学位論文全文要約

Impact of the distribution of epicardial and visceral adipose tissue on left ventricular diastolic function

（左室拡張機能における心外膜および内臓脂肪の分布の影響）

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Introduction

Left ventricular (LV) diastolic function has been recognized as an important marker of heart failure development. Obesity particularly with visceral fat accumulation has been reported to be associated with LV diastolic dysfunction (LVDD) in addition to aging, hypertension, diabetes, ischemic heart disease, and atrial fibrillation. Ectopic adipose tissue accumulates various parts of body such as abdomen and epicardium. The abdominal visceral adipose tissue (VAT) and epicardial adipose tissue (EAT) are metabolically active and can secret some adipokines resulting in systemic inflammation, development of coronary artery disease (CAD), and inducible LV structural and functional alteration. The evidence has been accumulating on the association between increased EAT and LVDD. Previous studies have suggested the differences in the impact of distribution of VAT on coronary artery plaque. Both abdominal VAT and EAT can contribute to LVDD, but the impact of their distribution on LV diastolic function has not yet been fully elucidated. Therefore, we sought to evaluate the distribution of EAT and VAT and to investigate its association with LVDD assessed by tissue Doppler echocardiography. We hypothesized that the impact of the EAT on LVDD varies depending on the amount of VAT.

Methods

Study design and population

This is the single center cross-sectional study. We retrospectively examined the patients who were underwent both cardiac computed tomography (CT) angiography and echocardiography within a month between January 2007 and December 2013 for suspected ischemic heart disease. We included the patients with complete echocardiographic studies including tissue Doppler examination (bilateral early diastolic mitral annular velocity; e'). The patients with the following factors were excluded from the analysis: reduced LV contraction (LV ejection fraction <50 %), significant valvular heart disease more than moderate grade, significant mitral annular calcification (grade ≥2+), atrial fibrillation, asymmetrical LV hypertrophy,

primary cardiomyopathy, infiltrative cardiomyopathy such as cardiac amyloidosis, presence of pericardial disease, history of myocardial infarction and history of cardiac surgery.

Clinical status and Laboratory Data

We investigated the geographic and clinical information of all the subjects including comorbidity and medication from medical record. Hypertension was defined as a patient systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or the current use of antihypertensive treatments. Dyslipidemia was defined as a low-density lipoprotein (LDL) cholesterol level ≥140 mg/dl on direct measurement, a total cholesterol level ≥220 mg/dl, or the current use of lipid-lowering drugs. Diabetes mellitus was defined by self-reporting, a glycohemoglobin A1c (HbA1c) level ≥6.5%, or the current use of hypoglycemic agents. Patients who smoked regularly during the previous year were classified as current smokers.

Evaluation of visceral adipose tissue and coronary artery on CT image

Measurement of abdominal visceral adipose tissue

A 64-slice CT scanner (LightSpeed VCT, GE Healthcare, Waukesha, Wisconsin, USA) was used for the CT examination. Prior to coronary scanning, plain abdominal scans were performed at the 4th and 5th lumbar levels in the spinal position. We measured the abdominal VAT area at the level of umbilicus using commercial software (Virtual Place, AZE INC., Tokyo, Japan). We defined the intraperitoneal adipose tissue area with a CT density between −150 and −50 Hounsfield units as the VAT area.

Measurement of epicardial adipose tissue

Non-contrast cross-sectional scans with 2.5-mm slice thickness were used for EAT measurement. The EAT was defined as the adipose tissue between the epicardial surface of the myocardium and the pericardium with a density range between −250 and −30 Hounsfield units, and was automatically quantified using the same software as for the abdominal VAT. EAT volume was calculated as the total sum of the EAT

areas from the atrial appendage (*i.e.*, 1 cm above the left main coronary artery) to the apex with 1-cm thick spacing between each image. We corrected VAT area and EAT volume by body surface area and used as adiposity markers (VAT area index and EAT volume index, respectively).

Coronary CT angiography

Patients took orally 40 mg metoprolol 60 minutes before CT examination if the heart rate at rest was more than 60 beats/min, and then received 0.3 mg nitroglycerin just before scanning. Contrast-enhanced scanning was performed with the scan protocol and reconstruction methods previously described. The images were reconstructed with image-analysis software (CardIQ, GE Healthcare) on a dedicated computer workstation (Advantage Workstation Ver.4.2, GE Healthcare). Two experienced observers evaluated independently all coronary segments with >2 mm in diameter using curved multiplanar reconstructions and cross-sectional images rendered perpendicularly to the vessel center line. We defined a cross-sectional narrowing 75 % or more in epicardial coronary arteries as obstructive CAD.

Echocardiographic measurements

Echocardiography, including Doppler and tissue Doppler imaging, was performed by an experienced sonographer using an iE33 ultrasound system equipped with an S3 transducer (Philips Medical Systems, Andover, MA). LV ejection fraction was measured by Simpson's biplane method. LV mass was calculated by the following formula: LV mass=0.8×1.04((interventricular septum + LV internal diameter + inferolateral wall thickness)^3−(LV internal diameter)^3) +0.6 g indexed for body surface area (LV mass index: LVMI). Left atrial volume was measured in end systolic apical four and two chamber view using biplane disk summation method. Mitral inflow velocity was recorded using pulsed-wave Doppler echocardiography in apical three-camber view, and we measured trans-mitral early (E) and late (A) diastolic velocities at the leaflet tips. The early diastolic mitral annular velocity was measured by Doppler imaging with the sample volume positioned in the septal (septal e′) and lateral (lateral e′) mitral annulus in apical four-chamber view. We calculated the ratio of E to averaged e' velocity (E/e') and averaged the septal and lateral E/e'. Tricuspid

valve regurgitation velocity (TRV) was measured by continuous Doppler method. We used septal and lateral e', averaged E/e', indexed left atrial volume (LAVI) and TRV as the marker of the LV diastolic function.

Statistical Analysis

Statistical analyses were performed using EZR software version 1.36 (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html). A *p*-value of <0.05 was considered statistically significant. Categorical variables were expressed as number (%), and continuous variables as mean (±SD) or median (interquartile range: 25%, 75%). We performed Kolmogorov-Smirnov test to confirm the normal distribution and converted to natural logarithm if necessary. Pearson's correlation was calculated to confirm the correlation between VAT area index or EAT volume index and each component of diastolic function (bilateral e', E/e', LAVI and TRV). We performed univariate (model 1) and multivariate (model 2 and 3) linear regression analysis to examine the associations between these components and VAT area index. In the multivariate linear regression analyses, we adjusted by the patients' background and the conventional cardiovascular risk factors which can contribute to LV diastolic function including age, sex, body mass index, hypertension, dyslipidemia, and diabetes (model 2). In addition to the independent variables in model 2, obstructive CAD was adjusted in model 3. We also examined the association between these components and EAT volume index with similar procedure (model 1', 2' and 3'). Then, we confirmed whether EAT volume index was associated with LV diastolic function independently of VAT area index. Subgroup analysis was performed to investigate whether abdominal VAT affected the association of EAT and LVDD. The subjects were divided into two groups by the median value of VAT area index and the association of EAT volume index with LVDD was confirmed in each subgroup.

Result

A total of 411 patients underwent both cardiac CT angiography and echocardiography within the periods.

Of these 267 patients underwent complete echocardiographic studies including tissue Doppler examination. The following factors excluded patients from the analysis: reduced LV contraction (n = 15), significant valvular heart disease (n = 4), atrial fibrillation (n = 6), asymmetrical LV hypertrophy (n = 6), and the presence of pericardial disease (n = 1). There was no patient with history of cardiac surgery among the 267 patients. Finally, 235 patients were considered eligible for enrollment in this study. TRV was available only in 92 patents.

The association of abdominal VAT with LV diastolic function

VAT area index was significantly correlated with bilateral e' velocity, averaged E/e' and LAVI, while not with TRV (p = 0.29, n = 92). The results of linear regression analysis to investigate the association between e' and VAT area index are tested. In univariate analysis, higher VAT area index was significantly associated with bilateral e' impairment, E/e' and LAVI (model 1). The significant association were observed only in e' velocity after adjustment for conventional cardiovascular risk factors (model 2) and obstructive CAD (model 3).

The association of EAT with LV diastolic function

EAT volume index was not normally distributed, so we converted EAT volume index to natural logarithm (ln EAT volume index). A normal distribution was confirmed for ln EAT volume index. The ln EAT volume index significantly correlated with bilateral e', averaged E/e' and LAVI, while not with TRV (p = 0.35, n = 92). We performed the similar linear regression analysis to investigate the association between ln EAT volume index and e' velocity, E/e' and LAVI. There was a significant association of ln EAT volume index with decreased septal and lateral e' and higher E/e' and increased LAVI (model 1'). Higher ln EAT volume index was the independent determinant of decreased bilateral e' and increased LAVI in multivariate analysis adjusted for conventional cardiovascular risk factors (model 2') and obstructive CAD (model 3').

Impact of abdominal VAT on the association between EAT and e' velocity

We added VAT area index as the independent variable to the model 3'. There were significant association of ln EAT volume index with e' impairment independently of VAT area index. However, no significant association was observed in averaged E/e' and LAVI. Then we divided VAT area index to two groups by the median value and performed a subgroup analysis. There was significant correlation of ln EAT volume index with septal e' only in the lower VAT group. In contrast, ln EAT volume index was correlated with lateral e' in both VAT subgroups. E/e' did not correlated with ln EAT volume index in both subgroups. LAVI correlated with ln EAT volume index only in the higher VAT group. In multivariate linear regression analysis, higher ln EAT volume index was significantly associated with both septal and lateral e' impairment in the lower VAT group; whereas it was associated only with lateral e' and not with septal e' in the higher VAT group. E/e' was not associated with ln EAT volume index in both subgroups. There was significant association between ln EAT volume index and LAVI only in the higher VAT group.

Discussion

In the present study, the higher VAT area index was significantly associated with e' velocity independently of conventional cardiovascular risk factors and obstructive CAD. The higher ln EAT volume index was significantly associated with e' velocity and LAVI independently of these factors. Moreover, there was significant association of the higher ln EAT volume index with e' velocity even after adjusting for the VAT area index. In the subgroup analysis, the ln EAT volume index was significantly associated with lateral e' regardless of the amount of VAT. Interestingly, there was no association between the ln EAT volume index and septal e' in higher VAT area index subgroup. Meanwhile, the ln EAT volume index was associated with LAVI only in higher VAT.

Significance of LVDD in heart failure and determinants of LVDD

The previous observational study reported that half of the patients with heart failure (HF) had normal

ejection fraction. In Japan, the proportion of HF with preserved ejection fraction (HFpEF) has been increasing over time and expected to continue to increase with an aging society.

The diagnosis of HFpEF is generally based on the combination of clinical symptoms and/or signs of heart failure, normal LV ejection fraction, and LVDD. Detection of LVDD not only helps for diagnosing HFpEF but also can be a marker of prognosis. Aging, hypertension, diabetes, myocardial ischemia, obesity, and metabolic syndrome have been reported to be the determinants of LV diastolic function. Here, we confirmed the impact of EAT, VAT and those distribution on LVDD in this study.

Ectopic fat accumulation and LVDD

In the present study, VAT area index was significantly associated with decreased e' velocity. The previous study evaluating the relationship between visceral adiposity and LVDD in community-dwelling volunteers presented significant association of abdominal VAT with e' velocity independently of subcutaneous fat and cardiovascular risk factors. Although it has been shown that VAT is a risk factor for CAD, VAT area index was associated with impaired e' velocity independently of CAD in this study. In this study, VAT area was not associated with E/e' and LAVI as in the previous study. There was no association between VAT area and TRV although no previous report was found.

This study also showed that increased EAT was significantly associated with e' velocity impairment and LA enlargement, which is consistent with previous studies. The association between EAT and E/e' was no longer observed when adjusting for patient background. There was no association between EAT and TRV. Larger amount of the EAT has been reported to be associated with coronary artery atherosclerosis and plaque vulnerability and CAD can modify the association between EAT and LVDD. While Topuz, et al. reported that EAT was associated with LVDD in the patients with normal coronary artery. In this study, the significant association between increased EAT and impaired e' velocity or increased LAVI were independent of obstructive CAD.

The impact of distribution of EAT and abdominal VAT on LVDD

The higher ln EAT volume index was associated with impaired bilateral e' after adjusting the VAT area index in this study. In our subgroup analysis, only lateral e' was significantly associated with ln EAT volume index in the higher amount of the abdominal VAT group. To the best of our knowledge, few studies have directly examined the difference between the effects of EAT and abdominal VAT on LV function. Oikawa et al. reported that the EAT had a stronger effect on coronary calcium and coronary plaque than the abdominal VAT. Although both abdominal VAT and EAT contribute to the development of atherosclerosis or LV remodeling by secreting proinflammatory cytokines, the EAT may affect LV relaxation more strongly due to its proximity. The mechanical effect can also contribute because EAT has direct contact with myocardium with no separation by the pericardium. In the previous study investigating the association of EAT localization with LVDD, EAT on the LV lateral wall were more strongly associated with LVDD, and significantly associated not with septal e' but with lateral e'. Interestingly, EAT was significantly associated with LAVI only in higher VAT subgroup, suggesting a possible interaction between EAT and VAT on left atrial enlargement.

A recent study has reported that the EAT surrounding the atrium was significantly larger in paroxysmal atrial fibrillation group than in CAD group and healthy group and the ratio of atrium to ventricle EAT was significant associated with Atrial volume. The localization of EAT also may be an important factor related with LA remodeling.

Clinical implication

The diagnosis of HFpEF is mostly based on the signs and symptoms of congestion at rest. While, it has been challenging to detect the early stage of HFpEF, in which there was no congestive findings at rest, but increased intracardiac pressure presents during exercise and reduced exercise tolerance exists. In the recent study that examined the factors estimating the prevalence of such early HFpEF, obesity with body mass index $\geq$30 kg/m2 was one of the predictors. Obokata, et al. showed that the EAT was increased in

HFpEF group particularly with higher BMI compared to healthy control. They discussed that there is one of the phenotypes of HFpEF with pericardial constriction related with EAT. In this study, EAT was associated with impaired LV relaxation independently of body mass index. The regional adipose deposition may have an additional diagnostic value beyond total body adiposity in obese patients with HFpEF. Although there has not been an established therapeutic strategy targeting the ectopic fat, the interventions focusing on lifestyle modifications may be effective in patients with VAT and EAT, as it has been suggested that it may be a risk for the development of heart failure.

Limitation

This study had some limitations. First, this was single center, relatively small number cross sectional study. Secondly, we did not investigate the influence of inflammatory cytokines or adipokines on the association between EAT or VAT and LVDD. Third, we evaluated LV diastolic functional class based on the recent guideline in this study. However, we could obtain the TRV in the limited number of patients because majority of the patients did not have significant tricuspid regurgitation. Fourth, we could not confirm the detailed exercise capacity or functional class of HF in the medical records. Our patients were thought to have some cardiovascular risk factors but not have overt signs of heart failure. We were afraid that the severity of LVDD could not be determined due to the higher proportion of intermediate grade of the guideline. We therefore evaluated the association between individual components of LV diastolic function and ectopic fat accumulation.

Among the determinant factors of LVDD based on the guideline, E/e' and TRV reflect the information of the intracardiac pressure. LAVI reflects higher LV end diastolic pressure too, but it is also a marker of the LA deformation and remodeling. Moreover, e' velocity is an indicator of the LV myocardial relaxation, so it was thought to consistent with our purpose of the study estimating the impact of ectopic fat on LV myocardium itself. In addition, this study included the patients only with sinus rhythm and preserved ejection fraction. Our data is difficult to be applied to all situation due to the limited population.

Conclusions

EAT accumulation was significantly associated with e' velocity and LAVI independently of cardiovascular risk factors and obstructive CAD, and more strongly compare to abdominal VAT. The impact of EAT on LVDD may vary depending on the amount of abdominal VAT.