired muscle pump, as suggested by decreased P_{max}. This explanation is, however, unsatisfactory because, although arterial blood flow increases with increasing load (Rådegran 1997), the muscle pump is not dependent on muscle force, but rather is a function of muscle tension overcoming venous pressure, which occurs even in unloaded exercise. Moreover, the finding that SV increases after pericardectomy in dogs, indicating that filling pressures are more than adequate to maximize SV during exercise, is an important one (Stray-Gundersen et al. 1986). Therefore, it is uncertain whether the decrement in P_{max} in hypoxia had any effect on venous return and cardiac filling pressures in the present study.

To maintain myocardial oxygen consumption in hypoxia, the decrease in C_aO_2 is compensated for at rest by a more complete extraction of O_2 from the coronary blood in comparison with breathing at sea level. During maximal exercise the compensatory mechanism is an increased coronary blood flow, indicating that normal heart has a "coronary flow reserve" for use in hypoxia (Kaijser et al. 1990; Grubbstrom et al. 1991). As the increase in flow is accompanied by an increase in coronary arterial pressure and stiffness (Templeton et al. 1972), the stiffening of the ventricle could shift the end-diastolic pressure (EDP) – end-diastolic volume (EDV) curve to the left (Janicki et al. 1996). This leftward shift would mean a smaller EDV with a similar EDP and thus a smaller SV due to a smaller myocardial fiber length at the end of a diastole. However, this theoretical mechanism does not occur even during chronic hypoxia since the relationship between SV and EDV is the same during exercise at altitude as at sea level (Reeves et al. 1987b). Another possible explanation for the decreased SV in hypoxia could be sought in ventricular

interdependence. Acute hypoxia raises pulmonary arterial pressure (Cudkowicz 1970) and right ventricular pressure that causes bulging of the interventricular septum towards the left ventricular cavity (Ritter et al. 1993). This and the decreased pulmonary capillary wedge pressure (PCWP) representing lowered left atrial pressure and thus an impaired preload, results in a lower driving pressure across the mitral valve and, consequently, a lowering of early diastolic filling and a greater contribution to atrial contraction (Ritter et al. 1993; Boussuges et al. 2000). Although the present study does not offer data on cardiac dimensions or filling pressures, an intriguing possibility is that endurance athletes would be more vulnerable to a reduction in filling pressure than non-athletes. The rationale for this lies in the fact that endurance athletes have greater ventricular diastolic chamber compliance and distensibility than non-athletes and thus operate on the steep portion of their Starling curve, i.e. a small reduction in filling pressure would induce a large reduction in SV (Levine et al. 1991a). Thus, increased right ventricular dilation from hypoxic pulmonary vasoconstriction and the evident reduction in PCWP may impede left ventricular filling with a constrained pericardium. Were this mechanism to explain the observed results, it would expected to do so only under severe workloads, as the role of the right heart is not so critical during submaximal efforts (Garcia et al. 1999). Whether this reasoning explains the reduction of $\dot{Q}_{max}$ in acute hypoxia or not remains an open question.

An increased afterload is not a strong candidate with which to explain the decreased SV in acute hypoxia, as peripheral vascular resistance (Vogel et al. 1974) and mean arterial pressure (Wolfel et al. 1991) during exercise are elevated during chronic hypoxia only, and not during acute hypoxia (Rowell and Blackmon 1987).

6.4 Oxygen uptake on-response

The effect of workload on $\dot{V}O_2$ response is critical. The results (IV) indicated that power output during the first three minutes was similar and fairly constant across the three tests during Phases 1 and 2 (fast component of $\dot{V}O_2$). Thereafter, during Phase 3 (slow component of $\dot{V}O_2$) there were differences in power output that presumably induced corresponding changes in $\dot{V}O_2$. It should be noted that the mean power was only 3.0% higher in hyperoxia and 3.9% lower in hypoxia when compared with normoxia. If we accept an average oxygen cost of 11 ml per watt, the difference in $\dot{V}O_2$ between hyperoxia and hypoxia would then be theoretically 275 ml $\cdot$ min^{-1}. The measured values clearly exceed this value, indicating that power output alone cannot be responsible for all the observed differences in $\dot{V}O_2$ response. Moreover, previous studies have indicated that the time constant of the fast component of $\dot{V}O_2$ response exhibits no significant change as work rate increases, i.e., although the overall oxygen cost increases with work intensity, the time constant is invariant (Barstow and

Molè 1991). Thus, it is argued that the $\dot{V}O_2$ kinetics analysis can be used to study $\dot{V}O_2$ response during maximal exercise while F_IO_2 is undergoing modification, especially during the $\dot{V}O_2$ fast component phase. However, the differences in power output during the $\dot{V}O_2$ slow component phase affected $\dot{V}O_2$ response; hence the conclusions must be interpreted cautiously.

6.4.1 $\dot{V}O_2$ fast component

The similarity of $\dot{V}O_2$ response during Phase 1 in all three tests (IV) suggests an equal rate of increase in $\dot{Q}$, which is expected to be responsible for the increase in $\dot{V}O_2$ in this phase (Barstow and Molè 1987; Casaburi et al. 1989; Cochrane and Hughson 1992). This finding is also supported by the results of Grassi et al. (1996) that delivery of O_2 to the working muscles does not limit $\dot{V}O_2$ kinetics during the first 10-15 s of exercise. The similar $\dot{V}O_2$ kinetics may, despite F_IO_2 also reflect similar muscle PCr kinetics even at the onset of severe exercise, a situation that has previously been indicated to exist at lower exercise intensities (Barstow et al. 1994). On the contrary, more recent evidence from human muscle indicates that manipulations of intracellular PO_2 by the breathing of high and low O_2 gas mixtures is sufficient to modify the muscle concentrations of PCr during constant-load exercise (Haseler et al. 1998). These data are entirely consistent with the idea that O_2 consumption is limited by the relative rates of adjustment in metabolic controllers and O_2 supply, thus supporting the O_2 delivery and metabolic control hypothesis (Tshakovsky and Hughson 1999; Hughson et al. 2001). According to this hypothesis, under nonsaturating conditions of PO_2, the redox potential and phosphorylation potential must be increased (i.e. greater number of NADH, ADP and P_I) to sustain the required rate of ATP production. This hypothesis would also explain the greater lactate concentration during submaximal running in hypoxia and the lower concentration in hyperoxia despite similar VO_2 (I).

As an increase in $\dot{V}O_2$ response during Phase 2 indicates augmented O_2 extraction and a continued increase in pulmonary blood flow (Whipp et al. 1982), the present decreased A_2 in hypoxia reflects either a lower cardiac output and/or a narrower $(a\text{-}v)O_2$ difference. Of these, the latter is more likely because of the decrease in SpO_2% in hypoxia, and heart rate was higher than in hyperoxia from the 30 s mark until 210 s. A faster MRT (0-63%) in hypoxia is contrary to what was hypothesized on the basis of previous studies (Engelen et al. 1996; MacDonald et al. 1997), where hyperoxia speeded up and hypoxia slowed down $\dot{V}O_2$ kinetics during submaximal exercise. As $\dot{V}O_2$ leveled off during Phase 3 in hypoxia in most subjects, but continued to increase in hyperoxia and normoxia, a shorter MRT in hypoxia is plausible. Another possible explanation for the unexpectedly short MRT in hypoxia might be the fact that the increase in pulmonary ventilation was fastest at the beginning of hypoxic exercise. Consequently, the O_2 cost of breathing may be higher in

hypoxia (Benoit et al. 1997), which in turn could increase the $\dot{V}O_2$ of the whole body at the onset of exercise and shorten the MRT. It should be noted that MRT is not held to be a totally accurate measurement because $\dot{V}O_2$ has first-order exponential kinetics only for work rates below the anaerobic threshold (Wasserman et al. 1994). However, MRT has previously been used in studies using work rates above this level (Sietsema et al. 1989; MacDonald et al. 1997).

In the previous studies (Engelen et al. 1996; MacDonald et al. 1997), the differences in $\dot{V}O_2$ kinetics are related to similar steady state $\dot{V}O_2$ values despite F_IO_2. In the present study, $\dot{V}O_{2max}$ values differed significantly, probably attenuating the differences in the $\dot{V}O_2$ kinetic parameters. However, F_IO_2 in particular is expected to have a major influence on the results, as Engelen et al. (1996) reported a significant slowing of τ during the $\dot{V}O_2$ fast component at F_IO_2 0.12 but not at F_IO_2 0.15. Thus, the F_IO_2 0.166 used was not severe enough to induce changes in the time constants of the $\dot{V}O_2$ fast component. It is also concluded that hyperoxia failed to accelerate $\dot{V}O_2$ kinetics because the fractional concentration of O_2 was relatively low. A similar result was obtained in a study where exertion of lower intensity was used (Linnarsson 1974). If a higher F_IO_2 had been used in hyperoxia, the driving pressure for O_2 diffusion would have increased more than O_2 saturation due to O_2 dissolved in plasma, and the possibilities for a faster $\dot{V}O_2$ response would have been more favorable. In addition, it seems that the elevated SpO_2% found in hyperoxia was temporarily compensated for by a lower heart rate. Therefore, O_2 delivery was not necessarily higher than in the other trials at the beginning of exercise. It seems that the experienced athletes tended to start cycling at a similar power output despite F_IO_2, a phenomenon called teleoanticipation (Ulmer 1996). It can only be speculated whether the subjects would have cycled at a higher power and heart rate in hyperoxia if they had been informed of the available extra oxygen.

6.4.2 $\dot{V}O_2$ slow component

It should be noted that significant differences were observed in power output from the fourth minute onwards (IV), presumably inducing corresponding changes in $\dot{V}O_2$. A significantly decreased τ_3 for the $\dot{V}O_2$ response was found in hypoxia. In its broadest sense, the time constant is considered a measure of the sensitivity of respiratory control (Barstow 1994). With this assumption in mind and paying attention to the differences in power output, it seems that the $\dot{V}O_2$ response during maximal work shows faster adjustment to the prevailing conditions with a decreasing F_IO_2 during the slow-component phase of the $\dot{V}O_2$ response. A similar early plateau in $\dot{V}O_{2peak}$ in hypoxia has previously been seen during a progressive exercise (Drinkwater et al. 1979).

The mechanisms of the $\dot{V}O_2$ slow component are not fully understood, but the recruitment of fast-twitch (FT) fibers is expected to have a major impact (Barstow et al. 1996; Borrani et al. 2001). Thus, it might be possible that FT fibers were recruited at the beginning of exercise in hypoxia to compensate for

impaired O_2 delivery. The possible early recruitment of FT fibers and their concomitant fatigue may be the cause of the power decrement in hypoxia. This would leave less reserve for an increase in $\dot{V}O_2$ during the later parts of the test and may be one reason for the small $\dot{V}O_2$ amplitude and short τ_3 in hypoxia. Blood lactate levels are also considered a potential explanation for the $\dot{V}O_2$ slow component. A_3 has previously been shown to correlate significantly with end-exercise blood lactate concentration (Barstow et al. 1996), but there was no such interaction in any F_IO_2 situation in the present study. This result is in agreement with the conclusion that lactate may be correlated with, but is not a cause of the $\dot{V}O_2$ slow component (Gaesser and Poole 1996).

6.5 Evaluation of methods

Arterial O_2 saturation was measured with pulse oximetry, which is a standard non-invasive method. It has been indicated to be useful in estimating S_aO_2% in healthy subjects as there is a strong correlation between the results of pulse oximetry and arterial blood gas analysis (Powers et al. 1989a; Webb et al. 1991; Martin et al. 1992; Mengelkoch et al. 1994). However, the method contains possibilities for errors and the bias has been shown to become more negative in proportion to desaturation in the case of the pulse oximeter used in study I (Severinghaus et al. 1989). The opposite is also possible as oximetry estimates of S_aO_2% can be significantly higher than blood gas measurements at all times throughout exercise and no significant decrease from rest is seen until maximal cycling (Rice et al. 1999). The present data indicate a rather stable pattern of SpO_2% in transition from rest to submaximal and/or maximal exercise. Therefore, pulse oximetry readings are expected to provide relatively good estimate of the effects of F_IO_2 on arterial O_2 saturation.

When CO_2 is measured with an infrared method in respiratory gases, as in the present work in studies I-III, CO_2 measurements are susceptible to underreading in the face of high O_2 concentrations because of collision broadening (Hornby et al. 1995). This would cause an overestimation of $\dot{V}O_2$. Mass spectrometers (IV, V) are not prone to similar errors due to the high O_2 concentration and they also are used as a reference for other analyzers (Hornby et al. 1995). As the changes in $\dot{V}O_{2max}$ were of a similar magnitude in all studies (I-V) when judged against power and F_IO_2, it is assumed that the methodological error in studies I-III was negligible and that the results indicate a real effect of F_IO_2 on aerobic metabolism.

Breath-by-breath gas analysis is also susceptible to errors, especially in gas delay (i.e. transport time plus mass spectrometer response time) relative to flow signal (Noguchi et al. 1982; Hughson et al. 1991). The delay was determined according to the instructions of the manufacturer and controlled for each measurement. The method for calculating the delay of the gas sample line was

based on the Fowler algorithm for calculating anatomical dead space (Fowler 1948; Heller et al. 1999). Because of the effect of gas density on the flow rate in the sampling catheter, delay time was on average 20 ms longer in hyperoxia and 20 ms shorter in hypoxia than in normoxia (~300 ms).

The most potent errors in cardiac output measurement include inadequate mixing of the gases between the rebreathing bag and the lungs, recirculation, the calculation of lung tissue volume and the effect of the measurement procedure on cardiac output (Sackner et al. 1975; Triebwasser et al. 1977). The calculation of the disappearance of acetylene was started as soon as helium reached a constant value, normally after two or three breaths. The effect of recirculation was avoided by excluding breaths where the disappearance of acetylene indicated smoothening of the curve. The effect of lung tissue was controlled by calculating $\dot{Q}$ both with fixed (mean of the subject's values) and with variable (separate value for each measurement) lung tissue values. Although there was no significant difference between these two procedures, the variable method was chosen as the lung tissue value has been shown to increase as a function of power output (Sackner et al. 1975). The rebreathing method requires fast and deep breathing, which by itself will artificially increase $\dot{Q}$ at rest and at light workloads. However, the results are almost identical with the direct Fick method, as exercise intensity increases (Liu et al. 1997).

7 CONCLUSIONS

1. In addition to severe exercise, arterial desaturation can be observed at submaximal workloads in trained athletes. In comparison with normoxia, desaturation is more severe in hypoxia and enhances dramatically as the intensity of exercise increases. In hyperoxia, SpO_2% remains closest to the resting level, but may achieve significantly lower levels during exercise than at rest. Inadequate hyperventilation is a plausible explanation for the initial drop in SpO_2% during hyperoxia and normoxia. In hypoxia, oxygen diffusion limitation due to lowered P_AO_2 is expected to be the most likely explanation for the very fast drop in SpO_2%. In all situations, the very rapid red blood cell transit time in the pulmonary capillary bed of the trained athlete, possessing a high cardiac output, is expected to be a major contributor to the arterial hypoxemia and desaturation that occur during heavy exercise. At submaximal workloads, ventilation and heart rate are elevated in hypoxia in comparison to normoxia and hyperoxia to maintain adequate $\dot{V}O_2$. Blood lactate concentration is elevated during submaximal exercise in hypoxia despite adequate $\dot{V}O_2$. Athletes also perceive hypoxic exercise as more severe than either normoxic or hyperoxic exercise.

2. Hypoxia impairs and hyperoxia improves $\dot{V}O_{2max}$. Impaired $\dot{V}O_{2max}$ is accompanied by a reduction in exercise performance in hypoxia. There is also a tendency towards higher exercise performance in hyperoxia than in normoxia, although the improvement is not always statistically significant. The change in $\dot{V}O_{2max}$ exceeds the change in exercise performance.

3. In athletes, maximal cardiac output may decrease in acute hypoxia in a manner very similar to that seen during chronic hypoxia. Different interpretations can be offered for this result. First, under these circumstances, not all of the reduction in $\dot{V}O_{2max}$ is explained by a narrowing of the (a-v)O_2 difference, but impairment in $\dot{Q}_{max}$ is also involved. Secondly, reduced $\dot{Q}_{max}$ in acute hypoxia may be beneficial, as factors such as pulmonary and peripheral O_2 diffusion were limiting $\dot{V}O_2$. In this case, a greater $\dot{Q}_{max}$ would further reduce arterial saturation and impair peripheral O_2 extraction. Thirdly, the results may indicate CNS limitation and the existence of a central governor, suggesting that the reduced $\dot{Q}_{max}$ and $\dot{V}O_{2max}$ in acute hypoxia might be the result rather than the cause of the reduced P_{max} and reduced recruitment of skeletal muscles.

4. The time constants (τ) of $\dot{V}O_2$ were not shorter in hyperoxia and longer in hypoxia at the onset of maximal cycling, although this has been indicated to be the case during submaximal exercise. The differences in the work rate (submaximal vs. maximal exercise) and in VO_{2max} between the trials as well as the fact that F_IO_2 was modified only slightly in hyperoxia and hypoxia might explain the discrepancy between the previous studies and the present results. In addition, the explanation for the results in hypoxia may include the need to recruit FT fibers and the need to ventilate more than in normoxia and hyperoxia, both of which would increase total $\dot{V}O_2$ at the beginning of exercise. In hyperoxia, elevated SpO_2% was compensated for by a lower heart rate at the beginning of exercise. Thus, O_2 delivery was not necessarily higher than in the other trials at the beginning of hyperoxic exercise. It remains speculative whether the subjects would have cycled at a higher heart rate and accelerated their $\dot{V}O_2$ response had they been informed of the available extra oxygen.

5. Maximum force and impulse are impaired less in hyperoxia and more in hypoxia when compared with normoxia during maximal ergometer rowing, whereas neither peak force production rate nor neuromuscular efficiency change along with F_IO_2. Moreover, hypoxia has a tendency to diminish sum-IEMG in comparison with normoxia whereas hyperoxia has no effect on it. The strong correlation between F_{max} and $\dot{V}O_2$ in normoxia supports the idea of causal relationship between oxygen consumption and exercise performance, whereas the lack of a significant correlation in the cases of hypoxia and hyperoxia may suggest a partial uncoupling of these processes and the existence of other limiting factors besides $\dot{V}O_2$. In hyperoxia, this limitation may have a neuromuscular nature and/or indicate teleoanticipation with regard to the “normal” maximum performance. In hypoxia, metabolic limitation and/or inhibitory feedback from exercising muscles and/or CNS limitation may be prominent.

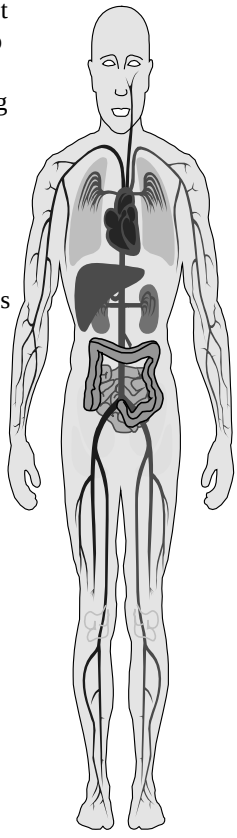
As a summary of the results of the previous as well as present studies the following simplified model is presented to indicate the possible limiting factors on exercise performance and $\dot{V}O_2$. The factors determining $\dot{V}O_{2max}$ are multiple and several combinations are possible. Factors such as type of exercise, subject's fitness, P_IO_2 and experience may modify the order of the limiting factors. The evidence that $\dot{V}O_{2max}$ is limited by the supply of O_2 is substantial. However, some previous results as well as the present ones provide a motivation for focusing research efforts on the operation of the CNS as a possible key determinant of cardiorespiratory responses and exercise performance during modification of F_IO_2. It is possible that the use of magnetic imaging techniques and near-infrared spectroscopy might uncover the possible existence, and mode of action of the proposed central governor.

"Central governor hypothesis"

Originally, the hypothesis was that the heart is able, to some extent, to regulate its own output, in accordance with S_aO_2%. According to this hypothesis, there is a "governor" either in the heart muscle itself or in the central nervous system, maintaining a reasonably high S_aO_2%.

A recent addition to the hypothesis is that the variable primary controlled during exercise is the recruitment of skeletal muscles, specifically to prevent myocardial ischemia. Thus, $\dot{V}O_{2max}$ is determined by the recruitment of muscles.

The results of the present study indicated reduced $\dot{Q}_{max}$ and sum-IEMG in acute hypoxia, together with a strong positive correlation between $\dot{Q}_{max}$ and peak work rate. These findings suggest that the central nervous system is among those factors that limit exercise performance and $\dot{V}O_{2max}$ in acute hypoxia.



"Classical hypothesis"

When a large muscle mass (2 legs or more) is working, both the circulatory and oxidative capacity of the muscle exceeds what the heart can supply. Thus, the pumping capacity of the heart limits O_2 delivery and $\dot{V}O_{2max}$.

Lung functions may limit $\dot{V}O_{2max}$ and exercise performance in some athletes already at sea level. In hypoxia, the role of the lungs in limiting $\dot{V}O_{2max}$ becomes greater.

The present study indicates, that maximal cardiac output may be reduced in acute hypoxia in trained athletes in a manner similar to that seen in chronic hypoxia. Both HR_{max} and SV_{max} have a tendency to decrease in acute hypoxia and increase in hyperoxia. Changes in the operation of the autonomic nervous system might explain findings concerning HR_{max}, whereas the changes in the function of the myocardium during diastole might offer an explanation for the modifications in SV_{max}.

TIIVISTELMÄ

Tässä väitöskirjassa tutkittiin kestävyyssuorituskyvyn ja hapenkulutuksen ($\dot{V}O_2$) välistä suhdetta. Sisäänhengitysilman hapen osuutta (F_IO_2) muuntelemalla vaikutettiin valtimoveren happisaturaatioon (SpO_2%), jolla on keskeinen vaikutus hapen jakeluun ja siten maksimaaliseen hapenottokykyyn ($\dot{V}O_{2max}$). Hengitys- ja verenkiertoelimistön vasteita sekä neuromuskulaarisia toimintoja tarkastelemalla pyrittiin mallintamaan niitä mekanismeja, jotka säätelevät ja rajoittavat suorituskykyä normaali-, niukka- ja runsashappisessa ympäristössä.

Tämän tutkimuksen koehenkilöjoukon muodostivat yhteensä 29 vapaaehtoista kansallisen / kansainvälisen tason kestävyysurheilijaa (24 miestä ja 5 naista), jotka edustivat seuraavia lajeja: soutu, hiihto, pyöräily, triathlon ja suunnistus. Jokainen koehenkilö kuormitettiin normobarisessa hyperoksiassa (F_IO_2 0.293 – 0.622), normoksiassa (F_IO_2 0.209) ja hypoksiassa (F_IO_2 0.150 – 0.166) randomisoidussa järjestyksessä. Käytetyt hypoksiset F_IO_2 tasot vastasivat 1900 – 2700 m korkeutta merenpinnasta.

Tutkimuksen päätulokset osoittivat että:

1. Arteriaalista desaturaatiota voi esiintyä urheilijoilla rasittavan kuormituksen lisäksi myös kevyessä kuormituksessa. Hypoksiassa desaturaatio on suurempaa kuin normoksiassa ja se lisääntyy merkittävästi suoritustehon noustessa. Hyperoksiassa SpO_2% säilyy lähimpänä lepotasoa. Riittämätön hyperventilaatio on todennäköisin syy SpO_2%:n laskulle kevyessä rasituksessa normoksiassa ja hyperoksiassa. Hypoksiassa alveoli-ilman happiosapaineen lasku aiheuttaa hapen diffuusiorajoituksen. Kovassa rasituksessa keskeinen desaturaatiota aiheuttava tekijä on punasolujen keuhkokapillareissa viettämän ajan lyheneminen merkittävästi urheilijoiden hyvin suuren sydämen minuuttitilavuuden johdosta. Tällöin hemoglobiinin lepotasoa vastaavan happisaturaation saavuttamiseen käytettävissä oleva aika on riittämätön.

2. Hypoksia heikentää ja hyperoksia parantaa $\dot{V}O_{2max}$:a. Hypoksiassa heikentyneeseen $\dot{V}O_{2max}$:iin liittyy heikentynyt suorituskyky. Hyperoksiassa havaittiin tendenssi suorituskyvyn paranemiseen normoksiaan verrattuna, mutta muutos ei ole aina tilastollisesti merkitsevä. $\dot{V}O_{2max}$:n muutos ylittää suorituskyvyssä havaitun muutoksen.

3. Urheilijoilla voi sydämen maksimaalinen minuuttitilavuus ($\dot{Q}_{max}$) laskea akuutissa hypoksiassa tavalla, joka on aikaisemmin havaittu vain kroonisessa hypoksiassa. Havainto mahdollistaa erilaisia tulkintoja: a) Kaikki $\dot{V}O_{2max}$:n lasku akuutissa hypoksiassa ei johdu valtimo-laskimo

happieron pienenemisestä, vaan $\dot{Q}_{max}$:n lasku vaikuttaa myös; b) $\dot{Q}_{max}$:n lasku voi olla edullinen ilmiö, koska suurempi $\dot{Q}$ lisäisi entisestään arteriaalista desaturaatiota ja heikentäisi myös hapen perifeeristä ekstraktiota; c) Havainnon voidaan tulkita tukevan keskushermoston rajoittuneisuutta siten, että $\dot{Q}_{max}$:n ja $\dot{V}O_{2max}$:n lasku olisivat seurausta vähentyneestä luurankolihasten rekrytoinnista.

4. Hapenkulutuksen nopean komponentin aikavakiot (τ) eivät eroa hyperoksian, normoksian ja hypoksian välillä maksimaalisessa kuormituksessa tässä tutkimuksessa käytetyillä F_IO_2-pitoisuuksilla. Aika 63% muutoksen saavuttamiseen koko $\dot{V}O_{2max}$ vasteesta on kuitenkin hypoksiassa lyhyempi kuin hyperoksiassa ja normoksiassa. Erot $\dot{V}O_{2max}$:ssa ja työtehossa $\dot{V}O_2$:n hitaan komponentin alueella selittänevät sitä miksi hyperoksia ei nopeuttanut ja hypoksia hidastanut $\dot{V}O_2$ vasteita maksimityössä, vaikka vasteiden on aikaisemmin havaittu käyttäytyvän siten submaksimaalisessa kuormituksessa.

5. Maksimaalisessa soutuergometrikuormituksessa säilyivät vedon voima ja impulssi hyperoksiassa korkeampana normoksiaan verrattuna, mutta heikkenivät enemmän hypoksiassa. Seitsemän lihaksen integroidun elektromyografiasignaalin summasignaalilla (summa-IEMG) oli taipumus olla hypoksiassa alempi kuin normoksiassa ja hyperoksiassa. Hypoksiassa summa-IEMG:n pienuuden todennäköisin syy on keskushermoston rajoittuneisuus, mahdollisesti suojamekanismi. Hyperoksian ja normoksian summa-IEMG:n samankaltaisuuden luontevin selitys on koehenkilöiden tottumattomuus työskennellä runsashappisessa ympäristössä ja siitä johtuva kykenemättömyys hyödyntää koko kapasiteettiaan uudessa tilanteessa.

Tämä tutkimus osoittaa, että suorituskyvyn ja hapenkulutuksen yhteydet ovat hyvin monitahoiset ja useat tekijät kuten suoritustapa ja –teho, sisäänhengitysilman happiosapaine ja henkilön suorituskyky vaikuttavat rajoittavien tekijöiden painotuksiin ja keskinäiseen järjestykseen. Tämä tutkimus osoittaa myöskin, että osa sellaisista fysiologisista muutoksista, joiden on aiemmin ajateltu tapahtuvan vain kroonisessa hypoksiassa, voi ilmetä myös akuutissa hypoksiassa, ainakin hyväkuntoisilla kestävyysurheilijoilla. Siten raja akuutin ja kroonisen hypoksian välillä suoritus- ja hapenottokykyyn liittyvien muutosten osalta ei ole niin jyrkkärajainen kuin aikaisemmin on ajateltu.

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