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Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure

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Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD) with and without chronic respiratory failure. P. Jakobsson, L. Jorfeldt, A. Brundin.

ABSTRACT: Eighteen patients with advanced COPD, 8 with chronic respiratory failure (RF) and 10 without (nonRF, NRF) were investigated using spirometry, arterial blood gas analysis and biopsies taken from the quadriceps femoris muscle. The biopsies were analysed for ATP, creatine phosphate (CrP), creatine (Cr), lactate and glycogen content. Muscle fibre composition was also studied. Low concentrations of ATP, glycogen and CrP were found in the RF patients. Significant correlations were found between muscle metabolites and arterial blood gas values with the strongest correlation between muscle glycogen and arterial Po_2 ($r=0.70$; $p<0.001$). A very low percentage of "oxidative" type I muscle fibres was found in both groups. Possible mechanisms causing depletion of muscle metabolites are discussed.

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Studies in mild to moderate COPD and COPD with acute respiratory failure (RF) have demonstrated changes in muscle metabolism not only in the respiratory muscles but also in other skeletal muscles [1, 2]. It is also known that patients with severe COPD often have a reduced skeletal muscle mass [3, 4]. The generalized deterioration of skeletal muscle metabolism in COPD patients with and without RF is of interest not only because of its effect on the general state of the patients but also because of the possibility that respiratory muscles are also affected which might worsen the respiratory situation.

Human skeletal muscle is built up of two main types of fibres; type I fibres, which have a slow twitch profile and a high oxidative capacity but a low glycogenolytic capacity, and type II fibres which have a fast twitch profile and a high glycogenolytic capacity [5]. In healthy subjects the percentage of type I and type II fibres in muscles such as the quadriceps femoris are approximately the same but there is considerable interindividual variation. In mild to moderate COPD a slight predominance of type I fibres has been demonstrated in leg muscle [1].

The respiratory muscles are only to a limited extent available for metabolic studies in man and measurement of the energy situation by muscle biopsy technique is associated with the great risk of pneumothorax, especially in advanced COPD patients. Studies involving COPD patients have therefore been limited to those patients undergoing thoracotomy or patients under intensive respiratory care.

Advanced COPD - with as well as without RF - is a common disease and this category of patient is of great clinical interest. The aim of the present investigation was to study skeletal muscle metabolites and fibre composition in patients with advanced COPD to see if there is a difference in this respect between patients without chronic RF (NRF group) and patients with chronic RF (RF group).

Patients and methods

The NRF group consisted of 7 men and 3 women with advanced COPD attending the department of lung medicine as outpatients. Criteria for inclusion were a compensated clinical status with no sign of infection at the time of study, chronic airflow limitation with a forced expiratory volume in one second (FEV_1) less than 1 *l* before administration of bronchodilator drugs, and arterial blood gas analysis at rest breathing air showing $Po_2 \geq 10$ kPa, $Pco_2 \leq 6$ kPa.

The chronic RF group consisted of 6 men and 2 women with advanced COPD treated with long-term oxygen therapy at home. The criteria at our department for starting oxygen therapy at home are COPD in a clinically stable state on optimal therapy and a Po_2 <8 kPa at rest breathing air.

Patients with malignancy, hepatic, metabolic or renal disease were excluded.

Informed consent was obtained and the study was approved by the Local Ethics Committee.

All patients were investigated using spirometry and arterial blood gas analysis at rest breathing air. Muscle biopsy specimens from the lateral part of the quadriceps femoris muscle were obtained by means of the muscle needle biopsy technique [6]. Two biopsies were taken on each occasion. The first biopsy was frozen in liquid nitrogen immediately after withdrawal and stored at -80°C or less pending subsequent analysis for ATP, creatine phosphate (CrP), Creatine (Cr), lactate and glycogen content [7, 8]. The second biopsy was used for histochemical analysis. The activity of myofibrillar ATPase was estimated according to PADYKULA and HERMAN [9]. Muscle fibre types I and II were identified. The percentage of each type was calculated.

Reference material

Muscle metabolite concentrations were compared with data obtained from eight healthy male military conscripts using an identical procedure in our own laboratory reported elsewhere [10]. The present patients were older than the reference material but the muscle metabolic situation does not change with age [11–13]. The muscle metabolite concentrations in our reference material do correspond well with other reports of normal values in the literature [1, 8, 14]. We therefore consider this comparison to be adequate.

Statistical analysis

The unpaired Student t-test was used for comparison between the two groups and with the reference material. Mann-Whitney U-test was used to compare the lactate values. Linear regression analysis with one or more independent variables was used to study the relationship between metabolic variables and arterial blood gases as well as lung function variables.

Table 1. – Characteristics of the COPD patients in the respiratory failure (RF) and non respiratory failure (NRF) groups.

	Group RF		Group NRF		
	m	SD	m	SD	
Age, yrs	63	7	63	7	
Height, cm	172	8.7	173	11.5	
Weight, kg	68.8	10.8	69.9	18.8	
Men/Women	6/2		7/3		
FEV_1 *l*	0.69	0.21	0.99	0.23	p<0.05
VC *l*	2.2	0.6	2.7	0.8	NS
Pao_2 kPa	7.7	0.9	10.4	0.9	p<0.001
$Paco_2$ kPa	7.2	1.4	5.4	0.4	p<0.001

Results

The characteristics of the groups investigated and the results are summarized in table 1 and table 2.

The average age was 63 yrs in both group. All but one patient were former smokers. In the RF group oxygen had been administered for at least 16 hours a day over the previous 3–21 months, (mean 11.3). Two patients in the RF group were on oral steroids, 4 in the NRF group.

FEV_1 was significantly lower ($p<0.05$) in the RF group than in the NRF group, while vital capacity (VC) did not differ significantly between the two groups. Arterial Po_2 and Pco_2 differed between the RF and NRF patients ($p<0.001$) (table 1).

The percentage of type I muscle fibre (slow twitch) was very low in both groups, the difference between the groups being insignificant (table 2). Glycogen concentration was 347±67 mmol glycosyl units·kg d.m. in the NRF group. In the RF group it was 22% lower ($p<0.05$). The CrP concentration was also significantly lower in

Table 2. – Percentage of type I muscle fibres and muscle metabolites in the respiratory failure (RF) and non respiratory failure (NRF) groups.

	Group RF		Group NRF		
	m	SD	m	SD	
Type I muscle fibre%	17.0	9.6	22.3	12.6	NS
Glycogen*	269	68	347	67	p<0.05
CrP**	50	12	72	15	p<0.01
Cr**	69	19	58	11	NS
ATP**	18.0	3.8	19.5	1.9	NS
	median	range	median	range	
Lactate**	11.1	1.4–59.8	4.2	1.6–25.4	NS

*: mmol glycosyl units·kg d.m; **mmol·kg d.m.

the RF group than in the NRF group (31%, $p<0.01$) in which it was 72±15 mmol·kg d.m. Lactate values demonstrated a considerable interindividual variation in both groups with some extensively high values in the RF group. The median was nearly three times higher in the RF group compared with the NRF group. ATP was 19.5±1.9 and 18.0±3.8 mmol·kg d.m. in the NRF and RF groups respectively.

Compared with the reference material the NRF group demonstrated no significant differences in glycogen, CrP, creatine and lactate concentrations but a somewhat lower ATP concentration ($p<0.001$). In the RF group the glycogen ($p<0.05$) and CrP ($p<0.05$) concentrations were also lower than the controls, while the lactate concentrations did not differ significantly because of great interindividual variation in the RF group.

There was a significant linear correlation between most muscle metabolites and arterial blood gas values (table 3). The correlation was strong between muscle glycogen concentration and arterial Po_2 ($p<0.001$) (fig. 1). Furthermore there were positive correlations between CrP as well as percentage of type I fibres and arterial Po_2 ($p<0.05$) (fig. 2) and a negative correlation between Cr and arterial Po_2 ($p<0.05$). Muscle glycogen concentration and CrP correlated negatively with Pco_2 ($p<0.05$ and $p<0.01$ respectively) whereas there was a positive correlation between muscle lactate as well as Cr and Pco_2 ($P<0.05$ and $P<0.01$ respectively).

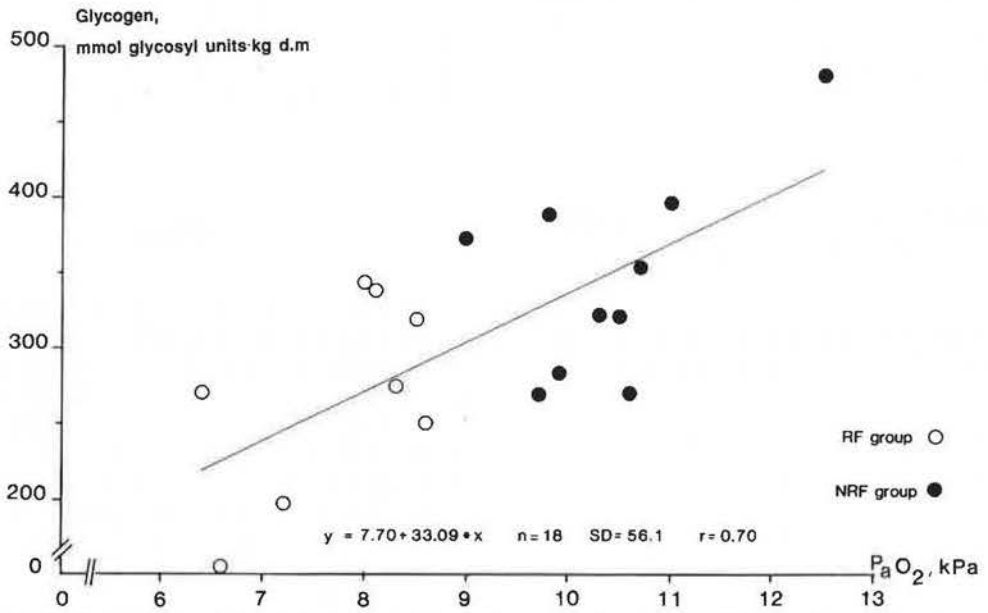

Fig. 1. – The relationship between glycogen content in the quadriceps femoris muscle and arterial Po_2 at rest breathing air.

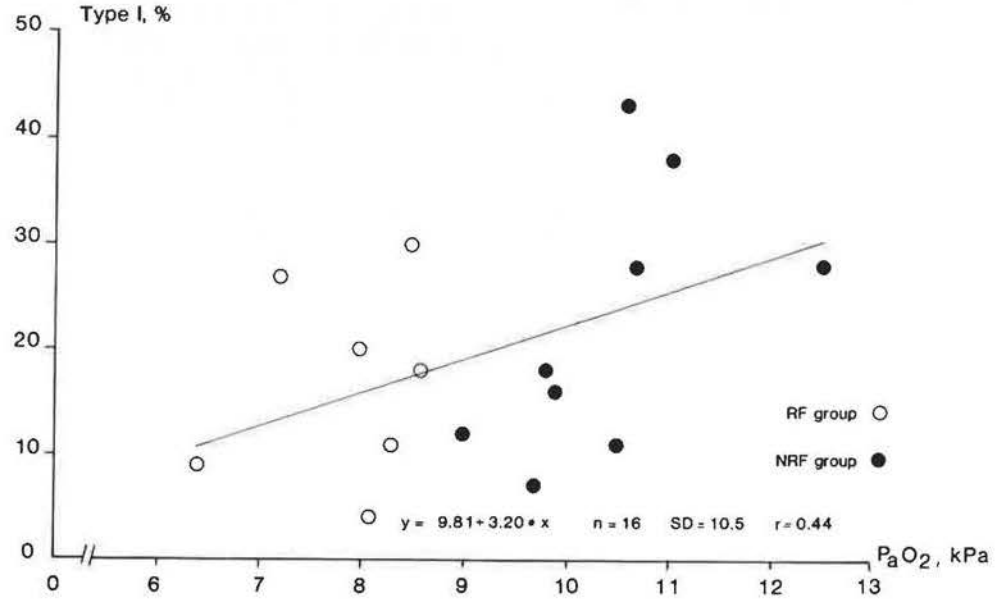

Fig. 2. – The relationship between percentage of type I fibres in muscle biopsies from the quadriceps femoris muscle and arterial Po_2 at rest breathing air.

Table 3. – Correlations between muscle metabolites as well as type I muscle fibre and arterial blood gases (y=f(x)).

x	y	r	
Pao_2	Glycogen	0.70	p<0.001
	Lactate	-0.33	p=0.08
	CrP	0.53	p<0.05
	Cr	-0.49	p<0.05
	Type I	0.44	p<0.05
$Paco_2$	Glycogen	-0.50	p<0.05
	Lactate	0.51	p<0.05
	CrP	-0.57	P<0.01
	Cr	0.64	p<0.01
	Type I	-0.18	p=0.24

Discussion

In the NRF group we found low concentrations of ATP in the quadriceps femoris muscle while glycogen, CrP and creatine did not differ significantly from the young healthy male controls [10]. In the RF group we, on the contrary, found low concentrations of glycogen, CrP and ATP. The present patients with chronic RF demonstrated significantly lower muscle glycogen and CrP than the NRF patients.

The results in the RF group are in agreement with data from another study of patients with COPD demonstrating low concentrations of CrP in the quadriceps femoris muscle [1] and a study of acutely ill patients with circulatory and respiratory insufficiency where there was an increase in lactate content, a decrease in the CrP concentration as well as decreases in ATP [15]. Like GERTZ *et al.* [2] in COPD and acute RF, we found low concentrations of ATP and CrP and increased lactate concentrations.

The reason for glycogen depletion in the vastus lateralis muscle in COPD patients with RF is not obvious. In this respect the strong positive correlation between muscle glycogen concentration and arterial Po_2 for the whole material (fig. 1) is of interest. As there was a correlation between Po_2 and FEV_1 and a small but statistically significant difference in FEV_1 between the RF and NRF groups as well as a close to significant correlation between muscle glycogen concentration and FEV_1 it can be argued that the difference in muscle glycogen between the NRF and RF groups merely reflects a difference in FEV_1. However, stepwise analysis of multiple linear regression with muscle glycogen concentration as y-variable and FEV_1 and arterial Po_2 as x-variables did show that arterial Po_2 was able to significantly (p=0.003) reduce the residual variance for glycogen likewise when the influence of FEV_1 was considered. This indicates that the difference in arterial Po_2 between the RF and NRF groups is of importance for the difference in muscle glycogen concentration between the groups and that there may exist a causal relationship between the decrease in muscle glycogen and arterial Po_2. The situation was similar for CrP concentration although the difference in arterial Po_2 between the groups did not contribute as much as with muscle glycogen.

From our results it is not possible to state which is the primary factor in the process of decreasing arterial Po_2 and muscle glycogen concentration, *i.e.* whether muscle energy depletion in the vastus lateralis muscle in COPD patients represents a generalized process in skeletal muscle including respiratory muscles and contributes to worsened ventilatory function which in turn lowers arterial Po_2 or if hypoxia due to advanced obstruction of the airways leads to depletion of muscle energy stores.

Following trauma and surgery there is a decrease in skeletal muscle glycogen concentration which has been attributed to the stress situation. Even moderate surgical trauma such as cholecystectomy is followed by a fall in muscle glycogen concentration to the same level as observed in the present RF group [16]. Furthermore, raised concentrations of the stress hormones adrenaline and noradrenaline have been reported in chronic RF [17]. The hypothesis can therefore be put forward that the RF situation induces a stress reaction possibly *via* hypoxia which leads to a deterioration in muscle energy metabolism.

One way of investigating the interrelationships between arterial blood gas values and muscle metabolites is to study the possible influence of long-term oxygen therapy on muscle energy content and endocrine stress factors.

Patients with advanced COPD are inactive and a difference in physical activity may well exist between the RF and NRF groups thus influencing the skeletal muscle energy situation and contributing to the differences found.

Our study of patients with advanced COPD with and without RF has shown a very low percentage of "oxidative" type I muscle fibres in patients with advanced COPD irrespective of RF or not. This is in contrast to studies of patients with mild to moderate COPD in which a slight predominance of type I fibre has been described [1]. The latter is also the case in normal individuals of this age [18]. The percentage of type I fibres was correlated to arterial Po_2 (fig. 2). The reason for the very low percentage of "oxidative" type I muscle fibres in these cases is not known.

In our study 6 patients were on oral steroids, two in the RF group and 4 in the NRF group. In steroid myopathy, necrotic changes have been demonstrated in type I fibres and atrophy of type II fibres [19] but little is known about the influence of steroids on muscle metabolites. If the patients on oral steroids are excluded there are still positive significant correlations between muscle glycogen and CrP concentrations *vs* arterial Po_2 and a close to significant correlation between the percentage of type I muscle fibres and arterial Po_2. This indicates that the minor difference between the groups in steroid therapy cannot explain the results in our study.

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Les métabolites des muscles striés et les types de fibres chez les patients atteints de bronchopneumopathie chronique obstructive avancée (COPD), avec et sans insuffisance respiratoire chronique. P. Jakobsson, L. Jorfeldt, A. Brundin.
RÉSUMÉ: Nous avons investigué par spirométrie, analyse des gaz du sang artériel, et biopsie du muscle quadriceps crural, dix-huit patients atteints de COPD avancée, dont 8 avec insuffisance respiratoire chronique (RF) et 10 sans cette insuffisance (non RF, NRF). Les biopsies ont été analysées pour l'ATP, la phosphate créatine (CrP), la créatine (Cr), les lactates et le glycogène. La composition des fibres musculaires a également été étudiée. De faibles concentrations d'ATP, de glycogène et de CrP ont été mises en évidence chez les patients RF. Des corrélations significatives ont été trouvées entre les métabolites musculaires et les valeurs des gaz du sang artériel, la corrélation étant la plus marquée entre le glycogène musculaire et Po_2 artérielle ($r=0.70$; $p<0.001$). Un pourcentage très faible des fibres musculaires oxydatives de type 1 a été décelé dans les deux groupes. Les mécanismes susceptibles d'expliquer la déplétion des métabolites musculaires sont discutés.
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