

Lymphocyte beta-adrenergic receptors in young subjects with peripheral or central obesity: relationship with central haemodynamics and left ventricular function

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This study was designed to evaluate total (t) and surface (s) β -adrenergic receptor (BAR) density and their relationship with central haemodynamics and left ventricular function in young subjects with central or peripheral obesity.

A total of 31 obese subjects (BMI ≥ 30.5 kg \cdot m⁻² for males and ≥ 27.3 kg \cdot m⁻² for females) aged less than 40 years and without other risk factors for cardiovascular diseases (smoking, hypertension, diabetes and lipid abnormalities) were studied. Nine had peripheral obesity and 22 central obesity according to WHR values; there were 20 lean controls (BMI < 25 kg \cdot m⁻² for males and < 24.7 kg \cdot m⁻² for females).

Casual (c) and 24 h ambulatory mean blood pressures (MBP-24 h) were determined. BAR density was evaluated according to Böyum and De Blasi methods. Plasma catecholamines by high perfusion liquid chromatography and fasting immunoreactive plasma insulin (IRI) were also measured by RIA.

Radiionuclide angiocardiology was used to determine central haemodynamics and both systolic and diastolic left ventricular function. Total peripheral resistances (TPR) and intravascular volumes were also determined. Echocardiographic study was used to measure LVM, LVM \cdot h⁻¹, LVDD and IVS. Left ventricular ejection fraction (LVEF), peak filling rate (PFR), BART and BARs were significantly lower (P < 0.05) and cardiac output, cardiac volumes, LVM, LVM \cdot h⁻¹ and time to PFR significantly higher (P < 0.05) in both obese groups than in lean controls. Plasma IRI was significantly (P < 0.05) higher in both obese groups whereas plasma norepinephrine was higher only in central obese. Comparisons between the two obese groups indicated that only LVEF was significantly lower (P < 0.05) in subjects with central obesity than in subjects with peripheral obesity. BART and BARs correlated inversely with BMI, SV, LVDD and total blood volume. Multiple regression analysis indicated that BMI and SV remained the best predictors of BAR measurement even when epinephrine, IRI and MBP-24 h values were considered.

These results indicate that obese subjects have signs of hyperkinetic circulation and depressed lymphocyte BAR densities.

Introduction

Some epidemiological data indicate a close relationship between central obesity and cardiovascular diseases^[1–3]. The deleterious effects of overweight on left ventricular function have been reported by some authors^[4–9].

Although an impaired left ventricular function related to the degree and duration of obesity was reported in overweight individuals^[5,7,8], the mechanisms of left ventricular dysfunction in obese subjects are still unclear^[7–10]. Our previous data indicated a depressed ejection fraction at rest and after exercise in young normotensive obese subjects without major risk factors for cardiovascular diseases^[7–11]. In the same subjects, radiionuclide peak filling rate was impaired and inversely correlated to the degree and duration of obesity^[8].

The β -adrenoceptor system has recently been shown to play an important regulatory role in the modulation of cardiac inotropy^[12]. Circulating lymphocytes containing a homogeneous population of β_2 adrenoceptors coupled in an excitatory manner to the adenylate cyclase system are a frequently used model to study alterations in β -adrenoceptor function in man^[13].

Although it is still uncertain whether lymphocyte β -adrenoceptors (BAR) can reflect the entire population of myocardial BAR, there exists some evidence that β_2 type adrenoceptors are also present and involved in the chronotropic and inotropic stimulation of the heart, even though these properties have traditionally been ascribed to β_1 adrenoceptors^[14]. In any case, BAR density measurement in young obese but otherwise healthy subjects can, for obvious ethical reasons, be performed only on circulating lymphocytes.

There is an increasing interest in BAR population alterations associated with cardiovascular diseases^[13–16]; no investigation, however, has reported alterations in

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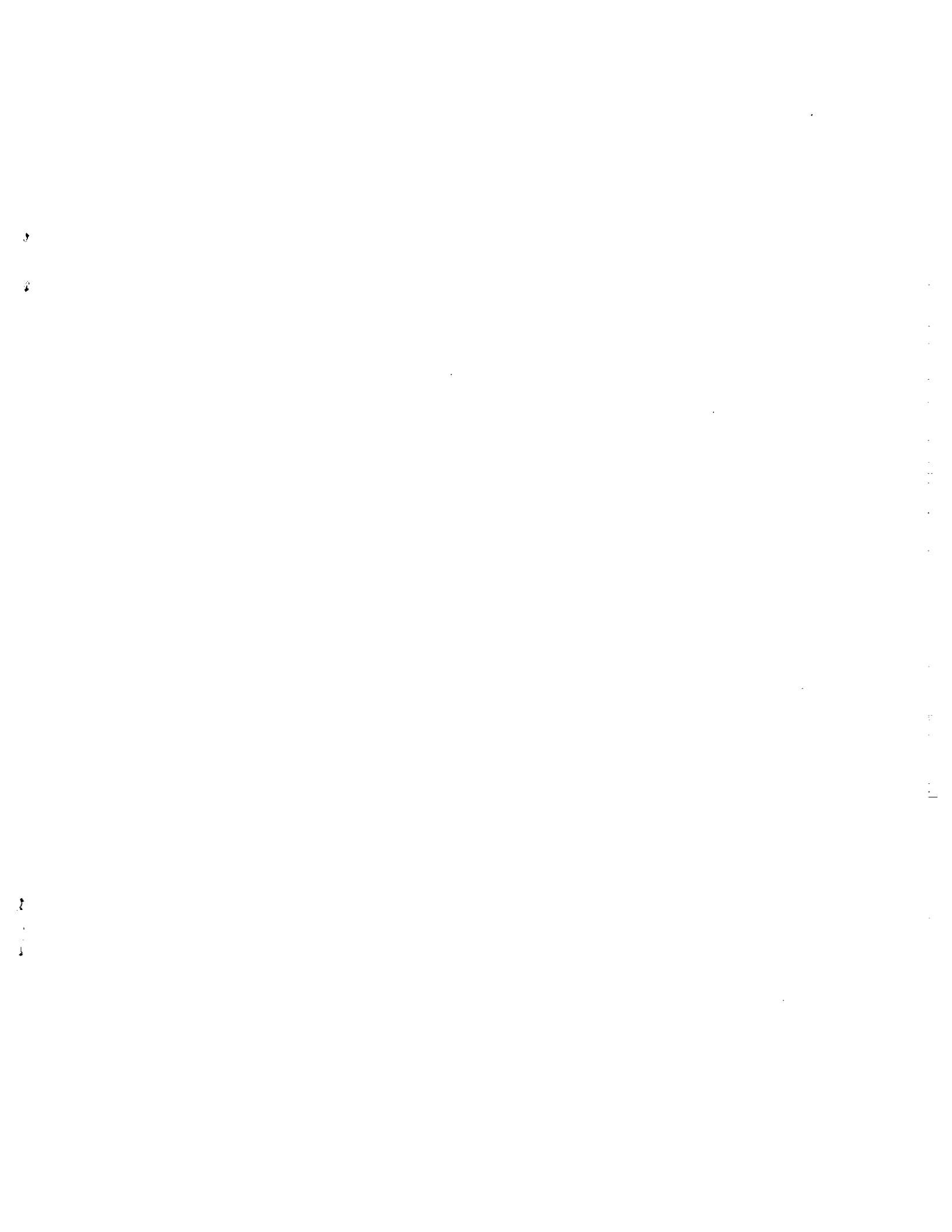


Table 1 Details of study groups (mean value \pm SD)

	Group 1 (n=20)	Group 2 (n=9)	Group 3 (n=22)
Gender (M/F)	10/10	5/4	11/11
Age (years)	36.9 \pm 3.5	36.0 \pm 3.7	36.3 \pm 3.9
Height (m)	1.60 \pm 0.09	1.66 \pm 0.08	1.60 \pm 0.09
BMI (kg . m ⁻²)	22.2 \pm 2.1	33.5 \pm 4.0*	35.9 \pm 5.9**
WHR	0.85 \pm 0.07	0.87 \pm 0.04	0.97 \pm 0.07**a
DO (months)	//	136.8 \pm 26.3	255.3 \pm 178.1
cMBP (mmHg)	92.7 \pm 6.9	95.8 \pm 3.1	96.9 \pm 5.3
MBP-24h (mmHg)	83.5 \pm 4.5	88.0 \pm 2.3*	89.3 \pm 4.7**
HR (beats . min ⁻¹)	70.2 \pm 4.1	74.2 \pm 4.8*	75.0 \pm 4.4**
IRI (μ U . ml ⁻¹)	9.1 \pm 3.2	13.3 \pm 6.3*	16.5 \pm 7.7**

BMI=body mass index; WHR=waist to hip girth ratio; DO=duration of obesity; cMBP=casual mean blood pressure; MBP-24h=24 h mean blood pressure; HR=heart rate; IRI=immunoreactive plasma insulin. * P <0.05 vs group 1. ** P <0.05 vs group 1. ^a P <0.05 vs group 2.

the BAR population in obese subjects and investigated its relationship with the degree of obesity or body fat distribution.

This study was designed to evaluate the influence of degree of obesity and body fat distribution on lymphocyte BAR density in young obese subjects without major risk factors for cardiovascular disease, i.e. smoking, hypertension, insulin dependent or independent diabetes mellitus or lipid abnormalities.

In view of this, obese subjects were subgrouped according to their body fat distribution, by evaluation of their waist to hip girth ratio.

Our goal was to evaluate a possible relationship between degree of obesity, body fat distribution and cardiovascular or neurohormonal abnormalities.

Subjects and methods

SUBJECTS

A total of 51 subjects, 31 with obesity and 20 lean, healthy controls, were included in this study. The obese subjects were recruited from individuals aged less than 40 years attending the obesity centre of the Internal Medicine Department of the University of Palermo (Italy). Lean controls were chosen from a group of individuals undergoing a clinical check-up and found to be healthy.

Obese subjects were totally unselected as far as duration and degree of obesity, body fat distribution, glucose tolerance, blood pressure and other known cardiovascular risk factors.

Subjects were considered obese according to BMI values proposed by the Italian Consensus Conference on Obesity^[17]. The cut-off values for obesity were ≥ 30.5 kg . m⁻² for males and ≥ 27.3 kg . m⁻² for females. Lean subjects were selected on the basis of BMI values of less than 24.7 kg . m⁻² for females and 25 kg . m⁻² for males. Obese subjects were further subdivided according to their body fat distribution, as

assessed by measuring the waist-to-hip girth ratio (WHR)^[7,8,11], and on the basis of the sex-specific 85th percentile of WHR values reported by the Italian Consensus Conference on Obesity^[17]. In view of this, central obesity was diagnosed when the WHR was higher or equal to 0.81 in women and higher or equal to 0.92 in men. According to these criteria the following groups were considered: Group 1, lean subjects: 10 males and 10 females aged 29–38 years (36.9 \pm 3.5), with BMI 22.2 \pm 2.1 kg . m⁻² and WHR 0.85 \pm 0.07 (mean values \pm SD); Group 2, subjects with peripheral obesity: five males and four females aged 29–39 years (36 \pm 3.7) with BMI 33.5 \pm 4 kg . m⁻² and WHR 0.87 \pm 0.04 (mean values \pm SD); Group 3, subjects with central obesity: 11 males and 11 females aged 29–39 years (36.3 \pm 3.9) with BMI 35.9 \pm 5.9 kg . m⁻² and WHR 0.97 \pm 0.07 (mean values \pm SD).

All the obese and lean subjects were normotensive and matched as closely as possible with regard to age, gender and body height (Table 1).

Exclusion criteria included smoking habits, diabetes mellitus, hyperlipoproteinaemia, endocrine and cardiovascular diseases, hypertension, alcoholism, drug addiction and psychiatric problems.

Systolic, diastolic and mean blood pressure (cMBP) were recorded by averaging three measurements after 5 min in a comfortable supine position, using a mercury sphygmomanometer with an appropriately wide cuff for obese subjects^[3,18].

Ambulatory blood pressure was also recorded by the portable fully automatic Takeda TM 2420 system connected through the serial interface (RS 232) to an IBM personal system for the evaluation of 24 h mean blood pressure (MBP-24h).

Resting heart rate (HR) was measured from the electrocardiogram. MBP-24h values, heart rate and fasting insulin levels were mildly, but significantly, higher in both obese groups than in lean subjects. Only WHR was, by definition, significantly different in central obese in comparison with peripheral obese subjects (Table 1).

All obese subjects had been left untreated for at least 2 weeks before the study. During this withdrawal period no significant changes in body weight were observed.

The duration of obesity was evaluated by accurate clinical history^[7,8,11] and was 136.8 ± 26.3 months in subjects with peripheral obesity and 255.3 ± 178.1 months in subjects with central obesity (Table 1).

This study was approved by the Ethics Committee of our Institution 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 plasma immunoreactive insulin (IRI) and blood sugar, oral glucose tolerance test, serum cholesterol, triglyceride levels and liver function tests.

Methods

LYMPHOCYTE BAR DETERMINATION

Following insertion of an intravenous catheter, all subjects rested quietly in the supine position for 30 min, then 35 ml of heparinized blood was obtained to measure lymphocyte BAR density and plasma catecholamines. Human mononuclear leukocyte (MNL) isolation and BAR determination were performed according to the methods described by Böyum^[19] and De Blasi *et al.*^[20] and then also utilized and validated in our laboratory^[21,22].

Briefly, peripheral blood MNL were prepared by density gradient centrifugation on Ficoll-Hypaque (Lymphoprep, Immuno, Pisa, Italy). To eliminate residual contaminating platelets, the cells were centrifuged at 200 *g* for 10 min and the supernatant was discarded. Finally, the MNL were resuspended in Dulbecco's modified eagle medium (pH 7.4 at 20 °C containing 20 mM HEPES and 1 mg . ml⁻¹ bovine serum albumin (GIBCO-Biocult, Glasgow, Scotland).

β -Adrenergic receptor binding experiments were performed as previously described^[23]. MNL ($0.2 \text{ ml } 7\text{--}10 \times 10^6 \text{ cells . ml}^{-1}$) was added to 50 μl of ¹²⁵I-pindolol (¹²⁵I-PIN; specific activity 2,200 Ci . mmol⁻¹; New England Nuclear, Boston, Massachusetts). At the end of the incubation (45 min at 37 °C) 10 ml ice-chilled phosphate-buffered saline (PBS) was added and the samples were quickly filtered through Whatman GF/C glass fibre filters (Whatman, Clifton, New Jersey) with an additional 10 ml cold PBS wash. Non-specific binding was defined in the presence of 1 μM (-)-propranolol (Imperial Chemical Industries Pharmaceuticals, Cheshire, U.K.). Total receptors (BART) were defined by the difference between total binding and non-specific binding; surface receptors (BARs) were defined by the difference between total binding and binding in the presence of 1 μM Ciba Geigy Production (CGP) 12177 (Ciba Geigy, Origgio, Italy), a hydrophilic ligand specific for surface receptors. A single saturating concentration of ¹²⁵I-PIN (200 pM) was used since it is able to identify over 90% of the receptors^[20].

PLASMA CATECHOLAMINES AND PLASMA INSULIN

Samples were prepared and assayed by high perfusion liquid chromatography, as described by Goldstein *et al.*^[24]. Sensitivity for detection of norepinephrine (NEP) was 15 pg and for epinephrine (EP) 25 pg.

Fasting plasma immunoreactive insulin (IRI) was detected by the radioimmunoassay double antibody method using a commercial kit (Sorin, Saluggia, Italy). Sensitivity for detection of insulin was $2.5 \mu\text{U . ml}^{-1}$.

RADIONUCLIDE STUDY

Systolic and diastolic functions were evaluated by radionuclide angiocardigraphy using the blood gated method according to Bonow *et al.*^[25]. A computerized large field scintillation camera (Starcam 400; General Electric) with a high resolution 1.5 inch parallel hole collimator was utilized. This method has been validated in our laboratory, in particular in obese subjects^[7,8,11,26].

Using radionuclide angiocardigraphy the following parameters were calculated: cardiac output (CO; ml . min⁻¹); left ventricular ejection fraction (LVEF; %); stroke volume (SV=CO/HR); end-diastolic volume (EDV=SV/EF \times 100; ml); end-systolic volume (ESV=EDV-SV; ml); peak filling rate (PFR=EDV . s⁻¹) and time to PFR (tPFR; ms).

Total peripheral resistances (TPR) were calculated by formula $\text{MBP} \times 60 \times 1332/\text{CO}$ and expressed as dynes . s . cm⁻⁵.

Total plasma volume (TPV; ml) was determined from the dilution of iodine 125 labelled human albumin. Total blood volume (TBV; ml) was estimated using the TPV determination and the total haematocrit^[27,28].

Since TPV and TBV in obese subjects expand when corrected for body height and contract when corrected for weight, absolute values only were used in this study^[7,10].

ECHOCARDIOGRAPHIC STUDY

Two-dimensional and M-mode echocardiography examination was performed using an ESAOTE Biomedica computer-aided ultrasound system equipped with 2.5 and 3.5 MHz phased-array transducers, and a standard VHS video system.

Left ventricular mass (LVM; g) was calculated according to the Devereux method from necropsy validation studies^[29]. LVM was also related to body height (LVM . h⁻¹) using the recommendation that LVM should be indexed to height instead of body surface area for a more accurate evaluation of left ventricular hypertrophy (LVH)^[30]. Left ventricular diastolic dimension (LVDD; mm) and interventricular septal (IVS; mm) thickness were also determined.

LVH was assumed in the presence of a LVM . h⁻¹ > 2 standard deviations of the sex-specific mean of a group of 110 normotensive subjects without a family history of hypertension, who provided the normal values for our laboratory. LVH was considered present if LVM . h⁻¹

Table 2 Left ventricular function, lymphocyte beta adrenergic receptors and plasma catecholamine levels in all the groups studied (mean value \pm SD)

	Group 1 (n=20)	Group 2 (n=9)	Group 3 (n=22)
LVEF (%)	65.5 \pm 4	61.2 \pm 1.1*	57.1 \pm 4.6***
PFR (EDV . s ⁻¹)	3.55 \pm 0.8	2.7 \pm 0.4*	2.6 \pm 0.6**
tPFR (ms)	145.3 \pm 13.7	152.4 \pm 6.2	165.1 \pm 26.9**
BART (receptors/cell)	1497 \pm 115	1056 \pm 96*	1034 \pm 295**
BARs (receptors/cell)	1160 \pm 179	812 \pm 258*	881 \pm 283**
Norepinephrine (pg . ml ⁻¹)	267.3 \pm 31	277.4 \pm 46	307.7 \pm 56**
Epinephrine (pg . ml ⁻¹)	144.7 \pm 38	172.3 \pm 30	173.5 \pm 43

LVEF=left ventricular ejection fraction; PFR=peak filling rate; tPFR=time to peak filling rate; BART=total lymphocyte β -adrenergic receptors; BARs=surface lymphocyte β -adrenergic receptors. * P <0.05 vs group 1. ** P <0.05 vs group 1. *** P <0.05 vs group 2.

exceeded 150 g . m⁻¹ in women and 163 g . m⁻¹ in men^[26].

According to these criteria, only one subject with central obesity presenting mild LVH was found.

STATISTICAL ANALYSIS

Comparisons between lean and both obese groups were performed using one-way analysis of variance. When the differences were statistically significant, the Student-Newman-Keuls test was also used. Linear and multiple regression analyses were utilized to calculate coefficients of correlation between BART or BARs and obesity measurements or hormonal and cardiovascular parameters.

Independent variables in multiple regression analysis were body mass index, plasma epinephrine, fasting immunoreactive insulin, 24 h mean blood pressure and stroke volume. A P value <0.05 was considered statistically significant. All results in text and in tables are expressed as mean value \pm Standard Deviation (SD).

Results

Lymphocyte β -adrenergic density was studied in young lean and obese subjects with peripheral or central obesity. Age and height did not differ between the groups. MBP-24h, HR and IRI levels were significantly (P <0.05) higher in both obese groups than in lean subjects (Table 1).

LEFT VENTRICULAR FUNCTION, BAR DENSITY AND PLASMA CATECHOLAMINE LEVELS

Obese groups vs lean controls

LVEF, PFR, BART and BARs values were significantly (P <0.05) lower in both obese groups than in lean controls; tPFR was significantly (P <0.05) higher only in subjects with central obesity (Table 2).

Norepinephrine levels were higher in both obese groups but significantly (P <0.05) only in central obesity. The epinephrine values did not differ significantly between the groups (Table 2).

Central obese vs peripheral obese subjects

Small differences only were observed between central and peripheral obese subjects. In particular, LVEF values were significantly (P <0.05) lower, whereas BART and BARs were lower but not significantly so in subjects with central obesity. Norepinephrine values were moderately but not significantly higher in central obese subjects. No other significant difference was found (Table 2).

HAEMODYNAMIC PARAMETERS, INTRAVASCULAR VOLUMES AND ECHOCARDIOGRAPHIC MEASUREMENTS

Cardiac output, diastolic, systolic and stroke volumes were significantly higher in the obese groups compared to the lean subjects (P <0.05). On the other hand, the decreased TPR values and the increased intravascular volumes seen in both obese groups were not statistically different from the values obtained in the lean controls (Table 3).

LVM and LVM . h⁻¹ were significantly (P <0.05) higher in peripheral and central obese subjects, whereas LVDD and IVS did not differ between the groups (Table 3).

Correlations

In peripheral and central obese subjects BART and BARs were inversely correlated with BMI (r = -0.68, P <0.001; and r = -0.60, P <0.001, respectively) (Fig. 1), TBV (r = -0.40, P <0.05; and r = -0.41, P <0.05), SV (r = -0.40, P <0.05; and r = -0.42, P <0.05), LVDD (r = -0.36, P <0.05; and r = -0.41, P <0.05).

No correlation between BAR and WHR, duration of obesity, plasma catecholamines and plasma insulin levels, LVM or LVM/h was found. Multiple regression analysis was performed to ascertain whether BMI showed an independent correlation with BAR. BART and BARs values decreased with both body mass index and stroke volume but not with plasma catecholamines, insulin levels and MBP-24h values (Table 4).

Table 3 Haemodynamic parameters, intravascular volumes and echocardiographic measurements in all the groups studied (mean value \pm SD)

	Group 1 (n=20)	Group 2 (n=9)	Group 3 (n=22)
CO (ml . min ⁻¹)	6792 \pm 1050	8077 \pm 806*	7905 \pm 1181**
TBV (ml)	5003 \pm 993	5011 \pm 370	5111 \pm 864
TPV (ml)	2890 \pm 498	2954 \pm 190	3010 \pm 502
TPR (dynes . s . cm ⁻⁵)	1093 \pm 207	955 \pm 91	1015 \pm 173
EDV (ml)	133 \pm 26.1	182.1 \pm 25.4*	175.8 \pm 29.8**
ESV (ml)	45.7 \pm 13.9	74.6 \pm 18.5*	72.0 \pm 15.4**
SV (ml)	87.4 \pm 17	107.5 \pm 11.0*	103.8 \pm 18.5**
LVM (g)	134.9 \pm 15.5	177.0 \pm 6.3*	184.6 \pm 19.0**
LVM . h ⁻¹ (g . m ⁻¹)	84.3 \pm 15.1	106.1 \pm 3.2*	114.6 \pm 10.3**
LVDD (mm)	49.9 \pm 5.1	50.4 \pm 3.8	53.1 \pm 5.4
IVS (mm)	8 \pm 1.3	8.2 \pm 0.7	9.1 \pm 2.1

CO=cardiac output; TBV=total blood volume; TPV=total plasma volume; TPR=total peripheral resistances; EDV=end-diastolic volume; ESV=end-systolic volume; SV=stroke volume; LVM=left ventricular mass; LVM . h⁻¹=left ventricular mass/body height; LVDD=left ventricular diastolic internal dimension; IVS=interventricular septal thickness. * P <0.05 vs group 1. ** P <0.05 vs group 1.

Discussion and conclusions

This study confirms previous results indicating that obesity is characterized by signs of a hyperkinetic circulation and of an impaired left ventricular function^[3-9,11,31]. These abnormalities are associated with a decreased density of lymphocyte β -adrenergic receptors. In fact, in the current study, total or surface BAR correlated inversely with BMI but not with WHR. This indicates a higher influence of the degree of obesity than body fat distribution on BAR population: a fact that has not been previously reported. This was

observed in selected young obese subjects who were non-smokers and were free of hypertension, diabetes and lipid abnormalities.

The lack of correlation between BAR and WHR is not surprising. In fact, even though central obesity has been reported to be more frequently associated with cardiovascular disease than peripheral obesity^[1-3], Jern *et al.*^[32] have recently demonstrated that resting central haemodynamics was correlated with BMI but not with WHR in normotensive individuals. This finding is very important. In fact, changes in central hemodynamics could account for the BAR reduction seen in our obese

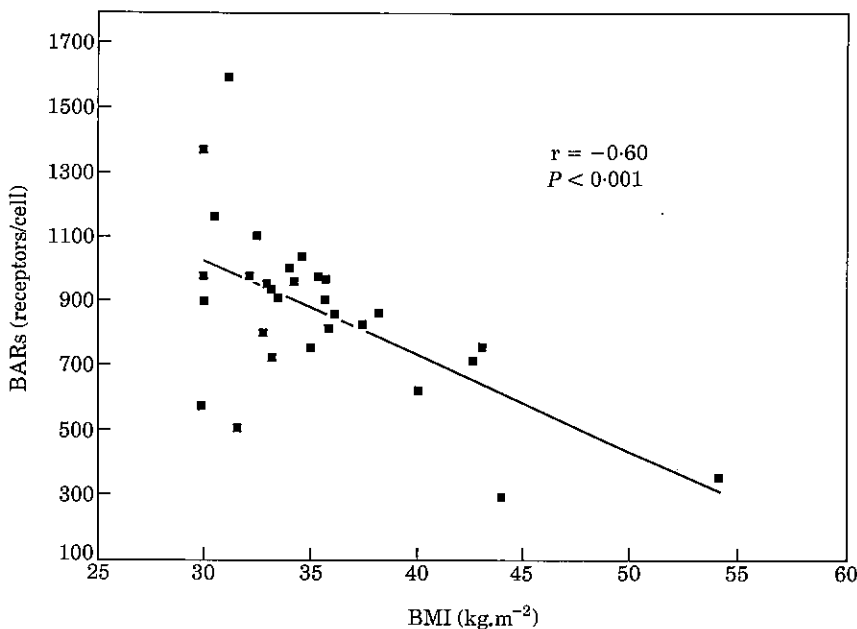


Figure 1 Correlation between surface lymphocyte β -adrenergic receptors (BARs) and body mass index (BMI) in obese subjects.

Table 4 Multiple regression analysis

Dependent variables	Predictors						Analysis of variance
	Constant	BMI	Epin	SV	MBP-24h	IRI	
BARt	2232	-26	-1.6	-5.9	6.7	1.1	P=0.002
	P=0.01	0.006	ns	0.04	ns	ns	
BARs	2065	-24.8	-0.7	-5.5	3.9	1.7	P=0.01
	P=0.08	0.01	ns	ns	ns	ns	

BARt=total lymphocyte β -adrenergic receptors; BARs=surface lymphocyte β -adrenergic receptors; BMI=body mass index; Epin=plasma epinephrine; SV=stroke volume; MBP-24h=24 hours mean blood pressure; IRI=immunoreactive plasma insulin.

subjects. Since body fat distribution is currently considered the best predictor of cardiovascular disease in obese subjects, we must stress that in selected young obese individuals one may hypothesize that, in this age group, the degree of obesity is more important than body fat distribution, to explain the reduced BAR population; we cannot exclude that, later in life, body fat distribution might also play an important role in BAR impairment, which could relate to the higher cardiovascular risk associated with central obesity.

Moreover, inverse correlations between BAR density and stroke volume, total blood volume and left ventricular diastolic dimension were found in obese subjects, suggesting that these parameters, rather than catecholamines, could predict BAR population measurement in this population. This hypothesis was supported by the multiple regression analysis, which indicated that body mass index and stroke volume remained the best predictors of BAR population measurement even when epinephrine, insulin and 24 h mean blood pressure values were considered.

Although higher insulin levels were reported to be associated with an increased cardiovascular risk in obese subjects^[3], there was no indication in the present study that a direct influence of insulin on BAR alterations might exist.

BAR population did not correlate with either plasma norepinephrine or epinephrine, as also reported by Mancini *et al.*^[15] in subjects with congestive heart failure. This finding could support the idea that modulation of β -receptor density is not simply a function of resting sympathoadrenal activity; it could also take place in obese subjects, even if we cannot rule out that the lack of correlation between BAR and catecholamines resulted more from methodological problems rather than true pathophysiological differences.

Our study was not designed to solve this question and at present there are no data explaining the physiological consequences of the changes of BAR in obese subjects compared to lean, healthy individuals.

It is possible that modifications in adenylate cyclase activity could explain the reduced BAR population in obese subjects. Whereas more data on β -adrenoceptor

density are being collected, there is an increasing interest in the possibility that post-adrenoceptor changes of the β -adrenoceptor-adenylate-cyclase complex could contribute to changes of adrenergic responsiveness^[33]. A study of post-adrenoceptor events, for example alterations in G-protein, in adenylate-cyclase and in protein-kinase, requires more elaborate and complicated techniques. Until now, most data on G-proteins have been obtained with lymphocytes and not with myocardial tissue. These lymphocyte data suggest important changes in the stimulatory G-protein levels in subjects with congestive heart failure^[34,35]. Moreover, our preliminary unpublished data indicate that exercise produces no change in isoproterenol-stimulated adenylate-cyclase activity in obese patients, suggesting that β -receptors are more rapidly desensitized in these subjects.

Although it should be emphasized that changes in lymphocyte BAR density and function cannot necessarily be extrapolated to the myocardium, our results are consistent with those reported in subjects with congestive heart failure^[36-38].

The physiological role of BAR and its relationship with left ventricular function in obese subjects still remain unclear, but our results suggest that haemodynamic changes associated to a high degree of obesity could affect BAR population more than body fat distribution.

Finally, additional data on the effects of exercise or isoproterenol stimulation of BAR have to be provided for a reliable explanation of the reduced BAR population in obese subjects.

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