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Cardiac Remodeling with Excessive Visceral Adiposity beyond Anthropometrics in Asymptomatic Asians

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Abstract

Purpose:

Visceral Adipose Tissue (VAT) as a source of pro-inflammatory and biological mediators is implicated in adverse cardiac structure remodeling, functional alternations, and results in Heart Failure (HF) in central obese patients. However, the impact of different distributions of visceral fat on cardiac structural/functional changes still remains unclear.

Methods:

This retrospective analysis includes 354 subjects free from previous myocardial infarction, coronary arterial disease, stroke, or clinical HF. Regional VAT including Pericardial Fat (PCF) and Thoracic Periaortic Fat (TAT) volumes, fatty liver grades were all measured by Multi-Detector Computed Tomography (MDCT) (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA) and abdominal sonography (Toshiba Nemio SSA-550A). We measured Left ventricular mass/mass index (LVM/LVMI), LV Mass to Volume ratio (LVMVI), Left Atrium (LA) diameter represented as cardiac remodeling, and analyzed their association with adiposity measures.

Results:

All VAT are significantly associated with worsening cardio-metabolic profiles (hs-CRP, metabolic scores, coronary calcium score) (all $P<0.05$). Excess PCF/TAT wassignificantly associated with larger LVM/LVMI, LVMVI, and LA diameter (all $P<0.05$); presented in LV concentric remodeling, it further worsens LV diastolic function. In multivariate models, this effect on LA remodeling was attenuated in TAT after adjusting for the clinical variable ($P=0.052$). However, there was no correlation between hepatic fat and LV/LA structural/functional alternations.

Conclusion:

Accumulated visceral adiposity, especially PCF deposits, was associated with certain cardiac structural/functional remodeling characterized by impaired LV diastolic function. PCF may exhibit a local effect on adjacent cardiac structure more than TAT and hepatic fat. Our data suggested that PCF may serve as an independent predictor to screen subclinical heart failure in asymptomatic population.

Keywords: Cardiac Remodeling; Visceral Adipose Tissue (VAT); Pericardial Fat (PCF); Thoracic Periaortic Fat (TAT); Fatty Liver Grade

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Introduction

Obesity is an independent risk factor for the development of left ventricular structure remodeling and functional changes which further results in heart failure with preserved ejection fraction (HFpEF) through hemodynamic and non-hemodynamic mechanisms mediated [1-5].The mechanisms may include indirect cardiovascular risk factors or direct obesity hyper-hemodynamic adaptation, with increasing left ventricular wall stress leads to adverse cardiac structure remodeling or induced myocardial injury through adipokines and inflammatory mediators [6-8].

Recently, focus on the role of Visceral Adipose Tissue (VAT) as a source of pro-inflammatory and biological mediators implicated in adverse cardiac structure remodeling. Therefore, we suspected that VAT (such as Pericardial Fat (PCF), Thoracic peri-Aortic Fat (TAT) especially with their anatomic proximity to cardiac structure), not only plays a central role on mediating inflammation and oxidative stress but also may trigger certain adverse cardiac structure remodeling that be more accentuated in HFpEF [9-11].

In addition to PCF and TAT, recent studies demonstrated that abdominal fat accumulation, especially non-alcoholic fatty liver disease is closely linked to not only metabolic syndrome but also subclinical left ventricular structure remodeling and increase cardiovascular risk [12-15]. However, the impact of different distribution of visceral fat on cardiac adverse structure remodeling is not fully understood.

Thus, this study aimed to assess whether there was association between regional VAT and cardiac structural and functional abnormalities, especially after adjusted possible cardiovascular risk factors. We hope this study to provide clinical application to early prediction on subclinical heart failure in obese, especially central obesity.

Methods

Subjects

In this retrospective analysis, echocardiography, liver ultrasound, and coronary artery calcium scoring with Computed Tomographic (CT) imaging were performed in 362 consecutive subjects who participated in a primary cardiovascular health survey at a tertiary medical center in Taipei, Taiwan, from January 2007 to August 2009. Patients with previous myocardial infarction, stroke, coronary arterial disease, peripheral arterial disease or prior hospitalization for congestive heart failure were excluded. The presence of a history of hypertension was defined as systolic blood pressure>140mmHg, diastolic blood pressure >90mmHg, or previously diagnosed Hypertension under pharmaceutical control. Diabetes mellitus was defined as fasting glucose level >126mg/dL or previously diagnosed diabetes mellitus under pharmaceutical control. Hyperlipidemia was defined as known history and/or the use of lipid lowering drugs, such as statins or fibrates, on a daily basis. Nonalcoholic fatty liver disease was defined on abdominal echocardiography after the exclusion of excessive alcohol use, hepatitis B or C confirmed by serologic tests, and other known etiologies of liver disease.

Anthropometric Measurements and Lab Data Acquisition and Analysis

All baseline characteristics and information regarding anthropometric measures were collected. Standardized cuff sphygmomanometer–defined resting blood pressures were measured by medical staff members blinded to other test results. Body weight and height were measured and body mass index (body weight/height ^{2}) was calculated.

A Hitachi 7170 Automatic Analyzer (Hitachi Corporation, Hitachinaka Ibaraki, Japan) was used to measure fasting and postprandial glucose levels (hexokinase method), glycosylated hemoglobin, creatinine (kinetic colorimetric assay), total cholesterol and triglyceride, and alanine aminotransferase (enzymatic method). Lipid profiles including low-density lipoprotein and high-density lipoprotein cholesterol were obtained using homogenous enzymatic colorimetric assay. Hs-CRP levels were determined using a highly sensitive, latex particle–enhanced immunoassay (Elecsys 2010; Roche Diagnostics GmbH, Mannheim, Germany), and Nt-proBNP levels (N- terminal brain – type natriuretic peptide) were measured by commercially available assays (ECLIA Elecsys 2010 analyzer, Roche Diagnostics) in plasma samples. We calculated metabolic score for all participants, based on metabolic scores as defined by NCEP ATP III criteria. Waist circumference ≥80cm for women or ≥90cm for men (1 point); serum fasting glucose concentration ≥100mg/dL (≥5.5mmol/L) (1 point); serum high-density

lipoprotein (HDL) level <40mg/dL(<1.03mmol/L) for men or <50mg/dL (<1.29mmol/L) for women (1 point); serum triglyceride level >150mg/dL (>1.69mmol/L) (1 point); and/or blood pressure >130/85mmHg (1point).

Echocardiography protocol for assessing conventional echocardiography parameters

Each subject underwent two-dimensional (2D) and color Doppler transthoracic echocardiography using a commercially available ultrasound system (Vivid 7, GE Medical System, Vingmed, Norway) equipped with 2–4 MHz transducer at the left decubitus position. All recorded images were measured and analyzed with clinical information blinded using a computerized off-line software (TomTec Image Arena, Munich, Germany). All measurements were averaged from three consecutive cardiac cycles. LV wall thickness and mass were determined from M-mode method. LV volumes, ejection fraction and endocardial/middle wall fractional shorting were obtained via the modified biplane Simpson method from the apical four- and two-chamber views according to American Society of Echocardiography recommendations.

CT-defined visceral adiposity: pericardial fat, thoracic peri-aortic fat

Multi-detector CT (MDCT) study was performed using a DualSource CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) with 32x0.6mm per tube with double sampling by z-flying focal spot, rotation time of 330 ms, tube voltage of 120kV, and full tube current of 625mA pertube (independent of patient size).Contrast injection (iopamiro 370mg/mL, Bracco, Italy) was administered (60–85mL) at an injection rate of 5mL/s with a delay calculated during the timing bolus scan. Overlapping transaxial images were reconstructed using a medium sharp convolution kernel (B25f) with an image matrix of 512x512pixels, slice thickness and increment of 0.75/0.4mm using an ECG-gated half-scan algorithm. Image reconstruction was retrospectively gated to ECG. Reconstructed image data were transferred to a dedicated workstation (Aquarius 3D Workstation, TeraRecon, San Mateo, CA) for subsequent visceral adipose tissue, Pericardial Fat (PCF), and thoracic periaortic (TAT) analysis. The semiautomatic segmentation technique was developed for quantification of fat volumes. We traced the region of interest manually and defined fat tissue by using Hounsfield Units (HU) as pixels with the attenuation of -190 to-30 HU, which corresponded to adipose tissue in contrast-enhanced cardiac CT scans. PCF was defined as any adipose tissue volume (unit: mL) located within the pericardial sac. TAT tissue was defined as the volume (unit: mL) of the adipose tissue surrounding the thoracic aorta, which extended67.5mmfrom the level of the bifurcation of pulmonary arteries as starting point, with cranial-caudal coverage of the thoracic aorta to the diaphragm as its lower anatomical limit.

Coronary Artery Calcium Measurement

We measured the calcification of the coronary arteries by using a dedicated offline workstation (Aquarius 3D Workstation; TeraRecon, San Mateo, CA). A coronary calcified lesion was defined as an area with a density >130 Hounsfield units and covering≧6 pixels. The Agatston scoring method was applied by multiplying each lesion (area) by a weighted CT attenuation score in the lesion.

Liver Ultrasound

We used ultrasound, a widely used surrogate for liver biopsy, for the assessment of fatty liver. Abdominal sonography was performed using a Toshiba Nemio SSA-550A instrument (Toshiba, Tochigi-ken, Japan) by hepatology specialists completely blinded to other laboratory results. In brief, liver pathology was further graded semi-quantitatively as absent (grade 0), mild (grade 1), or moderate to severe (grade 2and 3) according to the level of echoes arising from the hepatic parenchyma, as suggested in previous studies.

In our acknowledgment that the interpretation of fatty liver by abdominal ultrasound may tend to be subjective, so for convenient of statistical analysis, we further defined subjects with at least moderate fatty liver disease as having significant fatty liver disease in this study. This study design was approved by the local ethics committee in accordance with the Declaration of Helsinki (12MMHIS052).

Statistical Analysis

Data of clinical characteristics were presented as frequency and percentage for categorical variables or as mean and standard deviation for continuous variables. Patients were equally divided into three groups (tertiles) according to their levels of PCF, TAT or fatty liver grade. The trend of clinical characteristics (including baseline characteristics, biochemical data, comorbidities, and echo parameters) across the ordinal groups (i.e. tertiles of PCF, TAT or fatty liver grade) was tested using

linear contrast in the general linear model for continuous variables or using Cochran–Armitage chi-square trend test for categorical variables (i.e. prevalence of hypertension). Outcomes of primary interest in this study were parameters represented as cardiac structure remodeling included LVMI, LV mass to volume ratio and LA diameter. The association between values of PCF/TAT (or the presence of fatty liver grade) and LV structure changes was tested using multivariable linear regression analysis. In the regression analyses, we first adjusted for age, sex, body mass index (model 1), and further adjusted for systolic blood pressure, fasting glucose, estimated glomerular filtration rate, total cholesterol and high-density lipoprotein (model 2), and finally adjusted for hypertension and diabetes mellitus (model 3). We illustrated the relationship between PCF/TAT/fatty liver grade and LV structure/LA diameter using scatter plot with a Pearson's correlation. A *P* value < 0.5 was considered to be statically significant. Data analysis was performed using SPSS 22 (IBM SPSS, Armonk, NY: IBM Corp).

Result

1. Basic information , cardiometabolic profiles and adiposity measures

A final total 354 participants (mean 51.6 +/-8.8 years old, 69.2% male) enrolled from annual health evaluation study and completed all examination. Baseline demographic, anthropometric characteristics and metabolic parameters divided into groups according to the trend of various visceral fat are summarized in table 1, 2 and 3.

In table 1, lists patient's clinical characteristics stratified by tertiles of PCF. We observed that among male patients, both systolic and diastolic blood pressure and BMI were highly correlated to the increase of PCF level, (all trend p<0.05).In addition, increasing PCF were significantly associated with graded increase in fasting glucose, Hba1c, total cholesterol, hs-CRP and metabolic score as well as decrease in HDL, (all trend p <0.05).Furthermore, higher coronary calcium score was correlated with higher PCF level, (trend p <0.001).The prevalence of hypertension gradually increased with higher PCF levels, (trend p <0.05).

Table2 illustrates patient's clinical characteristics stratified by tertiles of TAT.

We still observed that increase level TAT were correlated with grades increase in BMI, total cholesterol, LDL, hs-CRP, metabolic score and coronary calcium score, (all trend p<0.05).

Table 3 shows patient's clinical characteristics stratified by fatty liver grade. The increasing fatty liver grade was positively associated with the increase of BMI, fasting glucose, HbA1c, triglyceride, coronary calcium score, metabolic score and hs-CRP. However, increase fatty liver grade was negatively correlated with HDL. The prevalence of hyperlipidemia and diabetes mellitus gradually increased with higher fatty liver grade, (all trend<0.05). We also noticed that increasing fatty liver grade was gradually increased with PCF levels, (trend P<0.05).

In this study, we documented that large amount of visceral fat (PCF, TAT and fatty liver grade) was associated with several unfavorable cardiometabolic and systemic inflammatory profiles including elevated BMI, metabolic score, and coronary calcium score and hs CRP.

2. The association between various echocardiographic parameters and visceral fat (PCF , TAT , fatty liver grade)

In the table1 and figure 1, increasing PCF levels were found to be positively correlated to grade increase in the following IVS, LVPWT, LVEDV, LVESV, LV mass, LVMI, LV mass to volume ratio and LA diameter, (all trend p<0.05), represented as LV concentric remodeling and impaired LV diastolic function. In addition, increasing amount PCF was significant decrease in midwall fractional shortening (trend p<0.05), represented as LV systolic function impaired.

In the table 2 and figure 2, we still observed the increasing TAT positively correlated with LVPWT, LVEDV, LVESV, LV mass and LVMI. However, no significant relationship was noted between LV midwall fractional shortening, LV mass to volume ratio, LA diameter and trend of TAT. In the table 3, we observed that there was no significant correlation between echocardiography parameters and trend of fatty liver grade. The impact on cardiac structure remodeling was attenuated in the trend of TAT and disappeared in fatty liver grade for anatomic far away from the heart.

3. The association between various visceral fat and LV structure remodeling and functional changes

Table 4 presents both univariate and multivariate models regarding the difference of association between LV structure /functional parameters and visceral fat measures.

In the univariate analysis, PCF volume was significantly related to increased thickness of IVS, volume of LVEDV, LV mass, LVMI, LV mass to volume ratio and LA diameter. In the multivariate analysis, PCF volume remained significantly associated with increased thickness of IVS, volume of LVEDV, LV mass, LVMI, LV mass to volume ratio and LA diameter after adjusting possible confounders (model 1through 3). Large amount of PCF is associated with concentric remodeling of LV and represented as worsening of LV diastolic function. The relationship between LV structure remodeling and TAT, we also noted that increase TAT was significantly related with increased thickness of IVS, volume of LVEDV, LV mass, LVMI, LV mass to volume ratio and LA diameter in the univariate analysis. However, this effect between TAT and LA diameter disappeared after adjusting possible confounders in the multivariate analysis.

In contrast, there were no associations between fatty liver grade and LV structure changes. In this study, we demonstrated that impact on the adverse cardiac structure remodeling effects mediated by visceral fat is attenuated by their deposition far away from the cardiac structure.

Discussion

Recently, increasing amount of evidence strongly linked central obesity to insulin resistance, the metabolic syndrome and abnormal adiopkine signaling which is particularly predictive of incidental heart failure [16-17]. In our study, we observed that greater amount visceral fat were associated with unfavorable anthropometrics, worsening cardio-metabolic profiles, including higher coronary calcium scores, metabolic scores and greater degree of systemic inflammation.

Indeed, subclinical myocardial dysfunction has been identified in obese subjects without cardiovascular risks factors, mediated by myocardial ultra-structure alternations and associated with ventricular remodeling [18]. In our knowledge, the more advanced impaired ventricular performance with increased risk for mortality when LV geometry becomes altered. The more evidences suggest that increased mortality in obese with altered ventricular geometry with highest mortality has seen in patients with concentric hypertrophy [19-21].These adverse cardiac geometry abnormalities are closely related to visceral adipose tissue [22-24]. However, the different distribution of visceral fat may play the different degree of influence on cardiac geometric alterations and functional abnormalities.

In our data, we demonstrated that grade increase of PCF volume was significantly related to the increase of LV wall thickness, mass index and mass to volume ratio. These geometric changes in LV are defined as concentric remodeling and like hypertensive cardiac remodeling [25-27]. Indeed, there was higher prevalence of hypertension noted in the trend of PCF. In addition, this effect still remained in spite of adjusting possible confounders especially hypertension. Moreover, we also noted the larger LA is correlated with PCF excess. LA is directly exposed to LV pressure during ventricular diastole. Increase LA size is the booster effect of increasing LV filling pressure.LA structural remodeling has been a clinical potential indicator to reflect the duration and severity of LV diastolic dysfunction. The larger LA has higher prevalence of atrial fibrillation that results in chronic heart failure [28-30].

Base on our data, the more PCF amount is related to a concentric LV remodeling phenotype and more severity of diastolic dysfunction. In addition to LV diastolic dysfunction, more studies demonstrated that the amount of PCF volume was correlated to systolic function impairment [31-34]. In this investigation, we show that worsened midwall contractility was significantly related to increasing PCF. The previous studies have been documented that midwall fractional shortening may be impaired in hypertensive patients with normal left ventricular ejection fraction. Furthermore, recent study recommended that reduced midwall function can predict reduced benefit of blood pressure control on cardiovascular morbidity and mortality [35-37]. Meanwhile, we noted that this effect exhibits in PCF, stronger than in TAT, and disappears in hepatic fat. Although the impact of TAT on LV concentric geometric alternations still exists, the effect on LA diameter disappeared after adjusted possible confounders. In addition, no evidence of systolic midwalll contractility changes was noted in trend of TAT. In spite of excess hepatic fat is significantly associated with high prevalence of metabolic syndrome, increasing systemic inflammatory markers, and the worsening of cardio-metabolic profiles; however, there is no association between hepatic fat and LV structural and functional alternation in our study. This mean that impact of various visceral adipose has each different degree of effect on LV geometric and functional alternations and this effect would be attenuated by the distance away from the

myocardium. Therefore, we suggest that PCF volume may be applied to be an independent predictor of subclinical LV diastolic and systolic dysfunction in central obese.

VAT such as PCF, deposed adjacent to myocardium not only plays a role of systemic inflammatory mechanisms, but also probably acts locally through autocrine or paracrine mechanisms mediated to adverse LV geometric remodeling and results in heart failure [38-40]. However, potential mechanisms remain incompletely defined. The challenge of understanding the association between VAT and LV geometric remodeling leading to heart failure is complicated by multiple pathways that ultimately impact the myocardium. There is currently potential importance of autocrine and paracrine effects mediated by adipokines derived by visceral fat tissue from myocardium itself or larger PCF mass in obese subjects. Adiopkines, such as adiopnectin, which promotes insulin sensitivity, normal endothelial function that protects against myocyte hypertrophy and ischemic injury, is reduced in obesity [41-43]. Conversely, other adiopkines such as leptin, which is pro-inflammatory, pro-atherogenic and promotes LV hypertrophy, has high level in obesity and is associated with the risk of incidental heart failure. In addition, circulating adiopkines that signal from epicardial fat or PCF may directly influence local myocardial metabolic and function [44-46]. Furthermore, the extent visceral fat is linked to pro-inflammatory cytokines such as Interleukin (IL)-6, IL-1β, Atrial Natriuretic Peptide (ANP), and Tumor Necrosis Factor (TNF)-α which can play a role in the myocardial remodeling process by directly influencing aspects such as hypertrophy, apoptosis, fibrosis, and ultimately contractility [47-51]. Previous literatures have been reporting that lipid accumulation in the myocardium may enhance mitochondrial reactive oxygen species generation and oxidative stress which is the risk of heart failure in obese [52]. In addition, numerous studies demonstrated that obese subjects have activation of the renin-angiotensin system mediated directly via signals from adipose tissue [53]. Engeli et al. have suggested that adipose tissue contains the major components of a local renin-angiotensin system. Angiotensin is thought to cause sympathetic excitation, so there may be additive effects of renin-angiotensin and sympathetic activation with respect to blood pressure elevation and cardiac remodeling in obesity [54]. Therefore, increased activity of this system has been implicated in human obesity hypertension, LV hypertrophy, even myocardium fibrosis mediated.

In the clinical application, it is tempting to speculate that therapeutic interventions for reversal of LV hypertrophy and diastolic dysfunction in obesity mediation by manipulating the PCF. Indeed, previous literatures have reported the weight loss either achieved by lifestyle changes or bariatric procedures which decreases LV mass and improves LV function regardless of blood pressure status. The multiple potential mechanisms of weight loss through improving myocardial energetic, decreasing myocardial lipotoxicity, reversal of normal circulating level of adiponectin/leptin and decreasing inflammatory mediators seem to be closely linked to improve myocardial diastolic function [55-57].

Study Limitations

There are several limitations in this study. First, this is retrospective and cross-sectional study without longitudinal follow up or verification with clinical outcomes. Second, our subjects who are male gender predominance may exist somewhat biased. Third, our data got from asymptomatic Asian subjects who to part in a primary cardiovascular healthy survey, and them therefore may not be fully representative of the broader general patients in daily outpatient clinics. Finally, in our study, we represent LA structural remodeling with LA diameter rather than 2-dimentsional echo-based volume measurement. Thus, further research based on LA volume measures may be further confirmation.

Conclusion

In our study, we demonstrated that excess VAT such as PCF is associated with concentric LV remodeling, enlarged LA and worsening LV systolic and diastolic function.

However, the impact of VAT on LV geometric and functional alternation exist autocrine and paracrine effects and these effects would be attenuated by the anatomic distance away from the myocardium. We showed that this effect exhibits in PCF, stronger than TAT, and disappears in hepatic fat. In the clinical tests, PCF volume may be applied to be an independent predictor of subclinical heart failure in central obese. Till now, LV geometric remodeling and functional changes mediated by multiple potential mechanisms from visceral fat remains understand incompletely and requires further research to evaluate.

Table 1: Clinical characteristics according to tertiles of pericardial fat (PCF)

Variable	Tertile 1 (<65.1 mm)	Tertile 2 (65.2-91.2 mm)	Tertile 3 (> 91.2 mm)	*P* trend
Sample size	118	118	118	-
Baseline characteristics				
Male sex, n (%)	74 (62.7)	82 (69.5)	89 (75.4)	0.035
Age, year	50.9±8.5	51.4±8.6	52.5±9.2	0.123
Systolic blood pressure, mmHg	118.4±18.8	122.0±15.9	124.9±15.2	0.002
Diastolic blood pressure, mmHg	74.8±10.8	76.3±10.7	77.3±9.9	0.048
Body mass index, kg/m^2	23.7±2.5	24.7±3.2	25.1±2.9	<0.001
Biochemical data				
Fasting glucose, mg/dL	99.0±24.5	98.9±16.3	101.8±17.5	0.024
HbA1c, %	5.92±0.84	5.95±0.74	6.03±0.67	0.034
Total cholesterol, mg/dL	201.6±35.6	204.5±38.2	191.9±34.2	0.047
Triglyceride, mg/dL	139.3±86.4	149.8±89.8	131.2±69.9	0.866
Low-density lipoprotein, mg/dL	132.5±32.4	133.9±33.9	126.4±28.9	0.174
High-density lipoprotein, mg/dL	51.7±13.1	50.5±13.1	47.6±12.9	0.021
eGFR, mL/min/1.73m^2	85.1±15.1	87.2±16.2	83.9±19.2	0.354
hs-CRP, mg/dL	0.15±0.18	0.22±0.34	0.26±0.35	0.003
Coronary calcium score	17.5±78.3	37.3±161.3	40.4±149.2	<0.001
Metabolic score	1.36±1.23	1.76±1.31	1.96±1.31	<0.001
Nt-ProBNP (pg/mL)	49.2±51.9	49.8±61.7	43.7±56.6	0.428
Comorbidities				
Hyperlipidemia, n (%)	11 (9.3)	18 (15.3)	15 (12.7)	0.431
Hypertension, n (%)	24 (20.3)	31 (26.3)	39 (33.1)	0.027
Diabetes mellitus, n (%)	12 (10.2)	17 (14.4)	21 (17.8)	0.093
Echo parameters				
IVS, mm	9.4±1.2	9.6±1.2	10.0±1.2	<0.001
LVPWT, mm	9.1±1.1	9.4±1.2	9.9±1.2	<0.001
LVEDV, mL	99.0±17.0	102.9±16.6	108.3±19.4	0.001
LVEDV/ht$^{2.7}$, ml/ht$^{2.7}$	26.3±4.0	26.6±3.8	27.1±4.4	0.32
LVESV, mL	30.7±6.4	32.0±6.1	34.6±8.1	<0.001
LVESV/ht$^{2.7}$, ml/ht$^{2.7}$	8.1±1.5	8.3±1.4	8.6±1.9	0.059
LV mass, g/m^2	145.7±32.8	155.1±35.5	170.7±40.8	<0.001
LV mass/ht$^{2.7}$, g/ht$^{2.7}$	38.5±7.6	40.0±8.3	42.6±9.6	0.002
LV mass to volume ratio	1.47±0.21	1.51±0.23	1.57±0.22	<0.001
LVEF, %	69.1±2.9	68.8±3.3	68.2±3.4	0.069
FS mmw, %	0.21±0.02	0.21±0.02	0.20±0.02	0.014
FS endo, %	38.8±2.31	38.6±2.57	38.2±2.67	0.152
LA diameter, mm	29.9±3.8	31.4±4.4	32.9±4.0	<0.001

eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein;; b-type natriuretic peptide; IVS, interventricular septum; LVPWT, left ventricular posterior wall thickness; BSA: body surface area; LVEDV, left ventricular end diastolic volume; LVESV, left ventricle end systolic volume; LVEF, left ventricular ejection fraction; FS mmw, middle myocardial wall; FS endo, endocardial fractional shortening; LVMI, left ventricular mass index;

LA, left atrial

Table 2: Clinical characteristics according to tertiles of thoracic periaortic fat (TAT)

Variable	Tertile 1 (<6.28 mm)	Tertile 2 (6.28-9.22 mm)	Tertile 3 (> 9.22 mm)	*P* trend
Sample size	117	119	118	-
Baseline characteristics				
Male sex, n (%)	71 (60.7)	89 (74.8)	85 (72.0)	0.06
Age, year	51.5±7.6	51.1±8.6	52.3±9.9	0.923
Systolic blood pressure, mmHg	120.8±18.1	120.6±16.0	123.9±16.3	0.072
Diastolic blood pressure, mmHg	76.2±10.3	76.2±11.1	75.9±10.2	0.918
Body mass index, kg/m^2	24.2±2.6	24.3±3.1	25.0±2.9	0.038
Biochemical data				
Fasting glucose, mg/dL	100.2±23.7	98.8±17.2	100.8±17.9	0.82
HbA1c, %	5.92±0.85	5.98±0.78	6.00±0.63	0.097
Total cholesterol, mg/dL	204.8±37.7	201.0±35.6	192.2±34.8	0.004
Triglyceride, mg/dL	140.7±86.2	139.8±79.2	139.5±82.8	0.974
Low-density lipoprotein, mg/dL	134.8±32.5	132.2±32.2	125.8±30.4	0.021
High-density lipoprotein, mg/dL	51.3±13.4	50.4±12.9	48.0±12.9	0.092
eGFR, mL/min/1.73m^2	87.0±13.9	85.2±16.7	84.0±19.7	0.081
hs-CRP, mg/dL	0.16±0.17	0.20±0.31	0.27±0.38	0.029
Coronary calcium score	14.2±42.2	32.7±159.1	48.2±164.3	0.003
Metabolic score	1.5±1.3	1.6±1.2	2.0±1.3	0.003
Nt_ProBNP (pg/mL)	47.1±46.0	41.8±59.0	52.2±62.9	0.982
Comorbidity				
Hyperlipidemia, n (%)	11 (9.4)	18 (15.1)	15 (12.7)	0.417
Hypertension, n (%)	30 (25.6)	29 (24.4)	35 (29.7)	0.794
Diabetes mellitus, n (%)	12 (10.3)	17 (14.3)	21 (17.8)	0.732
Echo parameters				
IVS, mm	9.5±0.1	9.7±0.1	9.8±0.1	0.219
LVPWT, mm	9.2±0.1	9.5±0.1	9.7±0.1	0.001
LVEDV, mL	99.5±1.5	102.6±1.6	108.1±1.8	0.001
LVEDV/ht$^{2.7}$, ml/ht$^{2.7}$	26.3±3.6	26.2±4.3	27.4±4.2	0.061
LVESV, mL	30.9±0.6	32.0±0.6	34.4±0.7	0.002
LVESV/ht$^{2.7}$, ml/ht$^{2.7}$	8.1±1.3	8.2±1.7	8.7±1.8	0.013
LV mass, g/m^2	148.8±3.1	156.5±3.5	166.1±3.7	0.002

LV mass/ht$^{2.7}$, ml/ht$^{2.7}$	39.3±8.1	39.8±8.9	42.0±9.7	0.014
LV mass to volume ratio	1.49±0.02	1.52±0.02	1.53±0.02	0.176
LVEF, %	69.0±0.3	68.8±0.3	68.3±0.3	0.179
FS mmw, %	20.8±0.1	20.7±0.1	20.7±0.1	0.256
FS endo, %	38.7±0.2	38.6±0.2	38.3±0.2	0.281
LA diameter, mm	30.9±4.0	31.3±4.5	32.1±4.2	0.061

eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; b-type natriuretic peptide; IVS, interventricular septum; LVPWT, posterior wall thickness; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESV, left ventricle end systolic volume; LVESV: left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; FS mmw, middle myocardial wall; FS endo, endocardial fractional shortening; LVMI, left ventricular mass index; LA, left atrial

Table 3: Clinical characteristics according to fatty liver grade

Variable	Grade 0	Grade 1	Grade 2-3	*P* trend
Sample size	212	80	62	-
Baseline characteristics				
Male sex, n (%)	148 (69.8)	49 (61.3)	42 (76.4)	0.742
Age, year	51.2±8.2	51.6±9.2	53.7±9.9	0.171
Systolic blood pressure, mmHg	120.1±16.6	125.1±17.5	123.6±17.2	0.136
Diastolic blood pressure, mmHg	75.7±10.7	77.5±10.0	76.1±10.8	0.77
Body mass index, kg/m^2	24.1±3.0	25.5±2.5	24.8±2.7	0.003
Biochemical data				
Fasting glucose, mg/dL	98.3±21.2	100.6±14.1	105.1±21.5	0.001
HbA1c, %	5.95±0.79	5.87±0.48	6.22±0.87	0.009
Total cholesterol, mg/dL	200.1±37.4	197.3±33.3	200.1±35.6	0.972
Triglyceride, mg/dL	128.7±78.8	152.6±81.0	162.8±91.2	<0.001
Low-density lipoprotein, mg/dL	130.9±32.5	130.6±30.5	132.2±30.0	0.825
High-density lipoprotein, mg/dL	51.9±14.2	47.2±11.2	46.7±9.8	0.002
eGFR, mL/min/1.73m^2	85.1±16.3	88.7±17.6	80.8±17.4	0.31
hs-CRP, mg/dL	0.20±0.33	0.21±0.26	0.26±0.31	0.006
Coronary calcium score	15.9±60.9	26.9±164.3	99.6±239.9	0.002
Metabolic score	1.36±1.21	2.28±1.14	2.18±1.43	<0.001
Nt-ProBNP (pg/mL)	47.5±58.9	48.8±55.3	43.4±51.4	0.776
Comorbidity				
Hyperlipidemia, n (%)	21 (9.9)	7 (8.8)	16 (29.1)	0.001
Hypertension, n (%)	50 (23.6)	30 (37.5)	13 (23.6)	0.413
Diabetes mellitus, n (%)	23 (10.8)	13 (16.3)	13 (23.6)	0.013
Echo parameters				
IVS, mm	9.6±1.3	9.6±1.1	9.8±1.0	0.347
LVPWT, mm	9.4±1.3	9.6±1.1	9.7±1.1	0.148
LVEDV, mL	102.7±18.7	104.7±15.9	103.9±18.7	0.462

LVEDV/ht$^{2.7}$, ml/ht$^{2.7}$	26.5±4.3	27.4±3.4	27.2±4.2	0.857
LVESV, mL	32.1±7.3	32.5±6.6	33.6±7.4	0.117
LVESV/ht$^{2.7}$, ml/ht$^{2.7}$	8.3±1.6	8.5±1.4	8.4±1.7	0.371
LV mass, g/m^2	156.0±41.3	158.4±32.1	160.5±32.9	0.28
LV mass/ht$^{2.7}$, g/ht$^{2.7}$	40.1±9.4	41.4±7.4	40.1±6.7	0.857
LV mass to volume ratio	1.51±0.23	1.51±0.20	1.55±0.22	0.248
LVEF, %	68.9±3.0	69.0±3.0	67.6±4.1	0.123
FS mmw, %	0.21±0.02	0.21±0.01	0.20±0.02	0.193
FS endo, %	38.6±2.37	38.8±2.33	37.7±3.17	0.21
LA diameter, mm	31.2±4.2	31.7±4.5	32.3±4.0	0.112
Pericardial fat, mm	77.7±24.7	86.2±28.7	84.7±27.4	0.023
Thoracic periaortic fat, mm	7.9±3.5	8.3±3.8	9.0±4.4	0.146

eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; b-type natriuretic peptide; IVS, interventricular septum; PWT, posterior wall thickness; LVEDV, left ventricular end diastolic volume; LVESV, left ventricle end systolic volume; LVEF, left ventricular ejection fraction; FS mmw, middle myocardial wall; FS endo, endocardial fractional shortening; LVMI, left ventricular mass index; LAVI, left atrial volume index; LAV; left atrial volume.

Table 4: The association of PCF, TAT, grading of fatty liver with LV structure changes

	Pericardial fat (PCF)		**Thoracic peri-aortic fat (TAT)**		**Fatty liver grade**	
Predictor	ß coefficient(SE)	*p* value	ß coefficient(SE)	*p* value	ß coefficient(SE)	*p* value
IVS, mm						
Univariate	0.220(0.052)*	<0.001	0.138(0.053)*	0.009	0.051(0.054)	0.349
Multivariate						
Model 1	0.126(0.049)*	0.011	0.056(0.049)	0.258	-0.009(0.050)	0.857
Model 2	0.106(0.050)*	0.033	0.042(0.050)	0.398	-0.012(0.051)	0.807
Model 3	0.134(0.059)*	0.025	0.120(0.058)*	0.041	0.012(0.060)	0.84
LVEDV, ml						
Univariate	0.254(0.052)*	<0.001	0.238(0.052)*	<0.001	0.036(0.054)	0.506
Multivariate						
Model 1	0.131(0.043)*	0.003	0.142(0.043)*	0.001	-0.027(0.044)	0.531
Model 2	0.111(0.044)*	0.012	0.116(0.043)*	0.008	-0.039(0.045)	0.381
Model 3	0.134(0.054)*	0.014	0.147(0.053)*	0.006	-0.045(0.054)	0.407
LV mass index, gm						
Univariate	0.239(0.032)*	<0.001	0.22(0.227)*	<0.001	0.051(0.054)	0.35
Multivariate						
Model 1	0.19(0.031)*	<0.001	0.177(0.218)*	0.001	-0.027(0.044)	0.623
Model 2	0.147(0.031)*	0.004	0.134(0.222)*	0.008	-0.033(0.045)	0.465
Model 3	0.173 (0.039)*	0.005	0.19(0.265)*	0.002	-0.013(0.054)	0.811

LV mass to volume ratio						
Univariate	0.192(0.052)*	<0.001	0.124(0.053)*	0.019	0.071(0.054)	0.188
Multivariate						
Model 1	0.122(0.052)*	0.019	0.062(0.052)	0.227	0.025(0.052)	0.627
Model 2	0.095(0.052)	0.068	0.043(0.052)	0.401	0.021(0.053)	0.688
Model 3	0.128(0.062)*	0.039	0.122(0.061)*	0.045	0.061(0.062)	0.33
LA diameter, mm						
Univariate	0.287(0.052)	<0.001	0.175(0.052)	0.001	0.079(0.054)	0.142
Multivariate						
Model 1	0.189(0.048)*	<0.001	0.084(0.048)	0.081	0.004(0.049)	0.932
Model 2	0.175(0.049)*	<0.001	0.070(0.049)	0.155	-0.016(0.050)	0.756
Model 3	0.125(0.055)*	0.024	0.105(0.054)	0.052	0.035(0.055)	0.529

Model 1 adjusted for age, sex, body mass index

Model 2 adjusted for age, sex, body mass index, systolic blood pressure, fasting glucose, estimated glomerular filtration rate, total cholesterol and high-density lipoprotein

Model 3 adjusted for age, sex, body mass index, systolic blood pressure, fasting glucose, estimated glomerular filtration rate, total cholesterol,

high density lipoprotein, hypertension, and diabetes mellitus

IVS: interventricular septum; LVEDV: left ventricular end-diastolic volume; LV: left ventricular

* $P< 0.05$.

Figure1: Association between tertiles of pericardial fat and cardiac structure changes

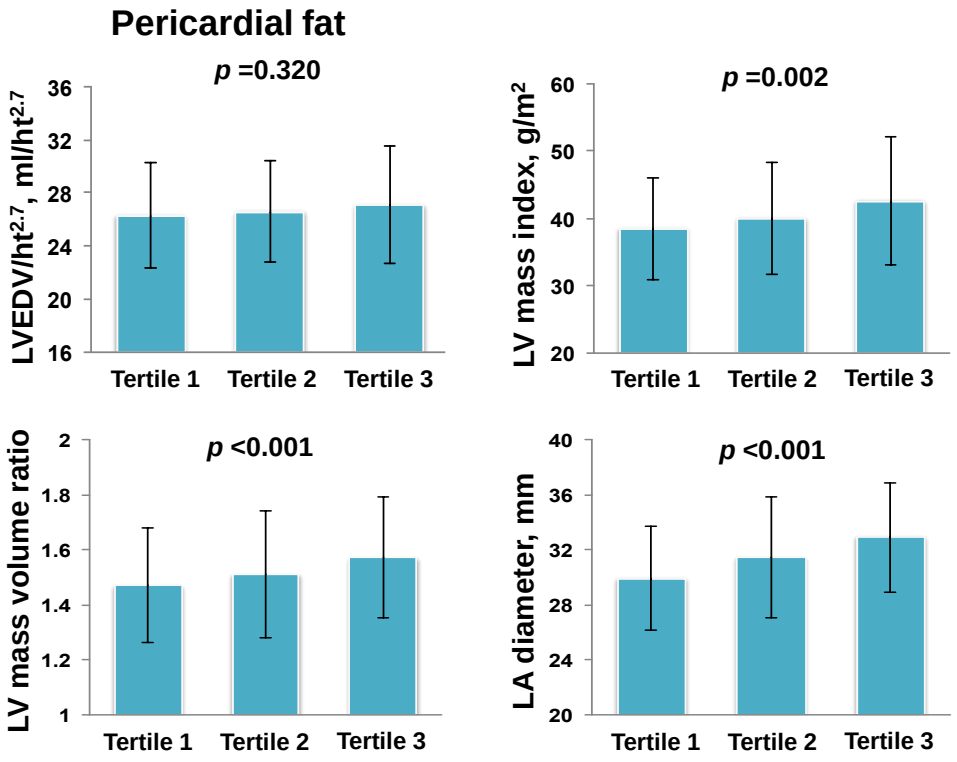
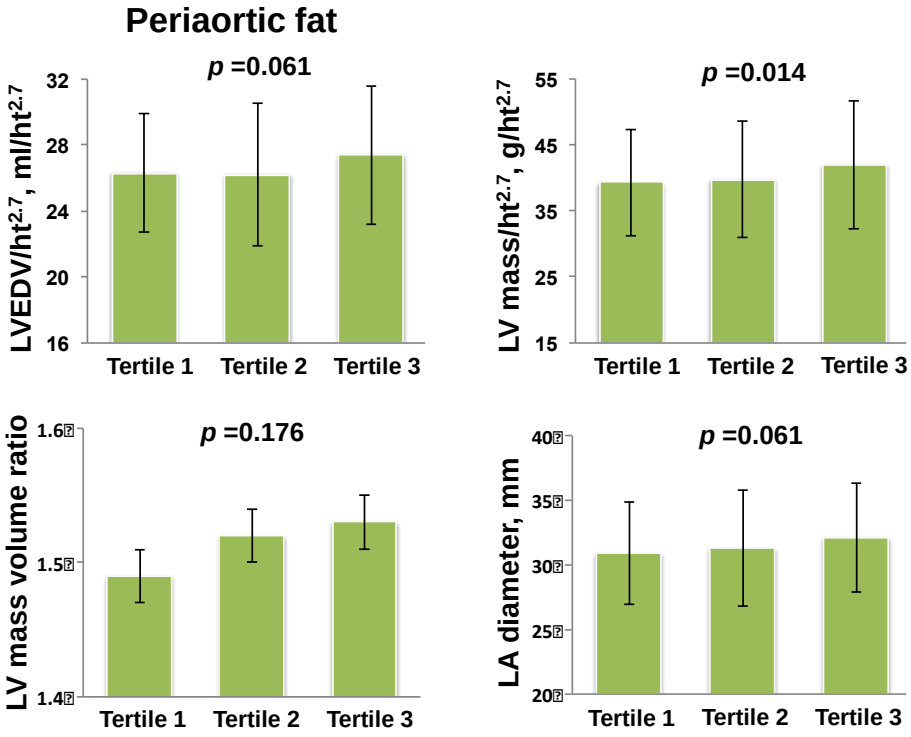


Figure2: Association between tertiles of periaortic fat and cardiac structure changes



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