Independent Effects of Body Fat and Inflammatory Markers on Ventricular Geometry, Midwall Function, and Atrial Remodeling

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ABSTRACT

Background: The effect of body fat distribution on left ventricular (LV) mass and geometry has been recently recognized. However, data regarding circulating inflammatory markers in relation to regional visceral fat deposits, which are metabolically active tissues that can impact cardiac structural remodeling, remain sparse.

Hypothesis: We hypothesized that obesity has adverse effects on cardiac function and structure.

Methods: We consecutively studied 1071 asymptomatic subjects (age 49.5 ± 10.5 years, 39.4% female) free from significant valvular disorders, chronic lung disease, or renal disease. Echocardiography-defined cardiac structures and LV geometries including LV mass, mass-to-volume ratio, and fractional shortening were all determined. Body fat composition (Tanita-305 Body-Fat Analyzer; Tanita Corp., Tokyo, Japan) was obtained and calculated. Multivariate regression models from various models were used to represent the independent association between body fat and echo-derived ventricular mass and geometries.

Results: In multivariable analysis, increasing body fat was significantly related to increase in left atrial (LA) and LV diameter, posterior wall thickness, relative wall thickness (RWT), LV mass, mass-to-volume ratio, and decreased midwall fractional shortening with or without stress correction (all $P < 0.001$). When LV mass and severity of mitral regurgitation was further added, the independent association between increased body fat composition and larger LA diameter remained significant (β coefficient = 0.37, $P < 0.001$). Elevated high-sensitivity C-reactive protein (Hs-CRP) level was associated with larger LA diameter, increased RWT, and worsened midwall mechanics in the female gender (all interaction $P < 0.05$).

Conclusions: Accumulated body fat seemed to be related to worse ventricular midwall contractility and atrial remodeling, particularly in the female gender, with high systemic inflammation. These gender and Hs-CRP-specific modification effects may potentiate the pathological mechanisms involved in heart failure with preserved ejection fraction.

Introduction

In recent years, there is increasing recognition of the impact of body fat composition and distribution on the

relationship between obesity and cardiovascular disease.¹ A large body of evidence documents that abdominal fat accumulation, as assessed by anthropometric indicators such as waist circumference or waist-hip ratio (WHR), is positively associated with occurrence of cardiovascular events.² Total body fat burden assessed by conventional bioelectrical impedance analysis (BIA) has the advantage of

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lower cost and clinical ease of use. However, the accuracy of such measures may not reflect real adipose tissue burden and could be confounded by several clinical variables.³ Furthermore, it provides no information on fat distribution at specific sites, therefore failing to describe the anatomy of visceral adipose depots.⁴

Through direct measurement of intra-abdominal fat, specifically visceral adipose tissue surrounding vital organs, investigators have demonstrated the link between its activity and cardiovascular diseases.^{5,6} Although visceral fat is biologically active and acts as a key mediator of various metabolic derangements and systemic inflammation⁷ with cytokine effects, the exact mechanisms that result in adverse cardiovascular events are not fully understood.^{8,9}

Methods

Subjects

In this retrospective analysis, we consecutively studied 1071 subjects who took part in a primary cardiovascular health survey in a tertiary medical center in Taipei, Taiwan, from 2006 to 2008. A detailed review of medical history through a structured questionnaire along with a physical examination was performed on all subjects. Patients with chronic lung disorders, atrial fibrillation, history of pacemaker implantation, significant valvular heart diseases, or end-stage renal disease were excluded. The presence of coronary artery diseases (CAD) was defined as a history of previous myocardial infarction, previous angioplasty, or more than 50% luminal narrowing on coronary angiography. Hypertension history (HTN) was defined as a history of systolic blood pressure above 140 mm Hg, diastolic blood pressure above 90 mm Hg, or previously diagnosed HTN under medication control. Diabetes (DM) was defined as a fasting glucose level above 126 mg/dL or previously diagnosed DM under medication control. Hyperlipidemia was defined as a history and/or use of lipid-lowering drugs such as statins or fibrates on a daily basis.

Anthropometric Measurements

All baseline characteristics and information regarding anthropometric measures were collected. Standardized sphygmomanometer cuff-defined resting blood pressures were measured at rest by medical staff blinded to the other test results. Body fat percentage was assessed by utilizing BIA from foot-to-foot using the Tanita-305 Body-Fat Analyzer (Tanita Corp., Tokyo, Japan), which provides a printout estimate of impedance and calculated body fat percentage. Measurements were performed in the standing position, through 2 footpad electrodes in contact with soles and heels on both feet. A 0.8-mA current with a 50-kHz frequency was applied via source electrodes on both soles, and the voltage drop compared with heel electrodes.

Echocardiographic Assessment

Each subject underwent 2-dimensional and M-mode transthoracic echocardiogram using a Hewlett-Packard Sonos 5500 series instrument (Hewlett-Packard Co., Palo Alto, CA) equipped with a 2.5 to 4.5 MHz transducer. Left ventricular (LV) end-diastolic and end-systolic volumes were

calculated by the *z*-derived method,¹⁰ which allows accurate quantification of LV volume and mass even in subjects with dilated cardiac chambers. LV geometry, including concentric hypertrophy, defined as relative wall thickness (RWT) ≥ 0.42 , and LV mass index ≥ 115 gm/m² for males and ≥ 95 gm/m² for females; eccentric hypertrophy, defined as the same LV mass index criteria with RWT < 0.42 , were assessed. For those subjects with RWT ≥ 0.42 and normal LV mass index were classified as concentric remodeling.

Endocardial and midwall fractional shortening was computed by a previously described formula.¹¹ Circumferential wall stress was also derived from end-systolic pressure representing mean arterial pressure as in the previously described equation.¹² Both midwall fractional shortening and circumferential wall stress were used to estimate stress-corrected LV afterload. Any patient with significant valvular heart disease or pulmonary hypertension (defined as estimated systolic pulmonary arterial pressure more than 50 mm Hg) was excluded. Mitral regurgitation (MR) was assessed by mapping jet expansion in the left atrium in 4-chamber views during the systole phase. MR was considered mild when the regurgitant jet area occupied $< 20\%$ of the left atrial area, moderate when it occupied 20% to 40%, and severe when it occupied more than 40% of the left atrial area.

Statistical Analysis

Continuous data were shown as mean and standard deviation, with categorical data expressed as the frequency and proportion of occurrence in all subjects. The association between LV structure, function, and body fat composition were presented with a univariable regression model with the standardized coefficient between 2 continuous variables reported. Multivariable regression models were used to determine the significance of clinical covariate-adjusted relations between body fat composition in relation to various LV geometric parameters, stratified by gender, and systemic inflammation status in terms of circulating high-sensitivity C-reactive protein (Hs-CRP) level (≥ 0.3 mg/dL). Because the LV geometric remodeling may be influenced by age, gender, body mass index (BMI), blood pressure, renal function, and hypertension, an analysis of covariance was also conducted to adjust these relevant covariates for comparison of mean values among the 3 groups.

All data were analyzed using a STATA 8.2 commercial software package (Stata Corp., College Station, TX). The significance of *P* level (α value) for all analysis was 2-sided, with a value < 0.05 considered statistically significant.

Results

Baseline Demographic and Anthropometric Data

Out of 1071 subjects, 1063 (age 49.5 ± 10.5 , 39.4% female) were selected for the final analysis. Among those excluded, 4 had atrial fibrillation, 1 had history of pacemaker implantation, and 3 had significant valvular heart disease (severe mitral regurgitation: 2; severe aortic stenosis: 1). Baseline demographic and anthropometric characteristics and metabolic parameters stratified by fat mass are summarized in Table 1. We observed that both systolic and diastolic blood pressures were significantly related to increasing body fat mass (both trend $P < 0.001$).

Table 1. Baseline Demographics, Anthropometrics, Metabolic Parameters, and Medical Histories of the Entire Cohort (n = 1063) Stratified by Body Fat Composition

Fat mass (kg)	1st Tertile	2nd Tertile	3rd Tertile	Trend <i>P</i>
	3.68–14.6	14.6–19.61	19.61–40.4	
Age (y)	50.5 ± 12.7	51.6 ± 9.1	50.9 ± 11.3	0.49
No. of females	164 (39.1%)	162 (38.7%)	177 (42.2%)	0.509
SBP (mm Hg)	116.3 ± 16.8	121.3 ± 16.5	125.7 ± 17	<0.001
DBP (mm Hg)	71.5 ± 9.6	75.7 ± 10.1	78.2 ± 10.4	<0.001
HR (bpm)	74.5 ± 10.2	74.8 ± 9.6	75.8 ± 11	0.03
Height (cm)	163.2 ± 8.2	163.7 ± 8.4	164.4 ± 9	0.04
Weight (kg)	56.7 ± 8.3	65 ± 8.5	75.4 ± 11.6	<0.001
BMI (kg/m ²)	21.2 ± 2.1	24.2 ± 1.8	27.8 ± 3.1	<0.001
WC (cm)	74.8 ± 7.7	82.6 ± 7.3	90.8 ± 8.8	<0.001
WHR	0.85 ± 0.07	0.89 ± 0.07	0.91 ± 0.07	<0.001
Fasting glucose (mg/dL)	96.7 ± 23.3	100.2 ± 21.2	106.6 ± 29.9	<0.001
HbA1c (mg/dL)	5.69 ± 0.94	5.8 ± 0.81	6.08 ± 1.18	<0.001
Cholesterol (mg/dL)	188.2 ± 33.3	198.5 ± 33	202.4 ± 43.1	<0.001
TG (mg/dL)	96 ± 51.8	136.7 ± 97.3	171 ± 102.5	<0.001
LDL (mg/dL)	118.9 ± 30.1	131.5 ± 30.2	134.1 ± 33.7	<0.001
HDL (mg/dL)	60.7 ± 16	54.1 ± 15	50.1 ± 14.1	<0.001
eGFR (mL/min/1.73m ²)	88 ± 17	87.2 ± 18.3	88.4 ± 18.5	0.83
Hs-CRP (mg/dL)	0.19 ± 0.25	0.21 ± 0.23	0.29 ± 0.4	<0.001
Hypertension (%)	58 (13.8%)	77 (18.4%)	114 (27.2%)	<0.001
Diabetes (%)	31 (7.4%)	25 (6%)	40 (9.6%)	0.145
Hyperlipidemia (%)	11 (2.6%)	20 (4.8%)	41 (9.8%)	<0.001
Smoking, current (%)	87 (20.7%)	77 (18.4%)	83 (19.8%)	0.691
CAD history (%)	11 (2.6%)	22 (5.3%)	35 (8.4%)	0.001

Abbreviations: BMI, body-mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

For anthropometric parameters, increasing body fat tertiles were significantly associated with graded increases in BMI, body weight, waist circumference, and WHR (all trend $P < 0.001$). With each increasing body fat tertile, there were stepwise increases in fasting glucose, HbA1c, all lipid profiles, and higher serum Hs-CRP level (all trend $P < 0.001$). Only estimated glomerular filtration rate was not significantly related ($P = 0.83$). Also, subjects in larger body fat tertiles were more likely to have hypertension, hyperlipidemia (both trend $P < 0.001$) or CAD ($P = 0.001$).

Table 2. Univariable Models Regarding the Association Between Body Fat Composition and Echocardiographic Parameters in the Whole Study Cohort by Different Genders (n = 1063)

	Females (n = 419)		Males (n = 644)		All (n = 1063)	
	β Coefficient	<i>P</i> Value	β Coefficient	<i>P</i> Value	β Coefficient	<i>P</i> Value
LA (mm)	0.46	< 0.001	0.33	< 0.001	0.36	< 0.001
IVS (mm)	0.4	< 0.001	0.21	< 0.001	0.25	< 0.001
PWT (mm)	0.44	< 0.001	0.23	< 0.001	0.3	< 0.001
LVIDd (mm)	0.34	< 0.001	0.14	< 0.001	0.25	< 0.001
LVIDs (mm)	0.26	< 0.001	0.13	0.001	0.20	0.001
RWT	0.28	< 0.001	0.14	< 0.001	0.16	< 0.001
LVEF (%)	−0.05	0.306	−0.02	0.661	−0.02	0.462
FSendo (%)	0.007	0.887	−0.02	0.569	−0.01	0.569
FSmw (%)	−0.14	0.004	−0.09	0.021	−0.07	0.015
FScmw (%)	−0.1	0.033	−0.08	0.04	−0.058	0.059
LV mass (gm)	0.54	< 0.001	0.27	< 0.001	0.35	< 0.001
MVR	0.32	< 0.001	0.17	< 0.001	0.22	< 0.001

Abbreviations: FScmw, stress-corrected midwall fractional shortening; FSendo, endocardial fractional shortening; FSmw, midwall fractional shortening; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diastolic dimension; LVIDs, left ventricular internal systolic dimension; MVR, mass-volume ratio; PWT, posterior wall thickness; RWT, relative wall thickness.

Echocardiographic Parameters

In Tables 2 and 3, we demonstrated the uni- and multivariable models between body fat composition and several cardiac structural and functional parameters by different genders in the whole cohort (n = 1063). Increasing body fat composition was associated with larger left atrial (LA) diameter, increased LV septal and posterior wall thickness, larger LV diameters, larger LV mass, increased RWT, and mass-to-volume ratio for both males and females (all $P \leq 0.001$), along with significant decrease in LV midwall fractional shortening without stress correction ($P = 0.015$). After adjustment for baseline clinical variables and hypertension, the multivariable models showed that for each standardized increase in body fat composition, there was significant increase in LA and LV diameter, posterior wall thickness, RWT, LV mass, mass-to-volume ratio, and decrease in midwall fractional shortening with or without stress correction (all $P < 0.001$). When LV mass and MR severity was further added, the independent association between increased body fat composition and larger LA diameter remained significant (β coefficient = 0.37, $P < 0.001$).

Figure 1 demonstrated the linear associations between LA diameter and different fat depots by genders. The association between LA diameter and body fat mass was more significant in the female gender ($R = 0.4$, $P < 0.001$). In Figure 2, the associations between LA diameter, LV relative wall thickness, and LV midwall function based on different genders and categorized by Hs-CRP interaction

Table 3. Multivariable Models Regarding the Association Between Body Fat Composition and Echocardiographic Parameters in the Whole Study Cohort (n = 1063)

	Model 1		Model 2		Model 3	
	β	P	β	P	β	P
	Coefficient	Value	Coefficient	Value	Coefficient	Value
LA (mm) ^a	0.35	< 0.001	0.38	< 0.001	0.37	< 0.001
IVS (mm)	0.25	0.001	0.28	< 0.001	0.24	0.011
PWT (mm)	0.29	< 0.001	0.32	< 0.001	0.28	0.003
LVIDd (mm)	0.25	< 0.001	0.29	< 0.001	0.28	< 0.001
LVIDs (mm)	0.20	< 0.001	0.23	< 0.001	0.24	0.029
RWT	0.16	< 0.001	0.17	< 0.001	0.13	< 0.001
LVEF (%)	-0.02	0.509	-0.03	0.278	-0.05	0.073
FSendo (%)	0.01	0.698	-0.02	0.421	-0.02	0.076
FSmw (%)	-0.07	< 0.001	-0.08	< 0.001	-0.07	< 0.001
FScmw (%)	-0.06	< 0.001	-0.06	< 0.001	-0.06	< 0.001
LV mass (gm)	0.35	< 0.001	0.39	< 0.001	0.35	< 0.001
MVR	0.22	< 0.001	0.24	< 0.001	0.19	< 0.001

Abbreviations: FScmw, stress-corrected midwall fractional shortening; FSendo, endocardial fractional shortening; FSmw, midwall fractional shortening; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diastolic dimension; LVIDs, left ventricular internal systolic dimension; MVR, mass-volume ratio; PWT, posterior wall thickness; RWT, relative wall thickness.

Model 1: adjusting for age; model 2: adjusting for age and gender; model 3: adjusting for age, gender, body mass index, blood pressure, renal function in terms of estimated glomerular filtration rate and hypertension history.

^aLV mass and severity of mitral regurgitation added in the model.

are illustrated. Higher Hs-CRP level was associated with larger LA diameter, increased RWT, and worsened midwall mechanics in the female gender (all interaction $P < 0.05$).

Discussion

Heart failure (HF) has emerged as a major public health issue in recent years.¹³ The effect of body mass composition and fat distribution on LV mass and geometry has also been well recognized.¹⁴ Accumulating evidence^{15,16} points to increased LV mass is an independent risk factor for cardiovascular morbidity and mortality, which actually rises continuously with increasing LV mass,^{17,18} indicating that these is no clear boundary between normal or abnormal LV mass values.

Obesity, defined as increased BMI, and the metabolic syndrome encompass a cluster of major and emerging risk factors for cardiovascular disease and HF. Central or visceral obesity can indirectly exert its negative cardiovascular effects through deleterious metabolic changes and systemic inflammation. In addition, visceral obesity can negatively impact ventricular mass and geometry, both potential precursors in HF development.^{19,20}

In the present study of over 1000 participants who underwent cardiovascular health evaluation, we found that

Figure 1. The positive linear association between body fat mass and left atrial (LA) diameter by different genders. The association between LA diameter and fat mass was more obvious in the female gender than male.

body fat mass was independently associated with adverse remodeling in LV geometry in terms of RWT and midwall function, which still holds true even after multivariable adjustment, especially in females. Although there seemed to be a paradoxical decrease in RWT among males (Figure 2), this variation was relatively negligible based on real clinical RWT data (only ranging between 40% and 41%, which can be regarded as clinically insignificant).

In recent years, exaggerated systemic inflammation and its strong link to metabolic disorders has been widely studied²¹; however, an established hypothesis bridging these observation has not been well proposed. Although metabolic syndrome accompanied by systemic inflammation has recently emerged as a clinical risk factor for HF incidence,²² the exact pathophysiologies linking it to cardiac structural and functional changes remained largely unexplored.

In previous literature, it has been well documented that endocardial fractional shortening may appear supranormal in hypertensive patients compared with normal adults, especially in the presence of left ventricular hypertrophy.^{23,24} On the other hand, midwall fractional shortening may be impaired in hypertensive patients with normal left ventricular ejection fraction.^{25,26} Recent findings of the LIFE (Losartan Intervention For Endpoint reduction) study suggested that reduced midwall function can predict reduced benefit of blood pressure control on cardiovascular morbidity and mortality.²⁷ As demonstrated in our data, it is worth noting that midwall function was more adversely associated with body fat mass in females. This may imply that females with higher body fat are more prone to develop unfavorable cardiac structural remodeling than males. This further supports the epidemiological findings of the preponderance of females and obesity in heart failure with preserved ejection fraction.²⁸

Limitations

There are several limitations in our study. First, our study has a male gender predominance, which may be somewhat biased. Second, this survey is retrospective and cross-sectional, without longitudinal follow-up or validation with

Figure 2. The distribution of left atrial (LA) diameter, relative wall thickness (RWT), and stress-corrected midwall mechanics (FScmw) by different genders, further categorized by high-sensitivity C-reactive protein (Hs-CRP) levels, with interaction presented (gender vs abnormally high Hs-CRP: ≥ 0.3 mg/dL), after accounting for clinical covariates, renal function, and hypertension history. Higher Hs-CRP level was associated with larger LA diameter, increased RWT, and worsened midwall mechanics in the female gender.

clinical outcomes. Third, our data come from asymptomatic Asian participants who took part in a primary cardiovascular health survey, and who therefore may not be fully representative of the broader general population in daily outpatient clinics. We also acknowledge that our data regarding LA structural remodeling were mainly focused on LA diameter rather than 2-dimensional echo-based volume measurements. Therefore, further research based on LA volume measures may be warranted to confirm our findings.

Conclusion

The current study showed that although body fat mass is negatively related to LV excursion in terms of reduced midwall contractile function, it can also exert independent effects on LV remodeling process, leading to subsequent LV mass increase and LA dilation. Worse ventricular

midwall contractility seems to be more prevalent in females with high systemic inflammation. These gender- and Hs-CRP-specific modification effects may potentiate the pathological mechanisms involved in heart failure with preserved ejection fraction. Because BIA and heart echo are relatively low-cost and effective tools, more screening tests based on these methods may be encouraged in obese or overweight individuals for cardiovascular risk stratification.

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