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CLINICAL INVESTIGATION

Effects of Acute Hypoxia on Body Substrate Utilisation During Progressively Increasing Work Rate Exercise Tests

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Abstract: Respiratory quotient (RQ) was used to assess the effectiveness of exercise interventions in shifting substrate utilisation. The body's RQ can be estimated non-invasively from the ratio of CO₂ production to O₂ consumption. In the present study, we examined the effects of acute hypoxia on the substrate utilisation of the body and its non-invasive estimation from ventilatory and pulmonary gas exchange variables during exercise. Eight male subjects performed two progressively increasing work rate exercise tests (15 W/min) until the limit of tolerance: in one test they were breathing room air (normoxia) and in the other 12% O₂ (hypoxia). Ventilatory and pulmonary gas exchange variables were measured using a turbine volume transducer and mass spectrometry and estimated breath-by-breath. During the warm-up period, RQ was found to be 0.79 ± 0.009 for normoxia, reflecting both carbohydrate and fat utilisation, and 0.94 ± 0.01 for hypoxia, reflecting predominant carbohydrate utilisation. At the metabolic transition point, RQ increased to 0.97 ± 0.04 in normoxia, reflecting predominantly carbohydrate utilisation. However, in the hypoxia study, RQ increased to 1.06 ± 0.01 , reflecting not only predominant carbohydrate utilisation but also extra CO₂ production and elimination. Consequently, substrate utilisation derives proportionally more from carbohydrate than from fat during exercise as the work rate increases. However, under conditions of acute hypoxia RQ estimation may not provide an accurate estimate of substrate utilisation.

Key Words: Exercise tests, respiratory quotient, substrate utilisation

Introduction

Fat and carbohydrate are the principal substrates that fuel aerobic ATP synthesis in human skeletal muscle. During exercise, the relative utilisation of fat and carbohydrate can vary enormously and depends strongly on exercise intensity. It is important to have an understanding of the relative energy sources needed for the types, intensities, and volumes of exercise.

Fatty acid is the major substrate for non-exercising skeletal muscle and the body at rest (1). During the steady state of moderate intensity constant load exercise (i.e. blood lactate concentration does not increase) fatty acid provides the majority of the substrate oxidised by skeletal muscle (2). In contrast, during the non-steady state of heavy exercise (i.e. blood lactate concentration increases), whole-body fatty acid oxidation rates decline

and muscle glycogen becomes the main fuel source utilised (2,3).

The substrate utilisation during the steady state of moderate intensity exercise can be estimated non-invasively from the relationships between the ratio of CO₂ output to O₂ uptake as measured at the mouth (respiratory exchange ratio, R), which accurately reflects the ratio of CO₂ production to O₂ consumption of the exercising muscle (respiratory quotients, RQ) (4). However, during the non-steady state of heavy exercise, R differs from RQ due to anaerobic metabolism and lactate production (4).

Substrate utilisation in response to progressively increasing work rate exercise, which contains aerobic, aerobic-anaerobic and anaerobic metabolisms, and its non-invasive determination become more specific in

contrast to the constant load exercise test (5). The ability to supply O₂, which depends on the interaction of the respiratory and cardiovascular systems, is strongly associated with substrate utilisation.

In the present study, we examined the influence of reduced inspired O₂ concentration on body substrate utilisation and its non-invasive determination from the pulmonary gas exchange variables during a progressively increasing work rate exercise test.

Materials and Methods

Eight male subjects (mean ± SE, age 22.3 ± 1.5 y, weight 75.6 ± 3.7 kg, height 179.5 ± 2.3 cm, body mass index 23.41 ± 0.8 kg/m²) volunteered for this study. They were not well trained but were healthy and active. Each subject was informed of the purpose, possible risks and benefits of the study prior to giving his written consent to participate. The protocol was approved by the local Ethics Committee.

The subjects were familiarised with the testing procedures and laboratory equipment before the experimental study. They took part in two progressively increasing exercise tests to the limit of tolerance with an electromagnetically braked cycle ergometer (Lode, Excalibur) on different days: in one they were breathing room air (normoxia) and in the other 12% O₂ (hypoxia). The subjects were not told which experiment (room air or 12% O₂) they were to participate in. The subjects were informed that they could stop the test whenever they felt the need to do so.

The test protocol started with a 20 W cycling at 60 rpm as a warm-up period. Then the work rate was increased by 15 W/min by a work rate controller and continued to the subjects' limit of tolerance as described by Whipp et al. (6).

During exercise, the subjects breathed through a mouthpiece attached to a low resistance (1.5 cmH₂O at 3 l/s) and low dead space (less than 90 ml) turbine volume transducer (Alpha Technology) to measure inspired and expired volumes. During the study, a turbine flowmeter was connected to a two-way breathing valve (Hans Rudolph). A 50 l meteorological balloon was used to store the humidified hypoxic gas mixture (12% O₂). The balloon was refilled from the gas tank as necessary during the study.

Respired air gas concentrations were measured by a quadruple mass spectrometer (CaSE, QP9000) for continuous monitoring of O₂, CO₂ and N₂. The calibration and validation of the system were performed prior to each study (7). Ventilatory and pulmonary gas exchange variables were estimated using a breath-by-breath Beaver algorithm (8). Heart rate was derived beat by beat from the R-R interval of a standard six-lead ECG (Quinton 5000) and monitored continuously throughout the all tests. The subjects' arterial O₂ saturation was carefully monitored by pulse oximetry (Ohmeda Biox 3740) throughout the hypoxia study. Arterial O₂ saturation was not allowed to fall below 70%.

The substrate utilisation of exercising muscles (metabolic RQ) was determined non-invasively from the ratio of CO₂ production to O₂ consumption ($\Delta VCO_2/\Delta VO_2$) during the warm-up period, aerobic phase and anaerobic phase of the exercise. The respiratory exchange ratio (R) was estimated from the CO₂ output to O₂ uptake ratio (VCO_2/VO_2).

During the incremental exercise test, aerobic to anaerobic transition (also called as an anaerobic threshold) was estimated non-invasively using the V-slope method (9), which is based upon the increase in CO₂ output due to the excess CO₂ production from bicarbonate buffering of metabolic (chiefly lactic) acidosis compared to the O₂ uptake during the incremental exercise test (Figure 1) (10). The V-slope method depends on metabolism and it was not affected by ventilatory response (4,9,11).

A paired-t test was used to evaluate the statistical significance of differences between values. Differences were considered significant at P < 0.05.

Results

Hypoxia resulted in marked reductions in peak exercise performance, O₂ uptake at peak exercise (VO₂ peak) and O₂ uptake at the metabolic transition point compared with normoxia: 208 ± 9 W, 2.63 ± 0.1 l/min and 1.65 ± 0.09 l/min (hypoxia) and 261 ± 12 W, 3.22 ± 0.2 l/min and 1.84 ± 0.1 l/min (normoxia), respectively.

The metabolic transition point, estimated from the plot of CO₂ output as a function of O₂ uptake during progressively increasing incremental exercise test, is illustrated in Figure 1. The aerobic to anaerobic metabolic

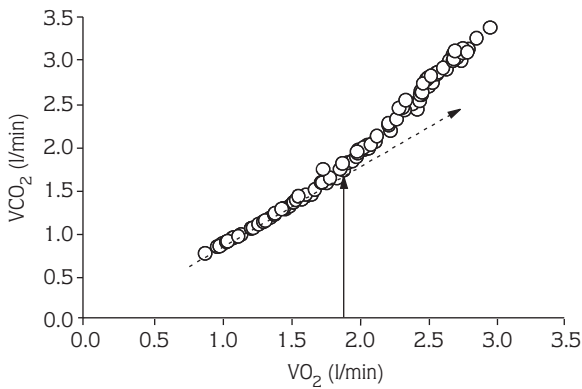


Figure 1. Representative responses in a typical subject of CO₂ output (VCO₂) as a function of O₂ uptake (VO₂) for a progressively increasing work rate exercise (15 W/min) test. The vertical solid line reflects the metabolic transition point.

transition occurred at $57.8 \pm 2.2\%$ of the VO₂ peak (normoxia) and $63.1 \pm 0.8\%$ of the VO₂ peak (hypoxia).

As can be seen in Figure 2, a reduced inspired O₂ concentration resulted in a marked increase in RQ in all subjects during the aerobic part of the exercise test. The relationships between R and RQ (mean \pm SE) in response to the progressively increasing work rate exercise tests with and without hypoxia are shown in Figure 3. During the warm-up period, R and RQ were 0.79 ± 0.009 and 0.79 ± 0.009 for normoxia, 0.94 ± 0.01 0.94 ± 0.01 for hypoxia, respectively (Table). When the work rate increased, RQ increased more rapidly relative to R. At the metabolic transition point, R and RQ increased to 0.87 ± 0.01 and 0.97 ± 0.04 in normoxia and 1.01 ± 0.01 and

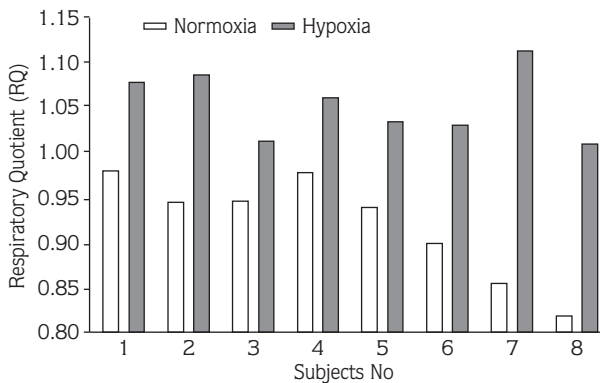


Figure 2. Individual values for the respiratory quotient (RQ) during aerobic phase of the progressively increasing work rate exercise tests with breathing room air (normoxia) and breathing 12% O₂ (hypoxia).

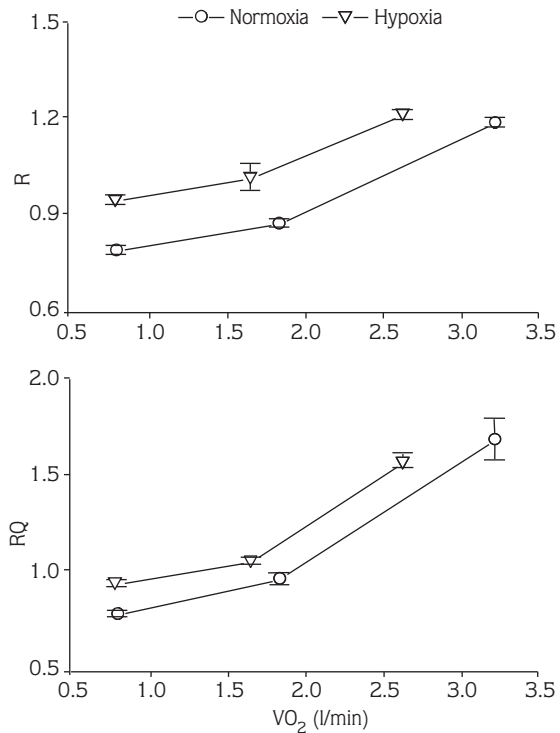


Figure 3. Mean (\pm SE) values of respiratory exchange ratio (R) and respiratory quotient (RQ) as a function of O₂ uptake (VO₂) response to the progressively increasing work rate exercise (15 W/min): during warm-up period, at the anaerobic threshold and at the end of the ramp phase for the normoxia study (o) and for the hypoxia study (∇).

1.06 ± 0.01 in hypoxia, respectively (Table). During the maximal exercise intensity, R and RQ were 1.19 ± 0.02 and 1.69 ± 0.1 in normoxia and 1.21 ± 0.01 and 1.57 ± 0.04 in hypoxia (Table).

Discussion

The present study examined the effects of hypoxia on the substrate utilisation rate and the determination of substrate utilisation from ventilatory and pulmonary gas exchange variables during a progressively increasing exercise test. RQ was used to assess the effectiveness of exercise interventions in changing substrate utilisation. The substrate utilisation of the exercising muscle can be affected by the fitness of the subjects, and trained subjects can utilise more fatty acids than unfit ones for a given work rate (12). Furthermore, it has previously been shown that substrate availability is also an important factor in the metabolism and exercising performance (13,14). Increased glycogen stores or slowed glycogen

Table. The respiratory exchange ratio (R) and respiratory quotient (RQ) in response to the progressively increasing work rate exercise tests with subjects breathing room air (N) and breathing 12% O₂ (H): during warm-up period, at the metabolic transition point (MTP) and at the maximal exercise performance.

		Warm-up	MTP	Maximal
R	N	0.79 ± 0.009	0.87 ± 0.01	1.19 ± 0.02
	H	0.94 ± 0.01*	1.01 ± 0.01*	1.21 ± 0.01
RQ	N	0.79 ± 0.009	0.97 ± 0.04	1.69 ± 0.1
	H	0.94 ± 0.01*	1.06 ± 0.01*	1.57 ± 0.04*

* significantly different from the normoxia study.

utilisation has been shown to provide clinical benefits to patients with heart disease by improving their exercise capacity (15).

Muscle energy demand throughout exercise at a work rate below the metabolic transition point is supplied from the oxidative metabolism. In this phase of the exercise, CO₂ comes from oxidative metabolism which consumes O₂ for energy production (4,5,14). However, with a work rate above the metabolic transition point, CO₂ output increases due to lactic acidosis (4,5,16). RQ is approximately 0.70 and is based exclusively on the metabolism of fat in resting conditions. An exclusive carbohydrate metabolism would yield an RQ of 1.00. However, during the aerobic phase of the exercise test, R does not accurately reflect muscle substrate utilisation due to the gas stores of the body, i.e. it is systematically lower than RQ (17). It has been shown that during the initial phase of exercise, metabolically produced CO₂ goes into the body CO₂ stores (4,5,16). Thus, the CO₂ output to O₂ uptake ratio measured at the mouth (i.e. R) becomes lower than the metabolic CO₂ production to O₂ uptake ratio measured at the tissue (i.e. RQ) (17).

During the warm-up period, RQ was 0.79 ± 0.09, suggesting mixed (i.e. both carbohydrate and free fatty acid) substrate utilisation. In agreement with previous studies, our results obtained in the normoxia study confirmed that carbohydrate is the major fuel at a work rate below the metabolic transition point, which was found to be slightly less than 1.00 (0.97 ± 0.04) (4,5,17). Substrate utilisation for the total body derives proportionally more from carbohydrate than from lipid stores during exercise as the work rate increases (4,17). However, during a constant load exercise test, fat

oxidation increases when the work rate increases from low to moderate intensity (18).

During exercise, the transition from aerobic to anaerobic metabolism occurred at 58% (normoxia) and 63% (hypoxia) of VO₂ peak, which is considered within the normal range for untrained subjects (19). It has been reported that muscle and blood lactate does not significantly increase at all levels of exercise and it increases after the work level of 60% of the subject's VO₂ peak is reached (20,21).

Above the metabolic transition point, RQ increased systematically above 1.00, reflecting CO₂ production from aerobic and also anaerobic metabolisms (4,5). This increase in CO₂ production results in a non-linear increase in CO₂ output compared to O₂ uptake. Substrate utilisation above the metabolic transition point could not be estimated validly due to excess CO₂ production from the anaerobic metabolism and hyperventilation.

It has previously been demonstrated that during exercise an increase in blood lactate concentration inhibits lipolysis and thus forces obligatory carbohydrate utilisation (22). Carbohydrate may be considered the preferred fuel for work rates above the region of anaerobic threshold, which is more efficient with respect to O₂ utilisation (4). It has been suggested that a greater dependence on glucose rather than the fatty acid metabolism would assist in maintaining homeostasis by optimising the energy yield per unit of O₂ (23). That is, compared with fatty acid oxidation, carbohydrate oxidation generates more ATP per molecule of O₂ consumed (4). Carbohydrate can also be metabolised non-oxidatively to yield ATP and lactate.

The contribution of muscle fibres type with increasing exercise intensity could also have important effects on substrate utilisation (24). During moderate and greater exercise intensities, increased recruitment of fast-twitch muscle fibres and sympathetic nervous system activity decrease the mitochondrial fatty acid uptake and increase muscle glycogenolysis and glycolysis (1).

In the hypoxic state, increases in RQ during the warm-up period of the exercise would support a shift of metabolism from both free fatty acid and carbohydrate utilisation to predominantly carbohydrate utilisation. The RQ value at the aerobic region of the exercise test involving breathing 12% O₂ was systematically greater than 1.00 (Figure 2). Reduced O₂ supply to exercising

muscle affects the metabolic paths and also maximal muscle performance (25,26). This effect naturally is likely to be more prominent during hypoxic exercise as the catecholamines are known to stimulate glycolysis through the activation of phosphorylase, which is the rate-limiting enzyme for glycogen breakdown (27,28). An increase in the arterial catecholamine level has been reported during exercise with hypoxic breathing (28).

It is also important to mention that increased carotid chemosensitivity could affect ventilatory and hence CO₂ output response as a function of O₂ uptake even in the aerobic region of the exercise test. There is a general agreement that carotid bodies characterise the primary site of hypoxic ventilatory responsiveness in humans (29,30).

On the basis of the present study, it is suggested that during exercise with reduced O₂ supply, non-invasive methods based on CO₂ production to O₂ consumption ratio (i.e. metabolic RQ) cannot validly assess body substrate utilisation due to the excess CO₂ production rate and also its elimination.

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