Original articles

Pulmonary venous flow and mitral inflow velocity pattern in uncomplicated obesity: evidence for late diastolic dysfunction

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Relaxation; Stiffness; Obesity; Doppler echocardiography; Cardiac hypertrophy.

Background. **Active left ventricular relaxation, assessed by Doppler isovolumic relaxation time, is impaired in obesity. There is little information on left ventricular passive properties during filling.**

Methods. **To evaluate left ventricular late diastolic stiffness in obesity, Doppler echocardiographic interrogation of mitral inflow tract and pulmonary vein flow velocities were obtained from 47 normotensive, young obese subjects (11 males, 36 females) and 43 normotensive, young normal-weight volunteers (13 males, 30 females) of comparable age.**

Results. **After controlling the effect of blood pressure and left ventricular mass, isovolumic relaxation time was prolonged in obese subjects ($p < 0.0001$ vs normal-weight controls). No difference was found in transmitral peak early and late flow velocities. Obese subjects exhibited prolonged pulmonary vein reverse flow velocity during atrial contraction ($p < 0.004$), and a higher difference or ratio between duration of pulmonary reverse flow and duration of transmitral forward late flow (6 – 31 vs -20 – 39 ms or 1.06 – 0.3 vs 0.84 – 0.3, $p < 0.002$ and $p < 0.001$, respectively). These differences were also confirmed after controlling blood pressure and left ventricular mass. Non-invasively estimated left ventricular end-diastolic pressure was higher in obese subjects than in controls ($p < 0.002$). At multivariate analysis a higher body mass index was the sole predictor of prolonged difference between duration of pulmonary reverse flow and duration of transmitral forward late flow ($\beta = 0.38$, $p < 0.001$).**

Conclusions. **Obesity is associated with prolonged left ventricular active relaxation and abnormalities of filling pressure not detectable by the sole mitral inflow velocity pattern. These latter abnormalities are consistent with the presence of early increased left ventricular passive stiffness.**

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Introduction

Assessment of pulmonary venous flow velocity pattern by transthoracic and transesophageal Doppler echocardiography is a reliable, non-invasive method to estimate left ventricular (LV) passive stiffness and has been used as a surrogate of LV filling pressures[1-8]. Thus, information obtained by integrating isovolumic relaxation time, mitral inflow and pulmonary venous flow velocities allows physiologically reliable evaluation of both active and passive phases of diastole. Full understanding of LV diastolic properties is clinically important, as impairment of diastole may lead to congestive heart failure also in the presence of apparently normal systolic performance[9-11].

Diastolic dysfunction has been described in obesity, characterized by the prolongation of isovolumic relaxation time[12-14], but little information is available on the passive phase of diastolic filling, a time of diastole that is difficult to examine non-invasively using analysis of mitral inflow velocity pattern[15]. Accordingly, this study was designed to evaluate LV passive diastolic phase in young, apparently healthy obese individuals using an integrated analysis of Doppler transmitral and pulmonary venous flows.

Methods

Subjects. Forty-seven normotensive, white, non-smokers, otherwise-healthy obese subjects (11 males, 36 females, mean age 28 – 9 years, body mass index 35 – 5 kg/m^2) were studied, together with 43 white normotensive, normal-weight volunteers (13

males, 30 females, mean age 31 – 9 years, body mass index 22 – 2 kg/m^2). All obese individuals came consecutively to the Outpatients Clinic of the Nutrition Unit of the Department of Clinical and Experimental Medicine of the Federico II University Hospital (Naples, Italy) with the sole purpose of losing weight for fitness and were classified as normal after an extensive clinical and laboratory test examination. Normal-weight individuals were volunteers recruited in a screening program by the Department Staff as previously reported[13]. Of 161 obese patients (age 17 to 69 years), consecutively referred to our laboratory, good quality pulmonary venous flow velocity could be recorded in 86 patients using an annular-array machine (53%). Percentage of feasibility increased to 80% when severe obesity (body mass index > 40 kg/m^2) was excluded.

Overweight was defined as body mass index > 27.8 kg/m^2 in men and > 27.3 kg/m^2 in women[16]. In addition to standard clinical screening, blood pressure was also measured at the end of the echocardiogram, in supine position, using arm-cuffs of appropriate size and a mercury sphygmomanometer. These values are reported in this study. Coronary artery disease was excluded on the basis of both a negative clinical history and examination (including 12-lead ECG), the absence of symptoms and conventional cardiovascular risk factors (arterial hypertension, dyslipidemia, smoking, diabetes), and evaluation of LV wall motion by two-dimensional echocardiography.

Echocardiography. A complete Doppler echocardiographic examination was performed in a dimly lit room with all patients in partial left decubitus position. Echocardiograms were recorded using a commercially available machine (SIM 7000 CFM Challenge or AU3, Esaote Biomedica, Florence, Italy) equipped with 2.5 to 3.5 MHz annular-array transducers. Two-dimensionally-oriented M-mode tracings were obtained from the parasternal LV short-axis view, recorded on videotape, printed out on strip-chart paper at 50 cm/s velocity, and reviewed by two independent observers, according to the standards of our laboratory[13,17]. LV chamber dimensions, septum and posterior wall thickness were measured according to the recommendations of the American Society of Echocardiography[18]. Left atrial dimension was measured by trailing edge to leading edge in parasternal short-axis view of the aorta at the level of valve leaflets. The Penn Convention[19] was used only to calculate LV mass. LV mass was thereafter normalized for height to the 2.7 power[20], an allometric measure of body size that has been shown to detect deviations of LV mass from normal also in obese individuals. Relative wall thickness was calculated as posterior wall thickness divided by LV end-diastolic radius[21]. Reproducibility of measurements of M-mode echocardiographic variables from our laboratory has previously been reported[22,23].

LV systolic function was evaluated by ejection fraction calculated using a method of estimation of LV volumes by M-mode echocardiography which was previously validated over a wide range of LV sizes[24]. This method allows reliable estimation of LV volumes also in the presence of LV dilation.

Doppler signals were recorded at high speed on videotape with the patient held in expiration and measured by two observers using electronic pointer devices. The average of three beats was used for the analysis.

Transmitral flow velocity was obtained from the apical 4-chamber view by pulsed wave Doppler interrogation of the LV inflow tract, with the sample volume placed at the tips of the mitral valve: peak early diastolic flow velocity (E), peak late diastolic flow velocity (A), deceleration time of early velocity, the duration of E velocity and the duration of A velocity were measured. The sample volume was then moved into the mitral valve annulus to measure the velocity time integral of E, A and that of total diastolic flow. Atrial filling fraction was calculated as the ratio of the velocity time integral of A and total diastolic flow.

Isovolumic relaxation time was obtained from the apical 5-chamber view with the sample volume placed between the LV outflow tract and the anterior mitral leaflet as the interval between the closing click of the aortic valve and the opening click of the mitral valve. When either the aortic closing click or the mitral opening click were unidentified, continuous wave Doppler of the LV inflow-outflow tract allowed identification of the interval between the end of aortic and the onset of mitral flows[13].

Pulmonary venous flow velocities were obtained from the apical 4-chamber view, by pulsed wave Doppler interrogation of the right upper pulmonary vein, using a 3 to 5 mm sample volume placed 1 to 2 cm into the vein lumen, as previously recommended[1-7], in order to record a clear laminar flow pattern. Measures of the peak systolic forward flow velocity, peak diastolic forward flow velocity and relative velocity time integrals, peak velocity and velocity time integral of reverse flow at atrial contraction were obtained. From these primary variables, the systolic fraction of pulmonary vein flow velocities was calculated as the ratio of peak systolic forward flow velocity to the sum of peak systolic and peak diastolic forward flow velocities. The duration of pulmonary vein reverse flow at atrial contraction (PVa duration) and the duration of transmitral late forward flow velocity (A) were measured and their difference (PVa-A)[1-7] and ratio (PVa/A)[8] were also calculated. Left ventricular end-diastolic pressure (LVEDP) was also estimated, by using a multivariate equation which takes into account PVa-A, peak systolic (s) and peak diastolic (d) pulmonary vein (PV) velocities and left atrial dimension (LA) as follows:

$$\log_{10}(\text{LVEDP}) = 1.36 + 0.01\,(\text{PVa-A}) - 0.17\,(\text{PVs/PVd}) + 0.01\,(\text{LA}).$$

This equation was invasively validated in a previous study[6], and found to be closely related to directly measured LVEDP (r = 0.90).

Intraobserver and interobserver variabilities were blindly obtained for peak systolic forward flow veloci-

ty, peak diastolic forward flow velocity, peak backward velocity at atrial contraction and PVa duration.

Statistical analysis. All data were expressed as mean – 1 SD. One-factor analysis of variance was used to compare measures of LV geometry, relaxation and filling, between normal-weight and obese individuals.

Correlates of LV Doppler transmitral flow and pulmonary venous flow were identified by least squares linear correlation analysis. Analysis of covariance was performed to control the between-group differences in pulmonary venous flow pattern for blood pressure and LV mass. Stepwise multiple regression analysis was used to identify independent determinants of PVa-A and PVa/A.

Bland and Altman plots and intervals of agreement[25] were used for evaluation of reproducibility of Doppler pulmonary vein flow parameters.

The null hypothesis was rejected at a two-tailed p 0.05.

Results

Interobserver and intraobserver variabilities were assessed using 20 randomly selected pulmonary vein Doppler velocity flow patterns among normal-weight (n = 12) and obese (n = 8) subjects. Table I shows mean interobserver and intraobserver differences – SD of Doppler pulmonary flow velocities and PVa duration and the corresponding intervals of agreement.

General characteristics of the study sample. Table II shows the general characteristics of the study population. Although comprised in a normal range, obese subjects exhibited higher systolic and diastolic blood pressure than normal-weight individuals whereas heart rate was not statistically different. LV chamber dimension, LV mass index, relative wall thickness, aortic root and left atrial dimension were also greater in obese than in normal-weight subjects ($0.04 < p < 0.0001$, Table III). After controlling blood pressure, obese subjects still exhibited higher LV mass index (adjusted mean 41 $g/m^{2.7}$) and relative wall thickness (adjusted mean 0.36) than normal-weight controls (adjusted means 29 $g/m^{2.7}$ and 0.31 respectively, both $p < 0.0001$). Ejection fraction was comparable to values in normal subjects.

Left ventricular relaxation and filling. Isovolumic relaxation time was markedly prolonged in obese individuals (Table IV) even after controlling blood pressure and LV mass index (adjusted mean 92 vs 72 ms, $p < 0.0001$). Obese subjects also exhibited prolonged duration of E flow velocity and increased deceleration time of E velocity, but these abnormalities were offset by controlling LV mass index. Peak E velocity, peak A velocity and both E and A velocity time integrals were comparable between groups: as a consequence, no between-group difference was found either in E to A ratio or in atrial filling fraction.

Table I. Interobserver and intraobserver variability for pulmonary vein flow velocities (n = 20).

Variables	Average interobserver variability	Average intraobserver variability	Interobserver interval of agreement	Intraobserver interval of agreement
Peak systolic PV velocity (cm/s)	0.6 – 1.2	0.05 – 0.8	1.91/-3.01	1.61/-1.71
Peak diastolic PV velocity (cm/s)	0.25 – 1.2	0.02 – 1.08	2.07/-2.57	2.16/-2.16
Peak PVa velocity (cm/s)	0.5 – 1.5	0.2 – 1.7	3.44/-2.44	3.4/-3.0
PVa duration (ms)	0.5 – 8	1.6 – 4	17.2/-16.7	10.2/-7.1

PV = pulmonary vein; PVa = pulmonary vein reverse flow at atrial contraction.

Table II. General characteristics of the study population.

Variables	Normal-weight (n=43)	Obese (n=47)	p
Age (years)	31 – 9	28 – 9	< 0.1
M/F	13/30	11/36	NS
Body weight (kg)	61 – 11	94 – 16	< 0.0001
Body height (m)	1.65 – 0.08	1.65 – 0.08	NS
Body mass index (kg/m^2)	22 – 2	35 – 5	< 0.0001
Systolic blood pressure (mmHg)	113 – 11	121 – 12	< 0.001
Diastolic blood pressure (mmHg)	72 – 7	77 – 7	< 0.002
Heart rate (b/min)	71 – 11	74 – 10	NS

Pulmonary venous flow. Table V shows that peak systolic forward flow velocity, peak diastolic forward flow velocity and their integrals, peak velocity of reverse flow at atrial contraction and its velocity time integral were comparable in obese and normal-weight individuals. Although obese subjects exhibited higher systolic flow fraction (derived from either peak velocities or velocity time integrals) than normal-weight individuals, these differences were largely offset after controlling blood pressure (obese: 54 and 56% respectively; normal-weight 51 and 52% respectively). In contrast, PVa duration, PVa-A difference and PVa/A ratio were higher in obese than in normal-weight subjects (Table V, all $p < 0.002$), even after controlling systolic and diastolic blood pressure. Further control of LV mass and LV end-diastolic dimension, as a crude index of preload, only attenuated these between-group differences (PVa duration 123 ms in obese, 101 ms in normal-weight, p

Table III. Left ventricular (LV) geometry and pump function.

Variables	Normal-weight (n=43)	Obese (n=47)	p
LV end-diastolic dimension (cm)	4.71 – 0.4	4.92 – 0.4	< 0.02
LV end-diastolic dimension index (cm/m)	2.85 – 0.2	2.98 – 0.2	< 0.004
LV mass (g)	113 – 39	157 – 38	< 0.0001
LV mass index ($g/m^{2.7}$)	29 – 8	41 – 10	< 0.0001
Relative wall thickness	0.31 – 0.04	0.36 – 0.04	< 0.0001
Aortic root (cm)	2.8 – 0.4	3.0 – 0.4	< 0.04
Left atrial dimension (cm)	2.9 – 0.4	3.4 – 0.5	< 0.0003
Ejection fraction (%)	65 – 5	64 – 4	NS

Table IV. Left ventricular relaxation and transmitral filling flow pattern.

Variables	Normal-weight (n=43)	Obese (n=47)	p
Isovolumic relaxation time (ms)	72 – 11	92 – 12	< 0.0001
Peak E velocity (cm/s)	73 – 15	73 – 13	NS
E velocity time integral (cm)	9 – 2	9 – 2	NS
E duration (ms)	206 – 32	224 – 33	< 0.01
E deceleration time (ms)	140 – 23	152 – 29	< 0.04
Peak A velocity (cm/s)	53 – 14	55 – 15	NS
A velocity time integral (cm)	4 – 2	4 – 2	NS
A duration (ms)	118 – 22	122 – 15	NS
A acceleration time (ms)	56 – 12	58 – 9	NS
E/A ratio	1.4 – 0.4	1.4 – 0.4	NS
Atrial filling fraction	0.30 – 0.07	0.29 – 0.06	NS

Table V. Pulmonary vein flow velocity pattern.

Variables	Normal-weight (n=43)	Obese (n=47)	p
Peak systolic flow velocity (cm/s)	47 – 11	47 – 10	NS
Systolic velocity time integral (cm)	10 – 3	11 – 3	NS
Peak diastolic PV velocity (cm/s)	48 – 13	48 – 10	NS
Diastolic velocity time integral (cm)	9.4 – 3.1	8.6 – 2.3	NS
Systolic PV flow fraction of peak velocities (%)	51 – 10	55 – 9	< 0.03
Systolic PV flow fraction of velocity time integral (%)	51 – 8	57 – 8	< 0.004
Peak PVa velocity (cm/s)	-18 – 10	-20 – 4	NS
PVa velocity time integral (cm)	-1.4 – 0.8	-1.7 – 0.7	NS
PVa duration (ms)	99 – 40	127 – 31	< 0.001
PVa-A duration difference (ms)	-20 – 39	6 – 31	< 0.002
PVa/A duration ratio	0.84 – 0.3	1.06 – 0.3	< 0.001

A = transmitral peak late flow velocity. Other abbreviations as in table I.

< 0.04; PVa-A -18 ms in obese, 4 ms in normal-weight, p < 0.02, and PVa/A 1.03 in obese, 0.84 in normal-weight, p < 0.02).

Although in this study population the values of estimated LV end-diastolic pressure were in the range of normality, obese subjects exhibited values significantly higher than controls (3.8 – 1.3 vs 3.0 – 1.1 mmHg, p < 0.002).

In a multiple linear regression model including body mass index, diastolic blood pressure, LV mass and isovolumic relaxation time, body mass index was the only independent predictor of either prolonged PVa-A (β = 0.38, SEE = 0.56 ms, p < 0.0004) or high PVa/A (β = 0.38, SEE = 0.005, p < 0.003).

Discussion

Uncomplicated obesity is characterized by near-normal pump function at rest[26], and a clear-cut impairment of active relaxation[12,13,27,28]. Although abnormalities of LV filling have been reported in invasive studies, performed on clinically selected patients with some indications to invasive procedures, these abnormalities could not be surely attributed to primary changes in passive properties of the myocardium, possibly also being due to altered loading conditions[29,30]. This is the first study performed on a relatively large group of young obese individuals, without any signs or symptoms of disease, coming to the Hospital only for fitness.

Pulmonary vein flow velocities were obtained in 53% of the obese cohort, because of insuperable technical problems (using our annular-array machines) in patients with a very thick thoracic wall, when body mass index > 40 kg/m^2. Although this relatively low proportion of patients might raise legitimate doubts about the feasibility of the procedure from the clinical point of view, from a pathophysiological point of view it reinforces the value of the findings, because the resulting selection bias could only reduce the magnitude of the reported association (as shown by the regression model).

Findings from this study demonstrate that, in addition to the known abnormal active relaxation[13], detectable also in this relatively young group of obese subjects, resistance of the left ventricle to atrial contraction is also increased, evidence that could not be detected by the sole Doppler interrogation of the mitral inflow velocities. This unsuspected abnormality was at least in part unrelated to hemodynamic factors measurable by echocardiography and was due to the combination of shorter atrial forward ejection with prolonged backward pulmonary flow. In the study of Rossvoll and Hatle[5], the duration of LV inflow velocity at the atrial contraction exceeded the duration of pulmonary backward flow by about 25 ms, as is average in subjects with normal end-diastolic pressure (i.e. below 5 mmHg). However, in the presence of LV end-diastolic pressure exceeding the limit of 5 mmHg, the duration of pulmonary backward flow tended to equalize or overcome the duration of LV filling. In the presence of more elevated values of LV end-diastolic pressure (> 10 mmHg), backward flow exceeded forward atrial flow by about 30 ms. The values of the difference between backward and forward atrial flow duration reported in the Rossvoll s study in subjects with mildly elevated LV end-diastolic pressure are similar to those found in our obese subjects in the present study. It is of note that similar to findings in the Rossvoll s study, the E/A flow velocity ratio was comparable between our normal-weight and obese subjects. In another study[6], prolongation of the duration of atrial backward flow in patients with elevated LV end-diastolic pressure was even more accentuated than in the Rossvoll s study or in our obese patients, likely because this study included older patients.

The reasons for the reduced difference or ratio between duration of the LV inflow and duration of the reverse flow in the pulmonary veins in our obese subjects can be well attributed to the relatively high resistance that the left ventricle opposed to mitral forward flow, as compared to the lower resistance offered by pulmonary veins (acting as a capacitance system). The mechanism of this small and early alteration of LV filling is therefore likely to be the increased LV passive stiffness yielding elevation of LV filling pressure especially at end-diastole. To verify the likelihood of this mechanism we applied to our population sample an invasively validated multivariate equation[6] used to generate estimates of LV end-diastolic pressure. The estimated LV end-diastolic pressure was indeed higher in obese subjects than in normal-weight controls, confirming that an elevation in filling pressure may be the most likely cause of the alteration of the physiological relation between forward and backward flows at atrial contraction.

Finally, the evidence that the prolonged duration of backward pulmonary flow as to the forward LV inflow is at least partially unrelated to LV load and geometry, suggests mechanisms more directly linked with obesity. These mechanisms underlying the increased late passive LV filling resistance in these young obese subjects might include remodeling of the collagen network or fat deposition in the intercellular matrix which lead to an increase in chamber stiffness, initially limited to the phase of atrial contraction (late diastole).

In conclusion, uncomplicated obesity is characterized by alteration of active relaxation with normal LV filling pattern in the early filling phase. Comparison of LV inflow and pulmonary vein flow patterns indicates that LV resistance to filling at atrial contraction (late diastole) is also precociously increased in obese subjects. This abnormality is relatively independent of LV load and geometry, and is a very precocious marker of late diastolic dysfunction.

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