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Left ventricular function response to exercise in normotensive obese subjects: influence of degree and duration of obesity

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This study has been designed to evaluate whether duration and severity of obesity can influence lef ventricular function response to exercise in obese subjects without other known cardiovascular ris factors such as hypertension, diabetes or hyperlipoproteinemia. A total of 29 obese subjects wer included and they were divided, according to their body mass index and to Garrow's criteria as follows *Overweight or mildly obese subjects*: body mass index from 25 to 30 kg/m^2; *moderately obese subjects* body mass index > 30 and < 40 kg/m^2. Both obese groups were further subdivided according to thei duration of obesity evaluated by accurate anamnesis in subgroup A (duration of obesity less than 12 months) and subgroup B (duration of obesity more than 120 months). Left ventricular ejection fractio was detected by blood pool gated radionuclide angiocardiography both at rest and after symptom-limite bicycle ergometer procedure. At peak exercise left ventricular ejection fraction increased significantl ($p < 0.05$) only in overweight subjects. Exercise produced an increase of left ventricular ejection fractio in 14 overweight and in 5 moderately obese subjects and a decrease in 2 moderately obese subjects. A peak exercise mean heart rate and mean blood pressure increased significantly ($p < 0.001$) in bot groups. When obese subjects were subgrouped according to duration of obesity, left ventricular ejectio fraction increased significantly ($p < 0.05$) only in overweight subjects with duration of obesity less tha 120 months. Duration of obesity correlated inversely with percent change in left ventricular ejectio fraction (EF) at peak exercise (ΔEF) ($r = -0.59$; $p < 0.001$). No correlation between body mass inde and ΔEF and between EF at rest and ΔEF was observed.

Our results suggest that higher degree and higher duration of obesity can impair left ventricula function response to exercise. In view of this, a noninvasive evaluation of left ventricular function coul

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be useful to detect cardiac dysfunction early in subjects with higher degree and higher duration of obesity.

Key words: Left ventricular function; Obesity

Introduction

Obesity is often associated with modifications in cardiac function, including increased cardiac output, blood and cardiac volumes, elevated left ventricular filling pressure, decreased peak filling rate and presence of left ventricular hypertrophy even in the absence of systemic hypertension [1–5].

Previous studies have also demonstrated that resting left ventricular dysfunction can occur in asymptomatic obese subjects [3,6,7]. In addition, Alpert et al. [8] have recently reported that increased left ventricular mass could predispose morbidly obese subjects to impairment of left ventricular systolic function during exercise.

On the other hand, few data are available about the influence of degree and duration of obesity on left ventricular function both at rest and after exercise, in obese subjects without other associated cardiovascular risk factors, such as hypertension, diabetes, hyperlipoproteinemia. In a previous study we described an inverse correlation among resting left ventricular ejection fraction and both body mass index and duration of obesity in normotensive obese subjects selected to other known risk factors for cardiovascular disease. In this study ejection fraction values were lower in the subgroup of obese subjects with a higher degree and higher duration of obesity [3]. Since ejection fraction at rest is not necessarily synonymous to an impairment of left ventricular function, the present study has been designed to evaluate the effects of exercise on left ventricular ejection fraction in normotensive and healthy subjects with overweight or moderate obesity, with special reference to subgroups with higher or lower duration of obesity.

Our final goal was to investigate whether degree and duration of obesity can influence left ventricular function exercise response. Therefore, an attempt has been made to eliminate confounding factors such as diabetes, lipid abnormalities, hypertension and increased left ventricular mass.

Materials and Methods

Patient selection and protocol evaluation

A total of 29 obese subjects were recruited from all obese individuals attending the obesity centre of the Medical Pathology Institute at the University of Palermo (Italy). They were totally unselected regarding duration and degree of obesity, glucose tolerance, blood pressure and other known cardiovascular risk factors. After this recruitment phase, exclusion criteria included insulin-dependent or -independent diabetes mellitus, hyperlipoproteinemia, hypertension, cardiovascular diseases (including chest pain, myocardial infarction, valvular diseases, ventricular arrhythmias and heart failure), endocrine diseases, alcoholism, drug addiction and psychiatric problems.

A medical history, physical examination, resting and Holter electrocardiogram, chest X-ray, echocardiogram, 201-thallium myocardial scintigraphy, left ventricular function evaluated by equilibrium angiocardiography at rest and during supine bicycle exercise were performed on each patient.

Obese subjects were divided into two groups, according to their body mass index values and Garrow's criteria [9] as follows:

Overweight or mildly obese subjects. This group consisted of 15 subjects (6 males and 9 females) aged 30–51 yr (mean age: 41.13 ± 2.64) with body mass index ranging from 25 to 30 kg/m^2 (mean value: 26.84 ± 0.29).

Moderately obese subjects. This group consisted of 14 subjects (5 males and 9 females) aged 31–55 yr (mean age: 43.78 ± 2.52) with body mass index

TABLE 1

Details of overweight and moderately obese subjects (mean value ± SEM).

	Overweight ($n = 15$)	Moderately obese ($n = 14$)
Age (yr)	41.13 ± 2.64	43.78 ± 2.52
Sex (M/F)	6/9	5/9
BMI (kg/m^2)	26.84 ± 0.29	32.80 ± 0.78 *
Height (m)	1.65 ± 0.03	1.64 ± 0.04
DO (months)	95.1 ± 8.89	178.6 ± 27.44 **
HR (beats/min)	76 ± 1.2	80 ± 1.4
SBP (mmHg)	121.5 ± 1.9	124 ± 1.5
DBP (mmHg)	76.3 ± 1.4	80 ± 1.1
MBP (mmHg)	91.5 ± 1.4	94.6 ± 1.2
LVM (g)	160 ± 7.74	171.5 ± 6.97
LVMI (g/m^2)	84 ± 4.64	90 ± 3.87

BMI = body mass index; DO = duration of obesity; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; LVM = left ventricular mass; LVMI = left ventricular mass index. * $p < 0.05$; ** $p < 0.01$.

$> 30 < 40$ kg/m^2 (mean value: 32.80 ± 0.78). In both groups age, sex, body height, systolic, diastolic and mean blood pressure and heart rate were similar (Table 1).

The heart rate was detected from the electrocardiogram and systolic and diastolic blood pressures were measured from the average of three measurements after 5 min in a comfortable supine position, using a mercury sphygmomanometer. Diastolic blood pressure refers to Korotkoff phase V. Mean blood pressure was calculated from the sum of diastolic blood pressure plus one-third of the arterial pulse pressure. Arterial pressure was measured with an appropriate large cuff in obese patients [10]. Patients were considered to be normotensive if they had no history of systemic hypertension and had at least 3 blood pressure measurements less than 140/90 mmHg during out-patient visits at least 1 week apart.

All the obese subjects with increased left ventricular mass or left ventricular mass index, using M-mode echocardiographic criteria [11,12] or with unsatisfactory echocardiographic finding, were also excluded. Before the study started, 20 subjects (12 overweight and 8 moderately obese subjects) had been untreated, while 9 (3 overweight and 6 moderately obese subjects) had received a hypocaloric diet and 3 moderately obese subjects had taken fenfluramine (18 mg daily). All the overweight and moderately obese subjects were untreated for at least 4 weeks before the study. During this withdrawal period no significant changes in body weight were observed in either overweight subjects (body weight value from baseline to end of withdrawal period: 70.55 ± 1.72 vs 71.90 ± 1.50 kg) or in moderately obese subjects (79.25 ± 1.35 vs 81.25 ± 1.75 kg).

The subject's fat distribution was assessed by measurement of the waist to hip girth ratio to detect whether obese subjects suffered from abdominal or diffuse obesity, since abdominal obesity (waist to hip girth ratio > 1) has been reported to be a higher cardiovascular risk factor [13,14]. The waist girth was measured at the level of the umbilicus and the hip girth at the level of the superior iliac spine, as described by Larsson et al. [13].

No significant change in waist to hip girth ratio was observed between overweight subjects (0.96 ± 0.006) and moderately obese subjects (1.00 ± 0.005) or between males (1.01 ± 0.004) and females (0.97 ± 0.05), according to our preliminary unpublished data related to an epidemiologic study on the population of western Sicily (district of Palermo, Italy). The duration of overweight or obesity was evaluated by accurate anamnesis [15] and was 95.1 ± 8.9 months and 178.6 ± 27.4 months, respectively, in overweight and in moderately obese subjects.

Overweight and moderately obese subjects were further divided into two subgroups according to the duration of obesity: subgroup A included patients who had been obese for less than 120 months and subgroup B those who had been obese for more than 120 months. The chosen limit of 120 months was selected to provide a sufficient number of subjects among overweight and moderately obese subjects to evaluate the co-variance between degree and duration of obesity on left ventricular ejection fraction exercise response.

The study was approved by the Sicily Region Ethical Committee and each patient gave informed consent after a detailed description of the

study procedure. Preliminary investigations included measurements of blood and urinary electrolytes, creatinine clearance, fasting blood sugar and oral glucose tolerance test, serum cholesterol, triglyceride levels and liver function tests.

Methods

Left ventricular ejection fraction was measured using the radionuclide blood pool gated method according to Bonow et al. [16], a technique already validated in our laboratory and used in evaluation of cardiac function in obese individuals [4]. Radionuclide angiography was performed at 9.00 a.m. at rest and during maximal supine bicycle exercise using red blood cells labeled with 20–25 mCi Tc^{99m} and a conventional Anger Camera (Starcam 300; General Electric) equipped with a high sensitivity, parallel-hole collimator oriented in left anterior oblique position to isolate the left ventricle. A minimum of 300,000 counts was acquired for each study.

High temporal resolution (10–20 ms/frame) cardiac image sequences were constructed by computer-based ECG gating, with the use of list mode data acquisition with exclusion of extrasystolic and postextrasystolic cycles and combined forward and reverse gating from the R wave. Left ventricular time activity curves, representing relative changes in left ventricular volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction with a fixed left ventricular region of interest, which was constructed automatically to conform to the borders of the left ventricle as identified from the end-diastolic image, the stroke volume image, and the amplitude image. This latter functional image was created by approximating each single pixel time-activity curve with the first harmonic of its temporal Fourier expansion. The time-activity curve was constructed from the raw image sequence without spatial or temporal smoothing processes. Index of left ventricular function was derived by computer analysis of the background corrected time-activity curves. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. In our laboratory normal left ventricular ejection fraction is $\geq 55\%$ and normal exercise response is an increase in left ventricular ejection fraction $\geq 5\%$, according to others [8].

A maximal exercise test was performed on a supine bicycle ergometer and images were acquired in the same projection as the resting study. Using a supine bicycle ergometer, patients were exercised at 25 W workload increases. After an initial warming-up period of 2 min, the patients exercised at a constant speed; the initial workload was 25 W and the load was increased by 25 W every 3 min until the appearance of limiting symptoms. These symptoms were classified as dyspnea, chest pain or fatigue.

No patients developed high-grade ventricular arrhythmias necessitating termination of exercise. Heart rate (automatically) and blood pressure (by cuff sphygmomanometer) were monitored during exercise at each stage. Imaging was begun after the onset of exercise and data series that occurred during maximal exercise (including approximately the final 3 min of exercise) was selected to analyze the left ventricular ejection fraction response to exercise.

Statistical analysis

All results in the tables and in the text are expressed as mean value $\pm$ standard error of the mean (SEM). The differences among basal and at peak exercise left ventricular ejection fraction in both groups were analyzed by one-way analysis of variance. Correlation coefficients were performed using linear regression analysis. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

The study population consisted of 29 subjects, 11 males and 18 females. No significant differences in age, height, heart rate, systolic, diastolic and mean blood pressure, left ventricular mass and left ventricular mass index were observed between overweight and moderately obese subjects (Table 1). Body weight, body mass index and duration of obesity increased significantly in mod-

TABLE 2

Left ventricular ejection fraction (LVEF) at rest and at peak exercise in overweight and in moderately obese subjects (mean value ± SEM).

	LVEF (%)	
	Rest	Exercise
Overweight ($n = 15$)	60.4 ± 1.41	65.9 ± 1.20 *
Moderately obese ($n = 14$)	58.2 ± 1.17	59.8 ± 1.53

* $p < 0.05$ vs rest.

erately obese subjects in comparison with overweight individuals (Table 1).

Effect of exercise on left ventricular ejection fraction

A small and non-significant decrease in resting ejection fraction was found in moderately obese subjects in comparison with overweight subjects (Table 2). Exercise produced an increase in ejection fraction, but this was significant only in overweight subjects ($p < 0.05$) (Table 2).

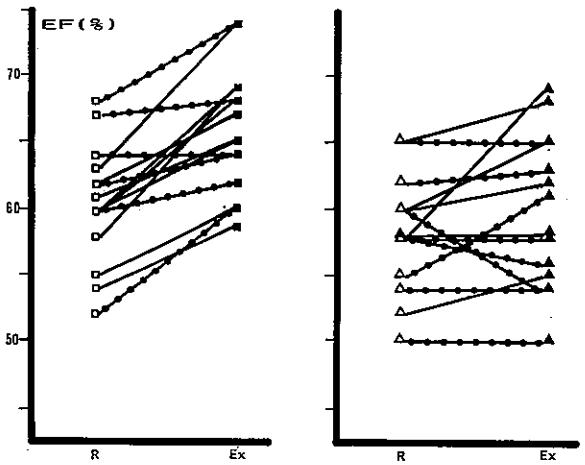

Fig. 1. Left ventricular ejection fraction at rest and after exercise in overweight and in moderately obese subjects. EF = ejection fraction; R = rest; Ex = Exercise; □ = overweight subjects; △ = moderately obese subjects; ——— = subjects with duration of obesity < 120 months; ●———● = subjects with duration of obesity > 120 months.

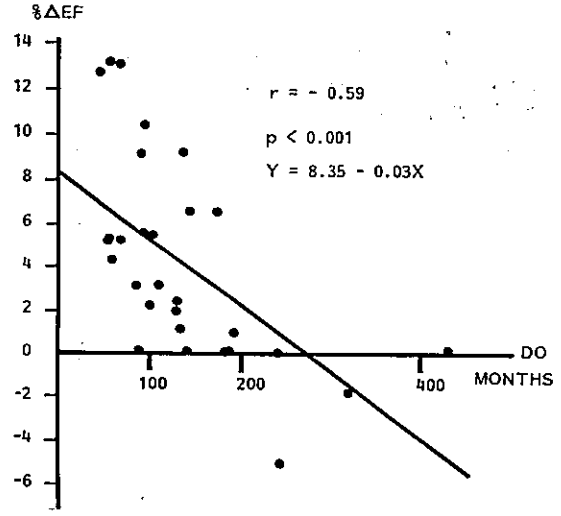

Fig. 2. Correlation between duration of obesity and percent change in left ventricular ejection fraction at peak exercise in all overweight and moderately obese subjects. %ΔEF = percent change in left ventricular ejection fraction at peak exercise; DO = duration of obesity.

A detailed analysis of our patients has shown that at peak exercise, ejection fraction increased in 14 overweight subjects (more than 5% in 10 subjects and less than 5% in 4 subjects) and only in 1 subject did it remain unchanged. At peak exercise ejection fraction increased in 7 moderately obese subjects (more than 5% in 3 subjects and less than 5% in 4 subjects), and it remained unchanged in 5 patients and decreased in the other 2 (Fig. 1).

In both groups exercise produced a significant increase ($p < 0.001$) both in mean heart rate (39.3 ± 3 beats/min and 40 ± 2 beats/min, respectively, in overweight and in moderately obese subjects) and in mean blood pressure (25 ± 1.9 mmHg and 30 ± 2.7 mmHg, respectively, in overweight and in moderately obese subjects).

The mean workload was 72 ± 1.8 W in overweight subjects and 70 ± 1.5 W in moderately obese patients.

Influence of duration of obesity on ejection fraction exercise response

When obese subjects were subgrouped according to duration of obesity, exercise produced a

TABLE 3

Left ventricular ejection fraction (LVEF) at rest and at peak exercise in obese subjects subgrouped according to the duration of obesity (mean value ± SEM).

Overweight		Moderately obese	
A ($n = 9$)	B ($n = 6$)	A ($n = 6$)	B ($n = 8$)
LVEF rest (%)			
59.2 ± 1.01	62.1 ± 2.37	58.8 ± 1.71	57.7 ± 1.67
LVEF exercise (%)			
66.2 ± 1.55 *	65.3 ± 2.04	62.8 ± 2.26	57.6 ± 1.79

Group A = duration of obesity < 120 months; Group B = duration of obesity > 120 months. * $p < 0.05$ vs rest.

significant increase ($p < 0.05$) in ejection fraction only in overweight subjects with a duration of obesity less than 120 months (Table 3).

A detailed analysis demonstrated that all the overweight subjects with a peak exercise ejection fraction increased less than 5% (4 patients) or unchanged (1 patient) had a duration of obesity more than 120 months (Fig. 1). Similarly, the two moderately obese subjects with a decreased peak exercise ejection fraction had a duration of obesity more than 120 months (Fig. 1).

Correlations

Duration of obesity correlated inversely with percent change in ejection fraction at peak exercise (ΔEF) ($r = -0.59$; $p < 0.001$). No correlation between body mass index and ΔEF ($r = -0.30$) and between resting ejection fraction values and ΔEF ($r = 0.04$) was found.

Discussion and Conclusions

Left ventricular function has been studied by several authors in obese subjects and despite data on increased cardiac output, intravascular and cardiac volumes in obesity [1,3,5–7], there is disagreement concerning the effects of obesity on left ventricular contractile state [7,17–19].

Previous studies assessing left ventricular systolic function in extremely normotensive obese subjects have focused on hemodynamic parameters obtained at rest. Garcia et al. [19] reported depressed left ventricular fractional shortening in 6 of 15 massively obese patients. In addition De Divitiis et al. [6] demonstrated that left ventricular V_{max} correlated inversely with body weight in 10 obese subjects, suggesting that impaired myocardial contractility may play a role in the development of left ventricular systolic dysfunction in such individuals.

We made similar observations in our previous investigation of 44 asymptomatic obese subjects subgrouped according to their degree and duration of obesity in comparison with 23 matched lean controls. Left ventricular ejection fraction at rest was reduced in obese subjects and was inversely related with body mass index and duration of obesity [3]. The use of exercise in this investigation has been chosen to extend these previous observations. It has recently been reported that abnormal exercise left ventricular ejection fraction response during radionuclide angiography may represent a sensitive prognostic index in the detection of cardiovascular disease [10].

The results of the present study seem to indicate that degree and duration of obesity could also influence left ventricular ejection fraction response to exercise in normotensive obese subjects with normal left ventricular mass: a fact that has not been previously reported. This is supported by the presence of a negative correlation between duration of obesity and percent change in ejection fraction at peak exercise. In fact, only in 3 of 14 obese patients with a duration of obesity of more than 120 months, did ejection fraction increase $\geq 5\%$ at peak exercise (a normal response suggesting adequate left ventricular function reserve). Conversely, in 11 of 14 obese subjects with a duration of obesity of more than 120 months, exercise produced a $< 5\%$ increase or a frank decrease in left ventricular ejection fraction (suggesting impaired left ventricular functional reserve). Moreover, in the obese subjects with a duration of obesity of less than 120 months, exercise revealed an impairment of left ventricular functional reserve only in 1 subject.

Our results indicate that some obese patients are unable to increase their ejection fraction on exercise. This study has not been designed to

explain this finding, but extends other data indicating that left ventricular function response to exercise can be inadequate in obese patients with increased left ventricular mass, as reported by Alpert et al. [8]. According to our results it is possible that an inadequate left ventricular function response to exercise can occur also in obese patients with normal left ventricular mass but with prolonged duration of obesity.

Our study seems to indicate, according to Alpert et al. [8], that resting left ventricular ejection fraction value cannot be considered a reliable predictor of left ventricular functional reserve in normotensive obese patients, as suggested by the lack of correlation between resting ejection fraction and its percent change at peak exercise reported in this study. In view of this it is possible that the degree and duration of obesity can be considered useful predictors of left ventricular ejection fraction response to exercise.

In conclusion, our study suggests that increases in the duration and severity of obesity are associated with evidence of an impairment of left ventricular function and it is possible, as suggested by Bjorntorp [21] and the Framingham [22] and Manitoba studies [23], that obesity could represent an independent risk factor for cardiovascular disease after a long-term incubation period. For this reason, noninvasive evaluation of cardiac function can be very useful in asymptomatic obese patients, especially when the duration of obesity is prolonged, to identify left ventricular dysfunction induced by overweight.

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