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Original article

Accumulation of pericardial fat correlates with left ventricular diastolic dysfunction in patients with normal ejection fraction☆

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KEYWORDS
Pericardium;
Obesity;
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Summary
Background: Left ventricular diastolic dysfunction (LVDD) plays an important role in heart failure with normal left ventricular ejection fraction (LVEF). Obesity is one of the major comorbid conditions of LVDD. Pericardial fat (PF) is an ectopic fat depot with possible paracrine or mechanical effects on the coronary circulation and myocardial function.
Methods: We measured PF volume on 64 slice computed tomography and analyzed echocardiographic parameters to confirm LVDD in 229 consecutive patients suspected of coronary artery disease with LVEF of more than 50% and no symptomatic heart failure (59% men, 67 ± 12 years). LVDD was defined as the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') >10.
Results: PF volume correlated significantly with E/e' ($r = 0.21$, $p < 0.01$), left ventricular mass index ($r = 0.23$, $p < 0.001$), and left atrial diameter ($r = 0.32$, $p < 0.001$). The mean PF volume was significantly greater in patients with LVDD (184 ± 61 cm^3, $n = 141$) than in those without LVDD

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(154 ± 58, $n = 88$, $p < 0.001$). Multivariate logistic regression analysis indicated that PF volume correlated significantly with the presence of LVDD (odds ratio: 2.00 per 100 cm^3 increase in PF volume, $p = 0.02$) independent of age, gender, abdominal obesity, hypertension, and diabetes.
Conclusions: PF volumes are significantly associated with LVDD, independent of other factors such as hypertension or diabetes. PF may be implicated in the pathogenesis of LVDD in patients with normal LVEF.

Introduction

Increasing evidence suggests that approximately half of all patients with heart failure have a normal left ventricular ejection fraction (LVEF) [1], and the mortality rate for this group is similar to those with heart failure and reduced LVEF [2]. Left ventricular diastolic dysfunction (LVDD) plays an important role in heart failure with normal ejection fraction (EF) [3]. However, there is no specific therapeutic strategy for LVDD partly because of the lack of understanding of its pathophysiological mechanism(s).

LVDD is most prevalent among elderly obese women with hypertension, diabetes, coronary artery disease, and/or atrial fibrillation [4,5]. Obesity is one of the important features of LVDD and fat tissue is known to secrete many adipokines that have local and systemic effects on the cardiovascular system [6]. Ectopic fat depots in muscle, liver, and pancreas are described as lipotoxic and pericardial fat (PF) is recognized as an ectopic visceral fat depot in close proximity to the myocardium and coronary arteries. PF volume is increased in obese patients and correlates with the presence [7,8] and incidence [9] of coronary atherosclerosis independent of other risk factors, indicating that PF may have paracrine or mechanical effects on the coronary circulation and myocardium. PF volume has also been reported to correlate with left atrial diameter, which is an indirect structural parameter of LVDD [10—12]. However, there is currently no report of a functional parameter of LVDD by tissue Doppler echocardiography that correlates with PF volume. The purpose of this study was to assess the association between PF volume and LVDD, as determined by tissue Doppler echocardiography.

Methods

Study sample

We analyzed consecutive inpatients in a stable condition who underwent 64-slice computed tomography (CT) coronary angiography and echocardiography between 2006 and 2009 on suspicion of coronary artery disease. None of the patients had history of previous thoracic surgery, percutaneous coronary intervention, or symptomatic heart failure. We screened 304 patients, each with LVEF more than 50%, and excluded those with previous pacemaker implantation ($n = 19$), chronic atrial fibrillation ($n = 12$), end-stage renal disease ($n = 14$), significant valvular disease ($n = 9$), poor image quality ($n = 17$), and incomplete data ($n = 6$). Thus, we measured PF volumes from CT images and examined echocardiographic parameters in 229 consecutive patients. The study was approved by the ethics review committee of our institution and a signed informed consent was obtained from each patient before participation. This study was registered at UMIN protocol registration system with the identification number UMIN000003361.

Cardiac CT scan protocol

The 64-detector CT (Brilliance-64, Phillips Medical Systems, Cleveland, OH, USA) was used with the following parameters: detector collimation 64 mm × 0.625 mm, table feed 19.7 mm/s, 0.2 beam pitch, rotation time 420 ms, tube current 429 mA, and voltage 120 kVp, as reported previously [7]. Reconstruction sets at 75% of the cardiac cycle or at a particular optimal phase were prepared from the raw data files. The contrast material (Omnipaque-350; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was administered using a mechanical power injector through a 20-gauge cannula inserted into the antecubital vein. To minimize differences in arterial enhancement across patients, we used a body-weight-tailored contrast material dose (0.7 mL/kg) and a fixed injection duration (9 s) [13]. An oral β-blocker (metoprolol, 20 mg) was administered 1 h prior to CT imaging, and nitroglycerin (0.3 mg) was administrated immediately prior to CT imaging. The reconstructed CT image data were transferred to a workstation for post-processing (ZIO M900, Amin/ZIO, Tokyo, Japan).

Cardiac CT image analysis

PF volume was measured three-dimensionally in all patients using contrast-enhanced images, as reported previously [7]. A predefined image display setting was used [window width = 150 Hounsfield units (HU), window center = −120 HU] to identify pixels that correspond to fat tissue [14]. The readers, who were blinded to the clinical results, trimmed along the pericardial sac using axial, coronal, and sagittal slices and volume-rendered images. PF was defined to be any adipose tissue located within the pericardial sac (Fig. 1). A slice 1 cm above the most cranial slice including the left anterior descending coronary artery was defined to be the superior border of the PF.

Three major coronary arteries were analyzed visually and quantitatively by contrast-enhanced coronary CT angiography. Coronary artery disease was defined to be ≥75% stenosis (according to the American Heart Association classification) on conventional coronary angiography ($n = 136$) analyzed quantitatively by coronary angiography software (CAAS, Pie Medical Imaging, Maastricht, Netherlands) or ≥50% luminal

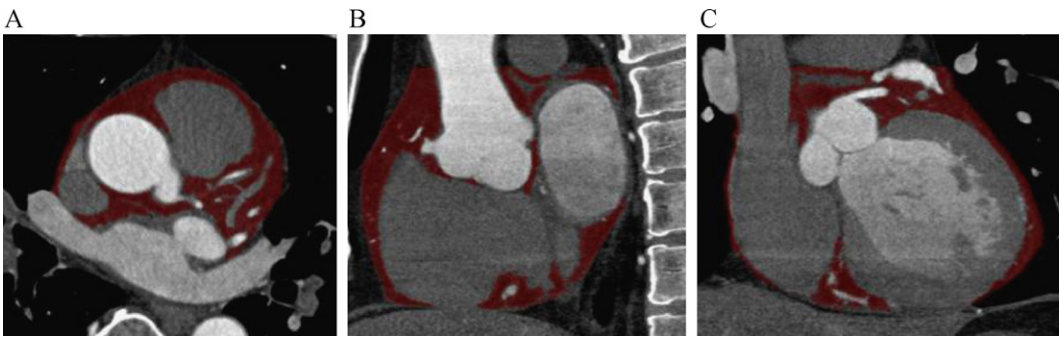

Figure 1 Representative computed tomography (CT) images of a 55-year-old male patient with hypertension, dyslipidemia, and diabetes. Red area is the pericardial fat (PF) within the pericardial sac quantified three-dimensionally by CT. The axial (A), saggital (B), and coronal (C) slice of the PF. His PF volume was 265 cm^3 and E/e' was 15. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

narrowing on CT images in patients without conventional coronary angiography ($n = 98$).

Echocardiography

For each patient, echocardiography was performed by a specialized echocardiologist. The cavity dimension and wall thickness were measured in a parasternal long axis view. Left ventricular mass was estimated using the formula recommended by guidelines [15]. Measurement of LVEF was performed in biplane apical (2-and 4-chamber) views using a modified Simpson's method. The pulsed Doppler sample volume was positioned at the opened leaflet tips of mitral valve. Early and late diastolic peak flow velocity and E-wave deceleration time were measured by transmitral Doppler imaging. The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') was also measured. LVDD was defined as the tissue Doppler oriented criterion using $E/e' > 10$ [16—18].

Assessment of risk factors and covariates

Obesity was defined as a body mass index of $\geq$25 kg/m^2. Abdominal obesity was defined as a waist circumference of $\geq$85 cm for Japanese males and $\geq$90 cm for Japanese females [19]. Blood was drawn after an overnight fast. Diabetes mellitus was diagnosed based on the criteria set by the World Health Organization or the use of hypoglycemic agents or insulin. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90 mmHg, or the use of an antihypertensive treatment. The estimated glomerular filtration rate was calculated using a modified formula from the Modification of Diet in Renal Disease study equation, which was proposed by the Japanese Society of Nephrology [20]. Metabolic syndrome was diagnosed according to the modified Adult Treatment Panel III criteria, which include the waist circumference cut-off values mentioned above and the presence of three or more metabolic abnormalities.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation. Differences in risk factors and adiposity traits in patients with or without LVDD were assessed. Differences between continuous variables were analyzed by the unpaired Student's *t*-test or the Mann-Whitney *U* test, as appropriate. Differences in categorical variables were analyzed by the chi-square test. Differences in PF volumes in patients with or without LVDD were analyzed by the unpaired Student's *t*-test. Pearson correlations and stepwise multivariate regression analysis among PF volume, metabolic risk factors, and echocardiographic parameters associated with LVDD were performed. Univariate and multivariate backward logistic regression analyses were used to assess the relationships among the presence of LVDD, PF volume, and other risk factors. We also tested the significant association between PF volumes and LVDD in multivariate logistic regression analyses using forced inclusion models of the following parameters: model-1, age and gender; model-2, age, gender, hypertension, and diabetes; model-3, age, gender, hypertension, diabetes, and abdominal obesity. The Hosmer—Lemeshow statistic was applied to assess model calibration. A p-value of <0.05 denoted statistical significance, and all tests were two-tailed. Variables were log-transformed if they had a skewed distribution. All analyses were performed using SPSS 17.0J for Windows (SPSS Inc., Tokyo, Japan).

Results

Study sample characteristics

Table 1 shows the characteristics of the participating patients ($n = 229$). Patients with LVDD ($n = 141$) had a higher age, body mass index, waist circumference, systolic blood pressure, fasting plasma glucose, and hemoglobin A1c, lower estimated glomerular filtration rate; were more likely to have hypertension, diabetes, metabolic syndrome, and coronary artery disease; and used aspirin more frequently than those without LVDD ($n = 88$). In the echocardiographic findings, patients with LVDD had a higher left ventricular mass index and left atrial diameter.

Table 1 Characteristics of patients with and without LVDD.

Parameters	Total	LVDD (+)	LVDD (−)	*p*-Value
Number	229	141	88	
Age, years	67 (12)	69 (10)	63 (12)	<0.001
Male gender, %	59	59	60	0.89
Obesity, %	30	33	26	0.37
Body mass index, kg/m^2	23.5 (3.3)	23.7 (3.2)	23.1 (3.6)	0.16
Abdominal obesity, %	56	60	50	0.17
Waist circumferences, cm	86.8 (9.3)	87.9 (8.6)	85.1 (10.0)	0.03
Hypertension, %	74	80	64	<0.01
Systolic blood pressure, mmHg	131 (20)	134 (20)	126 (18)	<0.01
Diastolic blood pressure, mmHg	74 (12)	73 (13)	74 (12)	0.62
Dyslipidemia, %	65	69	58	0.12
Total cholesterol, mg/dL	187 (33)	187 (33)	190 (34)	0.83
LDL cholesterol, mg/dL	110 (30)	108 (32)	112 (32)	0.58
HDL cholesterol, mg/dL	55 (17)	54 (16)	58 (19)	0.14
Triglycerides, mg/dL[a]	104 (74—149)	107 (77—156)	101 (71—146)	0.14
Diabetes mellitus, %	35	42	23	<0.01
Fasting plasma glucose, mg/dL	98 (26)	102 (29)	93 (19)	<0.01
Hemoglobin A1c, %[a]	5.8 (5.5—6.4)	5.9 (5.6—6.6)	5.7 (5.4—6.3)	0.02
Metabolic syndrome, %	43	49	33	0.02
Current smoker, %	20	18	23	0.50
Estimated GFR, mL/min/1.73 m^2	71 (19)	68 (20)	76 (17)	<0.01
B-type natriuretic peptide, pg/mL[a]	29 (15—63)	34 (15—71)	26 (14—46)	0.07
Medications				
Statins, %	37	42	30	0.07
Aspirin, %	48	54	38	0.02
β-Blockers, %	24	22	26	0.52
ACE inhibitors or ARBs, %	45	50	38	0.08
Thiazolidinediones, %	6	6	5	0.77
Atrial fibrillation, %	18	16	21	0.48
Coronary angiography, %	58	65	48	0.01
Coronary artery disease, %	40	46	31	0.03
Echocardiography				
LVEF, %	64 (6)	64 (6)	64 (6)	1.00
LV mass index, g/m^2	105 (27)	109 (27)	99 (25)	<0.01
Left atrial diameter, mm	38 (6)	38 (5)	36 (6)	<0.01
E/A[a]	0.8 (0.7—1.1)	0.8 (0.7—1.1)	0.8 (0.7—1.1)	0.98
E-wave deceleration time, ms	221 (65)	227 (71)	211 (53)	0.06

Data are mean (standard deviation) or number (percentage).
LVDD, left ventricular diastolic dysfunction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LV, left ventricle; E/A, early/late diastolic peak flow velocity ratio.
[a] Median and 25th to 75th percentiles.

Correlation between PF volume, risk factors, and LVDD

PF volume correlated positively with body mass index ($r = 0.51$, $p < 0.001$), waist circumferences ($r = 0.56$, $p < 0.001$), systolic blood pressure ($r = 0.16$, $p = 0.02$), log hemoglobin A1c ($r = 0.23$, $p < 0.001$), and log triglyceride ($r = 0.32$, $p < 0.001$), and negatively with high-density lipoprotein cholesterol ($r = -0.32$, $p < 0.001$). Multiple stepwise regression analysis identified age (beta = 0.13, $p = 0.02$) and waist circumference (beta = 0.56, $p < 0.001$) as significant and independent correlates with PF volume. PF volume correlated significantly with E/e' ($r = 0.21$, $p < 0.01$; Fig. 2A). PF volume also correlated positively with left ventricular mass index ($r = 0.23$, $p < 0.001$; Fig. 2B) and left atrial diameter ($r = 0.32$, $p < 0.001$; Fig. 2C), negatively with the log early/late diastolic peak flow velocity ratio ($r = -0.14$, $p = 0.03$), but not with LVEF ($r = -0.07$, $p = 0.31$). PF volume was larger in patients with LVDD ($n = 141$; 184 ± 61 cm^3) than those without LVDD ($n = 88$; 154 ± 58 cm^3, $p < 0.001$; Fig. 2D).

Factors associated with LVDD

Univariate logistic regression analysis found significant relationships between the presence of LVDD and age, hypertension, diabetes, estimated glomerular filtration rate, left

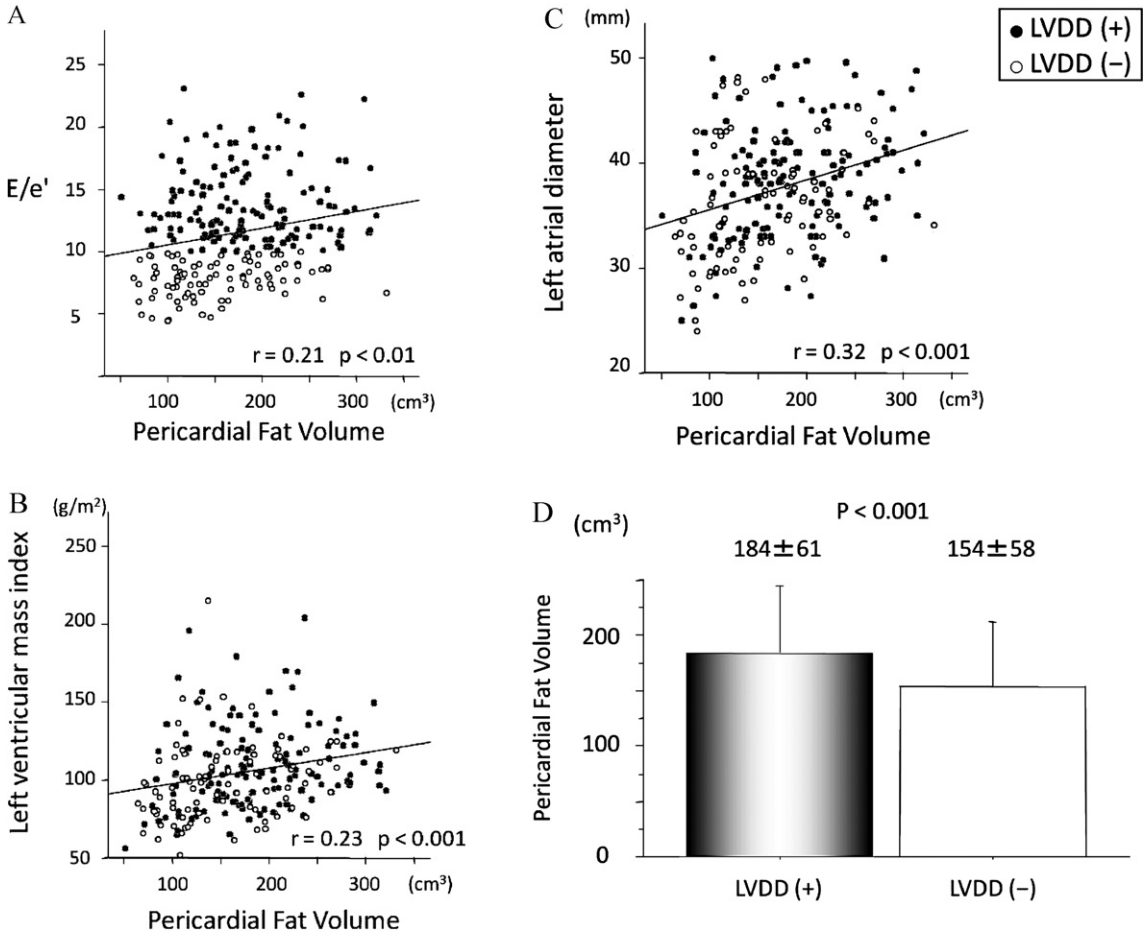

Figure 2 Correlation between pericardial fat (PF) volume and left ventricular diastolic dysfunction (LVDD). Correlation between PF volume and echocardiographic parameters: E/e' (A), left ventricular mass index (B), and left atrial diameter (C). PF volume had a significant positive correlation with E/e' ($r = 0.21$, $p < 0.01$), left ventricular mass index ($r = 0.23$, $p < 0.001$), and left atrial diameter ($r = 0.32$, $p < 0.001$). Filled and open circles indicate patients with and without LVDD, respectively. (D) PF volume in patients with or without LVDD. Bar graph indicates mean + standard deviation. PF volume was significantly larger in patients with LVDD ($184 \pm 61\ cm^3$) than in those without LVDD ($154 \pm 58\ cm^3$, $p < 0.001$).

Table 2 Univariate and multivariate backward stepwise logistic regression analyses of pericardial fat volume and risk factors associated with the presence of LVDD.

Factors	Univariate		Multivariate	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Age (per 10 years)	1.60 (1.25—2.04)	<0.001	1.50 (1.16—1.95)	0.02
Male gender (yes)	0.95 (0.55—1.63)	0.84	Not selected	
Body mass index (per kg/m^2)	1.06 (0.98—1.15)	0.16	Not selected	
Abdominal obesity (yes)	1.47 (0.86—2.52)	0.16	Not selected	
Hypertension (yes)	2.30 (1.27—4.20)	<0.01	Not selected	
Dyslipidemia (yes)	1.60 (0.92—2.78)	0.10	Not selected	
Diabetes mellitus (yes)	2.44 (1.34—4.46)	<0.01	2.24 (1.16—4.33)	0.02
Coronary artery disease (yes)	1.25 (0.89—1.75)	0.20	Not selected	
Estimated GFR (per $10\ mL/min/1.73\ m^2$)	0.81 (0.70—0.94)	<0.01	Not selected	
B-type natriuretic peptide (per 100 pg/mL)	1.73 (0.95—3.18)	0.07	Not selected	
LVEF (per %)	1.00 (0.96—1.04)	0.99	Not selected	
LV mass index (per g/m^2)	1.02 (1.00—1.03)	<0.01	Not selected	
PF volumes (per $100\ cm^3$)	2.36 (1.46—3.80)	<0.001	2.06 (1.22—3.47)	<0.01

LVDD, left ventricular diastolic dysfunction; OR, odds ratio; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LV, left ventricle; PF, pericardial fat.

Table 3 Multivariate-adjusted odds ratio for the presence of LVDD.

Model adjustments	Model 1		Model 2		Model 3	
	Odds ratio (95%CI)	*p*-Value	Odds ratio (95%CI)	*p*-Value	Odds ratio (95%CI)	*p*-Value
Age (per 10 years)	1.54 (1.20—1.97)	<0.01	1.55 (1.20—2.00)	<0.01	1.54 (1.19—1.99)	<0.01
Male gender	0.77 (0.42—1.41)	0.39	0.74 (0.40—1.37)	0.33	0.74 (0.40—1.38)	0.35
Hypertension	—	—	1.35 (0.69—2.65)	0.38	1.36 (0.70—2.67)	0.37
Diabetes mellitus	—	—	2.02 (1.04—3.92)	0.04	2.09 (1.06—4.12)	0.03
Abdominal obesity	—	—	—	—	1.23 (0.63—2.40)	0.54
PF volume (per 100 cm^3)	2.38 (1.43—3.97)	<0.01	1.95 (1.13—3.34)	0.02	2.09 (1.15—3.79)	0.02

LVDD, left ventricular diastolic dysfunction; CI, confidence interval; PF, pericardial fat.

ventricular mass index, and PF volume (Table 2). Multivariate backward logistic regression analysis identified age [odds ratio (OR): 1.50, 95% confidence interval (CI): 1.16—1.95 per 10 years, $p = 0.02$], the presence of diabetes (OR: 2.24, 95% CI: 1.16—4.33, $p = 0.02$), and PF volume (OR: 2.06 per 100 cm^3, 95% CI: 1.22—3.47, $p < 0.01$) as significant and independent factors associated with the presence of LVDD. This model was reliable ($p = 0.17$ by the Hosmer—Lemeshow test). In the forced entry models, we confirmed the significant association between PF volume and the presence of LVDD (OR: 2.09 per 100 cm^3, 95% CI: 1.15—3.79, $p = 0.02$) independent of age, gender, hypertension, diabetes, and abdominal obesity (Table 3). This model was also reliable ($p = 0.71$ by the Hosmer—Lemeshow test).

Discussion

The present study demonstrates that PF volumes correlate significantly with E/e', indicating the association between PF volumes and LVDD. Furthermore, multivariate analysis indicated that PF volume correlates significantly with the presence of LVDD, independent of other risk factors such as age, gender, hypertension, diabetes, or abdominal obesity.

PF has been reported to correlate with left atrial dimensions [12] and left ventricular diastolic filling [21], neither of which are recommended as first-line diagnostic parameters for LVDD [22]. However, recent guidelines recommend the evaluation of tissue Doppler E/e' in the assessment of LVDD [22]. To our knowledge, the present study is the first to report the significant association between PF volume and LVDD using tissue Doppler echocardiography.

Potential mechanisms

The potential mechanisms underlying the direct correlation between PF volumes and LVDD are mechanical and paracrine processes. Compression of PF on the myocardium may induce LVDD [12] by disturbing the dilation of the left ventricle and impairing cardiac filling through a pathophysiology similar to the thickening of the pericardium in constrictive pericarditis [23]. Previous studies also reported the paracrine effects of PF. Pericardial and perivascular fat, but not subcutaneous fat, contain high levels of various cytokines [24] that may induce inflammation and increase subsequent collagen turnover, leading to LVDD [25]. Myocardial dysfunction may be induced by a loss of adiponectin secretion or reduced nitric oxide synthase activity in perivascular fat [26]. Both may act directly on cardiomyocytes [27] and indirectly through impaired microvascular relaxation in the myocardium [28]. Thus, it is possible that a similar mechanism operates through paracrine processes. The systemic effects of obesity, diabetes, and other metabolic disorders on LVDD have also been described in previous studies [5].

PF has been observed inside and outside the pericardial sac, which was also reported to be associated with aortic calcification [14]. The PF outside the sac potentially has some effects on left ventricular function. We measured PF volume by trimming along the pericardial sac using axial, coronal, and saggital slices and volume-rendered images by 64-slice CT. In the present study, we could not precisely distinguish PF distribution inside or outside the sac. Further studies might be required to determine the effects of the PF outside the sac on LVDD.

Cardiac CT and echocardiography

We originally quantified PF volume three-dimensionally using multislice CT. This technique yielded highly reproducible measurements (CV = 7.1% and 8.9% for inter- and intra-observer variability, respectively) [7,29]. In addition, 64-slice CT is commonly used in cardiovascular clinical practice in Japan.

Noninvasive diagnostic evidence for LVDD is preferably derived from myocardial tissue Doppler. E/e' is reported to correlate closely with LV filling pressure, and this correlation has been confirmed in patients with pseudo-normal mitral valve flow velocity filling patterns [22]. We defined LVDD simply as $E/e' > 10$ according to the previously described cut-off value [16,17] partially because of lack of data concerning duration of reverse pulmonary vein atrial systole flow, duration of mitral valve atrial wave flow, and left atrium volume index used in recent guidelines [22].

Limitations

The clinical study design was cross-sectional, and the results do not imply causality. Because the subjects were not randomly selected but rather inpatients suspected to have coronary artery disease, they were more likely to have coronary artery disease than the general population, their risk factors were considered to have been modified by

medications, and some selection bias may influence the result of the present study (B-type natriuretic peptide level and left ventricle mass index are less than expected). The lack of data regarding the extent of coronary artery disease severity is also a limitation because it may largely affect LVDD. E/e' is a marker of increased left ventricular filling pressure, but may occur due to reasons other than primary myocardial disease, affecting the findings. The value of E/e' depends on the technician's experience. Because it depends also on fluid status and medications, the lack of data about time frame between CT and echocardiography may also be a limitation. The lack of data about duration of reverse pulmonary vein atrial systole flow, duration of mitral valve atrial wave flow, and left atrial volume index, which are used in recent guidelines to diagnose LVDD, is also a major limitation on defining LVDD. We have no data about the distribution of body fat (especially abdominal visceral fat and fat outside the pericardial sac) but only have waist circumference though this would help to get more insight into the differential pathophysiologic mechanisms. The correlations between PF volume and parameters of LVDD ($r = 0.21—0.32$) are weak, although statistically significant, so clinical significance of these correlations should be considered cautiously. The multivariate statistical models incorporated both abdominal obesity and PF volume, whose close correlation may affect the results of the analyses.

Clinical implications

In settings where the causality between PF volume and LVDD is demonstrated by a prospective study, PF volume may serve as a potential therapeutic target to prevent LVDD or heart failure in patients with normal EF. PF volume measurement may be useful in selecting therapeutic strategies. For example, thiazolidinediones have been reported to increase PF [30] and such medications may not be beneficial in patients with LVDD. It may also be useful to assess the effect of low-calorie diet on PF volume [31] or the effect of surgical removal [32] of PF on LVDD.

Conclusions

The present study demonstrated that PF volume correlated significantly with LVDD, independent of other risk factors such as age, gender, diabetes, hypertension, or abdominal obesity. PF may play a role in the pathogenesis of LVDD.

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