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Metabolic enzymatic activities in the intercostal and serratus muscles and in the latissimus dorsi of middle-aged normal men and patients with moderate obstructive pulmonary disease

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Metabolic enzymatic activities in the intercostal and serratus muscles and in the latissimus dorsi of middle-aged normal men and patients with moderate obstructive pulmonary disease. J. Sanchez, A. Brunet, G. Medrano, B. Debesse, J.Ph. Derenne.

ABSTRACT: The glycolytic and oxidative enzyme activities (lactate dehydrogenase (LDH), hexokinase (HK), citrate synthase (CS) and 3-hydroxyacyl-CoA-dehydrogenase (HAD)) were measured in the fifth internal and external intercostal muscles, in the vertical and horizontal parts of the serratus, an accessory inspiratory muscle, and in a non-respiratory muscle, the latissimus dorsi (LD) of twenty middle-aged men: nine subjects with normal lung function and eleven patients with moderate chronic obstructive pulmonary disease (COPD). In the normal subjects the enzyme activities of the respiratory muscles were similar to those of the LD, and there were no differences between the internal and the external intercostal muscles. In the COPD patients the metabolic activities of HK, CS and HAD were kigher in both intercostals than in LD. Furthermore, there was a significant inerease in these enzymatic activities as compared to the intercostals of the normal subjects. These data support the hypothesis that the internal and external intercostal muscles play a more important role in COPD patients than in normal subjects. They are consistent with the hypothesis tkat COPD has an endurance training effect on both intercostal muscles which could compensate for diaphragmatic disuse.
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The respiratory muscles are the only skeletal muscles on which life depends and which contract rhythmically for a lifetime. In spite of this continual activity, there is no difference in muscle fibre size in normal subjects between the latissimus dorsi (LD), a non-respiratory muscle on the one hand, and the costal diaphragm (DI), the internal (IIC) and external (EIC) intercostals and the vertical (VS) and horizontal (HS) parts of the serratus, an inspiratory accessory muscle, on the other hand [1]. Nevertheless, the metabolic enzymatic activities of hexokinase (HK), lactate dehydrogenase (LDH), citrate synthase (CS) and 3-hydroxyacyl-CoA-dehydrogenase (HAD) are significantly higher in DI than in LD in normal subjects [2]. These increased activities may be a consequence of the continual phasic activity of the diaphragm.

Chronic obstructive pulmonary disease (COPD) affects the respiratory muscles in two ways. Firstly, disorders of the lung and airways are responsible for an increased airways resistance; the respiratory muscle must generate more pressure for a given ventilation. Secondly, the development of COPD is associated with increased residual volume (RV) and functional residual capacity (FRC) with diaphragmatic flattening. Since diaphragmatic efficiency decreases when lung volume increases [3], the combined effects of the increased resistance and chest wall distention result in increased load and decreased muscular efficiency. We have previously shown that these increased loads did not induce a 'training effect' in the diaphragm: in fact muscle fibre size and HK and LDH activities are decreased in COPD patients [1, 2], suggesting that the diaphragm may be disused or detrained.

Since it has been shown that minute ventilation is normal and that the pleural pressure swing during tidal breathing and occlusion pressure are increased at rest in COPD patients [4–6], it is likely that the other muscles of respiration increase their activity to compensate for diaphragmatic disuse. Yet no modification of fibre size in IIC, EIC, HS and VS was observed in COPD patients [1]. However, endurance training may fail to induce significant changes in fibre diameter of the skeletal muscles whereas metabolic enzymatic activities may be markedly increased [7].

In order to evaluate the possibilities of such phenomena in the intercostal and serratus muscles we have measured the metabolic enzymatic activities of HK, LDH, CS, and HAD in IIC, EIC, VS, HS and LD in subjects with normal lung function and in

patients with moderate COPD. The data reported here show: firstly, that in the normal subjects the enzymatic activities of the intercostal and serratus muscles were not increased as compared to LD, and secondly, that the metabolic activities of HK, CS and HAD in both intercostals were higher in COPD patients than in normal subjects.

Methods

Muscle specimens were obtained during surgical procedure in nine subjects with normal lung function (N) and in eleven patients with moderate chronic obstructive lung disease (O). With the exception of four subjects in group N and two in group O, the patients studied here are different from those previously reported [1, 2]. The physical characteristics of the two groups are listed in table 1 together with their lung function data.

None of the patients had been treated with agents likely to modify muscle metabolism such as steroids, chemotherapy and radiotherapy. The nature and purpose of the study were explained to the subjects, and all voluntereed to take part in it. They were operated on for various reasons: 16 patients for resection of lung carcinoma, 2 for resection of bullae and 2 for pleural effusions. All patients fasted for at least 14 h before surgery. They were all in good physical condition and did not present any significant complication after surgery. All patients were smokers or ex-smokers.

Biopsies were taken from the internal and external intercostals, the vertical and horizontal bundles of serratus anterior and from the latissimus dorsi, a non-respiratory muscle. They were rapidly frozen in liquid nitrogen and stored at −80°C for later enzymatic analysis. They were given a code number and the enzymatic activities were measured without knowing if the subjects were normal or obstructive. The code number was broken by an independent technician after all the enzymatic analyses had been performed.

Preparation of samples

The muscle specimens were freeze-dried at −40°C, dissected under a microscope, freed from blood, connective tissue and fat, and then weighed on an automatic electrobalance (Cahn 25). This dissection and weighing procedure took place in a special room (less than 25% humidity) at 20°C. Freeze-dried material absorbs oxygen, nitrogen and moisture when exposed to room air and reaches an equilibrium very rapidly [8, 9]. In our low humidity room, this phenomenon accounted for an increase of approximately 3% of the sample's initial weight. The dissected samples were then homogenized (1:400), by using a Potter-Elvehjem homogenizer, in ice-cooled 0.3 M phosphate buffer at pH 7.7 and containing 0.05% bovine serum albumin (BSA). Enzymatic activities were measured threefold and expressed per gram of protein. Protein was determined according to LOWRY *et al.* [10], with bovine serum albumin as the standard. Enzyme activities were determined using NAD^+/NADH enzymatic fluorometric assays at 25°C with a Gilson spectra/glofluorometer (reagent volume 1 ml), according to LOWRY and PASSONNEAU [11].

Table 1. - Physical characteristics of the subjects

	Normal subjects	COPD patients	
	n=9	n=11	p
Age yr	52.6±2.4	51.6±1.8	NS
Body weight kg	71.8±2.7 (95.4%)	70.6±3.1 (93.1%)	NS
VC ml	4437±188 (95.9%)	4302±265 (95%)	NS
FEV_1 ml	3192±165 (92.9%)	2236±177 (66.5%)	p<0.001
FEV_1/VC %	71.7±1.8	52.3±3	P<0.001
FRC ml	3634±196 (96.2%)	4406±186 (126%)	p<0.001
RV ml	1787±227 (100%)	3006±199 (148%)	p<0.001
TLC ml	5713±686 (96.7%)	7326±342 (113.2%)	p<0.01
FRC/TLC %	54.3±0.9	60.5±1.7	p<0.01
RV/TLC %	32.2±1.3	40.8±2.1	p<0.01
Pa_{O_2} mmHg	84.2±3.6	81.7±2.3	NS
Pa_{CO_2} mmHg	37.7±1.6	36.6±0.6	NS

VC: vital capacity; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension. Values in brackets are % predicted values. Statistical differences between both groups are shown by p.

Enzymes studied

Hexokinase (HK:E.C.2.7.1.1.). The homogenate was added to a reagent solution containing 0.1 M tris buffer pH 8; 8mM $MgCl_2$; 1 mM glucose; 0.15 mM $NADP^+$; 0.01% DTT; 250 µg G-6-PDH, 2 mM ATP. Glucose-6-phosphate was used as a standard with the blank being handled in the same way as the sample but without ATP.

Lactate dehydrogenase (LDH:E.C.1.1.1.27). The homogenate was diluted 4 times in 0.3 M phosphate buffer pH 7.7 and 3mM NADH. The diluted homogenate was then added to the reagent solution containing imidazole 20 mM; BSA 0.02%; 17.25 µM NADH; 1 mM pyruvate. NADH was used as a standard with the blank being handled in the same way as the sample but without pyruvate.

Citrate synthase (CS:E.C.4.1.3.7). The homogenate was added to a reagent solution containing 0.1 M tris buffer pH 8; 25 mM EDTA; 0.5 mM NAD^+; 1 mM L-malate; 0.1 mM acetyl-CoA and 400 µg of malate dehydrogenase (MDH:E.C.1.1.1.37). NADH was used as a standard with the blank being handled in the same way as the sample but without acetyl-CoA.

3-Hydroxyacyl-CoA-dehydrogenase (HAD:E.C. 1.1.1.35). The homogenate was added to a reagent solution containing 0.04 M imidazole buffer pH 7.0; 0.06 mM EDTA; 0.02 mM NADH and 0.05 mM S-acetoacetyl-CoA. NADH was used as a standard with the blank being handled in the same way as the sample but without S-acetoacetyl-CoA.

Chemicals and enzymes

Chemicals used in the measurement of enzymatic activities were obtained from Sigma Chemical Co. (St. Louis, Mo, USA), and auxiliary enzymes used in these measurements were from Boehringer, Mannheim, GmbH Biochemica.

All values are expressed as mean ± one standard deviation. Enzymatic activities are expressed as $U \cdot g^{-1}$ protein.

A non-parametric statistical procedure was used to test variations between the two groups: Mann-Whitney U test [12]. Linear regression was calculated by the least squares method.

Results

Normal subjects

The enzymatic activities in IIC, EIC, VS, HS and LD in normal subjects are represented on the left of table 2, and are expressed in $U \cdot g^{-1}$ protein (µmol of substrate transformed per minute and per gram of protein at 25°C). Enzymatic activities were not systematically higher in the respiratory muscles than in the latissimus dorsi, but HK was higher in both parts of the serratus. CS and HAD were increased only in the vertical serratus.

COPD patients

The metabolic enzymatic activities of the same muscles in the COPD patients are shown on the right of table 2. Unlike normal subjects, the metabolic activities were higher in the respiratory muscles than in LD, with the exception of LDH in the intercostal muscles.

Comparison between normal and obstructive subjects

The individual values for the four enzymatic activities of the five muscles in both groups of subjects are represented in figure 1. Significant increases in

Table 2. - Enzymatic activities in internal intercostal (IIC), external intercostal (EIC), vertical (VS) and horizontal serratus (HS) and for latissimus dorsi (LD) muscles of normal subjects and COPD patients

	Normal subjects				COPD patients			
	HK	LDH	CS	HAD	HK	LDH	CS	HAD
IIC	6.07	1156	26	34.5	6.9*	965	33.6*	47.1**
SD	0.33	154	2.5	4.5	0.5	118	4.0	4.9
EIC	6.06	1163	30	40.5	6.7*	881	37.8**	53.9**
SD	0.35	140	2.6	5.0	0.37	277	4.33	5.6
VS	6.82*	1525	32.3*	45.4*	7.2**	1552	33.6*	49.4**
SD	0.76	427	3.6	4.4	0.6	467	3.0	3.5
HS	7.35**	1397	31.7	42.9	7.5**	1268	34.6*	46.5*
SD	0.6	419	3.96	4.35	0.77	314	3.5	4.1
LD	5.54	1090	26.48	37.09	5.52	958	28.6	36.6
SD	0.51	385	3.7	6.21	0.59	269	4.5	5.7

Mean enzymatic activities ± standard deviation are expressed in $U \cdot g^{-1}$ protein. Statistical significance in both group of subjects between values measured in LD and in other muscles is represented by *: $p<0.05$; **:$p<0.01$. HK: hexokinase; LDH: lactate dehydrogenase; CS: citrate synthase; HAD: 3-hydroxyacyl-CoA-dehydrogenase.

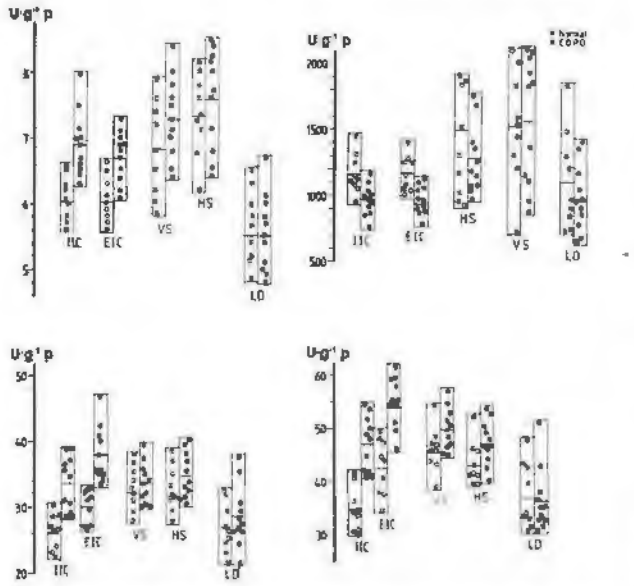

Fig. 1. Individual values of metabolic enzymatic activities in the two groups of subjects. For explanation see text.

HK, CS and HAD were found in the intercostals of the COPD patients ($p < 0.05$ to $p < 0.001$). In contrast LDH was significantly smaller in both intercostals of the COPD group ($p < 0.05$).

Correlation between enzymatic activities and ventilatory parameters

No correlation was found between the metabolic enzymatic activities of LD and any of the ventilatory parameters listed in table 1. In contrast HK, CS and HAD activities in the external intercostal muscles were negatively correlated to forced expiratory volume in one second (FEV_1) and FEV_1/VC (VC = vital capacity). Furthermore, they were positively correlated to FRC and RV (figs 2–4). In addition they were also positively correlated to other indices of distension; total lung capacity (TLC), RV/TLC and FRC/TLC (table 3).

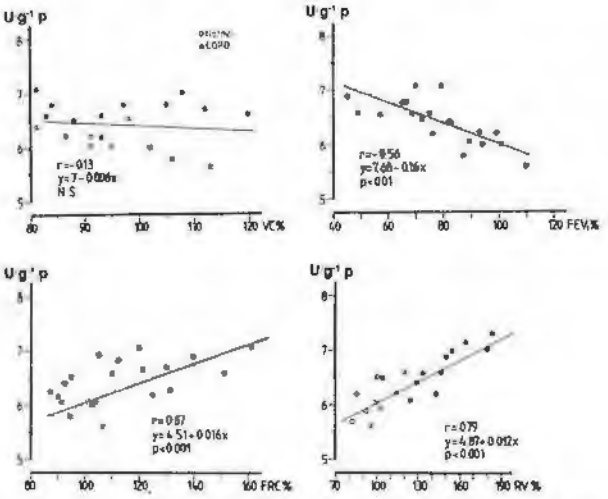

Fig. 2. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and hexokinase (HK) activity in the external intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

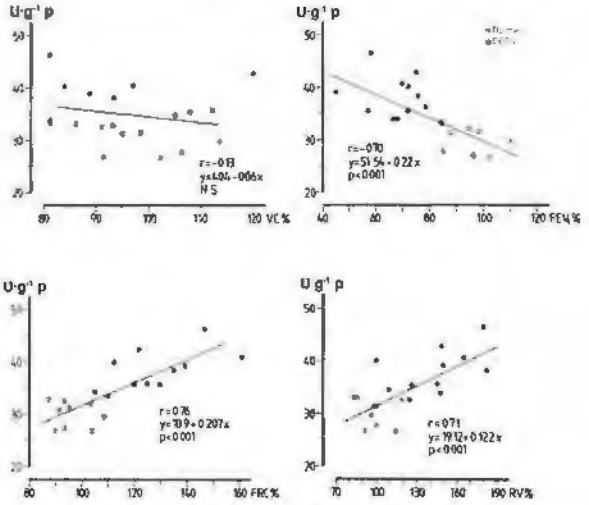

Fig. 3. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and citrate synthase (CS) activity in the external intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

LDH exhibited an inverse pattern (fig. 5). LDH activities were positively correlated to FEV_1 and FEV_1/VC and negatively correlated to FRC, RV, TLC, FRC/TLC and RV/TLC (fig. 5 and table 3).

A similar pattern was observed in the internal intercostal muscle (figs 6–9 and table 3).

Such findings were not observed in any part of the serratus. Significant correlations were not found between HK, LDH, CS and HAD activities and

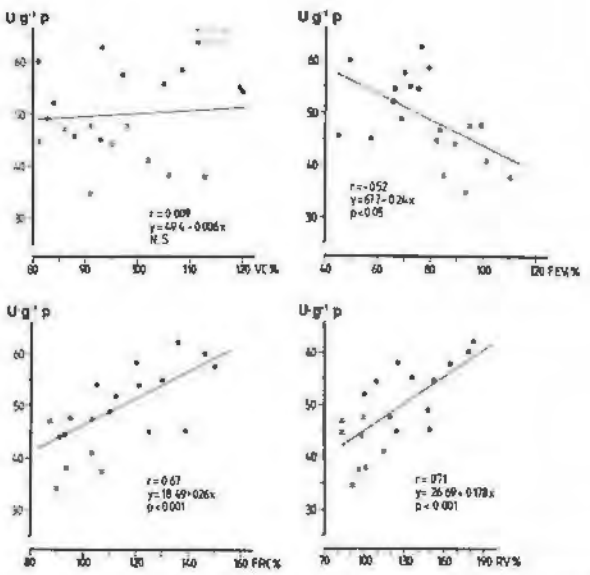

Fig. 4. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and 3-hydroxyacyl-CoA-dehydrogenase (HAD) activity in the external intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

Table 3. - Correlation coefficients between enzymatic activities of the internal and external intercostal muscles and ventilatory parameters.

	Internal Intercostal				External Intercostal			
	HK	LDH	CS	HAD	HK	LDH	CS	HAD
VC %	–0.14	–0.26	–0.08	–0.05	–0.13	–0.04	–0.13	–0.009
FEV_1 %	–0.63**	0.47*	–0.70***	–0.75***	–0.56**	0.48*	–0.70***	–0.52*
FEV_1/VC %	–0.62**	0.35	–0.45*	–0.55**	–0.48*	0.53*	–0.45*	–0.45*
FRC %	0.86***	–0.67**	0.77***	0.79***	0.67**	–0.59**	0.76***	0.67***
RV %	0.87***	–0.59**	0.79***	0.76***	0.79***	–0.49*	0.71***	0.71***
TLC %	0.49*	–0.50*	0.59**	0.53*	0.52*	–0.52*	0.53*	0.61**
FRC/TLC %	0.77***	–0.44*	0.47*	0.45*	0.44*	–0.53*	0.51*	0.48*
RV/TLC %	0.64**	–0.57**	0.44*	0.48*	0.47*	–0.64**	0.44*	0.49*

The symbols are the same as in table 1. Significant correlations are shown by: *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. Ventilatory parameters used were expressed as % predicted values.

ventilatory parameters. None of these correlations were greater than 0.39.

Effects of age, blood gases and body weight

Statistical analysis did not show systematic correlation between enzymatic activities and age, arterial oxygen tension (Pao_2), arterial carbon dioxide tension ($Paco_2$) and body weight. LDH activity had a negative correlation with age only in HS ($r=-0.47$; $p<0.05$). CS activity had a negative correlation with body weight only in HS ($r=-0.49$; $p<0.05$). Pao_2 was not correlated to any enzymatic activity. $Paco_2$ was positively correlated to LDH in VS ($r=0.57$; $p<0.01$) and LD ($r=0.44$; $p<0.05$) and negatively correlated to HK in HS ($r=-0.44$; $p<0.05$). None of the other correlations was statistically significant.

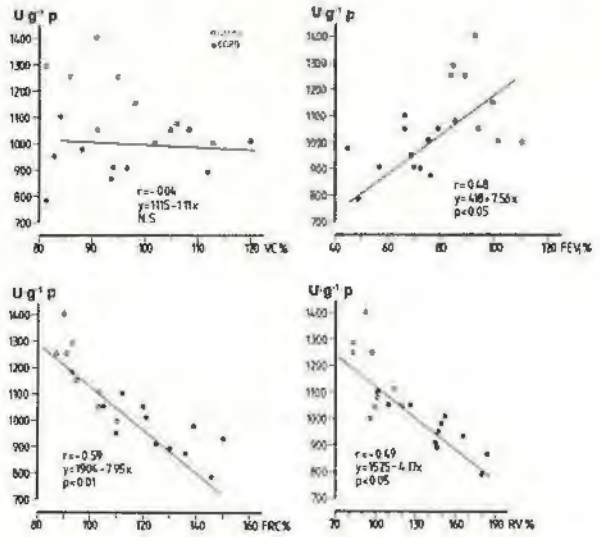

Fig. 5. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and lactate dehydrogenase (LDH) activity in the external intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

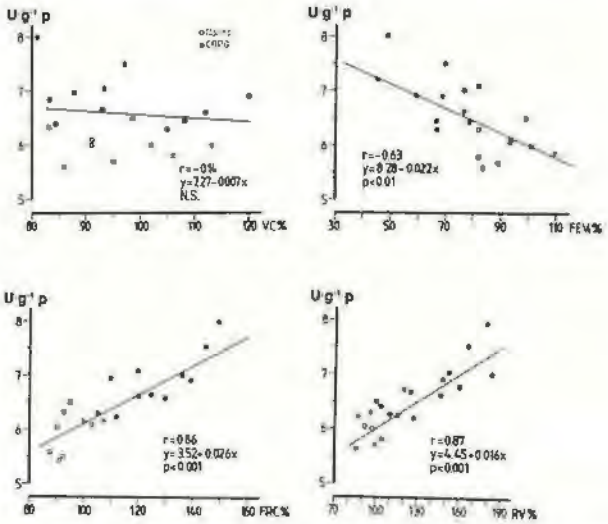

Fig. 6. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and hexokinase (HK) activity in the internal intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

Discussion

Enzymes studied

The enzymes studied here are representative of glucose phosphorylation (HK) and lactate metabolism (LDH); CS is responsible for the entry of acetyl-CoA into the citric acid cycle, thus representative of

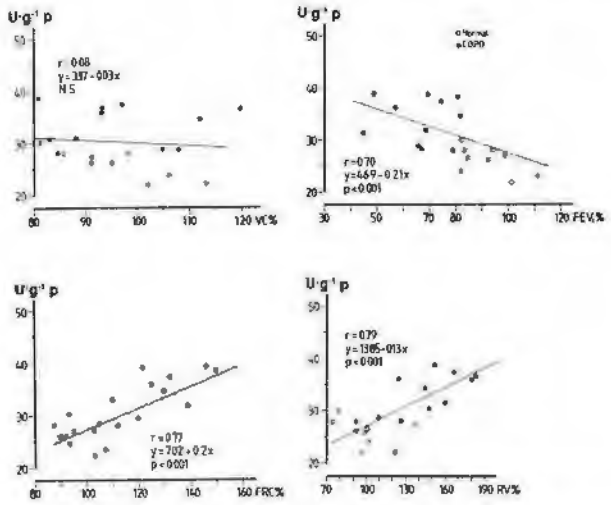

Fig. 7. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and citrate synthase (CS) activity in the internal intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

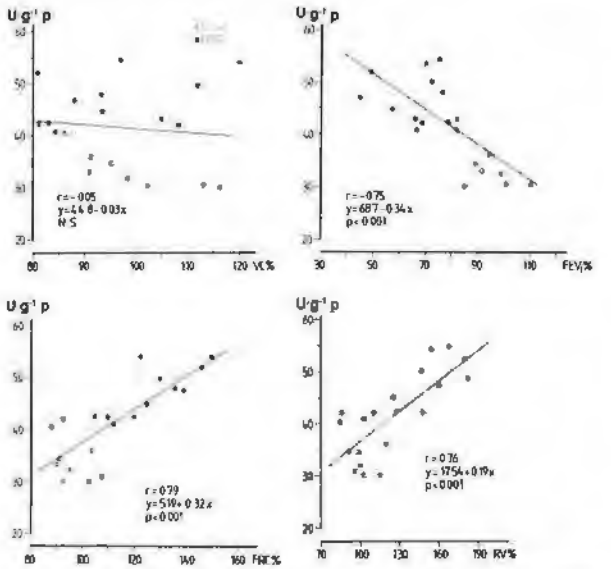

Fig. 8. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and 3-hydroxyacyl-CoA-dehydrogenase (HAD) activity in the internal intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

the Krebs cycle activity, and HAD activity is a marker of the capacity for β-oxidation of fatty acids in the muscle. It is well known that type I fibres have high oxidative enzymatic activities (HAD and CS). Type II fibres have a higher LDH activity. Endurance training increases HAD, CS and HK activities in human skeletal muscle [7, 13–15]. Detraining and disuse have opposite effects [16–18].

Enzymatic activities in normal subjects

Enzymatic activities were not systematically higher in the intercostal and serratus muscle than in the

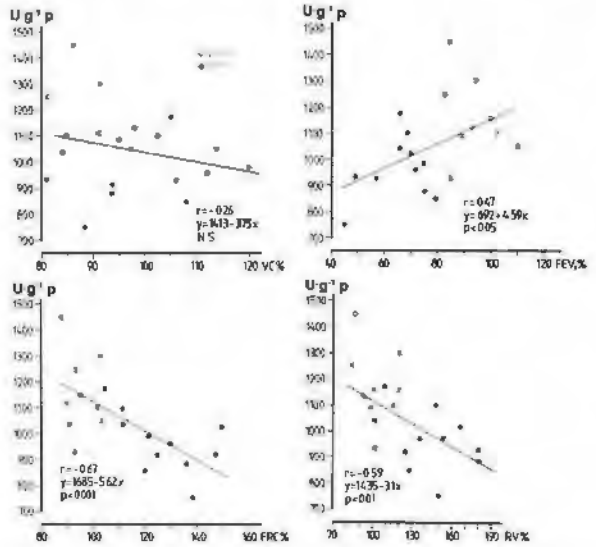

Fig. 9. Correlation between vital capacity (VC), forced expiratory volume in one second (FEV_1), functional residual capacity (FRC), and residual volume (RV) and lactate dehydrogenase (LDH) activity in the internal intercostal muscle. The ventilatory parameters are expressed as % of predicted values.

latissimus dorsi. The latter is a non-respiratory muscle and the values reported here are similar to those of other skeletal muscles in normal middle-aged sedentary subjects [18, 19], and to those previously measured in LD in a different group of patients [2]. The present results suggest that the intercostal and serratus muscles are moderately used in normal subjects. These findings are consistent with the idea that the diaphragm is the main agonist of inspiration normally and that the intercostal and serratus muscles are less important as respiratory pressure generators.

Effects of age, blood gases and body weight

There was no significant difference between age, Pao_2, $Paco_2$ and body weight (expressed in kilograms or as % ideal weight) between the two groups. The differences observed between normal and COPD patients cannot be explained by these parameters. The lack of systematic correlations between age and body weight and the metabolic enzymatic activities strongly suggests that the differences observed between normal and obstructive subjects are independent of these factors. These findings support previous observations in the diaphragm [2]. The lack of correlation between age and metabolic enzymatic activities is due to the small dispersion in age: thirteen patients were between 47 and 57 yrs old. The others were 38, 41, 44, 45, 60, 62 and 63 yrs old.

Effects of chronic obstructive pulmonary disease

Chronic obstructive pulmonary diseases are characterized by an increased inspiratory and expiratory resistance and by changes in the chest wall configuration, with increased RV, FRC or TLC. We have previously reported that the diameter of type I and II

fibres and the actvity of HK and LDH were smaller in the diaphragm of COPD patients than in normal subjects, showing that obstructive disease has no endurance training effect on the diaphragm and even suggesting that the diaphragm may be disused in COPD patients [1, 2].

In the present study there was no consistent change in the serratus. This is an inspiratory accessory muscle which is generally considered to be relatively unimportant in the act of breathing. It has been suggested that chronic airways obstruction and chest wall overinflation is associated with an increased contribution of the inspiratory accessory muscles. In fact, the main inspiratory accessory muscles are the scalene and sternomastoid muscles [20] which have not been analysed in the present study because they could not be sampled during the surgery.

Concerning IIC and EIC, we found that the activities of two aerobic enzymes CS and HAD increased by 29 and 36% respectively in IIC and by 26 and 32% in EIC. Such increases are similar to those observed in skeletal muscles after endurance training in man and other mammals [7, 21]. On the other hand, LDH activities were smaller in COPD patients: −17% in IIC and −24% in EIC. LDH (lactate fermentation) may be unchanged or even decreased with training [13], showing that the glycolytic capacity of skeletal muscles does not increase in response to endurance training. Recently ACKER *et al.* [22] reported that after one year of continous electrical stimulation of dog diaphragm, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity decreased to 50% of control values whereas HAD increased by 53%. GAPDH is another marker of glycolysis. Similarily, a shift to a more oxidative metabolism in chronically stimulated fast twitch muscle has been extensively documented in the rabbit [23, 24]. Hexokinase (HK) is unique among the glycolytic enzymes in that its activity in different types of muscle varies with respiratory capacity. It has been extensively documented in this context that exercise training, which induces an increase in the mitochondrial content of skeletal muscle, also results in an increase in hexokinase activity [13]. The increased HK activity observed in COPD patients is consistent with the hypothesis of a training effect of the disease on the intercostal muscles. Therefore, the results reported in the present study support the hypothesis that the internal and external intercostal muscles play a more important role in COPD patients and suggest that COPD has a training effect on both intercostal muscles. In a previous study we did not find any correlation between the mean least diameters of both type I and II fibres in the external intercostal muscles and any of the ventilatory parameters in a similar group of patients. The dissociation between changes in fibre size and enzymatic activities is often observed after training: the increase in enzymatic activities is a more sensitive index of the effects of training than changes in fibre size [7]. Our patients had only mild to moderate COPD (average FEV_1 2.2 *l* in the COPD patients compared to 3.2 *l* in normals). This suggests that the enzyme changes are relatively sensitive to small changes in lung function, and presumably would be much more marked in severe COPD.

There has been a longstanding controversy about the functions of the intercostal muscles. Nevertheless, it is generally agreed that the internal are expiratory and the external inspiratory. However, more recent work in the dog [25] suggests that the respiratory function of the intercostals depends essentially upon the loads and configuration of the chest wall. DE TROYER *et al.* [25] have shown that the external and internal intercostal muscles have a similar effect on the ribs, suggesting that the non-linear compliance of the ribs rather than the orientation of the muscle fibres is the primary determinant of the mechanical action of the intercostal muscles.

Therefore, the precise explanation for the 'training effect' that we have observed in COPD patients is not easy to establish. One could speculate that the increased activity in the external intercostal is related to a greater contribution of this muscle to the inspiratory act and that the increased activity observed in the internal intercostal is due to an increased expiratory activity, in order to compensate for the increased airways resistance. An alternative hypothesis would be that both intercostals act synergistically as inspiratory or expiratory agonists. A third explanation would be related to an increased postural activity of the intercostals. However, the precise nature of the compensation observed here requires further investigation.

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RÉSUMÉ: Les activités de l'hexokinase (HK), de la lactate déshydrogénase (LDH), de la citrate synthase (CS) et de la 3-hydroxyacyl-CoA-déshydrogénase (HAD) ont été mesurées dans les muscles intercostaux (5ème espace) et dans la partie horizontale et verticale du grand dentelé et dans le grand dorsal (latissimus dorsi–LD), chez 20 sujets: 9 patients à fonction respiratoire normale et 11 malades porteurs de bronchopathie chronique obstructive. Le grand dorsal est un muscle non respiratoire et sert de référence. Chez les sujets normaux, toutes les activités enzymatiques dans les muscles respiratoires sont similaires à celles du LD. De plus, il n'y a pas de différence entre l'intercostal interne et l'intercostal externe. La maladie obstructive chronique induit une augmentation des activités enzymatiques (HK, CS, HAD) dans les muscles intercostaux. Ces résultats suggèrent que les muscles intercostaux jouent un rôle plus important chez les sujets porteurs d'une maladie obstructive que chez les sujets à fonction respiratoire normale et ils sont consistants avec l'hypothèse que la bronchopathie chronique obstructive produit un effet d'entraînement dans les muscles intercostaux.