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Effect of Obesity and Overweight on Left Ventricular Diastolic Function: a Community-based Study in an Elderly Cohort

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Abstract

Objectives—To assess the independent effect of increased body size on left ventricular (LV) diastolic function.

Background—Obese and overweight individuals are at increased risk of heart failure. LV diastolic dysfunction is an asymptomatic condition associated with future heart failure. It is unclear whether obesity and overweight are independently associated with LV diastolic dysfunction.

Methods—LV diastolic function was evaluated in 950 participants from the Cardiovascular Abnormalities and Brain Lesions (CABL) study by traditional and tissue-Doppler imaging. Peak early and late trans-mitral diastolic flow velocities (E, A) and early diastolic mitral annulus velocity (E′) were measured, and E/A and E/E′ were calculated. The study sample was divided into three groups: normal weight [body mass index (BMI)<25.0], overweight (BMI 25.0–29.9) and obese (BMI≥30).

Results—In multivariate analyses, BMI was independently associated with higher E, A, and E/E′, an indicator of LV filling pressure (all p≤0.01). Overweight and obese had lower E′ (both p<0.01) and higher E/E′ (both p<0.01) than normal weight participants. E/A was lower in obese than normal weight subjects (p<0.01). The risk of diastolic dysfunction was significantly higher in overweight (adjusted odds ratio: 1.52, 95% confidence intervals 1.04–2.22) and obese (adjusted odds ratio: 1.60, 95% confidence intervals 1.06–2.41) compared to normal weight individuals.

Conclusions—Increased BMI was associated with worse LV diastolic function independent of LV mass and associated risk factors. The increased risk of LV diastolic dysfunction in both

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overweight and obese individuals may partially account for the increased risk of heart failure associated with both conditions.

Keywords

obesity; overweight; diastolic dysfunction; echocardiography; risk factors

INTRODUCTION

The prevalence of obesity is steadily increasing worldwide, and constitutes a major health issue because of its association with morbidity, mortality and cardiovascular diseases (1–3). Obesity is an independent predictor of incident heart failure in the general population, and evidence exists that overweight also carries an increased risk of heart failure, which is intermediate between that of obese and lean individuals (4,5). An increase in body size, besides being associated with cardiovascular risk factors such as hypertension, diabetes and hyperlipidemia, directly affects cardiac structure and function. The excess in body fat determines an increase in both preload and afterload due to a hyperdynamic circulation, chronic volume overload and increase in peripheral resistance (6,7). In addition, it has been demonstrated that increased adiposity enhances the effect of blood pressure on LV mass growth (8). As a result, left ventricular (LV) dilation and increased LV mass are frequent findings in individuals with increased body weight, with both eccentric and concentric LV geometric patterns described in these conditions (9–11).

LV diastolic dysfunction is a condition that reflects an impairment of the filling properties of the LV that has been demonstrated to be a predictor of future development of heart failure in population settings (12–15). LV diastolic dysfunction might therefore represent one of the pathophysiological links between an increased body weight and the future occurrence of heart failure. Cardiovascular risk factors and cardiac structural changes associated with obesity/overweight are also major determinants of LV diastolic function (16,17). Whether an increased body weight is associated with an impairment of LV diastolic mechanics, independent of associated risk factors, has not been fully established. Accordingly, the aims of our study were: 1) to analyze the association between body size and LV diastolic function, assessed by transthoracic echocardiography, in a community-based cohort of subjects over age 50, 2) to evaluate the impact of associated risk factors on this relationship, and 3) to investigate the effect of different degrees of increased body size on the risk of LV diastolic dysfunction.

METHODS

Study population

The study cohort was derived from the Northern Manhattan Study (NOMAS), a population-based prospective study evaluating the incidence, risk factors, and clinical outcome of stroke in the population of Northern Manhattan. Study design and methodological details have been described previously (18). From September 2005, NOMAS subjects over age 50 that voluntarily agreed to undergo a brain MRI study and a more extensive echocardiographic evaluation including diastolic function assessment were included in the Cardiac Abnormalities and Brain Lesion (CABL) study. This subset of individuals constitutes the study population of the present report. Informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Columbia University Medical Center.

Risk factors assessment

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at the time of the visit (mean of two readings), or patient's self-reported history of hypertension or of anti-hypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or patient's self-reported history of diabetes or of diabetes medications. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dL, a patient's self-report of hypercholesterolemia or of use of lipid-lowering treatment. Body mass index (BMI) was calculated as: weight (kilograms)/height^2 (meters^2). According to a standard definition, overweight was defined as BMI between 25.0 and 29.9, and obesity as BMI ≥ 30 (19).

Echocardiographic assessment

Transthoracic echocardiography was performed using a commercially available system (iE 33, Philips, Andover, MA) by a trained registered sonographer following a standardized protocol. LV linear dimensions were measured from a parasternal long-axis view according to the recommendations of the American Society of Echocardiography (ASE) (20). LV mass was calculated with a validated formula (21) and indexed both for body surface area (BSA) and height$^{2.7}$ (22). LV relative wall thickness (RWT) was calculated as: (2×posterior wall thickness)/end-diastolic diameter (23). LV ejection fraction was calculated by biplane modified Simpson's rule.

LV diastolic function assessment has been described previously in detail (17). Briefly, from an apical 4-chamber view, trans-mitral flow was sampled by pulsed-wave Doppler at the level of mitral valve leaflet tips. Peak velocities of the early (E) and late (A) phases of the mitral inflow were measured and their ratio (E/A) was calculated. LV myocardial velocities were evaluated by tissue Doppler imaging (TDI). Pulsed TDI sample volume was placed at the level of the lateral and septal mitral valve annulus and the peak early diastolic (E′) velocities were measured and the averaged (24). The ratio between the E and E′ (E/E′) was calculated as an index of LV filling pressures (25). Diastolic dysfunction was defined as: 1) E/A ≤ 0.7 (impaired relaxation, grade I); or 2) E/A > 0.7 and ≤ 1.5 and E′ < 7 cm/s (pseudo-normalized pattern, grade II); or 3) E/A > 1.5 and E′ < 7 cm/s (restrictive pattern, grade III) (17,24).

Statistical analysis

Data are presented as means ± standard deviation for continuous variables and as proportions for categorical variables. Differences between groups were assessed by one-way analysis of variance (ANOVA) and post-hoc multiple comparisons were performed using the Bonferroni correction. The Fisher's exact test was used to test differences between proportions. Multiple linear regressions were used to assess the independent association of BMI with diastolic function parameters. The predictors and the outcome variables were standardized with corresponding standard deviations and both unstandardized (B) and standardized (β) coefficient estimates and relative standard errors were reported. Covariates (age, sex, LV mass/height$^{2.7}$, heart rate, hypertension and diabetes) were entered in the models in a stepwise fashion, with entry and removal criteria set at a $p<0.1$. Analysis of covariance (ANCOVA) was conducted to assess differences in diastolic function parameters between groups after adjusting for covariates. Estimated marginal means adjusted for covariates and 95% confidence intervals (CI) were derived. Multivariate logistic models were used to assess the risk of diastolic dysfunction associated with body size measures, and odds ratios (OR) and relative 95% CI were derived.

For all statistical analyses, a 2-tailed $p<0.05$ was considered significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Study population

The study population consisted of 950 participants. The study sample was divided into three groups: those with a BMI < 25.0 kg/m^2 (normal weight group, n=242), those with a BMI between 25.0 and 29.9 kg/m^2 (overweight group, n=403) and those with a BMI ≥ 30 kg/m^2 (obese group, n=305). Demographic, clinical, and echocardiographic characteristics of the three groups are shown in Table 1.

BMI, LV mass and cardiovascular risk factors

Since obese and overweight participants showed higher LV mass when indexed by height$^{2.7}$, but also greater prevalence of cardiovascular risk factors, which may in turn be responsible for an increased LV mass and worse diastolic function, we explored the independent association of BMI and cardiovascular risk factors with LV mass. A higher BMI was the strongest independent predictor of increased LV mass/height$^{2.7}$ (β=0.28, p<0.001). Other independent predictors in the model were: age (β=0.15, p<0.001), hypertension (β=0.17, p<0.001) and diabetes (β=0.07, p=0.02). Sex was not associated with LV mass index after adjustment for BMI (β=−0.03, p=0.23). When LV mass was indexed by BSA instead of height$^{2.7}$, no significant residual association was found between BMI and LV mass (β=0.008, p=0.81).

BMI and diastolic function parameters

The correlation between BMI and echocardiographic diastolic function parameters was tested in stepwise multivariate linear regression models (Table 2). Higher BMI was associated with higher peak E wave (R^2=0.05; p=0.006), higher peak A wave (R^2=0.22; p<0.001), lower E/A (R^2=0.08; p=0.01) and higher E/E′ ratio (R^2=0.20; p=0.001), independent of factors influencing LV diastolic function including age, sex, LV mass, hypertension, diabetes and heart rate.

In separate sub-analyses by sex adjusted for age and LV mass index, we found that in men BMI was significantly correlated with higher A (β=0.14, p=0.01), lower E/A (β=−0.12, p=0.03) and lower E′ (β=−0.12, p=0.02). In women, BMI was significantly correlated with higher E (β=0.15, p<0.001), higher A (β=0.17, p<0.001) and higher E/E′ (β=0.12, p=0.003).

In a sub-analysis in individuals without hypertension and diabetes (n=223), the relation between BMI and E/E′ ratio was still significant (β=0.13, p=0.04) independent of age, LV mass index and heart rate (variables that were selected in the stepwise model; data not shown).

LV diastolic function in overweight and obesity

In multivariate comparisons (Table 3), peak E was significantly higher in obese than in normal weight subjects (p<0.01). Peak A was significantly higher in the overweight and obese (both p<0.01) groups compared to the normal weight group. E/A was significantly lower in obese patients compared with normal weight participants (p<0.01). Peak E′ was significantly lower in overweight and obese compared to normal weight individuals (both p<0.01). E/E′ was significantly higher in overweight and obese compared to the normal weight individuals (both p<0.01).

Prevalence of LV diastolic dysfunction in the overall sample was 53.5% (n=508). Diastolic dysfunction was present in 50.8% of the normal weight, in 54.2% of the overweight and in 57.1% of the obese subjects (p=0.34). A pseudo-normalized diastolic pattern was present in 16.7% of the normal weight, 17.7% of the overweight and 24.3% of the obese subjects

(p=0.04). A multivariate logistic model was used to assess the risk of LV diastolic dysfunction associated with the presence of overweight and obesity (Table 4). After adjusting for covariates, both the overweight (OR: 1.52, 95% CI: 1.04–2.22, p=0.03) and the obese (OR: 1.60, 95% CI: 1.06–2.41, p=0.02) groups had a significantly higher risk of diastolic dysfunction compared to the normal weight group. BMI as a continuous variable was also significantly associated with increased risk of diastolic dysfunction (adjusted OR for each BMI unit increase: 1.04, 95% CI: 1.01–1.07, p=0.04) and of pseudo-normalized diastolic pattern (adjusted OR for each BMI unit increase: 1.05, 95% CI: 1.01–1.08, p=0.02). No significant interaction was found between sex and BMI on LV diastolic dysfunction (p value for the interaction=0.61).

Waist circumference and LV diastolic function

All the previous analyses were also performed using the waist circumference as a measure of abdominal adiposity, in lieu of the BMI. In the multivariate linear regression analysis, waist circumference was significantly associated with peak A (β=0.11, p<0.001) and with E/A (β=−0.06, p=0.05). In the multivariate logistic model, an increased waist circumference (defined as ≥88 cm in women and ≥102 cm in men) was associated with a significant increase in risk of diastolic dysfunction (adjusted OR: 1.69, 95% CI 1.22–2.35, p=0.002). Waist circumference as a continuous variable was also significantly associated with an increased risk of diastolic dysfunction (adjusted OR for each unit increase: 1.03, 95% CI 1.01–1.04, p=0.01). No significant interaction was found between sex and waist circumference on LV diastolic dysfunction (p value for the interaction=0.88).

DISCUSSION

We analyzed the association between measures of body size and LV diastolic function, measured by traditional Doppler analysis of mitral inflow and TDI-derived parameters, in an elderly randomly-derived community cohort. Our findings indicate that: 1) the relationship between BMI and diastolic function parameters is continuous and independent of cardiovascular risk factors that cluster with obesity, such as hypertension, diabetes and LV hypertrophy; and 2) the overweight status is already associated with an impairment of LV diastolic function, close to that observed in obese individuals. In fact, no significant differences were found in most parameters of diastolic function between obese and overweight subjects. This observation was also confirmed by the similar odds ratio for diastolic dysfunction associated with both conditions. Overweight and obese subjects had also higher risk of a pseudo-normalized diastolic pattern. The use of TDI parameters, less load-dependent than trans-mitral Doppler flow (26), allowed us to detect diastolic abnormalities in 183 subjects (19.6% of the study sample) that would otherwise have been classified as normal by Doppler flow analysis alone. Furthermore, the use of E/E′ ratio, a widely used indicator of LV filling pressure (25) and an independent predictor of cardiac events including heart failure and myocardial infarction (27), revealed higher LV filling pressures in obese and overweight patients than in normal weight subjects. Cardiovascular risk factors were significantly more prevalent in overweight and obese individuals than in normal weight subjects. It is established that hypertension, diabetes and increased LV mass negatively affect LV diastolic function (16,17). However, BMI was still associated with LV diastolic function parameters after controlling for hypertension and diabetes. A sub-analysis performed in subjects without hypertension and diabetes further confirmed these findings. Moreover, the increased LV mass that we observed in overweight/obese patients was not just the result of the greater prevalence of cardiovascular risk factors in these subgroups. In fact, BMI was the main predictor of LV mass, independent of the presence of hypertension and diabetes. Although the increased LV mass might be a contributor to the impairment of diastolic function observed in the overweight and obese groups, the relationship between

BMI and diastolic function parameters was only slightly weakened by the adjustment for LV mass and other covariates, suggesting that different mechanisms may link the increase in BMI with the impairment in LV diastolic properties. In fact, there is ample evidence that the accumulation of adipose tissue may determine cardiovascular alterations in several metabolic and neuro-hormonal pathways, causing abnormalities in sodium handling, neuro-endocrine activation, renin-angiotensin-aldosterone system, and increasing myocardial oxidative stress (28,29). Changes in myocardial metabolism have been demonstrated in obese patients, with a shift toward free fatty acid utilization and subsequent cardiac lipotoxicity, resulting in cardiomyocyte apoptosis and reduced cardiac efficiency (30,31). In particular, myocardial fatty infiltration in obese patients may affect the cardiac structure and function, leading to the development of severe diastolic dysfunction (32,33).

This is the first large-scale study to evaluate the relation between increased body weight and LV diastolic function, in a randomly-selected elderly cohort, and to account for many factors that would have potentially affected diastolic function. In particular, we are the first to demonstrate that an impairment of diastolic function may already be present in overweight subjects. Previous reports had shown a relationship between obesity and diastolic function in extremely selected samples of young women (34–36), in subjects without cardiovascular risk factors (37), or in extremely obese subjects (38,39). In a large study in patients that underwent diagnostic coronary angiography, LV end-diastolic pressure was significantly higher in obese patients than in patients with a BMI < 25 (40). Surprisingly, in that study no adjustment for associated risk factors and co-morbidities affecting diastolic function was performed. Another study reported that waist circumference, but not BMI, was correlated to lower ventricular filling (41), which is in agreement with our findings. That study however, did not perform TDI evaluation, which in our study allowed us to reveal a correlation between BMI and LV filling pressure.

Our study has several limitations. Our evaluation of LV diastolic function by Doppler flow analysis did not include parameters such as isovolumic relaxation time, mitral valve deceleration time, or pulmonary venous flow. However, those parameters suffer from high load dependence, and the use of tissue Doppler parameters allowed us to detect diastolic abnormalities even when a pseudo-normalized flow pattern was present. The mean age of the study cohort was high, and so was the prevalence of cardiovascular risk factors; therefore, our results may not be extrapolated to younger populations with lower cardiovascular risk profiles.

In conclusion, LV diastolic dysfunction may be one of the pathophysiological link between overweight/obesity and the associated risk of developing heart failure (4). While in the past attention was paid essentially to obesity, our study demonstrates that subclinical signs of LV diastolic function impairment are present in overweight subjects too, and that these abnormalities are independent of associated risk factors. Therapeutic strategies aimed at promoting optimal body weight resulted in improvements in LV systolic and diastolic function (42,43), and might have a beneficial effect in preventing or delaying the future development of heart failure, a hypothesis that deserves further investigation.

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ABBREVIATIONS

LV	Left ventricular
BMI	Body mass index
BSA	Body surface area
CABL	Cardiac Abnormalities and Brain Lesions
NOMAS	Northern Manhattan Study
TDI	Tissue Doppler imaging

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Table 1

Characteristics of the study population by BMI categories

N=950	Normal weight (BMI < 25.0) N=242	Overweight (BMI 25.0–29.9) N=403	Obese (BMI ≥ 30.0) N=305
Clinical/demographic			
Age, years	73.9±10.3	70.9±8.9**	70.7±8.8**
Women, n (%)	135 (55.8)	233 (57.8)	216 (70.8)**‡
BMI, kg/m^2	22.6±1.9	27.4±1.5**	33.8±3.4**‡
Waist circumference, cm	85.4±8.7	95.0±8.3**	106.4±10.7**‡
Systolic BP, mmHg	132.4±18.3	135.9±16.1*	138.5±18.2**
Diastolic BP, mmHg	75.2±9.8	78.6±9.4**	79.8±9.3**
Hypertension, n (%)	149 (61.6)	284 (70.5)*	251 (82.3)**‡
Diabetes, n (%)	47 (19.4)	112 (27.8)*	116 (38.0)**‡
Hypercholesterolemia, n (%)	142 (58.7)	254 (63.0)	197 (64.8)
Echocardiographic data			
End-diastolic diameter, cm/m	2.71±0.28	2.77±0.28*	2.86±0.29**‡
LV mass, g	172.4±52.5	179.2±47.5	196.2±47.8**‡
LV mass/height$^{2.7}$, g/m$^{2.7}$	46.1±14.2	49.3±13.1**	56.0±14.0**‡
LV mass/BSA, g/m^2	104.5±30.4	101.7±24.8	104.3±24.4
Relative wall thickness	0.49±0.09	0.49±0.09	0.51±0.09
LV ejection fraction, %	62.2±8.2	63.2±7.4	64.5±6.7**
Heart rate, bpm	68.4±10.7	70.7±11.4*	70.1±11.6

*p<0.05 and

**p<0.01 vs. normal weight.

†p<0.05 and

‡p<0.01 vs. overweight

Multiple comparisons were carried out with the Bonferroni's correction method

Table 2

Relationship of LV diastolic function parameters with BMI - Multivariate linear regression

	Peak E			Peak A			E/A ratio			Peak E′			E/E′		
Model 1	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P
BMI	0.42 (0.12)	0.11	<0.001	0.93 (0.13)	0.22	<0.001	−0.006 (0.002)	−0.09	0.005	−0.05 (0.01)	−0.14	<0.001	0.14 (0.02)	0.19	<0.001
Age	−0.03 (0.06)	−0.02	0.58	0.74 (0.07)	0.33	<0.001	−0.01 (0.001)	−0.19	<0.001	−0.09 (0.006)	−0.45	<0.001	0.12 (0.01)	0.33	<0.001
Model 2	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P	B (SE)	β	P
BMI	0.33 (0.12)	0.09	0.006	0.57 (0.14)	0.13	<0.001	−0.005 (0.002)	−0.08	0.01	−0.01 (0.01)	−0.03	0.29	0.05 (0.02)	0.08	0.01
Age	−0.05 (0.06)	−0.03	0.38	0.68 (0.07)	0.30	<0.001	−0.01 (0.001)	−0.19	<0.001	−0.07 (0.005)	−0.38	<0.001	0.10 (0.01)	0.26	<0.001
Male sex	−4.01 (1.19)	−0.11	0.001	−5.54 (1.28)	−0.13	<0.001	-	-	-	-	-	-	−0.72 (0.22)	−0.10	0.001
LV mass index	-	-	-	0.11 (0.05)	0.08	0.01	-	-	-	−0.03 (0.004)	−0.24	<0.001	0.05 (0.01)	0.20	<0.001
Heart rate	−0.22 (0.05)	−0.14	<0.001	0.37 (0.06)	0.20	<0.001	−0.006 (0.001)	−0.20	<0.001	-	-	-	−0.03 (0.01)	−0.09	0.003
Hypertension	-	-	-	-	-	-	-	-	-	−0.61 (0.11)	−0.16	<0.001	0.61 (0.24)	0.08	0.01
Diabetes	3.19 (1.28)	0.08	0.01	5.63 (1.37)	0.12	<0.001	-	-	-	-	-	-	0.71 (0.23)	0.09	0.002

Values in table are non-standardized (B), standardized correlation coefficients (β) and p values. Dashes indicate the exclusion of the variable from the stepwise model. SE: Standard error. Model 2 adjusted-R^2 values: 0.05 for peak E, 0.22 for peak A, 0.08 for E/A ratio, 0.29 for peak E′, 0.20 for E/E′.

Table 3

Diastolic function parameters by BMI categories

	Normal weight (BMI < 25.0) N=242	Overweight (BMI 25.0–29.9) N=403	Obese (BMI ≥ 30.0) N=305
Peak E, cm/s	69.1 (1.2)	70.9 (0.9)	73.0 (1.0) c
Peak A, cm/s	84.2 (1.2)	89.1 (1.0) †	92.7 (1.1) †‡
E/A ratio	0.87 (0.02)	0.84 (0.02)	0.81 (0.02) †
Peak E′, cm/s	7.5 (0.1)	7.2 (0.08) †	7.0 (0.09) †
E/E′ ratio	9.9 (0.2)	10.7 (0.2) †	11.1 (0.2) †

† p<0.01 vs. normal weight.

‡ p<0.05 vs. overweight

Values in table are means adjusted for covariates. Covariates: Age, sex, LV mass index, heart rate, hypertension and diabetes (standard error in parentheses).

Table 4

Risk of diastolic dysfunction associated with the presence of overweight and obesity

	Odds ratio†	95% CI	P	Odds ratio‡	95% CI	P
Normal weight	Reference	-	-	Reference	-	-
Overweight	1.66	1.15 – 2.40	0.006	1.52	1.04 – 2.22	0.03
Obese	1.92	1.30 – 2.83	0.001	1.60	1.06 – 2.41	0.02

† Adjusted for age and sex.

‡ Adjusted for age, sex, LV mass index, heart rate, hypertension and diabetes. CI: Confidence interval.