Hemostatic Function in Young Subjects With Central Obesity: Relationship With Left Ventricular Function

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This study was designed to evaluate coagulation and fibrinolysis activity and their relationship with left ventricular function in young obese subjects with central fat distribution. We assessed coagulation and fibrinolysis activity by evaluation of factor VII activity, fibrinogen and plasminogen, plasminogen activator inhibitor (PAI), and tissue plasminogen activator antigen basally (tPA1) and after venous occlusion (tPA2). These measures were evaluated in young (<40 years) obese subjects with central fat distribution (n = 19) and in comparable lean subjects (n = 20). Blood glucose, triglycerides, total and high-density lipoprotein (HDL) cholesterol, apolipoprotein (apo) A1 and apo B, fasting immunoreactive insulin, and lipoprotein(a) levels were also measured by current methods. Left ventricular ejection fraction (LVEF) and peak filling rate (PFR) determined by radionuclide angiocardiography and left ventricular mass (LVM) and LVM indexed for body height (LVM/H) determined by echocardiographic study were calculated. Central obesity was evaluated by the waist to hip ratio (WHR) according to the criteria of the Italian Consensus Conference of Obesity. Factor VII ($P < .001$), fibrinogen ($P < .001$), plasminogen ($P < .001$), PAI activity ($P < .001$), tPA1 ($P < .02$), fasting blood glucose ($P < .01$), apo B ($P < .02$), and immunoreactive insulin ($P < .01$) were significantly higher in obese than in lean subjects. In contrast, HDL cholesterol ($P < .01$), tPA2 ($P < .01$), LVEF ($P < .001$), and PFR ($P < .02$) were significantly lower in obese than in lean subjects. In all subjects, WHR correlated directly with fibrinogen and inversely with tPA2; LVEF correlated inversely with tPA1, PAI, and fibrinogen; and PFR correlated inversely with factor VII activity. Multiple regression analysis indicated that WHR and PAI were independent predictors of LVEF. These results indicate that obese subjects with central fat distribution are characterized by a hypercoagulable state associated with a silent left ventricular dysfunction. Such alterations might be responsible for the higher cardiovascular risk in subjects with central obesity.

OBESITY is an important risk factor for cardiovascular disease, especially when there is a central fat distribution. Several indications suggest an independent role of obesity in promoting cardiovascular disease; however, this has not been universally accepted.[1] In addition, recent follow-up results of the Harvard Growth Study indicate that the risk of morbidity from coronary heart disease and atherosclerosis increased among men and women who had been overweight in adolescence.[2] The effects of obesity in adolescence on adult mortality have been demonstrated to reflect the central deposition of fat that occurs in adolescence.[3,4]

On the other hand, alterations in hemostatic function are emerging predictors of coronary heart disease or cardiac events. In fact, some epidemiological data indicate that activated coagulation and impaired fibrinolytic function might be associated with an increased risk of dying of cardiovascular disease.[5-8] In some of these studies, coagulation or fibrinolysis activity was also related to body mass index (BMI) or waist to hip ratio (WHR).[6,8]

These data might suggest an early connection between obesity and atherosclerosis and its clinical manifestations. Our previous data indicated a depressed ejection fraction at rest and after exercise in young normotensive obese subjects without major risk factors for cardiovascular disease.[9,10] In the same subjects, a decrease in β-adrenergic receptor density and an impaired diastolic function were found.[11,12]

Nevertheless, few data are available on the relationship between obesity, hemostatic activity, and left ventricular function.[8,13-15]

In the present study, coagulation and fibrinolysis function have been evaluated in young normotensive obese subjects with central fat distribution and without major risk factors for cardiovascular disease or events, ie, smoking, hypertension, diabetes, and lipid abnormalities. Our final goal was to recognize relationships among body fat distribution, hemostatic measurements, and left ventricular function in obese subjects with central fat distribution.

SUBJECTS AND METHODS

Subjects

A total of 39 subjects, 19 obese and 20 lean healthy controls, younger than 40 years were included in this study. Obese subjects were recruited from individuals attending the obesity center of the Internal Medicine Department at the University of Palermo. Lean controls were chosen from a group of subjects undergoing a clinical evaluation and found to be healthy. Subjects were considered obese according to BMI values proposed by the Italian Consensus Conference on Obesity.[16] Cutoff values for obesity were a BMI of at least 30.5 kg/m^2 for men and 27.3 kg/m^2 for women. Lean subjects were selected on the basis of BMI values of less than 24.7 kg/m^2 for women and 25 kg/m^2 for men. Each subject's fat distribution was assessed by measuring WHR in the standing position as previously reported.[9,10,12] Central fat distribution was defined on the basis of the sex-specific 85th percentile of WHR values.[16] In view of this, the cutoff value for central obesity was considered at least 0.81 for women and 0.92 for men. According to

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these criteria, obese subjects with peripheral fat distribution (WHR < 0.81 for women and < 0.92 for men) were excluded. Following this procedure, subjects were subdivided into two groups: group 1 (lean subjects), 10 men and 10 women aged 24 to 39 years (mean, 34 ± 5) with a BMI mean value of 23.3 ± 0.8 and a WHR mean value of 0.75 ± 0.04; and group 2 (obese subjects with central fat distribution), nine men and 10 women aged 28 to 38 years (mean, 33 ± 4) with a BMI mean value of 36.3 ± 4.7 and a WHR mean value of 0.93 ± 0.06.

All subjects were normotensive (systolic blood pressure consistently < 140 mm Hg and diastolic blood pressure < 90 mm Hg) and matched as closely as possible with regard to age, gender, and height (Table 1). Arterial blood pressure was measured with an appropriately large cuff in obese subjects.[1,9,10,12]

Exclusion criteria included smoking habits, insulin-dependent or -independent diabetes mellitus, hyperlipoproteinemia (total cholesterol > 220 mg/dL), endocrine and cardiovascular disease, hypertension, electrolyte imbalance, alcoholism, drug addiction, and psychiatric problems.

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. This study was approved by the Ethics Committee of our Institute, and each patient gave informed consent after a detailed description of the study procedure.

Preliminary investigations included determination of blood and urinary electrolytes, creatinine clearance, blood glucose, oral glucose tolerance, total serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Creatinine clearance, serum and urinary electrolytes, and the oral glucose tolerance test were used to exclude subjects with renal impairment, electrolyte imbalance, and diabetes mellitus, respectively. These measurements did not differ significantly between lean and obese subjects.

Laboratory Methods

Venous blood samples were drawn after an overnight fast using a 1.2-mm siliconized needle without or with minimal stasis. We determined the following in serum using conventional enzymatic methods (Boehringer Mannheim, Milano, Italy): blood glucose (Glucose Oxidase), triglycerides (Glycerol Phosphate Oxidase), total cholesterol (Cholesterol Oxidase), and HDL cholesterol (after precipitation by dextran-magnesium chloride). Apolipoprotein (apo) A1 and B levels were measured by radioimmunodiffusion (Behring, Scoppito, Italy).

Immunoreactive insulin levels were measured by the radioimmunoassay double-antibody method using a commercial kit (Sorin, Saluggia, Italy). Intrassay variation was 7.5%, and interassay variation was 8%; sensitivity for detection of insulin was 2.5 μU/mL.

Lipoprotein(a) levels were assayed by two-site anti-apo(a) immunoradiometric assay with antisera standards and control materials supplied by Pharmacia Diagnostic (Uppsala, Sweden). Cross-reactivity with plasminogen and apo B is absent up to a concentration of 8.5 g/L for plasminogen and 7 g/L for apo B in this assay. Interassay and intrassay variations were less than 9% and less than 5%, respectively.[17]

Table 1. Characteristics of Lean and Obese Subjects

Characteristic	Lean (n = 20)	Obese (n = 19)
Gender (M/F)	10/10	9/10
Age (yr)	34 ± 5	33 ± 4
Height (cm)	165 ± 8.3	163 ± 8.5
BMI (kg/m²)	23.3 ± 0.8	36.3 ± 4.7*
WHR	0.75 ± 0.04	0.93 ± 0.06*
FBG (mg/dL)	89 ± 4	93 ± 4.5†
Cholesterol (mg/dL)	176 ± 18	193 ± 24
HDL cholesterol	47.3 ± 3	41 ± 6†
TG (mg/dL)	120 ± 21	133 ± 42
Lp (a) (mg/dL)	10.3 ± 5.4	18 ± 7†
Apo A1 (mg/dL)	150 ± 12	153 ± 24
Apo B (mg/dL)	105 ± 15	146 ± 68‡
IRI (μU/mL)	9.8 ± 3	21.2 ± 8.3†

Abbreviations: M, males; F, females; FBG, fasting blood glucose, TG, serum triglycerides; Lp (a), lipoprotein (a); IRI, fasting immunoreactive insulin.

*$P < .001$ *v* lean.

†$P < .01$ *v* lean.

‡$P < .02$ *v* lean.

Hemostatic Measurements

Blood samples for coagulation and fibrinolysis tests were drawn in polypropylene tubes containing one tenth final volume of 3.8% sodium citrate and kept on crushed ice until centrifugation (4°C at 2,500 × *g* for 15 minutes), and plasma was stored in small aliquots at −70°C until use. A venous occlusion test was also performed in all subjects. A sphygmomanometer cuff was applied to the contralateral arm and inflated midway between systolic and diastolic pressure for 10 minutes. A further blood sample was obtained before deflating the cuff from the occluded arm and separated as previously described.[18]

Tissue plasminogen activator antigen before (tPA1) and after (tPA2) venous occlusion by enzyme-linked immunosorbent assay with a commercially available kit (Innogenetics NY, Antwerp, Belgium), plasminogen activator inhibitor (PAI) activity by chromogenic substrate assay with reagents obtained from Behring (using an automated device, Behring Chromo Time System; Scoppito, Italy), factor VII by a chromogenic substrate assay (Behring Chromo Time System), and fibrinogen and plasminogen by radioimmunodiffusion (Behring) were determined.

Analyses were performed in duplicate following the manufacturer's instructions and, in one series for each participant, within 6 months of sampling.

Assay of all parameters has been well validated in our laboratory.[18] Normal values were as follows: tPA antigen, 5 ± 0.5 ng/mL; PAI activity, 3.7 ± 0.3 U/mL; factor VII activity, 88% ± 5.2%; plasminogen, 10 ± 1.2 mg/dL; and fibrinogen, 3.4 ± 0.4 g/L.

Radionuclide Study

Systolic and diastolic functions were evaluated by radionuclide angiocardiography using the blood-gated method reported by Bonow et al.[19] A computerized, large-field scintillation camera (Starcam 400; General Electric, Horsholm, Denmark) with a high-resolution, 1.5-in parallel-hole collimator was used. This method has been validated in our laboratory, in particular in obese subjects.[9,10,12,20] Left ventricular ejection fraction (LVEF) and peak filling rate ([PFR] = end diastolic volume per second) were measured.

Echocardiographic Study

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

Left ventricular mass (LVM) was calculated according to the

Devereux method from necropsy-validated studies.[21] LVM was also related to body height (LVM/H) 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).[22]

LVH was assumed in the presence of a LVM/H greater than 2 standard deviations from 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 was greater than 120 g in men and 103 g in women.

According to these values, none of the obese and lean subjects had LVH.

Statistical Analysis

Comparisons between lean and obese subjects were performed using an unpaired t test. Linear and multiple regression analyses were used to calculate correlation coefficients between measurements of left ventricular function and tests of coagulation or fibrinolysis. Independent variables in multiple regression analysis were WHR, immunoreactive insulin, factor VII, and PAI, whereas dependent variables were LVEF and PFR. P less than .05 was considered statistically significant. All results are expressed as the mean ± SD.

RESULTS

Lean and obese subjects were comparable with regard to gender, age, and height. BMI and WHR were obviously significantly ($P < .001$) higher in obese than in lean subjects. In addition, fasting blood glucose ($P < .01$), lipoprotein(a) ($P < .01$), apo B ($P < .02$), and serum insulin ($P < .01$) levels were significantly higher and HDL cholesterol values ($P < .01$) were significantly lower in young subjects with central obesity than in lean controls. Total cholesterol, serum triglycerides, and apo A1 did not differ significantly between obese and lean groups (Table 1).

Hemostatic Activity and Left Ventricular Function and Structure

Coagulation and fibrinolytic tests were significantly different between obese and lean subjects. In particular, factor VII, fibrinogen, plasminogen, and PAI activity were significantly ($P < .001$) higher in obese than in lean subjects. In addition, tPA1 was significantly higher ($P < .02$) and tPA2 significantly lower ($P < .05$) in obese than in lean subjects. LVEF ($P < .001$) and PFR ($P < .02$) were significantly lower in obese subjects with central fat distribution than in lean controls. In contrast, LVM and LVM/H did not differ between the two groups (Table 2).

Correlations

WHR correlated directly with fibrinogen ($r = .47$, $P < .05$) and inversely with tPA2 ($r = -.48$, $P < .05$); duration of obesity correlated directly with factor VII activity ($r = .49$, $P < .05$) and tPA1 ($r = .48$, $P < .05$). In addition, LVEF correlated inversely with tPA1 ($r = -.55$, $P < .001$), PAI ($r = -.69$, $P < .001$), and fibrinogen ($r = -.51$, $P < .002$) (Fig 1). PFR correlated inversely with factor VII activity ($r = -.50$, $P < .05$).

Table 2. Measurements of Hemostatic Function and Left Ventricular Structure and Function in Lean and Obese Subjects

Measure	Lean (n = 20)	Obese (n = 19)
Factor VII activity (%)	79 ± 11	105 ± 18*
Fibrinogen (g/L)	3.4 ± 0.7	4.5 ± 0.8*
Plasminogen (mg/dL)	9.7 ± 0.8	13.2 ± 2*
PAI (U/mL)	3.2 ± 0.3	4.9 ± 2*
tPA1 (ng/mL)	4.8 ± 0.7	5.9 ± 1.6†
tPA2 (ng/mL)	29 ± 4	23 ± 12‡
LVM (g)	135 ± 35	155 ± 42
LVM/H (g/m)	81 ± 25	95 ± 20
LVEF (%)	65.5 ± 4	56 ± 10*
PFR (EDV/s)	3.55 ± 0.8	2.9 ± 0.6†

Abbreviation: EDV, end diastolic volume.
*$P < .001$ *v* lean.
†$P < .02$ *v* lean.
‡$P < .05$ *v* lean.

Multiple regression analyses indicated that WHR and PAI were independent predictors of LVEF levels.

DISCUSSION

This study indicates that obese subjects with central body fat distribution may be characterized by abnormalities in coagulation function and fibrinolytic activity. These included higher levels of factor VII antigen, fibrinogen, plasminogen, PAI activity, and basal tPA, and lower levels of post–venous-occlusion tPA.

Some of these abnormalities were correlated with measurements of left ventricular function such as LVEF and PFR. These data are consistent with the indication that the risk of cardiovascular disease is higher in centrally obese than in lean subjects.[1,23,24]

In fact, elevated fibrinogen and factor VII are reported as risk factors for cardiovascular disease.[5,7] Moreover, either may be considered an expression of elevated turnover of the coagulation pathway and may be involved in the pathogenesis of ischemic heart disease.[5,25] In the current study, increased levels of these coagulation factors have been found in subjects with central obesity. Moreover, fibrinogen was directly correlated with WHR and factor VII was directly correlated with duration of obesity, indicating an association among long duration of obesity, body fat distribution of central type, and changes in coagulation function. In these subjects, fibrinogen was also inversely correlated with LVEF, and this may support a relationship between coagulation activity and silent left ventricular dysfunction. These data may be of interest, since general epidemiological studies suggest that high levels of fibrinogen and factor VII may be of casual significance in the development of ischemic heart disease.[26] Unlike factor VII, fibrinogen is an acute-phase protein and increases in response to a number of stimuli.[27] However, clinical situations in which fibrinogen levels are high are also characterized by an increase in incidence of venous thrombosis, indicating that this factor has an important role in thrombogenesis.[5] Fibrinogen is also a major determinant of blood viscosity, which, if

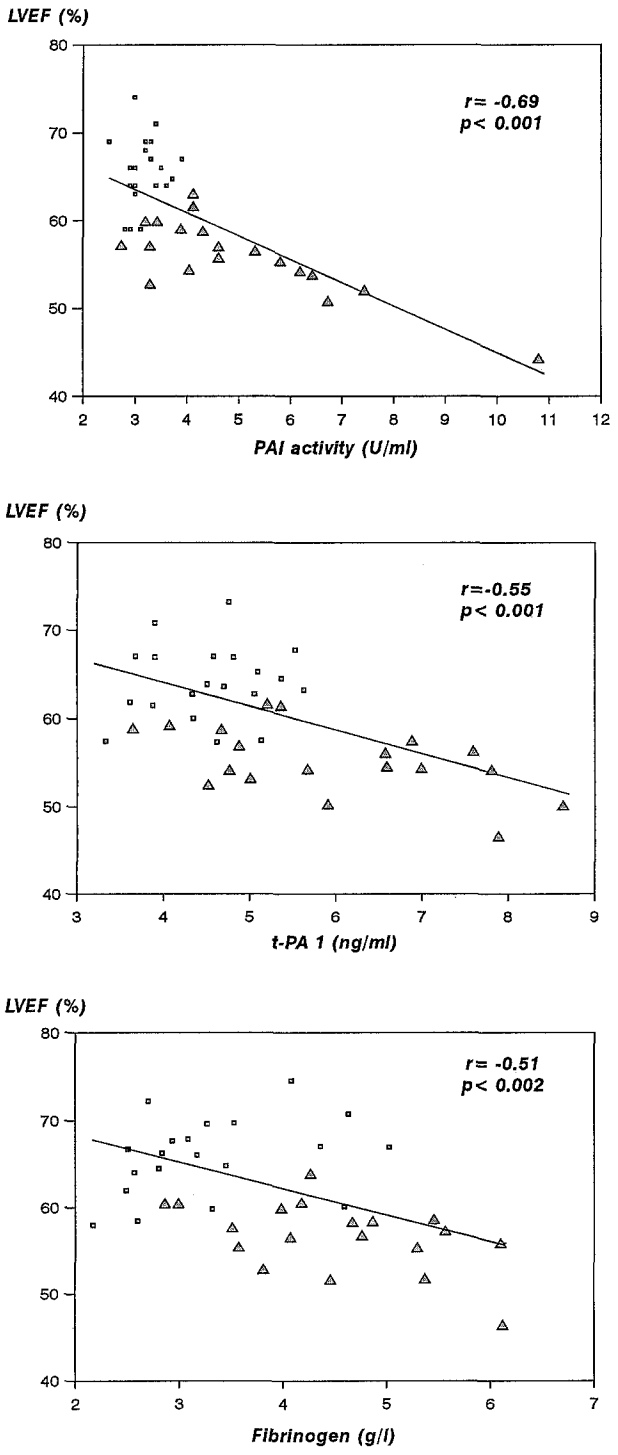

Fig 1. Correlation between LVEF and coagulation and fibrinolytic measurements in lean (□) and obese (△) subjects.

increased, probably has a casual role in coronary heart disease.[28]

Our data indicate a hypercoagulable state associated with a depressed left ventricular function in subjects with central obesity.

It has been recently reported that elevated PAI levels are associated with an increased recurrence of myocardial infarction.[29,30] In addition, increased PAI levels may be detectable in patients with coronary spastic angina.[31]

The relationships between central obesity and fibrinolytic activity have been well investigated by Landin et al.[8] They reported that a high WHR in obesity was associated with an impaired fibrinolytic activity. In addition, Vague et al[32] have provided evidence that hyperinsulinemia may be an important reason for the impaired fibrinolytic activity.

In our study, the role of hyperinsulinemia in promoting depressed fibrinolytic activity remains uncertain. In fact, despite insulin levels that were higher in obese than in lean subjects, no evidence indicated an independent effect of fasting insulin on the change in fibrinolytic activity.

In the present study, increased PAI and a depressed fibrinolytic activity have been demonstrated in subjects with central obesity. WHR and PAI activity remained the best predictors of LVEF in multiple regression analysis. This indication is further supported by results of the European Concerted Action on Thrombosis and Disabilities (ECAT) study.[6] In this study, a decreased pump function associated with increased PAI and decreased fibrinolytic activity both before and after stimulation by venous occlusion has been reported. An explanation for the mechanisms responsible for the abnormalities in hemostatic function detectable in our obese subjects remains unclear. They might indicate that it is possible to detect early suitable markers of atherosclerosis in subjects with central obesity. This is also supported by lower HDL levels and higher apo B and lipoprotein(a) values in obese than in lean comparable subjects.

In conclusion, obese subjects with central body fat distribution showed an atherogenic profile characterized by metabolic and hemostatic abnormalities associated with silent left ventricular dysfunction. Further prospective data must be provided to demonstrate if cardiac events occur more frequently in obese than in lean subjects.

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