Obesity and cardiovascular diseases

Giuseppe Licata, Salvatore Corrao, Gaspare Parrinello, Rosario Scaglione

Obesity and overweight have great clinical and social significance and are associated with a number of medical and surgical complications. We attempt here to summarize current knowledge on the subject and describe the research we are presently carrying out in this field. After a brief introduction, definition, and discussion of etiopathogenesis, the indexes of ponderal excess and epidemiology are illustrated. The cardiovascular adjustments and the relationships between obesity and hypertension, ischemic heart disease and congestive heart failure are then treated.
One aim of our investigation was to study the modifications of an entire set of biological and clinical parameters which could concretely formulate and/or identify some pathophysiological links between obesity and heart disease. We thus studied obese subjects with hypertension, diabetes and multiple cardiovascular risk factors. We also studied a group of asymptomatic obese subjects, whom we define as "the healthy obese". Our results, supported by the medical literature, led to the conclusion that obesity is an important and/or independent cardiovascular risk factor. We think, however, that it would be prudent to await for the results of interventional trials and follow-up studies involving a large number of young, healthy obese subjects in order to monitor the most important biological variables over the long term.

(Ann Ital Med Int 1994; 9: 27-31)

Introduction

Most of the concepts at the basis of current research on obesity were formulated before or during the 19th century. In fact, the hazards of obesity to health were clearly indicated in Greek and Roman medical treaties. Hippocrates stated that "sudden death is more common in those who are naturally fat than in the lean"[1]. With regard to treatment, he underscored the importance of restricting food intake, increasing physical activity and reducing sleep time[2]. In the 19th century, the frequently used terms "corpulence" and "polysarcia" were almost entirely replaced by "obesity". During this period, too, acquisition of scientific information by use of epidemiological studies became more and more frequent.

The Consensus Conferences in Bethesda (1985)[3] and Italy (1991)[4] sum up the most significant scientific knowledge and epidemiological data gathered in recent years. The Italian Society of Internal Medicine (SIMI) has also taken deep interest in this area: the reports by R. Galdi (1936), A. Dalla Volta (1962), L.A. Scuro (1977) which were presented respectively at the XLII, LVIII, LXXVIII SIMI Congresses represent interesting contributions to this theme.

Definition

The terms obesity and overweight designate a condition characterized by an excess of body fat. Obesity frequently leads to significant impairment of health and is currently the most common pathology of Western society. Its cause is, for the most part, the ingestion of a greater quantity of nutritional substances than the individual needs for support.

The clinical and social significance of this condition is momentous inasmuch as obesity, particularly in its severest form, is linked to a number of medical and surgical complications which often cause serious health problems, e.g. respiratory complaints, Pickwick's syndrome, arterial hypertension, diabetes mellitus, abnormalities of lipid and hormonal metabolism, arthritis of the knee, gallstones and cancer.

The approach to this pathological condition is difficult, and neither cultural nor scientific interpretations should be neglected. The role of the internist is fundamental for correct management of a clinical state characterized by complex pathophysiology and various complications.

Etiopathogenesis

The etiopathogenesis of obesity involves both genetic and environmental factors. The former may induce changes in eating behaviour (bulimia) and or modifications in energy expenditure which lead to the loss of normal body weight regulation mechanisms. The latter factors are more complex and derive from the interaction of both psychosocial and economic-cultural determinants inducing abnormalities in the energetic metabolism balance.

For practical purposes, we classify obesity as primary or secondary (in which the etiology can be established). The primary forms constitute the overwhelming majority of cases and seem essentially to stem from the interaction of several pathogenetic events.

Indexes of ponderal excess and determination of body mass

Various indexes enable quantification of ponderal excess. They are based essentially on anthropometric data (relative weight, Quetelet's index) and plicometry. Recently, great interest has arisen in fat distribution indicators such as the waist-hip ratio and the visceral/subcutaneous fat ratio calculated by computerized axial tomography since they identify central obesity which is mainly correlated to a higher cardiovascular risk[5-7]. There are

Cattedra di Patologia Medica I, Divisione di Medicina Interna, Università degli Studi di Palermo (Direttore: Prof. Giuseppe Licata)

Sintesi della Relazione presentata al XCIII Congresso Nazionale della Società Italiana di Medicina Interna (Firenze, 17-21 ottobre 1992).

various other methods to evaluate body composition although not all of them are easily applicable in clinical practice.

Epidemiology

Ponderal excess is present in a significant percent of the population in the Western world. Some American studies have reported a prevalence of about 23% for men and 30% for women[8-10]. These epidemiological data have been partially confirmed by two important Italian investigations: the Emilia Romagna Obesity Study (EROS)[11] for adults and the Italian Nutrition Examination Survey on the Elderly (INESE)[12] for the aging population.

The involvement of a great portion of the population has important repercussions on public health. In fact, obesity is clearly associated with both higher general mortality and cardiovascular morbosity and mortality.

In the late 1950s, American insurance companies began conducting research on obesity[13-15]. They found that increased ponderal excess corresponds to increased mortality, chiefly as the result of cardiovascular complications. The relationship between ponderal excess and mortality (for all causes) is described by a U or J-shaped curve, even when relative weight or body mass index (BMI) are used as indexes of ponderal excess.

Although the data from the medical literature are not unanimous, longitudinal studies such as the Framingham Study[16] and the Seven Countries Study[17] have evidenced increased cardiovascular mortality. In a recent study of 115 000 American nurses, Manson et al.[18] underscored the importance of ponderal excess over the years. The risk of myocardial infarction (both fatal and non-fatal), adjusted for age and initial BMI, is higher in women with a weight increase of more than 10 Kg after the age of 18 years than in women whose body weight remains stable.

Data from important follow-up studies such as the Pooling Project, the Framingham and Manitoba studies[16,19,20] show that obesity is an independent cardiovascular risk factor, evident chiefly after a long period of observation.

The Göteborg study[21] is one of the few presently available follow-up studies that has evaluated cardiovascular morbidity in relation to body fat distribution. After a 13-year follow-up of male subjects, the ratio between waist and hip circumference (WHR) resulted predictive for ischemic heart disease which was independent of BMI but not of smoking, arterial pressure or serum cholesterol.

Cardiovascular alterations

The improvement and reliability of non-invasive techniques such as echocardiography, echo-Doppler evaluation and radioisotope techniques, have permitted, in recent years, the rapid acquisition of a number of data concerning indexes of hemodynamic and cardiac function in a large number of subjects. These methods have allowed both correct evaluation of central hemodynamics and effective analysis of left ventricle function and structure in obese subjects.

It has been demonstrated that obesity (in its severest form) induces the expansion of intravascular volumes which is expressed in an increase in both cardiac output and left ventricular mass as well as derangement and even enlargement of left ventricle internal dimension.

A characteristic structural alteration, commonly described as eccentric left ventricular hypertrophy, can come about: it is characterized by increased loading conditions with consequent impairment of left ventricular performance[22,23].

It has recently been reported that the increment of cardiac output in the obese subject is caused not only by ponderal excess but also by visceral fat distribution[21,24]. When subjects with visceral obesity are compared to those with subcutaneous obesity and the same body weight, they evidence a major vascular volume overload due to the fact that blood flow in mesenteric adipose tissue is greater than that in subcutaneous inguinal adipose tissue[25]. Moreover, the hemodynamic importance of visceral fat distribution is increased by the evident emphasis that is frequently associated with metabolic disorders such as impaired glucose tolerance, hyperinsulinism and hyperlipidemia which represent further valid cardiovascular risk factors in obese subjects.

Obesity and hypertension

Recently, the results of important epidemiological studies (Framingham and others) and some interesting clinical observations have encouraged many investigators, including our group[26,27], to study more thoroughly the relationship between overweight and hypertension. This research line was begun 10 years ago, although the existence of a relationship between obesity and hypertension was pointed out in 1924 by Faber[28] in a study of prevalence carried out in 1000 healthy Scandinavian subjects, 20-25 years old.

Various epidemiological studies confirm a frequent association between obesity and hypertension. Moreover, recent data have confirmed the hypothesis made by Vague[29] who first spoke of the relationship between upper body obesity and hypertension and demonstrated a positive correlation between WHR and systolic and diastolic arterial pressure values.

A number of possible pathogenetic mechanisms can determine the development of hypertension in obese subjects. A paramount role is currently attributed to genetic and environmental factors, hyperinsulinism, insulin resistance, sympathetic activity, intracellular ion concentrations, sodium intake, sodium regulating hormones and adjustments for both intravascular volumes and cardiac hemodynamics.

Resnick et al.[31,32] recently made the hypothesis that the common basis for the clinical association between arterial hypertension and cardiac diseases with dysmetabolic syndromes such as obesity, impaired glucose tolerance and non-insulin-dependent diabetes mellitus, should be sought not so much in the levels of circulating insulin or a specific condition of insulin resistance but rather in a previous phase, that is, in the alteration of free cytosolic ion concentrations. The role of calcium in the maintenance of blood pressure balance and the pathophysiology of arterial hypertension has undergone significant investigation in recent years. Moreover, the basic importance of calcium in the contraction process of heart and vessel muscular cell, in the process of endocrine secretion, in the release of neurohormones and in the regulation of renal function is understood. It follows that cardiac output, peripheral vascular resistances, the secretion of various hormones such as insulin and those of the renin-angiotensin-aldosterone system, can be influenced by the intracellular concentration of calcium. In a recent study

with Resnick et al.[31], we used nuclear resonance spectroscopy to confirm higher levels of free cytosolic erythrocyte calcium and plasma insulin in obese as compared to lean subjects. A direct correlation between the levels of free cytosolic erythrocyte calcium and BMI ($r = 0.66$; $p < 0.001$) was also demonstrated.

Analysis of a sample of young hypertensive obese subjects free from other cardiovascular risk factors, enabled us to document the existence of a direct correlation between BMI and norepinephrine ($r = 0.55$) and between WHR and norepinephrine ($r = 0.59$). In the same sample group, both plasmatic norepinephrine and epinephrine were correlated to urinary sodium excretion with a value of $r = 0.69$ in hypertensive obese subjects and of $r = 0.59$ in normotensive obese subjects, confirming Dahl's hypothesis of a higher sodium-intake diet in overweight subjects[32]. WHR was also found to be correlated to urinary sodium excretion ($r = 0.58$). The existence of direct correlations between body fat mass and urinary sodium excretion ($r = 0.66$), both hematic and plasmatic intravascular volumes ($r = 0.88$ and $r = 0.82$, respectively) and cardiac output were also observed.

Our investigations as well as current medical literature indicate that at least five pathophysiological situations characterize hypertensive obese subjects: hyperinsulinism and insulin resistance; increased sympathetic activity; altered intracellular sodium concentration; abnormal ion transport across the cellular membrane which determines impaired Na^+/K^+ and Na^+/Ca^{++} exchange consequently causing increased free cytosolic calcium; increased activity of the renin-angiotensin-aldosterone system associated with a failure of atrial natriuretic factor (ANF) responsiveness.

The possible genetic mechanisms potentially responsible for the association between obesity and hypertension require further study; it is still difficult to identify indexes which serve as markers of the development of hypertension in the obese subject.

In our opinion, more emphasis should be placed on the systematic study of abnormal pathophysiological mechanisms so that we may identify other factors, chiefly those concerned with visceral obesity, in an attempt to make a distinction between "benign obesity" and "malignant obesity" (which is prevalently visceral).

This leads to an interesting problem: the treatment of hypertensive obese subjects. The restriction of energy-intake and effective weight loss associated with a behaviour program involving controlled physical activity are obligatory. The aim of treatment is to modify the altered mechanisms which play an important role in the genesis and maintenance of hypertension in obese subjects, i.e., hyperinsulinemia, increased sympathetic activity and increased sodium intake. Often compliance to this regimen is not good, and pharmacological treatment becomes essential.

Obesity and ischemic heart disease

Obesity is without a doubt an important risk factor for ischemic heart disease, especially in the case of abdominal fat distribution on account of its frequent association with hypertension, hyperlipidemia and diabetes mellitus. Yet it has not been fully proven that obesity is an independent risk factor.

We thus carried out a research to identify the pathophysiological relationships which might concretely evidence that obesity by itself could be considered an atherogenic condition, able to cause autonomously the development, over time, of ischemic and atherothrombotic events.

We found that obese but otherwise healthy subjects (in whom no functional or structural disorders had emerged), termed the "healthy obese", differ from lean subjects in the following ways:

- with regard to the atherogenetic lipidic pattern, the healthy obese subjects had higher plasmatic levels of Apo-B and reduced HDL cholesterol and Apo-A_1 levels;
- with regard to the prothrombotic and hypofibrinolytic pattern, the healthy obese subjects had higher plasmatic levels of factor VII, fibrinogen, PAI and t-PA. The obese subjects also had higher plasmatic levels of endothelin and no signs of coagulation and/or platelet "in vivo" activation.

We also carried out a retrospective study of the prevalence of acute myocardial infarction which evidenced that among subjects who had had acute myocardial infarction, there was a high frequency of overweight and overt obesity, and that these classes of patients were stricken by acute myocardial infarction more frequently and at a younger age than lean subjects. Moreover, in the obese, the infarction was more frequently localized at multiple sites, at least in males < 65 years.

We found various significant correlations between the different parameters examined, e.g.: t-PA, Lp(a); leukocytes, ANF, aldosterone, left ventricle internal diameters and ejection fraction, left ventricular mass and duration of obesity.

We thus believe that long-term and severe obesity, which usually implies biohumoral, hemodynamic and clinical alterations, could be considered a principal determinant of cardiovascular events, particularly in subjects with upper-body obesity.

Obesity and congestive heart failure

The relationship between obesity and congestive heart failure has been noted in prestigious epidemiological studies[16,20,21]. In this case, the pathological link - aside from the characteristic hemodynamic alterations found in obese subjects - seems to consist in a number of neurohormonal alterations as well as the evident abnormalities in diastolic and systolic function caused by excess weight. Alexander et al.[33-35] described a particular form of cardiac disease in severely obese subjects which they defined as "obesity cardiomyopathy": hemodynamic alterations (increased extravascular volumes, cardiac output, left ventricular pressure and filling volumes, etc.) which had been noted in the severely obese were also found, to a proportionally lower degree, in subjects with mild to moderate obesity[36].

Further non-invasive investigations in young obese subjects with no other cardiovascular risk factors confirmed that moderate visceral obesity is also frequently associated with effective alterations of systolic and diastolic function. Abnormalities of diastolic function seem to precede those of systolic function. Frequently seen is myocardial hypertrophy which is insufficient to ventricular distension, a situation causing impairment of systolic function, chiefly under conditions of physical stress.

Many of these hemodynamic and functional indexes are correlated to the duration of obesity[37,38]: this leads us to the conviction that obese subjects carry, apart from the known associated mixed pathologies, the hemodynamic

and functional origin of the evolution to congestive heart failure.

Non-invasive assessment of cardiovascular hemodynamic and left ventricular function in obese subjects, even when asymptomatic, is obligatory for the surveillance and monitoring of early alterations of left ventricular function and the verification of hemodynamic benefits of therapeutic or preventive programs. The majority of hemodynamic alterations and alterations of left ventricular function are reversible after adequate weight loss. Gradual, long-term weight loss is indicated for these subjects, with more restrictive regimens reserved for extreme cases as they are often intolerable when extended over time.

In conclusion, cardiovascular function in the obese subject can be preserved by a dietetic and psychological approach which fosters a more correct relationship between the patient and food and the patient and himself.

Study on a group of "healthy obese" subjects

Over the past two years we have recruited obese subjects to study the modifications of a set of biological and clinical parameters which might concretely formulate and/or identify some pathophysiological links between obesity as an autonomous entity (that is, independent of other risk factors) and heart disease. We were perfectly aware of the limits of this study. Although it would have been better to carry out a longitudinal study to evaluate the independent role of obesity as a cardiovascular risk factor, we had no choice at that time.

In January 1990, 157 male and female obese subjects (BMI $\geq$ 30 Kg/m^2) aged $\leq$ 50 years (range 18-50 years) were recruited, according to Garrow's criteria for moderate obesity. A control group of 20 young healthy lean subjects (10 males and 10 females), age range 20-50 years, was randomly selected from a large group of healthy volunteers.

During the recruitment phase we evaluated the following parameters: duration of obesity, WHR, body fat and fat free mass. All obese subjects with secondary obesity and/or other conditions that could invalidate the results of our research were excluded from the study. We studied 106 obese subjects, grouped as follows: 30 obese subjects, free from all other cardiovascular risk factors (termed the "healthy obese"), 15 obese subjects with only diabetes mellitus, 11 obese subjects with only essential arterial hypertension, and 50 obese subjects with different cardiovascular risk factors. The healthy obese subjects were sub-grouped according to the duration of obesity: more of less than 180 months.

All subjects underwent a complete assessment of metabolic, coagulative and fibrinolytic profiles, plasma ions, catecholamines, sodium regulating hormones, left ventricular function, cardiovascular and renal hemodynamics. Furthermore, in a randomly selected group of healthy obese subjects, we evaluated cardiac hemodynamic and function parameter response to a standardized acute saline load, evaluation of "in vivo" platelet activation by the measurement of urinary 11-dehydro-TCB2 excretion, evaluation of cardiac functional and morphological modifications in response to weight loss by a Mediterranean hypocaloric balanced diet.

We hoped that the study of a group of young healthy obese subjects, in whom the most important cardiovascular risk factors had been ruled out, would enable us to identify the alterations of the principal homeostatic systems involved in the determination of some cardiovascular diseases.

In the healthy obese group, in fact, we found a series of hormonal modifications similar to those verified in subjects with cardiovascular diseases (increased levels of insulin, plasmatic and urinary catecholamines and sodium regulating hormones). Moreover, we found direct correlations between BMI, body fat mass and urinary excretion of sodium, body fat mass and epinephrine, duration of obesity and ANF, WHR and systolic blood pressure/24 h. We also noted an impaired response of the sodium regulating hormone to an acute saline load in the healthy obese group.

We confirmed that the principal markers of cardiovascular injury, including a statistically significant increase in microalbuminuria, are also present in young healthy obese subjects, and that the hormonal modifications found in this group can definitely be an important predictor of the hemodynamic adjustments which, even if they are a response to functional requirements of the cardiovascular apparatus of the obese, are the protagonists of the injury. Moreover, most of the metabolic, hormonal and hemodynamic alterations are present in both men and women and are related to WHR levels which are predictors of visceral obesity. This further confirms that the type of obesity rather than sex *per se*, is responsible for the possible differences noted in the medical literature between obese men and women. Finally, our data confirm the negative role of protracted obesity: in our healthy overweight subjects, a longer duration of obesity was associated with exacerbation of a number of functional and morphological metabolic, hemostatic, hormonal and cardiac parameters.

Conclusions

In conclusion, although we believe that obesity is an important and independent cardiovascular risk factor, we think it prudent to await for the results of both interventional trials and possible follow-up studies which include long-term monitoring of these variables in healthy obese subjects.

These investigations could clarify the relationship between pathophysiological alterations and atherothrombotic events. Moreover, it would be possible to detect the real risk of obesity, particularly visceral obesity, since the particular neuroendocrine abnormalities of this type seem to act as a principal biopathogenetic starter.

Riassunto

L'obesità ed il sovrappeso hanno un notevole significato clinico e sociale, comportando diverse complicanze mediche e chirurgiche. In questo articolo presentiamo e riassumiamo le attuali conoscenze sull'argomento e descriviamo le ricerche da noi perseguite. Dopo una breve introduzione, definizione e discussione sull'eziopatogenesi, vengono illustrati gli indici utilizzati per la valutazione dell'eccesso ponderale e gli aspetti epidemiologici relativi. In seguito vengono trattati gli adattamenti cardiovascolari ed i rapporti tra ipertensione, cardiopatia ischemica, scompenso cardiaco congestizio ed obesità.

Scopo della ricerca è lo studio delle modifiche di un complesso di parametri biologici e clinici che possono concretamente formulare e/o identificare alcuni legami fisiopatologici tra obesità e cardiopatie.

Un gruppo di soggetti obesi affetti da ipertensione, diabete e con fattori di rischio cardiovascolare multipli ed un gruppo di soggetti obesi asintomatici convenzionalmen-

te denominati come "obesi sani", sono stati studiati e confrontati.

I risultati dello studio, confortati dai rilievi della letteratura, fanno concludere come l'obesità sia un importante e/o indipendente fattore di rischio cardiovascolare. Si ritiene comunque necessario considerare i risultati dei trial di trattamento e gli studi di follow-up coinvolgenti un elevato numero di soggetti giovani obesi sani in modo da valutare queste importanti variabili biologiche nel lungo periodo.

References

1. Hippocrates. The genuine works of Hippocrates translated from the Greek with a preliminary discourse and annotations (translated by Francis Adams). London: The Sydenham Society, 1849.
2. Precope J. Hippocrates on diet and hygiene. London: Zenò, 1952.
3. Burton BT, Foster WR, Hirsch J, Van Tallie TB. Health implication of obesity: an NIH Consensus Development Conference. Int J Obes 1985; 9: 155-69.
4. Consensus Conference Italiana. Sovrappeso, obesità e salute. Recenti Prog Med 1991; 82: 417-34.
5. Bjorntorp P. Obesity and the risk of cardiovascular disease. Am Clin Res 1985; 17: 3-9.
6. Bouchard C, Bray GA, Hubard VS. Basic and clinical aspects of regional fat distribution. Am J Clin Nutr 1990; 52: 946-50.
7. Depres JT. Obesity and lipid metabolism: relevance of body fat distribution. Curr Opin Lipidology 1991; 2: 5-15.
8. Abrahams S, Carroll MD, Naijar MF. Overweight and obese adults in the United States. Vital and Health Statistics. DHHS publication No. (PHS) 83-1680, National Health Survey Series 11, 1983; 230: 1-28.
9. National Center for Health Statistics 1973. Plan and operation of the Health and Nutrition examination survey, United States, 1971-1973, Washington, DC, Health Services and Mental Health Administration. Vital and Health Statistics, series, No. 10A and 10B. DHEW Publ. No. (HSM) 73-1310.
10. Van Itallie TB. Health implications of overweight and obesity in the USA. Ann Intern Med 1985; 103: 983-8.
11. Descovich GC, Cavicchi S, Conti D, et al. Sulla frequenza delle malattie cardiovascolari in una popolazione emiliano-romagnola. Nota I: relazione tra parametri antropometrici, età e sesso. G Aterosclerosi 1976; 1: 59-64.
12. Melchionda N, Enzi G, Caviezel F, et al. Epidemiology of obesity in the elderly: CNR Multicentric Study in Italy. Diabetes Res Clin Pract 1990; 10 (10 Suppl): 11-6.
13. Metropolitan Life Insurance Company. Build and Blood Pressure Study 1959. Chicago: Society of Actuaries, 1960; 1: 11.
14. Build and Blood Pressure Study 1979. Chicago: Society of Acturaries and Association of Life Insurance Medical Directors of America, 1980.
15. McCue H Jr. The 1979 Build and Blood Pressure Study. In: Bostrom H, Ljungstedt N, eds. Medical aspects of mortality statistics. Stockholm: Almquist and Wiksell International, 1981: 182-98.
16. Hubert HB, Feinleib M, McNamara PM, Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67: 968-77.
17. Keys A. Seven countries. A multivariate analysis of death and coronary heart disease. London: Harvard University Press, 1980.
18. Manson JE, Graham AC, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990; 322: 882-9.
19. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidences of major coronary events: final report of the Pooling Project. J Chron Dis 1978; 31: 201-306.
20. Rabkin SW, Mathewson FAL, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26-year observation period: The Manitoba Study. Am J Cardiol 1977; 39: 452-8.
21. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjiorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death; 13 year follow-up of participants in the study of men born in 1913. BMJ 1984; 288: 1401-4.
22. De Divitiis O, Fazio E, Petitto M, et al. Obesity and cardiac function. Circulation 1981; 64: 477-82.
23. Alexander JK, Dennis DW, Smith WG. Blood volume, cardiac output and distribution of systemic blood flow in extreme obesity. Cardiovasc Res Center Bulletin 1962; 1: 39-44.
24. Stern MP, Hafner SM. Body fat distribution and hyperinsulinemia and risk factors for diabetes and cardiovascular disease. Arteriosclerosis 1986; 6: 123-8.
25. Herd JA, Goodman M, Grose S. Blood flow rates through adipose tissues of unanesthetized rats. Am J Physiol 1968; 214: 263-8.
26. Licata G, Scaglione R, Capuana G, et al. Hypertension in obese subjects: distinct hypertensive subgroup. J Hum Hypertens 1990; 4: 37-41.
27. Licata G, Scaglione R, Parrinello G, et al. Rapid ventricular filling in untreated hypertensive subjects with or without left ventricular hypertrophy. Chest 1992; 102: 1507-11.
28. Faber A. Readings of blood pressure of 1000 healthy individuals aged 20-25 years: an anthropometric study. Scand Arch Physiol 1924; 45: 189-203.
29. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. Am J Clin Nutr 1956; 4: 20-34.
30. Resnick LM. Calcium metabolism in hypertension and allied metabolic disorders. Diabetes Care 1991; 14: 505-20.
31. Resnick LM, Gupta RK, Bhargava KK, et al. Cellular ions in hypertension, diabetes and obesity. Hypertension 1991; 17: 951-7.
32. Dahl LK, Silver L, Christie RW. The role of salt in the fall of blood pressure accompanying reduction in obesity. N Engl J Med 1958; 258: 1186-92.
33. Alexander JK, Amad K, Call WW. Observation on some clinical features of extreme obesity with particular reference to cardiorespiratory effects. Am J Med 1962; 32: 512-8.
34. Alexander JK. Obesity and the circulation. Mod Concepts Cardiovasc Dis 1963; 132: 799-807.
35. Alexander JK, Pettigrove JR. Obesity and congestive heart failure. Geriatrics 1967; 22: 101-8.
36. Licata G, Scaglione R, Barbagallo M, et al. Effect of obesity on left ventricular function studied by radionuclide angiocardiography. Int J Obes 1991; 15: 295-302.
37. Licata G, Scaglione R, Paterna S, et al. Left ventricular function response to exercise in normotensive obese subjects: influence of degree and duration of obesity. Int J Cardiol 1992; 37: 223-30.
38. Scaglione R, Dichiara MA, Indovina A, et al. Left ventricular diastolic and systolic function in normotensive obese subjects: influence of degree and duration of obesity. Eur Heart J 1992; 13: 738-42.

Address for correspondence:
Prof. Giuseppe Licata, Cattedra di Patologia Medica I, Università degli Studi, Piazza delle Cliniche 2, 90127 Palermo.