

# Ventilation and Its Control during Incremental Exercise in Obesity

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## Key Words

Insulin resistance · Obesity · Potassium · Ventilation

## Abstract

**Background:** In obesity, the addition of mass loading of the chest wall by adipose tissue decreases compliance, but its ventilation does not seem to be a limiting factor to physical performance. Plasma K<sup>+</sup> and lactic acid are considered important determinants of ventilation during exercise. Obesity is characterized by insulin resistance. **Objectives:** The aim of this study was to assess ventilatory adaptations to sustained effort and the effects of lactic acid and potassium in young obese subjects. **Methods:** Twelve obese subjects with a body mass index of 40 (mean age 27 years, 6 males) and 12 normal subjects with a body mass index of 22 (aged 28 years, 6 males) performed a progressive cycloergometric test with increases of 20 W every 4 min to exhaustion while minute ventilation, oxygen consumption, carbon dioxide production, end-tidal oxygen pressure, and end-tidal carbon dioxide pressure were measured. Blood samples were collected at the end of every step to determine plasma K<sup>+</sup>. Lactic acid was measured at rest, 40, 80, 120 W and peak exercise (or only at peak exercise if <120 W). Before each exercise, we tested insulin sensitivity using the quantitative insulin sensitivity check index. **Results:** Obese subjects had lower insulin sensitivity (0.318 vs. 0.345, p < 0.01). Peak exercise was not

significantly different between both groups (125 W in the obese group vs. 137 W in the control group), but the ventilatory threshold was at lower power output in the obese group compared to the controls (76 vs. 107 W, p < 0.05). Ventilation increased less in the obese group but oxygen saturation of hemoglobin remained within normal limits up to exhaustion in both groups. Ventilation was appropriate for the CO<sub>2</sub> increase but less appropriate for the increased O<sub>2</sub> consumption. Both K<sup>+</sup> and lactic acid increased less in the obese group. **Conclusions:** In our obese subjects, ventilation was not a limiting factor during exercise. Its lower increase may be due, in addition to the characteristics of their chest walls, to insulin resistance which may limit the increase in lactic acid during effort, and to the hypertrophy of muscle fibers previously noted, which may be linked to a lower increase in plasma K<sup>+</sup> during physical exercise. Copyright © 2006 S. Karger AG, Basel

## Introduction

In severe obesity, the most easily understood notion is that the addition of mass or weight to the chest wall decreases its compliance so that more respiratory work must be done by the respiratory muscles to expand and ventilate the lungs adequately [1, 2]. When submitted to exercise testing, obese subjects generally reach ventila-

tory thresholds at lower power output than normal controls and therefore have a lower work capacity [3]. However, in obese subjects, ventilation is apparently not a limiting factor to physical performance, with the lower work capacity being probably mostly due to a reduced capacity to increase blood perfusion in their muscles [4]. During progressive exercise in healthy subjects, there is a manifold increase in minute ventilation (VE).

Metabolic production of lactate, an organic anion, is faster during intense exercise in contracting skeletal muscle, and plasma lactate levels are increased. Increases in lactate anions play an important role in changing hydrogen ion concentrations in the plasma and muscles [5]. Potassium is an inorganic cation released from contracting skeletal muscle during exercise due to electrical events at the sarcolemma. Lactate and potassium affect physicochemical properties and the acid-base state of plasma, involving central and peripheral chemoreceptors in the control of ventilation. In fact, the production of lactate anions with the resultant decline in arterial pH during strenuous exercise is associated with an additional ventilatory drive in VE above the lactate threshold [6, 7], and several studies have reported that during exercise plasma potassium and ventilation increase concomitantly [8–10].

In quadriceps muscular biopsies of obese subjects, intracellular amounts of neutral lipids were increased and hypertrophy of the fibers was noted [11]. In obese subjects, a low respiratory exchange ratio indicated a condition of insulin resistance, which persisted during physical activity, implying a preference for lipids [11]. We hypothesized that the amounts of neutral lipids might reflect insulin resistance [12], likely affecting the production of lactate anions, and that hypertrophy might control potassium release on the basis of an increased activity of membrane ATPase that has been described in hypertrophic muscular fibers [13].

In line with these considerations, the present study focuses on ventilation in obese subjects during progressive exercise testing, ventilatory adaptations to increasing effort, the changes in lactic acid and potassium levels and possible correlations.

## Methods

### Patients

Twelve sedentary obese subjects (6 males and 6 females), aged  $27 \pm 4$  years, with a body mass index of  $40 \pm 1.4$  kg/m<sup>2</sup> (SEM) and 12 untrained control subjects (6 males and 6 females), aged  $28 \pm 3$  years, with a body mass index of  $22 \pm 1.6$  kg/m<sup>2</sup> (means

$\pm$  SEM), all without any cardiac and/or respiratory disorders (including nocturnal snoring), volunteered to participate in this study. Before study entry, written informed consent was given by all subjects. The experimental protocol was approved by the Ethics Review Committee of the Institute.

### Methods

After overnight fasting, on the first morning, plasma insulin levels (radioimmunologic assay) and blood glucose were measured in each subject in order to obtain information on insulin sensitivity (quantitative insulin sensitivity check index, QUICKI) [14]. All the subjects reported to the laboratory 2–3 h after dinner, having abstained from alcohol and caffeine for more than 24 h. Nobody was habitual tobacco smoker.

Total lung capacity and its subdivisions were measured in every subject using the closed-circuit helium method, and spirometric flow-volume curves were recorded using a pulmonary function/cardiopulmonary exercise testing instrument (V<sub>max</sub> 229, Sensor Medics, Yorba Linda, Calif., USA). Reference values were those of Knudson et al. [15].

Fat-free mass (FFM) was assessed in every subject by means of a tetrapolar bioelectrical impedance method (BIA 101/S, Akern, Florence, Italy) [16] controlling hydration of each subject with bioimpedance vector analysis [17].

A continuous incremental exercise test was performed on a Gould cycle ergometer with power output increased by 20 W (at 60 rpm) every 4 min until the subject could no longer maintain the pedaling frequency despite verbal encouragement. After exercise termination, the subject was followed for up to 20 min during recovery in a sitting position.

The percutaneous oxygen saturation was determined every 20 s during the test using a Radiometer oximeter, and ECG signals were continuously monitored by a Shiller station AT 60.

The same V<sub>max</sub> 229 ergospirometer was used to collect and analyze respiratory data: VE, oxygen consumption (VO<sub>2</sub>), carbon dioxide production (VCO<sub>2</sub>), and end-tidal oxygen (PETCO<sub>2</sub>) and carbon dioxide pressure (PETCO<sub>2</sub>). Calibrations were performed before each test. Mean values were obtained at baseline and during the last minute of rest and at each power output increase. Ventilatory threshold (VT) was detected in each subject by the V-slope method [18].

Blood was sampled at baseline and during the last 30 s of each power output increase from an indwelling Teflon catheter placed in the right atrium. The catheter was kept patent by flushing with normal saline (0.9% NaCl) and heparin. K<sup>+</sup> concentrations in the samples were analyzed by means of a Radiometer KNA2 Na<sup>+</sup>/K<sup>+</sup> analyzer. Lactic acid was measured by means of Accusport (Boehringer Mannheim, Monza, Italy) at rest, 40, 80, 120 W, and at peak exercise (or only at peak exercise if <120 W).

### Statistical Analysis

All the values obtained at each step of the test were compared between groups by analysis of variance (ANOVA). Dunnett's method was used to determine statistically significant differences ( $p < 0.05$ ) between obese and normal subjects at each step of exercise [19]. Values are expressed as means  $\pm$  SEM. About the relationship between  $\Delta$ VE and  $\Delta$ K<sup>+</sup>, and  $\Delta$ VE and  $\Delta$ lactic acid, we have compared the calculated straight-line regressions considering body mass as a dummy variable Z equal to 1 and 0 for obese and normal subjects, respectively. The model is given by:

$Y = B_0 + B_1X + B_2Z + B_3XZ + E$ , where Y and X are the two considered variables and Z is the dummy variable indicating normal or obese subjects. Based on this approach, we performed appropriate tests for coincidence, parallelism and equal intercepts [20].

## Results

The anthropometric characteristics of the two groups are listed in table 1. Bioimpedance analysis demonstrated higher FFM in the obese subjects, and hydration was within normal limits in both groups. Blood glucose levels were normal ( $89.40 \pm 4.1$  and  $86.90 \pm 3.5$  mg/dl in obese and control subjects, respectively), but plasma levels of

insulin were increased in obese subjects ( $15.01 \pm 1.6$  vs.  $8.97 \pm 1.2$   $\mu$ U/ml,  $p < 0.005$ ). QUICKI indicated a significant reduction in insulin sensitivity in the obese group ( $0.318 \pm 0.004$  vs.  $0.345 \pm 0.003$ ,  $p < 0.01$ ). In both groups, percutaneous oxygen saturation was within the normal range at rest and during the subsequent power output increases up to peak exercise.

Of the spirometric data, expiratory reserve volume, functional residual capacity, residual volume and total lung capacity were significantly decreased in the obese subjects, but there was no significant difference in all the other lung function variables measured (table 2).

Similar to other studies of exercise testing [3], exhaustion was reached at power outputs not significantly different between obese and lean subjects ( $125 \pm 9$  and  $137 \pm 10$  W, respectively,  $p = 0.10$ ), and  $V_T$  was significantly lower in the obese group compared to controls ( $76 \pm 8$  and  $107 \pm 9$  W,  $p < 0.01$ ).  $VO_2$  was significantly higher in obese subjects during exercise and similar at rest, when overcoming  $V_T$  and at the respective peak output. At exhaustion, maximum oxygen uptake (calculated as suggested by Wasserman et al. [21]) was 94 and 83% of theoretical maximal  $VO_2$  in control and obese subjects, respectively.  $VCO_2$  was consistently higher in the obese subjects at every power output (table 3).

Minute ventilation  $VE$  was significantly higher in the obese subjects at lower power output, slightly higher at higher power output and slightly lower at peak exercise. During the test, the increase in  $VE$  was significantly lower in obese subjects ( $\Delta VE$  free pedaling vs. peak exercise: obese subjects  $35.4 \pm 2.9$  SEM, normal subjects  $47.4 \pm 3.2$  SEM,  $p < 0.05$ ). When referred to FFM ( $VE/FFM$ ), its

**Table 1.** Anthropometric and functional data

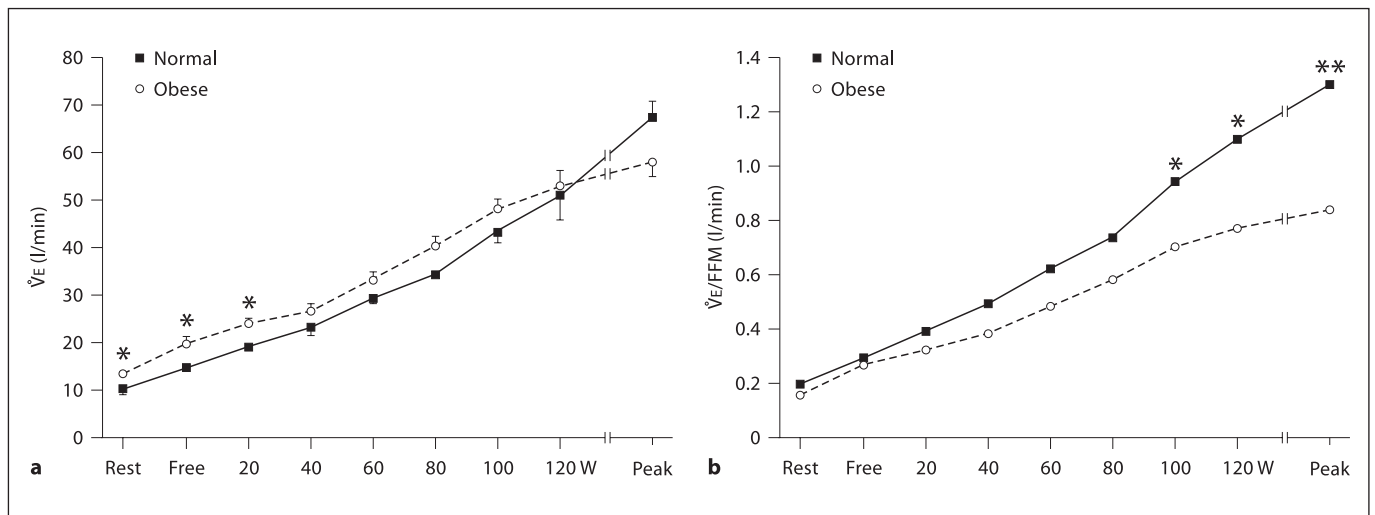
	Normal subjects	Obese patients	p value
Subjects	12	12	NS
Sex, males/females	6/6	6/6	NS
Age, years	$27 \pm 4$	$28 \pm 3$	NS
Weight, kg	$66 \pm 4$	$112 \pm 8$	$<0.001$
Height, cm	$171 \pm 4$	$168 \pm 2$	NS
Body mass index, kg/m <sup>2</sup>	$22 \pm 1.6$	$40 \pm 1.4$	$<0.001$
Fat-free mass, kg	$49 \pm 2$	$71 \pm 3$	$<0.01$
Exercise at exhaustion, W	$137 \pm 10$	$125 \pm 9$	NS
$V_T$ , W	$107 \pm 9$	$76 \pm 8$	$<0.01$

Two-tailed analysis of variance was performed. Values are means  $\pm$  SEM except for sex and number of subjects.

**Table 2.** Lung function data of the subjects

	Normal subjects	Obese patients	p value
VC, liters	$5.1 \pm 0.3$ (112%)	$4.8 \pm 0.3$ (1,087%)	NS
ERV, liters	$1.8 \pm 0.4$ (95%)	$0.9 \pm 0.2$ (78%)	$<0.05$
FRC, liters	$3.7 \pm 0.3$ (110%)	$2.0 \pm 0.1$ (96%)	$<0.001$
RV, liters	$2.3 \pm 0.2$ (135%)	$1.2 \pm 0.2$ (125%)	$<0.05$
TLC, liters	$7.6 \pm 0.7$ (122%)	$5.9 \pm 0.5$ (112%)	$<0.05$
HbO <sub>2</sub> Sat	$96.6 \pm 2.3$	$95.9 \pm 2.1$	NS
DLCO, ml/min/mm Hg	$37.7 \pm 4.3$ (132%)	$36.3 \pm 3.6$ (127%)	NS

Expiratory reserve volume (ERV), functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC) were reported at body temperature and pressure, saturated with vapor at these conditions. Diffusing capacity of the lung for CO (DLCO) was reported at standard conditions. HbO<sub>2</sub> Sat = Percutaneous O<sub>2</sub> saturation of hemoglobin in arterialized blood; VC = vital capacity. Percentages of the predicted lung function data are given in parentheses [15]. Two-tailed analysis of variance was performed. Means  $\pm$  SEM.



**Fig. 1.** VE (a) and VE/FFM (b) during exercise testing in obese and normal subjects. \*  $p < 0.05$ , \*\*  $p < 0.01$ , obese vs. control subjects (ANOVA with Dunnett's method). Free = Free pedaling.

**Table 3.**  $VO_2$  and  $VCO_2$  of normal and obese subjects during exercise testing (modified triangular protocol of Sjöstrand)

Power output	$VO_2$ , ml/min		$VCO_2$ , ml/min	
	normal controls	obese patients	normal controls	obese patients
Rest	380 ± 35	410 ± 40	260 ± 30	310 ± 28
Free pedaling	580 ± 38	820 ± 35**	410 ± 28	620 ± 23*
20 W	670 ± 31	940 ± 42**	580 ± 32	800 ± 28*
40 W	830 ± 30	1,150 ± 40**	710 ± 40	960 ± 36*
60 W	1,080 ± 29	1,400 ± 45**	990 ± 40	1,210 ± 38*
80 W	1,350 ± 29	1,610 ± 46**	1,220 ± 53	1,420 ± 50*
100 W	1,560 ± 32	1,860 ± 45**	1,520 ± 50	1,760 ± 43*
120 W	1,820 ± 48	2,040 ± 43*	1,790 ± 55	1,980 ± 52
Peak values at exhaustion	2,030 ± 153	2,190 ± 110	2,200 ± 135	2,160 ± 105
$V_T$	1,720 ± 146	1,590 ± 98	1,690 ± 122	1,440 ± 95*

Means ± SEM. Except for 120 W (10 normal controls and 8 obese patients), values were obtained from 12 controls and 12 obese subjects. \*  $p < 0.05$ , \*\*  $p < 0.01$ , vs. normal controls; two-tailed analysis of variance and Dunnett's method.

increase was markedly lower in the obese group, with a significantly lower value at peak exercise (fig. 1).

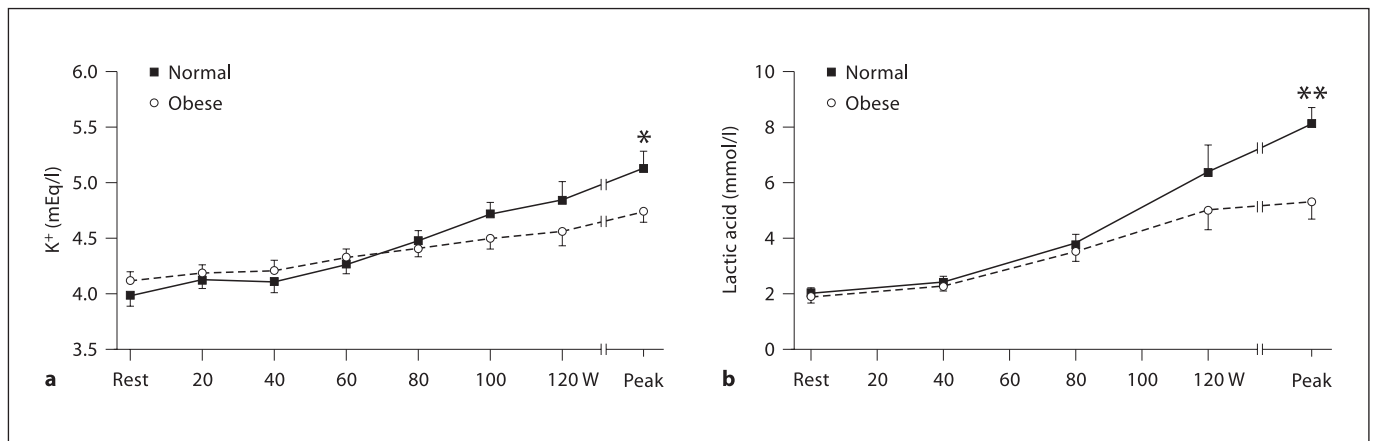
$PETO_2$  tended to be constantly lower in the obese group, while  $PETCO_2$  was quite similar in obese and control subjects at each power output of the exercise test (table 4).

Plasma  $K^+$  levels significantly increased in both groups, with significantly lower values in the obese subjects at maximum exercise (fig. 2a). Lactic acid increased in both

groups with significantly lower values in obese subjects at peak exercise (fig. 2b).

In 4 cases of the two groups (2 males and 2 females), we measured pH (IL Synthesis 25, Instrumentation Laboratory, Lexington, Mass., USA) before the beginning of the test and at peak exercise, and a biochemical correspondence of pH with plasma lactate values was found.

Considering VE and  $K^+$ , and VE and lactic acid, we analyzed their possible correlation by means of delta values



**Fig. 2.** Plasma K<sup>+</sup> (a) and lactic acid (b) during exercise testing in obese and normal subjects. \* p < 0.05, \*\* p < 0.01, obese vs. control subjects (ANOVA with Dunnett's method).

**Table 4.** PETO<sub>2</sub> and PETCO<sub>2</sub> of normal controls and obese patients during exercise testing (means ± SEM)

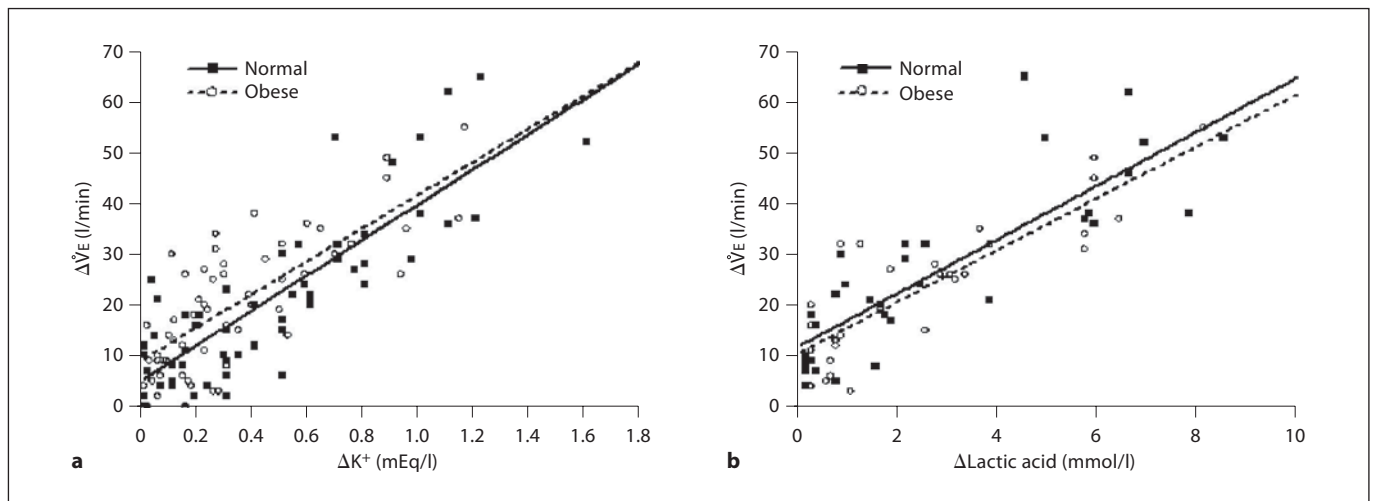
Power output	PETO <sub>2</sub> , mm Hg		PETCO <sub>2</sub> , mm Hg	
	normal controls	obese patients	normal controls	obese patients
Rest	92 ± 2	95 ± 3	37 ± 1	37 ± 1
Free pedaling	89 ± 1.5	82 ± 1*	38 ± 1	38 ± 1
20 W	90 ± 1	83 ± 1.5	38 ± 1.6	38 ± 0.5
40 W	90 ± 2	84 ± 1	39 ± 1	39 ± 0.5
60 W	91 ± 1.5	86 ± 1.5	40 ± 1	39 ± 0.5
80 W	91 ± 2	87 ± 2	40 ± 1.5	39 ± 0.5
100 W	92 ± 2	88 ± 3	40 ± 1	39 ± 0.5
120 W	93 ± 1	90 ± 3	40 ± 1.5	39 ± 1
Peak values at exhaustion	97 ± 2	91 ± 1*	38 ± 1	38 ± 1
V <sub>T</sub>	92 ± 1	87 ± 1	40 ± 1.5	39 ± 0.5

Means ± SEM. Except for 120 W (10 normal controls and 8 obese patients), values were obtained from 12 controls and 12 obese subjects. \* p < 0.05 vs. controls; two-tailed analysis of variance and Dunnett's method.

at rest up to maximal work capacity. In both cases, there was a linear correlation with similar slopes and intercepts between the obese group and the control group ( $\Delta V_E$  vs.  $\Delta K^+$ :  $r = 0.82$ ;  $p < 0.001$  in the control group, and  $r = 0.76$ ;  $p < 0.001$  in the obese group;  $\Delta V_E$  vs.  $\Delta$ lactic acid:  $r = 0.86$ ;  $p < 0.001$  in the control group and  $r = 0.85$ ;  $p < 0.001$  in the obese group; fig. 3a, b).

## Discussion

In the obese subjects, the increase in ventilation during progressive exercise testing up to maximal sustainable work capacity is less than that in normal subjects, especially when considering ventilation in relation to FFM. Nevertheless, ventilation does not appear to be a limiting factor for physical performance in obese subjects since percutaneous oxygen saturation is constantly within normal ranges during the test up to exhaustion. Probably, this may be due to an optimization of their ventilation-perfusion ratio.



**Fig. 3.** Correlation between  $\Delta V\dot{E}$  and  $\Delta K^+$  in plasma (a) and  $\Delta V\dot{E}$  and  $\Delta$ lactic acid (b) during exercise testing in obese and normal subjects. Least-square criterion applying ANOVA to the regression model to calculate straight-line regressions.

Ventilation of obese subjects seems appropriate to remove the increased amount of  $CO_2$  produced at every power output, as indicated by  $PETCO_2$ , being quite similar to controls. On the other hand, the higher  $O_2$  consumption of the obese subjects seems to be attained even through an increased tissue extraction, as indicated by a tendency for lower  $PETO_2$ . Altogether these data agree with the previously established strong correlation between  $VCO_2$  and  $\dot{V}E$  during exercise [22], but at every power output  $\dot{V}E$  is lower than that required to fulfill their increased need for  $O_2$ .

Obesity is classically linked to a condition of insulin resistance [23]. Subjects with insulin resistance have abnormal intramuscular neutral lipid storage, suggesting a major role for obesity in the pathogenesis of type 2 diabetes [12]. In muscular biopsies of the quadriceps vastus femoralis in obese men, one of the major findings was abnormal storage of intracellular neutral lipids [11]. This aspect, therefore, may be in agreement with the condition of insulin resistance in obesity, together with the lower values of the respiratory exchange ratio observed during physical exercise [11]. In the present study, QUICKI provided the information that the insulin sensitivity of the obese group was significantly lower than that of the control group. A lower insulin sensitivity was present in our obese subjects at rest and seemed to be confirmed by the lower increase in plasma lactic acid during physical exercise and at peak exercise.

It is well known that physical stress elicits a release of  $K^+$  from contracting muscles. Its plasma concentrations are regulated by two major mechanisms during and following exercise, i.e. the re-uptake by contracting muscles and the uptake by non-contracting muscles and kidneys [24]. The skeletal muscle  $Na^+-K^+$  pump is associated with  $\alpha$ - and  $\beta$ -adrenergic receptors [25].

In muscular biopsies of the quadriceps vastus femoralis in obese men, another major finding was nonselective hypertrophy of the fibers in the absence of predominance of any fiber type [11]. Hypertrophy may depend on an increased amount of work that is required to move heavier bodies. In agreement with data from a previous study [26], lower maximal plasma  $K^+$  levels were observed in the obese subjects during maximal exercise. It is conceivable that a difference of  $K^+$ , if any, should be in the opposite direction than that observed, due to the larger muscular mass of obese subjects releasing  $K^+$  (increased FFM, higher values of creatine kinase [27]). The results of  $K^+$  could be in line with the hypothesis of an increased density of the  $Na^+-K^+$  pump sites in their skeletal muscles, as it has been observed in trained dogs [13].

Even if peak activity on the whole did not result in significant differences between the two groups, in the present study we chose to study individual increases in  $\dot{V}E$  versus  $K^+$  and  $\dot{V}E$  versus lactate in each subject to obtain a more homogeneous and suitable analysis of the data (fig. 3a, b).

The significantly lower increase in ventilation in the obese subjects during progressive physical exercise may be explained by a reduced chest wall compliance and stiffness of the lungs, which may contain more blood than in a lean subject [1].

Two of the major factors regulating  $V_E$ , e.g. plasma potassium and plasma lactic acid, may be active even in obese subjects. Their lower increases seem to be due to different reasons, i.e. (1) muscular aspects, in accordance with the concept of 'integrative biology' [28], and (2) a condition of insulin resistance, which implies a preferential utilization of lipidic fuel and, thereafter, a reduced increase in lactic acid, especially during heavy work.

Usually, skeletal muscles adapt to exercise so that endurance training increases their capacity for clearance of plasma glucose, free fatty acids and triglycerides [29, 30]. Large intracellular lipid deposits are usually observed in athletes [31] without changes in expiratory exchange ratios and net lactate accumulation [32]. Muscle metabo-

lism plays a role in the health of nonmuscle tissues, and skeletal muscles may condition the regulation of cardiovascular variables such as control of heart rate and blood pressure, and probably other functions [28, 33].

Using a different experimental design based on a constant power output below  $V_T$  and a constant power output above  $V_T$ , Roe et al. [34] found that below  $V_T$   $K^+$  declined over the course of the test while ventilation remained stable, and above  $V_T$  ventilation showed the continued upward drift characteristic of these workloads while  $K^+$  remained constant.

In summary, there are many potential drives to breathe and their potential interactions remain to be elucidated. Nevertheless, in accordance with a number of previous studies, the data of our study seem to stress the involvement of  $K^+$  and lactic acid in the regulation of ventilation during progressive exercise up to exhaustion in light of some neuroendocrinological, morphological and metabolic peculiarities of the obese subject.

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