

## Left ventricular diastolic and systolic function in normotensive obese subjects: influence of degree and duration of obesity

R. SCAGLIONE, M. A. DICHIARA, A. INDOVINA, R. LIPARI, A. GANGUZZA, G. PARRINELLO, G. CAPUANA, G. MERLINO AND G. LICATA

*Institute of Medical Pathology, University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy*

**KEY WORDS:** Left ventricular function, systolic function, diastolic function, peak filling rate, obesity, radionuclide angiography.

*The present study was carried out to evaluate systolic and diastolic parameters in overweight and moderately obese, but otherwise healthy subjects, and in a lean control group, to determine whether degree and duration of obesity can influence left ventricular function. A total of 27 subjects, 17 overweight or with moderate obesity and 10 lean, healthy subjects were included. Patients were divided into three groups according to their body mass index (BMI) and to Garrow's criteria as follows: lean control group (BMI < 25 kg.m<sup>-2</sup>); overweight subjects (BMI from 25 to 30 kg.m<sup>-2</sup>); moderately obese subjects (BMI > 30 < 40 kg.m<sup>-2</sup>).*

*Systolic and diastolic parameters were measured using blood pool gated radionuclide angiography. Left ventricular (LV) ejection fraction (EF), peak ejection rate (PER), time to PER (tPER), peak filling rate (PFR) and time to PFR (tPFR) were evaluated. PER and PFR values were normalized for end-diastolic volume (EDV).*

*EF and PFR were significantly lower (P < 0.05) both in moderately obese and in overweight subjects and tPFR was significantly (P < 0.05) prolonged in both groups in comparison to lean controls. Only in moderately obese subjects was PER significantly (P < 0.05) decreased and tPER significantly (P < 0.05) prolonged in comparison to lean controls. As compared to overweight individuals, moderately obese subjects were characterized by a significant decrease (P < 0.05) in LVEF and PER and by a significant increase (P < 0.05) in tPER, without relevant change in PFR and in tPFR.*

*In all the obese subjects BMI was inversely correlated with PFR (r = -0.56; P < 0.05) and with EF (r = -0.48; P < 0.05); duration of obesity was inversely correlated with PFR (r = -0.64; P < 0.01) and with EF (r = -0.51; P < 0.05).*

*Multiple regression analysis indicated that PFR values decreased with BMI and duration of obesity, but not with mean blood pressure and LVEF.*

*Our results indicate that diastolic abnormalities could represent the early manifestations of the effects of obesity on the heart.*

### Introduction

Impaired left ventricular (LV) diastolic filling at rest is a common finding in several cardiovascular diseases, such as hypertension, coronary artery disease, dilated cardiomyopathy, even in the absence of depressed systolic function<sup>[1-4]</sup>.

Diastolic abnormalities can relate to the degree or duration of disease, or reversibility of LV hypertrophy, and to the adequacy of control of blood pressure<sup>[2,5]</sup>. Some authors<sup>[6-8]</sup> have reported that the risk of cardiovascular disease is higher in obese than in lean subjects, and recently we have found an inverse correlation between degree or duration of obesity and LV ejection fraction in normotensive obese subjects without other known risk factors for cardiovascular disease<sup>[9]</sup>.

Although previous studies using invasive or non-invasive methods showed the presence of a hypervolaemic and hyperdynamic state in obese patients<sup>[9-12]</sup>, no data are available concerning the simultaneous assessment of LV systolic and diastolic parameters in normotensive

obese patients. Since obesity is generally a long-standing condition, a non-invasive method is desirable and useful for repeated assessment of cardiac function. Radionuclide angiography is a sensitive method to evaluate non-invasively systolic and diastolic function in man<sup>[3,13]</sup>.

We therefore designed the present study to investigate the influence of degree and duration of obesity on cardiac function. This was accomplished by measuring indexes of systolic and diastolic LV function by radionuclide angiography in overweight and moderately obese but otherwise healthy subjects (with normal LV mass) and in a group of lean control subjects.

An attempt was made to exclude misleading factors, such as diabetes, lipid abnormalities and hypertension.

### Subjects and methods

#### SUBJECTS

A total of 27 subjects, 17 overweight or moderately obese and 10 lean, healthy subjects, were included in the study. Obese subjects were recruited from all obese individuals attending the obesity centre of the University of Palermo, Italy. Obese subjects were totally unselected in terms of duration or degree of obesity, glucose tolerance,

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Correspondence: Rosario Scaglione, MD, Patologia Medica, Piazza delle Cliniche 2, 90127 Palermo, Italy.

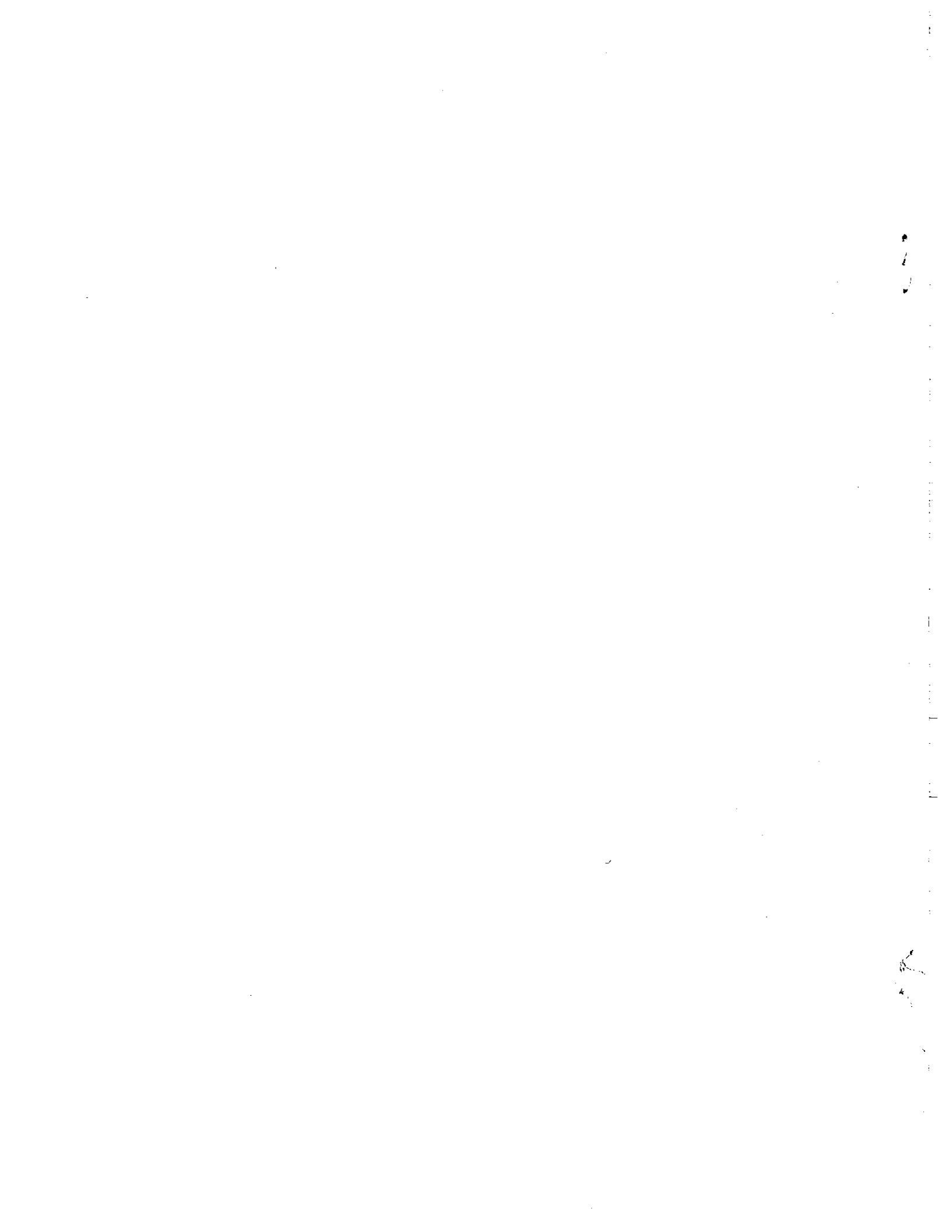


Table 1 Details of lean, overweight and moderately obese subjects (mean value  $\pm$  SEM)

	Lean (n=10)	Overweight (n=10)	Moderately obese (n=7)
Age (years)	44.7 $\pm$ 2.2	40.2 $\pm$ 3.5	48.6 $\pm$ 2.1
Sex (M/F)	4/6	5/5	3/4
BMI (kg.m <sup>-2</sup> )	23.1 $\pm$ 0.4	27.3 $\pm$ 0.4*	33.4 $\pm$ 1.4*†
Height (m)	1.66 $\pm$ 0.04	1.65 $\pm$ 0.02	1.61 $\pm$ 0.03
HR (b.min <sup>-1</sup> )	74.2 $\pm$ 1.2	76.2 $\pm$ 1.3	77.5 $\pm$ 1.7
SBP (mmHg)	120.2 $\pm$ 0.5	119.3 $\pm$ 2.1	124.4 $\pm$ 1.9
DBP (mmHg)	75.2 $\pm$ 1.9	74.7 $\pm$ 1.9	75.6 $\pm$ 1.7
MBP (mmHg)	90.3 $\pm$ 1.7	91.9 $\pm$ 2	92.3 $\pm$ 1.5
LVM (g)	168 $\pm$ 10.1	175 $\pm$ 12	183 $\pm$ 15.1
LVMI (g.mq <sup>-1</sup> )	93 $\pm$ 3.8	95 $\pm$ 6.3	97 $\pm$ 7.3

BMI=body mass index; 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 vs lean; † $P$ <0.05 vs overweight.

Table 2 Systolic and diastolic parameters in lean, overweight and moderately obese subjects (mean value  $\pm$  SEM)

	Lean (n=10)	Overweight (n=10)	Moderately obese (n=7)
LVEF (%)	65.0 $\pm$ 1.61	61.5 $\pm$ 2.11*	57.5 $\pm$ 2.24*†
PER (EDV.s <sup>-1</sup> )	3.90 $\pm$ 0.19	3.20 $\pm$ 0.26	2.38 $\pm$ 0.24*†
tPER (ms)	142.3 $\pm$ 4.77	150.4 $\pm$ 1.31	165.1 $\pm$ 2.06*†
PFR (EDV.s <sup>-1</sup> )	3.55 $\pm$ 0.20	2.65 $\pm$ 0.22*	2.40 $\pm$ 0.16*
tPFR (ms)	145.2 $\pm$ 6.68	162.2 $\pm$ 7.58*	167.5 $\pm$ 8.57*

EDV=end-diastolic volume; LVEF=left ventricular ejection fraction; PER=peak ejection rate; tPER=time to PER; PFR=peak filling rate; tPFR=time to PFR. \* $P$ <0.05 vs lean; † $P$ <0.05 vs overweight.

blood pressure or other known cardiovascular risk factors. After recruitment, exclusion criteria included insulin dependent or independent diabetes mellitus, hyperlipoproteinaemia, endocrine and cardiovascular disease, hypertension, alcoholism, drug addiction and psychiatric problems. Cardiovascular diseases were excluded on the basis of absence of chest pain or previous myocardial infarction. Cardiovascular investigations included chest X-ray, basal and 24 h ECG monitoring, and M and B mode echocardiography. In some patients 201-Thallium myocardial scintigraphy was also performed. Patients were divided into three groups according to their body mass index (BMI) values and Garrow's criteria<sup>[14,15]</sup> as follows. The lean control group consisted of 10 subjects (four males and six females) aged 30 to 52 years (mean  $\pm$  SEM: 44.7  $\pm$  2.2 years) and with a BMI less than 25 kg.m<sup>-2</sup> (mean  $\pm$  SEM: 23.1  $\pm$  0.4 kg.m<sup>-2</sup>); the overweight subjects comprised 10 subjects (five males and five females) aged 30 to 54 years (mean  $\pm$  SEM: 40.25  $\pm$  3.5 years) with a BMI ranging 25 to 30 kg.m<sup>-2</sup> (mean  $\pm$  SEM: 27.3  $\pm$  0.4 kg.m<sup>-2</sup>); the moderately obese subjects consisted of seven subjects (three males and four females) aged 40 to 58 years (mean  $\pm$  SEM: 48.6  $\pm$  2.1 years) with a BMI >30 and <40 kg.m<sup>-2</sup> (mean  $\pm$  SEM: 33.4  $\pm$  1.4 kg.m<sup>-2</sup>).

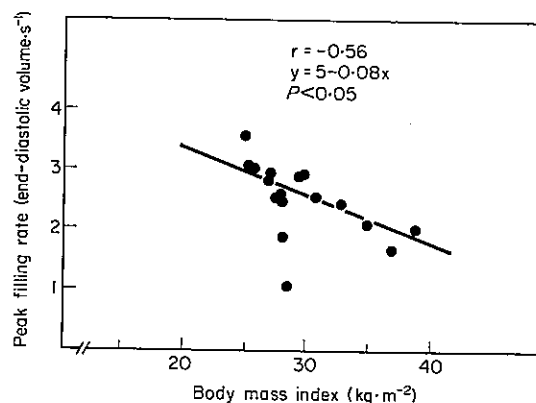


Figure 1 Correlation between body mass index and peak filling rate in overweight and moderately obese subjects (n=17).

In all the obese and lean subjects age, sex, body height, systolic (SBP), diastolic (DBP) and mean (MBP) blood pressure and left ventricular mass index (LVMI) were similar (Table 1). SBP and DBP were measured from the average of three measurements after 5 min in a comfortable supine position, using a mercury sphygmomanometer. DBP refers to Korotkoff V<sup>0</sup> phase, and MBP was calculated from the sum of DBP plus one third of the

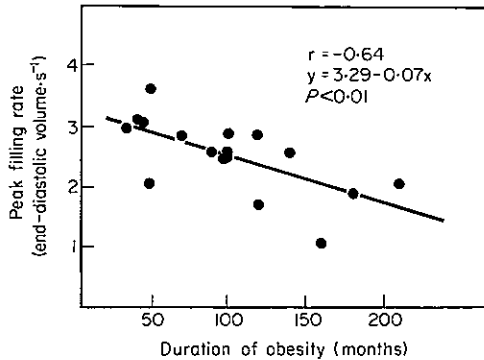


Figure 2 Correlation between duration of obesity and peak filling rate in overweight and moderately obese subjects ( $n = 17$ ).

arterial pulse pressure. Arterial pressure was measured with an appropriate large cuff in obese subjects<sup>[16]</sup>. Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated by echocardiography according to Devereux *et al.*<sup>[17]</sup>. All the subjects with unsatisfactory echocardiographic findings were also excluded.

Before the start of the study, 12 of the subjects had not been subjected to treatment, while three moderately obese had taken fenfluramine (18 mg daily) and two overweight subjects had received a conventional hypocaloric diet. None of the overweight and moderately obese subjects were administered any treatment for at least 4 weeks before the study. During this withdrawal period, no significant changes in body weight were observed in either overweight or moderately obese subjects.

Subject's fat distribution was assessed by measurement of the waist-to-hip girth ratio (WHR) to determine whether obese subjects showed abdominal or diffuse obesity, since abdominal obesity ( $WHR > 1$ ) has been reported to carry a higher cardiovascular risk<sup>[18]</sup>. 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.*<sup>[18]</sup>. No significant difference in WHR was observed between overweight subjects ( $0.99 \pm 0.004$ ) and moderately obese subjects ( $1.03 \pm 0.006$ ) or between males ( $1.02 \pm 0.004$ ) and females ( $1.0 \pm 0.006$ ) according to our preliminary unpublished data obtained during an epidemiological study on a population of western Sicily (Italy).

The duration of overweight or obesity was evaluated by accurate clinical history<sup>[19]</sup> and was  $90.4 \pm 16.8$  months and  $113.7 \pm 18.4$  months respectively in overweight and in moderately obese subjects.

The present 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.

#### METHOD

Systolic and diastolic function was evaluated by radionuclide angiography at rest with the blood pool

gated method according to Bonow *et al.*<sup>[3,20]</sup>, using a computerized large field scintillation Camera (Starcam 400 by General Electric) with high resolution (1.5 inch parallel hole collimator).

Radionuclide angiography was performed at 0900h in the supine position using red blood cells labelled with 20–25 mCi of  $Tc^{99m}$  in the left anterior oblique position to isolate the left ventricle (LV). A minimum of 300 000 counts.frame<sup>-1</sup> was reached before stopping data collection. High temporal resolution (10–20 ms.frame<sup>-1</sup>) cardiac image sequences were constructed by computer-based ECG gating, with the use of list mode data acquisition while excluding extrasystolic and post-extrasystolic cycles and combined forward and reverse gating from the R wave.

LV time activity curves, representing relative changes in LV volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction with an automatically fixed LV region of interest to the borders of the LV, as identified from the end-diastolic image, the stroke volume image and the amplitude image. The 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.

Indexes of LV function were derived by computer analysis of the background corrected time-activity curves. LV ejection fraction (EF) was computed on the basis of relative end-diastolic and end-systolic counts. Peak LV ejection rate (PER) and peak filling rate (PFR) were determined by fitting third order polynomial function to the systolic ejection squares technique<sup>[3]</sup>. The time of occurrence of the PER or PFR was obtained by setting the second derivative of the polynomial function to zero.

Time to PER (tPER) was measured from the R wave and time to PFR (tPFR) was measured relative to end-systole (minimal volume on the time-activity curve). Both PER and PFR were computed in LV counts.s<sup>-1</sup>, normalized for the numbers of counts at end-diastole and expressed as fractional end-diastolic counts (or EDV.s<sup>-1</sup>).

#### STATISTICAL METHODS

Comparisons between obese and lean subjects and between overweight and moderately obese subjects were undertaken using one-way analysis of variance. When differences were significant, the Student Newman Keuls test was also performed. Linear and multiple regression analyses were used to calculate coefficients of correlation among BMI, duration of obesity (DO) and systolic and diastolic parameters. Independent variables in multiple regression analysis were BMI, DO, MBP and LVEF. A  $P$  value  $< 0.05$  was considered statistically significant. All results in text and Tables are presented as the mean value  $\pm$  standard error of the mean (SEM).

#### Results

To assess the effect of obesity on systolic and diastolic parameters, we compared findings in lean, overweight

Table 3 Correlation coefficient in multiple regression analysis

	Partial coefficient correlation				Multiple coefficient correlation
	BMI	MBP	DO	LVEF	
PFR (EDV.s <sup>-1</sup> )	-0.470*	-0.175	-0.507	*0.215	-0.583*

\* $P < 0.05$ .

Explanatory variables were body mass index (BMI), mean blood pressure (MBP), duration of obesity (DO) and LV ejection fraction (LVEF).  $y = a + b \times \text{BMI} + c \times \text{MBP} + d \times \text{DO} + e \times \text{LVEF}$  where a, b, c, d and e are partial regression coefficients. The first value for partial correlation coefficient, for example, is the correlation coefficient between PFR and BMI after adjustment for MBP, DO and LVEF.

and moderately obese subjects. As shown in Table 1, age, height, heart rate, blood pressure and LV mass index did not differ significantly among all groups studied.

#### SYSTOLIC AND DIASTOLIC PARAMETERS

When compared to lean controls, overweight and moderately obese subjects were characterized by a significantly lower value ( $P < 0.05$ ) of LVEF and PFR and by a significantly ( $P < 0.05$ ) higher value of tPFR (Table 2).

PER was lower and tPER was lengthened both in overweight and in moderately obese subjects, but significantly only in moderately obese subjects ( $P < 0.05$ ) (Table 2). When compared to overweight subjects, moderately obese patients were characterized by a significant ( $P < 0.05$ ) decrease in LVEF, PER and by a significant ( $P < 0.05$ ) increase in tPER without significant change of PFR or tPFR (Table 2).

#### CORRELATIONS

In overweight and moderately obese subjects BMI was inversely correlated with PFR ( $r = -0.56$ ;  $P < 0.05$ ), Fig. 1, and with EF ( $r = -0.48$ ;  $P < 0.05$ ). Duration of obesity was also inversely correlated with PFR ( $r = -0.64$ ;  $P < 0.01$ ), Fig. 2, and with EF ( $r = -0.51$ ;  $P < 0.05$ ). No correlation between BMI and PER and between duration of obesity and PER was found.

Multiple regression analysis was performed to ascertain whether obesity showed an independent correlation with peak filling rate. Multiple and partial correlation coefficients are summarized in Table 3. PFR values decreased with body mass index and duration of obesity but not with mean blood pressure and LV ejection fraction.

#### Discussion and conclusions

The study has revealed that obesity can influence left ventricular function in normotensive subjects. A decreased LV ejection fraction, peak ejection rate and peak filling rate, and an increased time to PER and time to PFR were found in overweight and in moderately obese subjects as compared to lean controls. Many of these changes appeared to be related to the degree and duration of obesity and were more striking in moderately obese than in overweight subjects. Similar findings have been reported only in hypertensive obese subjects<sup>[21,22]</sup>.

Although most studies of obesity demonstrate an increased pre-load, there is a disagreement concerning the effects of obesity on after-load and contractile state<sup>[9-12,23,24]</sup>. It is likely that in obesity the presence of abnormal loading conditions, which confound the standard ejection phase, and the isovolumic phase indexes of ventricular function, contribute to the disparities found by different investigators. Coexistence of hypertension, diabetes and coronary artery disease with obesity may further complicate the study of this condition. For these reasons we evaluated LV systolic and diastolic functions in obese patients subgrouped according to severity of obesity and after excluding hypertension, diabetes, coronary artery disease and all other conditions that could influence cardiac function.

The presence of depressed PFR in overweight and moderately obese subjects without LV hypertrophy, related to severity and duration of obesity, seem to support previous studies indicating that obesity can impair cardiac function through an impairment of myocardial contractile activity<sup>[9,23,25]</sup>. In fact, it has been recently reported that altered diastolic parameters can correlate with myocardial contractile dysfunction<sup>[3,4]</sup>. It has also been found that abnormalities in diastolic parameters may be present in patients with coronary artery disease or hypertension without clearcut alterations of systolic function and also in the absence of LV hypertrophy<sup>[1-4]</sup>. Impaired LV filling in the absence of defined hypertrophy may represent an early marker of the pathological effects of some heart diseases<sup>[1,2,26]</sup>.

In this study an inverse relationship between peak filling rate and degree or duration of obesity has been found. These findings suggest that obesity can be associated with impaired diastolic function even in normotensive subjects: a fact that has not been reported.

However, the duration and degree of obesity can partially explain the changes in PFR. In fact,  $R^2$ , the square of the correlation coefficient is respectively 0.31 and 0.40 for PFR and BMI or duration of obesity, which means that respectively 31% and 40% of the variation of PFR can be explained by obesity. This study was not designed to determine the physiological basis of this association, but these data confirm previous findings by showing that overweight can play an important role in determining left ventricular function<sup>[9]</sup>. This conclusion is

further supported by a multivariate analysis which indicates that body mass index and duration of obesity are the best predictors of peak filling rate.

Our data have also shown that the decrease in left ventricular ejection fraction is more clearcut in moderately obese than in overweight subjects, while diastolic abnormalities are present in both obese groups. Therefore, diastolic abnormalities could represent an early marker of cardiac involvement also in normotensive obese subjects.

In view of this, it is difficult to interpret the reduction of EF as a primary disorder of systolic function. Ejection fraction is the ratio of the systolic ejection volume to the end-diastolic volume; thus a reduction in EF can be due to a reduced end-diastolic volume (constant end-systolic volume) as well as to an increased end-systolic volume (constant end-diastolic volume). Thus for a given reduced EF, it is impossible to decide whether this is due to a disorder of systolic function or to a disorder of diastolic function or even to both. Our results indicate that EF can be altered in obese subjects by altering the filling phase.

Impaired left ventricular function in obese subjects could be sustained by an increased pre-load that could determine changes in structure and dimensions of the left ventricle, according to Messerli *et al.*<sup>[10]</sup> and to previous data published by our group<sup>[9,11]</sup>.

This hypothesis is also supported by recent observations indicating a deterioration of the contractile state with increased weight in obese hypertensives<sup>[22]</sup> and by an inverse correlation between duration of obesity and EF, previously reported by us<sup>[9]</sup> in normotensive obese subjects with characteristics similar to those of the obese subjects reported in this study.

In conclusion, since obesity is generally a long-standing condition, non-invasive evaluation of cardiac function can be useful to assess and possibly to discern early the presence of cardiac dysfunction in obese subjects, above all when their obese state is prolonged or severe.

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