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ORIGINAL CONTRIBUTION

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Kinetics of catecholamines and potassium, and heart rate during exercise testing in obese subjects

Heart rate regulation in obesity during exercise

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Summary *Background* Obesity is characterised by a marked insulin resistance which involves an abnormal regulation of K^+ uptake and metabolism. Less is known about the effect of physical exercise on K^+ kinetics. *Aim of the study* To assess plasma catecholamines and potassium levels and their relationship with cardiac activity during a physical effort up to exhaustion in young obese subjects. *Methods* Blood samples for epinephrine (E), norepinephrine (NE), potassium (K^+) and heart rate (HR) were collected at the end of every step during a progressive cycloergometric test up to exhaustion in twelve obese subjects (6 males, aged 26 ± 2, BMI 39.9 ± 1) and twelve normal subjects (6 males, aged 28.2 ± 2, BMI 22 ± 1). In every subject anaerobic threshold (AT) was detected. *Results* In obese subjects plasma catecholamines rose faster but had a lower peak in correspondence of maximal work-loads, with respect to controls. Catecholamines had a linear correlation in the obese group and a quadratic one in the control group when plotted vs O_2 consumption. The increase of plasma potassium was less in obesity than in control. *Conclusions* During physical exercise K^+ and catecholamines kinetics differ significantly in obese subjects vs normals and they may justify a less prompt cardiac response at the higher work-loads and a lower work capacity. The present data can be interpreted in the light of the insulin resistance syndrome of obesity, which causes an abnormal regulation of the Na-KATPase and of K^+ channels during physical exercise. The results of the present study may be relevant to nutritionists when suggesting physical exercise to obese subjects.

Key words obesity – exercise testing – heart rate – catecholamines – potassium – insulin resistance

Abbreviations

BMI = body mass index
E = epinephrine
NE = norepinephrine
AT = anaerobic threshold
HR = heart rate

Introduction

Physical stress classically elicits an increase in plasma catecholamines, which contribute to increase heart rate and myocardial contractility [1] and a release of potassium ions from contracting muscles [2]. The sarcolemmal potential change during muscular contraction and the failure of the Na^+-K^+ pump to keep pace with the rate of K^+ loss is thought to be an important mechanism for

the exercise hyperkaliemia [3]. More recently, it has been proposed that the primary mechanism for the exercise hyperkaliemia is linked to a reduction in non-diffusible intracellular anions, which accompanies phosphocreatine hydrolysis in response to exercise, together with simultaneous acid-base changes [4]. Besides the release from contracting muscles, a decrease in plasma volume (hemoconcentration) and a possible release of K^+ from erythrocytes are the other main mechanisms responsible for the rise in plasma K^+ concentrations with exercise [5].

There are two major mechanisms for regulating plasma K^+ concentrations during and following exercise: the re-uptake by contracting muscles and the uptake by non-contracting tissues, including inactive skeletal muscle, and kidneys [5].

The skeletal muscle Na^+-K^+ pump is associated with α- and β-adrenergic receptors [6]. In general, β-adrenoceptor stimulation increases the pump activity, whereas β-adrenoceptor blockade and α-adrenoceptor stimulation reduces it [7]. Catecholamines tend to protect against hyperkaliemia through β-adrenergic stimulation and K^+ re-uptake [6]. It has been experimentally demonstrated that static muscular contractions increase heart rate and arterial pressure [8]. These increases are due to a reflex initiated by the stimulation of group III and IV afferents whose endings are located in the interstitium of the working muscle [9]. An important mechanism by which contractions activate the afferents may be the accumulation of K^+ in the interstitium of the muscle [10]. It can be hypothesized that extracellular K^+ is a well-controlled parameter, mainly connected to systemic limitations with regard to the regulation of arterial blood pressure, ventilation and myocardial stability [11, 12].

We have previously noted that obese subjects undergoing physical effort with increasing work-loads up to exhaustion show a smaller increase in heart rate [13] and a reduced increase of cardiac output relative to their oxygen consumption, when compared to normal subjects [14]. They reach a maximal power output similar to that of a normal subject and, at the same time, a lower AT which may mean a lower work capacity [13].

Because a lower increase in plasma catecholamines has been described during exercise in obese subjects [15], the aim of this study was to assess the kinetics of them and of K^+, which are strictly linked to one another, and look for the best correlation that might be between HR and catecholamines, and HR and K^+.

Methods

Subject population

Twelve obese subjects (6 males, 6 females aged 26 ± 2, BMI 39.9 ± 1) and 12 normal subjects (6 males and 6 females, aged 28 ± 2, BMI 22 ± 1), all untrained and without any cardiac and/or respiratory disorder, were studied.

Experimental protocol

Fat-free mass was assessed in each subject of the two groups by means of a tetrapolar bioelectrical impedance method (BIA 101/S, Akern, Florence, Italy) with an error of 2.7 % compared to densitometry, which is the reference method [16]. Each subject performed on a cycle ergometer Gould an exercise test, at least 3 hours after lunch, with progressive 20 W increases every four minutes until the subject could no longer maintain pedalling frequency (60 rpm). An ergospirometer MMC Horizon TM System 4400 TC (Sensor Medics) determined pulmonary ventilation $\dot{V}E$, O_2 uptake ($\dot{V}O_2$), and CO_2 production ($\dot{V}CO_2$) on a breath-by-breath basis. We used the average values from the last fourth minute of each step. Heart rate data were recorded at the end of every workload up to exhaustion by a Cardiovit AT-60 (Schiller).

The goal for each participant was to reach at least 85 % of maximal predicted HR.

AT was determined using the V-slope method (analysis of the straight line relations of $\dot{V}CO_2$ vs. $\dot{V}O_2$) [17], which has advantages over the traditional methods [18–20] that depend on regular breathing pattern and respiratory chemosensitivity.

Analytical determinations

One hour before the test, a catheter was inserted into a dorsal vein of the right forearm and driven up to the right atrium. The catheter was kept patent by flushing with normal saline (0.9 % NaCl). Blood samples for the determination of catecholamines and K^+ were collected in 5-ml heparinized syringes at rest in the sitting position, during the last 20 s of each 4-min work-load, at exhaustion and during the subsequent recovery.

Plasma was analyzed for K^+ concentrations with a Kodak Ektachem DT60 analyzer. A high-performance liquid chromatography (HPLC) [21] method was used to determine plasma E and NE. Using HPLC, our laboratory data on the same sample of plasma in a number of determinations over time have low coefficients of variation (5.4 % for E and 5.8 % for NE).

The institutional ethics committee approved the investigation, and each volunteer gave his informed consent.

Statistical analysis

$\dot{V}O_2$, heart rate and K^+ obtained at each step of the test were compared between groups by analysis of variance (ANOVA). Dunnett's method was used to determine the statistical difference of the above parameters between obese and normal subjects at each step of exercise [22]. A difference was considered statistically significant for $p < 0.05$. Values were expressed as mean ± SEM. We used the least-squares criterion applying ANOVA to the regression model to calculate the straight-line or quadratic regressions [23]. Considering the relationship between K^+ and HR, we 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: $Y = B0 + B1X + B2Z + B3XZ + E$, 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 [23].

Results

Anthropometry and body composition data are reported in Table 1.

Table 1 Anthropometric data*

	Normal subjects (range)	Obese subjects (range)	P Value[a]
No. of subjects	12	12	NS
Sex (M/F)	6/6	6/6	NS
Age (years)	28±2 (19–39)	26±2 (17–42)	NS
Weight (kg)	65±3 (49–85)	111±9 (91–144)	< 0.001
Height (cm)	170±3 (154–194)	165±3 (150–180)	NS
BMI (kg/m^2)	22.2±1 (19–25)	39.9±1 (35–46)	< 0.001
Body surface (m^2)	1.7±0.1 (1.4–2.1)	2.2±0.1 (1.9–2.5)	< 0.01
Fat-free mass (Kg)	50.1±3.9 (33–70)	70.7±4.1 (54–83)	< 0.01

* Values are mean ± SEM. In parentheses, the ranges of anthropometric data are given. *BMI* body mass index; [a] By two tailed analysis of variance

Exercise testing data

Exercise exhaustion was reached at power outputs not significantly different for obese and lean subjects (respectively 124 and 137 W). AT was at similar levels of $\dot{V}O_2$, but at significantly lower mean external work loads in the obese subjects (79 vs 109 W, $p < 0.05$).

$\dot{V}O_2$ was significantly higher in the obese subjects at each work load and similar at rest and at the respective peak exercise work rates (Table 2).

HR rose in obese as well as in control subjects, and it was higher in the obese subjects at rest, at free pedalling up to a work rate of 40 W; at exhaustion it was lower in obese than in controls (Table 2). Obese subjects were not able to attain 85 % of predicted maximum HR, in spite of the fact that the attained work-load did not permit the maintenance of the pedalling frequency of 60 rpm.

Analytical data

Both E and NE had a different time course: they rose faster and with a lower peak at maximal power outputs in the obese subjects, later and with a higher peak at maximal power outputs in controls (Fig. 1 A, B). If E is plotted vs $\dot{V}O_2$ and HR, a linear regression is detectable in the obese group (respectively: r: 0.48; $p < 0.001$ vs $\dot{V}O_2$ and r: 0.48 $p < 0.001$ vs HR) and a quadratic regression in the control group (respectively: r: 0.71; $p < 0.001$ vs $\dot{V}O_2$ and r: 0.57; $p < 0.001$ vs HR) (Fig. 2 A, B). NE plasma levels vs $\dot{V}O_2$ have a linear regression in the obese group

Table 2 Oxygen uptake ($\dot{V}O_2$), heart rate of normal and obese subjects during exercise testing (modified protocol of Sjöstrand)[a]

Work load	$\dot{V}O_2$ (ml/min)		Heart rate (beats/min)	
	Normal subjects	Obese subjects	Normal subjects	Obese subjects
Rest (n = 12.12)	360±40	450±30	78±2	92±3**
Free Pedalling (n = 12.12)	490±40	820±40**	85±3	106±4**
20 W (n = 12.12)	660±30	970±40**	99±4	114±3*
40 W (n = 12.12)	820±30	1100±40**	108±3	120±4*
60 W (n = 12.12)	1060±30	1370±40**	121±4	128±4
80 W (n = 12.12)	1280±30	1570±50**	133±7	137±4
100 W (n = 12.10)	1540±40	1810±50**	147±7	144±5
120 W (n = 10, 7)	1760±60	1970±40*	153±6	151±5
Max. peak (n = 12.12)	1990±170	2070±120	172±3	156±4*
AT (n = 12.12)	1760±190	1520±90	149±3	136±4*

[a] Values are mean ± SEM. *AT* anaerobic threshold; * = $p < 0.05$; ** = $p < 0.01$ by two-tailed analysis of variance and Dunnett's method

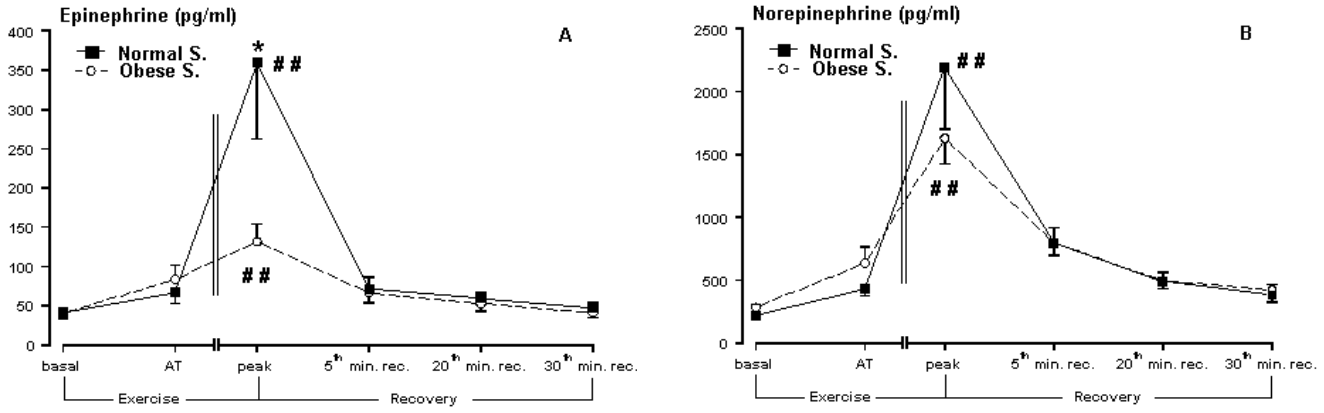

Fig. 1 Plasma epinephrine and norepinephrine during and after exercise testing in obese and normal subjects. Asterisks indicate the significance between rest values and peak activity values (# # $p < 0.05$), and between obese and control subjects at peak activity (* $p < 0.05$)(ANOVA with Dunnett's method)

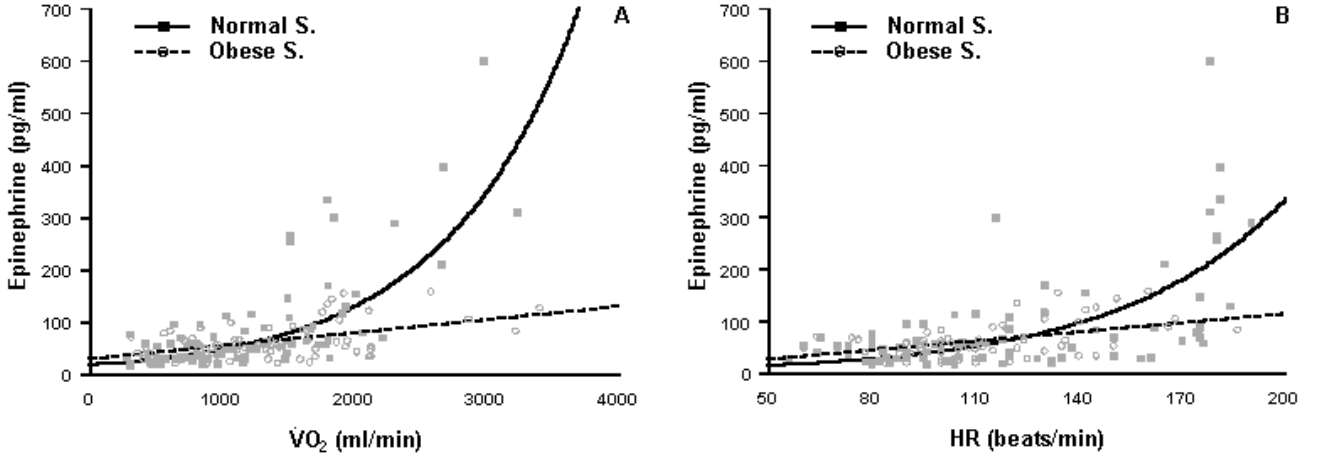

Fig. 2 **A** Relationships between plasma epinephrine and $\dot{V}O_2$ in normal and obese subjects; **B** Relationships between plasma epinephrine and HR in normal and obese subjects (data partly published in J Clin Basic Cardiol (1999), 2: 229–236) (Least-squares criterion applying ANOVA to the regression model to calculate the straight-line or quadratic regressions)

(r:0.77; $p < 0.001$) and a quadratic one in the control group (r: 0.63; $p < 0.001$) (Fig. 3 A), while NE vs HR have quadratic regressions in both groups (r: 0.73; $p < 0.001$ in the obese group and r: 0.72; $p < 0.001$ in the control group) (Fig. 3 B).

Basal serum K^+ levels were similar between obese and control subjects. In both groups they significantly increased during exercise and abruptly fell to levels equal to basal levels during recovery (Table 3). As a whole, the obese subjects had significantly lower increments in plasma K^+. In particular, they showed less increases at work-loads before AT, and higher increases at work-loads after AT, when compared to controls (Fig. 4).

In the normal subjects the ratio $\Delta K^+/\Delta$ work rate was 0.061 ± 0.012 mmol/L/10 W below the AT and 0.153 ± 0.034 mmol/L/10 W above the AT ($p < 0.05$); in the obese subjects the ratios were 0.011 ± 0.010 and 0.099 ± 0.031, respectively ($p < 0.05$). $\Delta K^+/\Delta$ work rate below AT was significantly higher in normal subjects when compared to obese subjects ($p < 0.05$) while it was not significantly different above AT. The increases in ΔK^+ above AT relative to those below AT were 251 % in the normal subjects and 825 % in the obese subjects, respectively.

Both in controls and in obese subjects there was a linear correlation with the same slope and the same intercept in the plot of HR vs plasma potassium (r: 0.61; $p < 0.001$ in the control group and r: 0.58; $p < 0.001$ in the obese group) (Fig. 5).

Discussion

In this study we describe heart rate, plasma catecholamines and potassium responses of obese, otherwise healthy, subjects to increasing workloads and compare them to normal control subjects matched for age

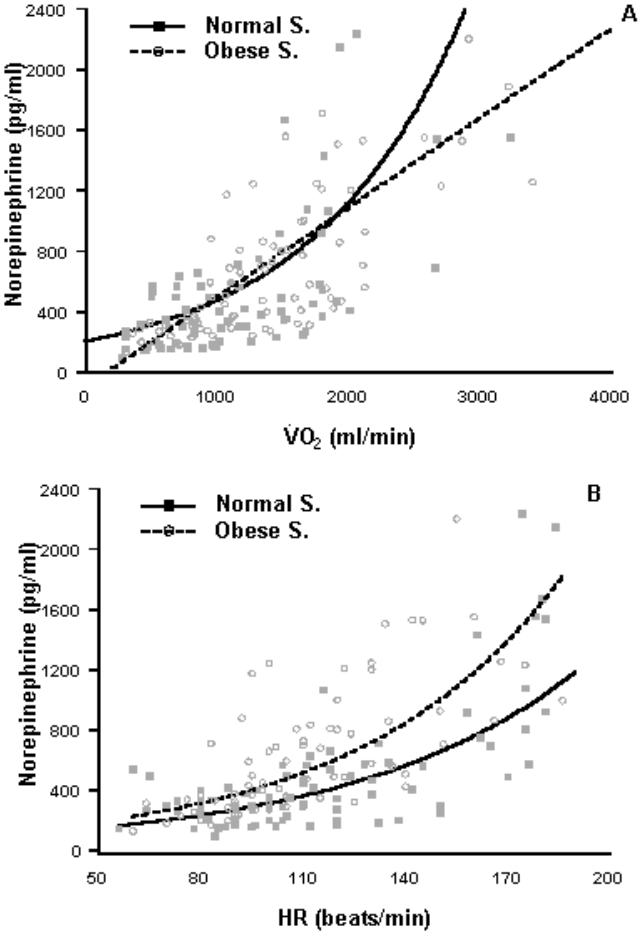

Fig. 3 **A** Relationships between plasma norepinephrine and $\dot{V}O_2$ in normal and obese subjects; **B** Relationships between plasma norepinephrine and HR in normal and obese subjects (Least-squares criterion applying ANOVA to the regression model to calculate the straight-line or quadratic regressions)

Table 3 K^+ (meq/l) during exercise testing and recovery[a]

Work load	Normal subjects	Obese subjects
Basal (n = 12.12)	4.06±0.1	4.19±0.09
20 W (n = 12.12)	4.06±0.1	4.12±0.09
40 W (n = 12.12)	3.94±0.1	4.16±0.08
60 W (n = 12.12)	4.23±0.08	4.30±0.05
80 W (n = 12.12)	4.46±0.08	4.41±0.08
100 W (n = 12.10)	4.62±0.11	4.49±0.09
120 W (n = 10.7)	4.73±0.17	4.53±0.14
Max. peak (n = 12.12)	5.07±0.15 °	4.71±0.11* °
AT (n = 12.12)	4.81±0.13	4.28±0.09**
5th min recovery (n = 12.12)	4.15±0.07	4.25±0.07
20th min recovery (n = 12.12)	3.98±0.12	4.00±0.08
30th min recovery (n = 12.12)	4.12±0.08	4.13±0.07

[a] Values are mean ± SEM. *AT* anaerobic threshold; * ° p values by two-tailed analysis of variance and Dunnett's method.
• significant difference compared to controls; ° significant difference compared to basal values; ° * = $p < 0.05$; ** = $p < 0.01$

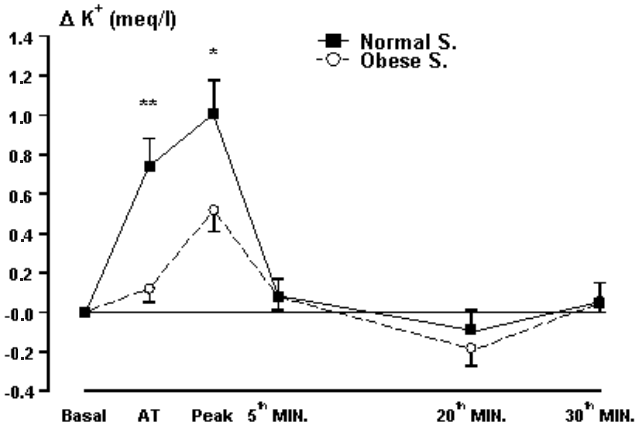

Fig. 4 Delta plasma potassium during exercise testing and the subsequent recovery in both groups. Asterisks indicate the significant difference between obese and normal subjects at AT and peak activity (* $p < 0.05$, ** $p < 0.01$)(ANOVA with Dunnett's method)

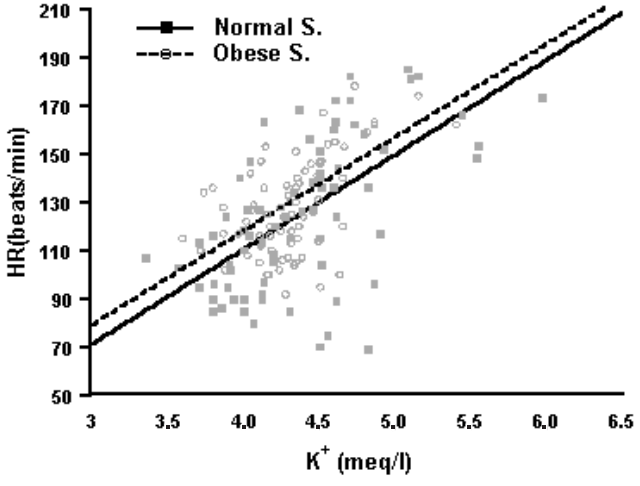

Fig. 5 Relationships between plasma potassium and HR in normal and obese subjects (Least-squares criterion applying ANOVA to the regression model to calculate the straight-line regressions)

and sex. The cycle ergometer test was used to obtain accurate information about performed work output and cardiac function [24].

It appears that in obese subjects, the increase in heart rate during a progressive physical exercise is less than that observed in non-obese subjects for two reasons: 1) basal heart rate and heart rate at low power outputs are higher, and 2) the maximal heart rate reached is lower than in controls. This observation may be in accordance with their reduced increase of cardiac output when plotted vs oxygen consumption and the reduced ratio cardiac output/fat-free mass when plotted vs external work rates [14]. The smaller slope of these correlations seems to make it reasonable to reduce their work capacity due to the unfavorable situation of muscle perfusion.

The present data on plasma potassium show a

smaller increase in obese subjects with respect to lean controls during exercise.

It is conceivable that a difference of K^+, if any, should be in the opposite direction due to the larger muscular mass of obese subjects releasing K^+. This assumption is confirmed by constantly higher values of CK enzyme previously found by us in obese subjects at rest and during physical activity [25]. Again, it has been shown that during maximal exercise two-thirds of an increase of plasma concentration of metabolites are due to hemoconcentration and one-third to its true increase in plasma content [26]. The decrease of blood volume is due to a shift of water from the plasma compartment into the interstitial and intracellular compartments of contracting muscles [27, 28]. Unfortunately, we have no direct or indirect measure of variation in hemoconcentration during exercise. Nevertheless, due to the probably larger muscular mass, it should be reasonable to suppose a more pronounced hemoconcentration in the obese group, and therefore higher, rather than a lower increase of K^+. Thus, possible explanations of the present data are 1) acute increase of K^+ uptake by contracting muscle during physical exercise (in contrast of the blunted K^+ uptake of basal condition secondary to insulin resistance) and 2) increased K^+ excretion as urine or sweat.

It has been previously demonstrated that the increase of K^+ is linear with exercise intensity [5] and that training results in a blunting of the exercise-induced rise [29]. This is probably due to an increased concentration of the Na^+-K^+ pump in skeletal muscles, as it has been observed in trained dogs [30]. The contraction of a larger muscular mass may justify the trend to higher values of plasma NE and E that we have reported at the lower power outputs in the obese subjects and, consequently, the initial lower increase in plasma K^+ before AT, likely due to a higher muscular re-uptake mediated by β-receptors activity. Subsequently, corresponding to submaximal and maximal power outputs, the low increase in plasma E and NE may be in line with the greater slope of increase in plasma K^+ in the obese subjects. The contrary seems to occur in the controls.

The data of plasma catecholamines in obese subjects that we present are substantially in accordance with those of previous reports [15], with a reduced response in correspondence of maximal power outputs when compared to controls. The obese subjects tend to have higher plasma levels at lower power outputs, that is below A. T., especially in NE, when compared to controls. Exercise-induced catecholamine responses are related to exercise intensity and affected by the preceding training regimen [31]. The relative exercise intensity is an important determinant of the catecholamine response because their concentration rises exponentially when exercise intensity progresses from moderate to maximal [32]. The absolute exercise intensity is also a determinant of their response because of the role played by the muscle mass involved in the activity. This is evident in one study in which the increments in plasma E and NE concentrations were more than twofold greater during two legs cycling than during one leg cycling [33], and in a second study where the increment in muscle sympathetic nerve activity in the leg was greater when isometric hand grip exercise was performed with both arms than when it was performed with one arm [34].

The linear correlations of E and NE vs $\dot{V}O_2$ in the obese subjects and the exponential ones in the control subjects may be indicative of different neuro-biological responses to physical exercise in the two groups that we have studied.

The plots of plasma E and NE vs HR during physical exercise were different in the two groups, while those between plasma K^+ vs HR correlated linearly in normal as well as in obese subjects, with no significant difference in intercepts and slopes.

These observations seem to agree with the possibility that K^+-mediated reflex responses to muscular contractions may play an actual role in the regulation of cardiac activity during physical exercise.

K^+ is likely related to the different behaviors of catecholamines below and above AT, in accordance with Tanabe et al. [35], who measured arterial K^+. Its overall lower increase may condition the less prompt cardiovascular answer of the obese subjects at the higher work-loads.

The lower maximal plasma K^+ levels reached by the obese subjects could be due to the increased amount of work that is always requested by the muscular mass to move heavier bodies, and therefore to an increased skeletal muscle Na^+/K^+-ATPase activity [36]. Recently, the observation of increased units of Na-KATPase was confirmed in leukocytes and erythrocytes of obese subjects [37, 38].

The data of the present work could be considered by nutritionists when suggesting the loads of physical exercise programs for obese subjects with respect to weight-reduction, since training generally assumes the attainment of a given heart rate.

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