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Skeletal muscle metabolism during exercise and recovery in patients with respiratory failure

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Abstract

***Background*—Patients with respiratory failure have early fatiguability which may be due to limitation of oxygen supply for oxidative (mitochondrial) ATP synthesis. Skeletal muscle in exercise and recovery was studied to examine the effect of chronic hypoxia on mitochondrial activity in vivo.**

***Methods*—The skeletal muscle of five patients with respiratory failure (Pa_{O_2} <9 kPa) was studied by phosphorus-31 magnetic resonance spectroscopy and compared with 10 age and sex matched controls. Patients lay in a 1·9 Tesla superconducting magnet with the gastrocnemius muscle overlying a six cm surface coil. Spectra were acquired at rest, during plantar flexion exercise, and during recovery from exercise. Relative concentrations of inorganic phosphate (Pi), phosphocreatine (PCr) and ATP were measured from peak areas, and pH and free ADP concentration were calculated. For the start of exercise, the rates of PCr depletion and estimated lactic acid production were calculated. For the post exercise recovery period, the initial rate of PCr recovery (a quantitative measure of mitochondrial ATP synthesis), the apparent Vmax for mitochondrial ATP synthesis (calculated from initial PCr resynthesis and the end exercise ADP concentration which drives this process), and the recovery half times of PCr, Pi, and ADP (also measures of mitochondrial function) were determined.**

***Results*—Considerably greater and faster PCr depletion and intracellular acidosis were found during exercise. This is consistent with limitation of oxygen supply to the muscle and might explain the early fatiguability of these patients. There was no abnormality in recovery from exercise, however, suggesting that mitochondria function normally after exercise.**

***Conclusions*—These results are consistent with one or more of the following: (a) decreased level of activity of these patients; (b) changes in the fibre type of the muscle; (c) decreased oxygen supply to the muscle during exercise but not during recovery. They are not consistent with an intrinsic defect of mitochondrial ATP synthesis in skeletal muscle in respiratory failure.**

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Patients with chronic obstructive airways disease (COAD) have limited exercise tolerance which is attributed mainly to breathlessness. The perceived symptom of breathlessness is thought to be due to afferent information from respiratory muscles as well as a centrally perceived sense of effort.[1] Incoordination between contraction of respiratory muscles and airflow, as well as early fatiguability of the muscles, may also contribute.[2–4]

In addition to breathlessness, intrinsic abnormalities of skeletal muscle could contribute to the limited exercise tolerance. Abnormalities of mitochondrial function in skeletal muscle have been shown in heart failure,[5] and there have been recent suggestions that there may be mitochondrial dysfunction in the calf muscles of patients with COAD.[6] Breathlessness and respiratory rate during heavy exercise are also correlated with the degree of anaerobic metabolism of working muscles.[7] Decreased oxidative capacity may contribute to early fatiguability of limbs and respiratory muscles.

Previous studies have shown that magnetic resonance spectroscopy (MRS) with phosphorus-31 (^{31}P-MRS) can be used to determine abnormalities of oxidative metabolism in the skeletal muscles of patients with mitochondrial myopathies.[8] We studied the skeletal muscle of five patients with chronic hypoxia and mild hypercapnia due to COAD and compared their bioenergetics with those of control subjects. Significantly altered metabolism was seen in respiratory failure during exercise without evidence of a significant defect in mitochondrial oxidation during recovery from exercise.

Methods

SUBJECTS

Five patients (two women, three men) of mean age 63 (range 61–68) years with COAD were recruited from the respiratory department of a local hospital. All were current or past smokers with spirometric evidence of severe airflow obstruction (table 1). Breathing room air, all were hypoxaemic (Pa_{O_2} tensions

Table 1 Mean (SD) results of spirometry and blood tests of patients.

	Results	*Reference data*
Spirometry		
FEV_1 (l/min)	0·75 (0·28)	2·69–4·73
FVC (l)	1·76 (0·39)	3·39–5·83
FEV_1/FVC	44 (17)	64–92
Blood tests		
Hb (g/dl)	13·4 (1·1)	13·5–18·0
Pa_{O_2} (kPa)	7·6 (1·2)	10·0–12·2
Pa_{CO_2} (kPa)	6·7 (0·6)	4·6–6·0
Arterial pH	7·40 (0·02)	7·35–7·45

less than 9 kPa, table 1). All complained of dyspnoea and had exercise tolerances between 20 and 500 m. All had palpable foot pulses and none had symptomatic peripheral vascular disease. Three patients were taking corticosteroids, of whom one was on diuretics, one was on digoxin, and one was on both diuretics and digoxin. The other two patients were not taking any medication.

Spirometry and haemoglobin measurements were performed on each patient and brachial arterial blood was collected for estimation of arterial blood gases (table 1). The results of ^{31}P-MRS were compared with those of untrained healthy controls (five women and five men) of mean age 63 (range 54–76) years. All subjects gave informed consent and the study had the approval of the local ethical committee.

STUDY DESIGN

Subjects were positioned supine in a 1·9 Tesla superconducting magnet with head and shoulders supported at 20–30° to the horizontal and with the right calf muscle overlying a 6 cm diameter surface coil tuned to 32·7 MHz. Pulse length was 80 μs (approximately equal to a 90° pulse at coil centre). Interpulse delay was two seconds.

The exercise protocol has been described before.[9] Two 64 scan (two minute) spectra were collected from the muscle at rest, then 16 scan (32 second) spectra were collected during exercise, which consisted of 30 plantar flexions of the right foot per minute, lifting a weight a distance of 7 cm. Time was divided equally between exercise and relaxation. No eccentric exercise was performed. The weight used was 10% of the lean body mass (assessed from skin fold thickness using standard biometric tables) for 8·8 minutes, increased to 16% of the lean body mass for a further 3·8 minutes if necessary. Subjects were asked to stop exercising when the concentration of phosphocreatine (PCr) had fallen to between 30% and 40% of resting levels. Below this level ATP becomes depleted[10] which results in fatigue and, more importantly, causes recovery abnormalities irrespective of the pathology being studied. To focus upon metabolic abnormalities specific to respiratory failure, patients were asked to stop exercising before this critical level of PCr was reached. All control subjects exercised for 12·5 minutes without the PCr falling to this critical level. In contrast, no patient exercised long enough for the weight to be increased above 10% of the lean body mass. Recovery was studied by collecting the following spectra sequentially: four of eight scans, four of 16 scans, three of 32 scans, and two of 64 scans (13 minutes in all). Spectra were quantified by manual triangulation and corrected for saturation and line shape to determine the concentrations of phosphocreatine (PCr) and inorganic phosphate (Pi) relative to that of ATP.

During exercise, PCr concentration [PCr] is more conveniently expressed as PCr/(PCr + Pi), which corrects for any signal loss due to leg movement with respect to the coil. Intracellular pH was calculated from the chemical shift of Pi relative to PCr, and free ADP concentration was calculated from the creatine kinase equilibrium assuming ATP concentration = 8·2 mmol/l cell water and total creatine = 42·5 mmol/l cell water.[8]

The half times of recovery of PCr, Pi, and ADP, which are sensitive to abnormalities of mitochondrial metabolism,[8] were calculated by graphical interpolation. To analyse mitochondrial function in more detail we also calculated the initial rate of PCr resynthesis (d[PCr]/dt) by linear regression using values of [PCr] at the end of exercise and over the first two data points in recovery (t = 0, 0·13, and 0·4 minutes). Any decrease in pH and PCr during the acquisition of the last exercise spectrum was estimated by linear extrapolation from the midpoints of the last two exercise spectra to the end of the last exercise spectrum. Initial d[PCr]/dt is a direct estimate of the rate of mitochondrial ATP synthesis,[11] which is driven by cytosolic ADP concentration according to a hyperbolic relationship $V = Vmax / (1 + Km/[ADP])$, where Km is the ADP concentration at which the oxidation rate is half maximal. To quantify abnormalities of mitochondrial function, this relationship was used to calculate the apparent maximum rate of oxidative ATP synthesis as $Vmax = (d[PCr]/dt)(1 + Km/[ADP])$. For this calculation Km was assumed to be normal (nominally 30 μmol/l).

To assess ATP production during exercise we calculated the initial rates of proton production and of PCr depletion ($-d[PCr]/dt$) between the resting state and the first data point in exercise (t = 0·5 minutes, midpoint). The initial rate of PCr depletion represents the shortfall between ATP demand and ATP production by oxidation and anaerobic glycolysis. The rate of proton production was calculated as the sum of two components: the rate of proton consumption by net hydrolysis of PCr, given by $-(d[PCr]/dt)/[1 + 10^{(pH-6.75)}]$ where 6·75 is the pK of phosphoric acid; and the rate at which protons are taken up by cellular buffers, given by $-\beta(dpH/dt)$ where β is the cytosolic buffer capacity, taken as 30 slykes.[12] This quantity represents the rate of lactic acid synthesis less the rate of proton efflux. Proton efflux is pH dependent,[12 13] but as resting pH changed little over this interval, it was assumed that the change in proton efflux was negligible. Calculated metabolic proton production was taken, therefore, as a

Table 2 Mean (SD) results of ^{31}P-MRS studies

	Controls	Patients	p
Resting muscle:			
pH	7·00 (0·02)	7·00 (0·02)	NS
Pi/ATP	0·31 (0·07)	0·33 (0·06)	NS
PCr/ATP	2·89 (0·13)	2·99 (0·33)	NS
[ADP] (μmol/l)	9 (3)	8 (6)	NS
Exercise:			
Exercise duration (min)	12·5 (0·0)	2·5 (0·4)	<0·01
Initial exercise			
PCr depletion (mmol/l/min)	10 (7)	32 (8)	<0·01
Proton production (mmol/l/min)	2 (3)	9 (4)	<0·01
End 2·5 min exercise			
ADP (μmol/l)	38 (18)	56 (36)	NS
PCr/(PCr + Pi)	0·61 (0·14)	0·34 (0·04)	<0·01
pH	6·99 (0·08)	6·68 (0·23)	<0·01
End exercise			
ADP (μmol/l)	67 (24)	56 (36)	NS
PCr/(PCr + Pi)	0·53 (0·14)	0·34 (0·04)	<0·05
pH	6·93 (0·11)	6·68 (0·23)	0·05
Recovery:			
Recovery half time (s)			
PCr	34 (14)	42 (14)	NS
Pi	38 (21)	42 (35)	NS
ADP	16 (5)	19 (6)	NS
Initial PCr recovery (mmol/l/min)	16 (5)	21 (10)	NS
Apparent Vmax (mmol/l/min)	24 (6)	34 (9)	0·05
Initial proton efflux (mmol/l/min)	2·4 (3·4)	2·8 (1·3)	NS

Differences assessed by Mann–Whitney U test.

measure of lactic acid production during this period.

Results

The results of ^{31}P-MRS studies are shown in table 2. There was no significant abnormality in resting muscle bioenergetics. Exercise duration was considerably reduced, and both pH and PCr/(PCr + Pi) at the end of exercise were significantly lower than in the controls, although ADP concentration was normal. The initial rates of PCr depletion and proton—that is, lactic acid—production were considerably increased. There was no significant difference, however, in the recovery half times of PCr, Pi, and ADP, nor in the initial rate of PCr recovery. The apparent Vmax for mitochondrial ATP synthesis was marginally higher than in controls.

Discussion

^{31}P-MRS permits non-invasive study of aerobic and anaerobic metabolism during exercise and recovery in vivo and offers a means of quantifying the oxidative capacity of muscle mitochondria. For a given work rate, decreased aerobic capacity of a muscle will result in increased anaerobic synthesis of ATP. Anaerobic glycolysis synthesises ATP less efficiently and necessitates increased lactic acid production which acidifies the cell, predisposing to muscle fatigue.[14 15]

These patients with COAD showed a greater and faster decrease in pH and PCr during exercise than normal subjects. The increased acidification of skeletal muscle during exercise principally reflects increased proton accumulation from lactic acid production. It is possible that this rapid cytosolic acidification is responsible for some of the fatiguability of these patients, since cytosolic pH is an important correlate of muscular fatigue.[14 15]

These exercise abnormalities are consistent with impaired oxidative metabolism. This limitation in ATP synthesis could be due to limited oxygen supply, decreased fitness of the patients, or a switch to anaerobic glycolytic fibres. We will consider these in turn.

Firstly, the reduced arterial P_{O_2}, which diminishes the gradient for oxygen diffusion from the red cell to the muscle mitochondrion, impairs oxygen supply to the proteins of the respiratory chain. We have seen a similar, although less significant, exercise abnormality in young patients with hypoxaemic congenital heart disease and arterial P_{O_2} levels similar to those of the patients in this study.[16] Exercise under conditions of acute hypoxia also causes increased PCr breakdown and lactate production,[17 18] but little impairment in submaximal work performance[19] or exercise duration.[20]

Secondly, these results could also reflect a predominance of anaerobic glycolytic (type II) muscle fibres.[21–23] Adaptations of skeletal muscle fibre type towards anaerobic rather than oxidative ATP synthesis are a feature of severe airways obstruction.[24] In a study of patients with COAD as severe as in the present study, the proportion of type II fibres was increased to 83% of total muscle fibres compared with about 50% in normal subjects.[24] The cause of this predominance is unknown and is likely to be multifactorial since many conditions are associated with type II fibre predominance, ranging from corticosteroid therapy[25] or hyperthyroidism[26] to intensive sprint training.[27] The relationship of change of fibre type to reduced exercise capacity remains unclear, but it is tempting to speculate that since anaerobic fibres synthesise ATP less efficiently and produce more lactic acid, a type II predominant muscle may be more prone to fatigue than a predominantly aerobic muscle.[15]

Thirdly, other factors are likely to contribute to the very large deficit in the capacity for muscular work. Respiratory failure is associated with decreased cross sectional area of leg muscle[6] and fibre atrophy,[24] and this will result in reduced muscle power. Since endurance training increases the aerobic capacity of muscle,[28] our results showing increased breakdown of PCr and acidification may reflect the decreased level of activity of these patients. This is controversial since disuse may affect the aerobic capacity of the muscle[29] but does not alter the proportion of fibre type within the muscle in patients with rheumatoid arthritis[25] or after prolonged immobility resulting from leg injury.[30] One ^{31}P-MRS study on patients with chronic fatigue syndrome with day to day activity levels lower than the normal control group showed no metabolic differences from normal controls.[31]

In spite of the profound abnormalities in exercise, recovery from exercise was not impaired and calculation of the absolute capacity for ATP synthesis (table 2) revealed little or no evidence for a defect of mitochon-

drial oxidation during recovery (indeed there was a slight increase in the apparent Vmax, which arises from a non-significant increase in initial PCr resynthesis and a small decrease in end of exercise ADP concentration compared with controls). This is in contrast to an earlier study of COAD (of similar severity to the present study) where the half time of PCr recovery was 2·7 times greater than in controls.[6]

In patients with known intrinsic defects of mitochondrial metabolism, PCr depletion is rapid during exercise, as in our patients, but PCr, Pi, and ADP recovery times are slow[8] and Vmax is low.[11] Furthermore, the lack of abnormality in recovery in our patients is also in contrast to the results of our study of hypoxaemic congenital heart disease, where the recovery half times of ADP and PCr were doubled, and both the initial rate and the calculated maximum rate of PCr resynthesis were reduced by nearly half.[16] These observations suggest that the exercise abnormalities we have identified in COAD (and the recovery abnormalities in hypoxic congenital heart disease) cannot be solely due to hypoxia. Moreover, a preliminary report shows that in most instances administration of oxygen to patients with COAD does not change the metabolic abnormality.[32]

It is difficult to exclude other factors (such as blood flow during exercise and recovery) that may contribute to the metabolic changes seen. Heart failure or subclinical peripheral vascular disease, or both, could be contributing to the exercise induced substrate limitation—for example, oxygen limitation—seen in our results. Patients with heart failure[5] or peripheral vascular disease[9] do have some of the metabolic characteristics seen here, but they are less pronounced and the patients exercise for longer than these patients with COAD. Heart failure does not alter the proportion of fibre types[33] and peripheral vascular disease probably causes a relative increase in type I fibres.[34 35]

In contrast to previous studies we found no evidence of a significant intrinsic defect in mitochondria or in substrate supply during recovery from exercise in patients with respiratory failure, but we have confirmed previously reported findings of decreased aerobic capacity and increased acidification of skeletal muscle when these patients exercise. This may be partly a result of decreased oxygen supply and decreased fitness, and the change to glycolytic fibres seen in skeletal muscle of patients with severe COAD. The increased acidification and rapid decrease in high energy phosphate content of muscle may contribute to the early fatigue and breathlessness experienced by patients with chronic airflow limitation.

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Adventitia

In the late 1950s and early 1960s a number of epidemiological studies were undertaken to ascertain why the UK had such a high rate of mortality and morbidity from chronic bronchitis compared with other European countries and the USA. I collaborated with Donald Reid, Geoffrey Rose and Charles Fletcher, and we applied the methods developed at the time which consisted of the MRC Respiratory Disease Questionnaire, and simple methods of measurement of lung function, blood pressure, and ECG.

The problem with an assessment of the distribution of disease is that one has to study a great many individuals if one wishes to take into account factors such as occupation and social standing, and to separate the effects of personal factors such as smoking from those of the environment. Donald Reid pioneered the use of occupational groups to undertake such studies. He studied Post Office and Telephone workers in the UK to examine the effects of the environment upon their health.

We extended these studies to the USA during the time that I spent working at Johns Hopkins University. I was responsible for undertaking studies in three locations with widely differing socioeconomic and geographical characteristics: namely, Westchester (New York), Washington, and Baltimore, to try to determine whether there really was a difference in the prevalence of chronic bronchitis between individuals doing the same work in the UK and the USA, after taking into account their smoking habits.

In the UK I, together with Donald Reid, had been responsible for the negotiations with the Post Office top management and unions and readily obtained the willingness of the management to cooperate with our study. When I went to the USA I therefore talked first with the medical side of the American Telephone and Telegraph Company, who were the comparable employer to the Telephone branch of the Post Office in this country.

The contrast, however, was stark. The medical branch was extremely helpful and was willing to take part in any of the studies but, unfortunately, had far less influence than the equivalent medical branch in this country. My meetings with the management in the USA, however, were pretty frosty. Following the British example I also went to see the union and was fortunate in getting to see the head of the Communication Workers of America direct in Washington—a man called Joe Beirne. The contrast with the head of the union in Britain was far greater than any other difference between our two countries. Beirne's office was palatial. As soon as I arrived I was served with an excellent cup of tea by a waiter from a trolley. During our conversation he received a telephone call from President Kennedy who wanted his help on something. I was not asked to leave the room. Beirne's response to my request for help was immediate and complete. When told that the management were not exactly cooperative his response was that if the management refused to help, the union would. Whatever happened, he said, the survey must take place. He promised that if necessary the union would provide the premises and would ensure that all the relevant communication workers would participate, whatever the management said. That message, when transmitted to the management, immediately produced a positive response. We were informed that, of course, we could use the work locations and that all possible assistance would be provided. As a result our response rate was outstanding.

The examinations were all very successful. I was the common examiner between the UK and the USA and therefore had to examine a sizeable proportion of Americans. The only real problem was the difference in accent between the British and Americans, the two questions that really caused difficulties being those on asthma and phlegm production. I had received many strange answers to my demand of "Have you ever had asthma?" until eventually one participant said "No, I never take those!" I then realised that they had all thought that I was talking about aspirin rather than asthma, so I had to adapt my pronunciation accordingly!

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