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【 ORIGINAL ARTICLE 】

Pulmonary Artery Diameter (PAD) and the Pulmonary Artery to Aorta Ratio (PAD/AAD) as Assessed by Non-contrast Cardiac CT: The Association with Left Ventricular (LV) Remodeling and the LV Function

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Abstract:

Objective Dilatation of the pulmonary artery itself (PAD: pulmonary artery diameter) or in relation to the ascending aorta (PAD/AAD: pulmonary artery diameter to ascending aortic diameter ratio) has been reported to be associated with pulmonary hypertension and with a prognostic outcome of either heart failure or cardiovascular events. We herein aimed to assess the correlations between pulmonary hypertension-related parameters PAD (or PAD/AAD) and left ventricular (LV) remodeling and LV function.

Methods This retrospective study included 193 patients (ages: 67±12 years) who underwent both coronary CT angiography (CCTA) and echocardiography. The PAD and the AAD were measured on a transaxial non-contrast CCTA image at the level of the pulmonary artery bifurcation. Left ventricular mass (LVM), relative wall thickness ratio (RWT), left ventricular ejection fraction (LVEF), left atrial volume (LAV), and early mitral inflow velocity to mitral annular early diastolic velocity ratio (E/e') were evaluated by echocardiography. The relationships between PAD (or PAD/AAD) and echocardiography parameters were assessed, and adjusted for the demographic data and cardiovascular disease (CVD) risk factors by a multivariable linear regression analysis.

Results PAD (mean±SD: 2.6±0.4 cm) was positively correlated with LVM (r=0.34, p<0.001), LAV (r=0.41, p<0.001), and E/e' (r=0.29, p<0.001). PAD/AAD (mean±SD: 0.76±0.12 cm) was positively correlated with LVM (r=0.12, p=0.09), LAV (r=0.24, p<0.001), and E/e' (r=0.15, p=0.04). These correlations remained significant after adjusting for demographic data and CVD risk factors. PAD (or PAD/AAD) did not correlate with LVEF or RWT (p>0.05).

Conclusion Greater PAD or PAD/AAD is significantly associated with LV remodeling and an impaired LV function.

Key words: pulmonary artery diameter, computed tomography, cardiac remodeling, cardiopulmonary interaction

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Introduction

The main pulmonary artery (PA) and the aorta are routinely imaged with chest computed tomography (CT). Previous studies have reported an increased main pulmonary artery diameter (PAD) and an increased ratio to the ascending aorta (PAD/AAD) as markers for pulmonary hypertension (PH), as the main PA accommodates increased pulmonary artery pressure (1, 2).

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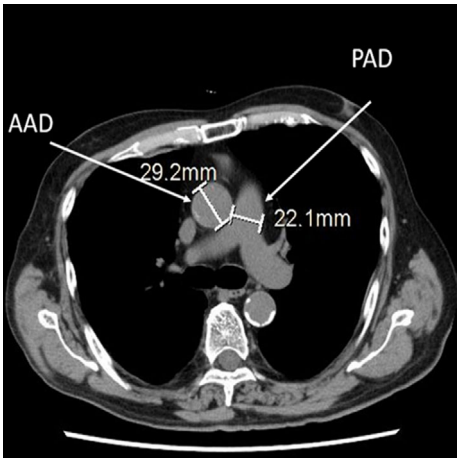

Figure 1. PAD and AAD measurements. Measurements were performed on a non-contrast trans-axial CT image at the level of the pulmonary artery bifurcation.

PH is prevalent among patients with heart failure (HF) and left heart diseases are the most common causes of PH, accounting for 65-80% of PH cases (3). Previous studies have reported that the pulmonary artery pressure strongly predicts an adverse outcome among patients with HF (4, 5). Moreover, PAD/AAD, the indicator for the presence of PH, has also been reported as a predictor of the outcome among patients with heart failure (6).

Identifying heart failure at its earliest and preclinical stages leads to early treatment, thereby preventing and delaying the onset of severe symptoms. Cardiac remodeling is the process of structural and functional changes in the left ventricle in response to cardiovascular damage or pathogenic risk factors, and precedes clinical heart failure (7, 8). Cardiac remodeling as presented with cardiac hypertrophy has prognostic value for future adverse cardiovascular events (9). Cardiac remodeling and an impaired cardiac function are related to an increased PA pressure mainly through passive backward transmission of left-sided filling pressure (3, 10).

Based on these results, we hypothesized that the easily measureable variables of PAD or PAD/AAD are potential markers for structural and functional changes in cardiac remodeling - a precursor of clinical left ventricle failure. We herein investigated whether PAD and its ratio to AAD as assessed by non-contrast CT are associated with LV remodeling and the LV function after adjusting for demographic and cardiovascular disease (CVD) risk factors.

Materials and Methods

1. Patients

Four hundred forty-four patients with clinical indications for the assessment of CVD or the cardiac function who underwent both coronary CT angiography (CCTA) and echocardiography from August 2014 to March 2017 at a single university hospital were retrospectively studied. Patients with intervals of over a month between CCTA, echocardiography and blood test (n=77) were excluded. In addition, patients with cardiac diseases related to PAD and AAD measurement or echocardiography parameters measurement (thoracic aortic aneurysm, aortic dissection, aortic stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, atrial fibrillation and moderate or severe mitral regurgitation) were excluded (n=16). Nineteen patients with coronary artery stents and 142 patients who did not have sufficient data on the demographics or CVD risk factors data were not enrolled. A total of 193 patients were included in this study. This study was approved by the ethical review board for medical research involving human subjects in our institution, with informed consent waived.

2. CT data measurements

CCTA was performed following the standard protocol in our institution on a 320-detector CT scanner (Aquillion One Vision Edition, Canon medical systems, Otawara, Japan) with a prospective ECG-gatingin diatolic phase. The parameters of pre contrast phase are: detector configuration, 320×0.5 mm; gantry rotation time, 275 ms; tube potential, 120 kV; and tube current, from 270 mA to 550 mA depending on patient's body weight. A non-contrast axial scan was performed with the crania-caudal scan direction from the level of the carina to the bottom of the heart (FOV, 240 mm; slice thickness, 0.5 mm; reconstruction thickness, 3 mm; gap 0.5 mm).

PAD or AAD was defined as the largest diameter of the pulmonary artery or ascending aorta including the arterial lumens and walls. PAD and AAD were measured on the same slice at the level of the pulmonary artery bifurcation on a non-contrast transaxial image (Fig. 1). A radiologist with ten years of experience [H.N-T] measured PAD and AAD. Four weeks later, a second reader [T.N-C], a radiographer with ten years of experience, measured PAD and AAD on 48 patients from the total of 193 patients in the study to assess the inter-observer reproducibility. Twelve patients from each of the four years of the study were randomly selected, and measurements were made in random order by the second reader. The two readers' measurements were blinded to each other and to the clinical and echocardiography information.

3. Echocardiography data measurements

Echocardiography parameters were measured using the American Society of Echocardiography recommendations (11). Measurements of the LV dimensions (internal diameter and septal and posterior wall thicknesses in diastole) were acquired from 2D-guided M-mode echocardiography obtained from optimized parasternal short-axis views. Left ventricular mass (LVM) was calculated by the Devereux formula (12). The LV relative wall thickness (RWT) was calculated using the following equation: RWT=2*(LVPWd)/LVIDd, where LVPWd was the LV posterior wall diameter in diastole, and LVIDd was the LV internal diameter in dias-

tole (12).

The left ventricular ejection fraction (LVEF) was calculated by the Teichholz formula. The left atrial volume (LAV) was measured using the apical four-chamber view (12). For the diastolic functional parameters, the peak velocity of early phase (E) of the mitral flow using pulsed-Doppler echocardiography and the early peak diastolic mitral annular velocity (e') at the septal and lateral mitral annulus using tissue-Doppler echocardiography were evaluated (12). The e' was calculated from the average of the septal and lateral mitral annulus. E/e' was calculated as a parameter of LV filling pressure (12).

4. Cardiovascular disease risk factors

The patient characteristics were retrospectively collected from medical records. Hypertension is defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg or current use of antihypertensive medications. Diabetes mellitus is defined as casual blood glucose ≥200 mg/dL or HbA1c ≥6.5%, or being treated with insulin or oral hypoglycemic medications. The criteria for dyslipidemia is high-density lipoprotein cholesterol ≤40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, triglyceride ≥150 mg/dL or the current use of hypocholesterolemia drugs. CKD is defined as a glomerular filtration rate (eGFR) of lower than 60 mL/min/m^2. These CVD risk factors were evaluated within one month of both echocardiography and CCTA. The diagnosis for coronary artery disease including old myocardial infarction and angina pectoris was based on the CCTA findings. The diagnosis of chronic obstructive pulmonary disease (COPD) was obtained based on clinical reports. There were no cardiac events among the participants during the interval between CCTA and echocardiography.

5. Statistical analyses

The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used to assess the strength of the relationships between PAD or PAD/AAD and the echocardiography parameters. The body surface area (BSA) indexed values (PAD/BSA, LVM/BSA, LAV/BSA) and height indexed values (PAD/height, LVM/height, LAV/height) were used to evaluate the influence of body size on the echocardiography parameters. A multivariate linear regression analysis was used to evaluate these associations, after adjusting for demographic covariates [age, gender, BSA, and CVD risk factors (heart rate (HR), CKD, hypertension, diabetes mellitus, dyslipidemia, smoking and coronary heart disease]. In the model including PAD index, BSA or height was not involved to avoid any over-adjustment.

Statistical analyses were performed using the R software program (R version 3.3.2 and EZR version 1.35, The R project for statistical analysis computing). The GraphPad Prism software program version 6.0 was used for graphing (GraphPad software, La Jolla, USA). The inter-observer variability was described using the intra-class correlation coefficient (ICC) using the SPSS software program version 25 (SPSS, Chicago, USA), where ICC <0.4 represented poor reliability; ICC between 0.4 and 0.75, fair- to-good reliability; and ICC >0.75, excellent reliability (13). A value of $p<0.05$ was considered to be statistically significant.

Results

1. Baseline characteristics

The patient characteristics are shown in Table 1. The average age of the patients was 67.2 years with 35% women. The mean values ±SD of height, BSA and HR were 1.61±0.09 (m), 1.69±0.19 (m^2), and 69.4±13.2 (beat per minute; bpm), respectively. The mean value of PAD was 2.6±0.4 cm, AAD was 3.4±0.4 cm. Supplementary material 1 shows indexed to BSA and height values of the pulmonary arterial and aortic parameters and the echocardiography data. The ICC of PAD measurement was 0.976 (95% IC, 0.957-0.987, $p<0.001$) and the ICC of AAD measurement was 0.953 (95% IC, 0.915-0.974, $p<0.001$). Inter-observer reliability between two separate readers was excellent.

The interval between CCTA and echocardiography was 4.7 days (0 to 28 days).

2. Relationships of PAD, PAD/BSA, PAD/height with the echocardiography parameters

There were significant positive correlations of PAD with LVM, LAV and E/e' ($p<0.001$, $p<0.001$ and $p<0.001$, respectively), although PAD was not correlated with LVEF or RWT (Fig. 2, Table 2). Multivariate linear regression analyses suggested that PAD was independently correlated with LVM, LAV and E/e' (Table 2). These positive correlations persistent when PAD/BSA and PAD/height values were used instead of original values, even after adjusting for CVD risk factors (Supplementary material 2).

3. Relationships of the pulmonary artery to aorta ratio (PAD/AAD) with the echocardiography parameters

PAD/AAD had positive correlations with LVM, LAV and E/e' ($p=0.03$, $p<0.001$ and $p=0.04$) (Fig. 3, Table 2). In the results of the multivariate linear regression, these correlations remained significant after adjusting for all demographic data and CVD risk factors (Table 2). Similar to PAD, there were no correlations between PAD/AAD with RWT and LVEF ($p=0.7$ and $p=0.4$, respectively) (Table 2).

Discussion

In the present study, we investigated the correlations of PAD and its ratio to the aorta with LV remodeling and function. This study found that a larger PAD or PAD/AAD had a positive correlation with the development of LV remodeling with higher LVM, and impairment of the left ventricular dia-

Table 1. Patients' Characteristics (n=193) and Baseline Data.

Patients' characteristics	
Age (yrs)	67.2±11.8
Women, n	67 (35%)
Height (m)	1.61±0.09
BSA (m^2)	1.69±0.19
Heart rate (bpm)	69.4±13.2
COPD, n	7 (3.6%)
Coronary heart disease, n	32 (16.5%)
CKD, n	47 (24.2%)
Hypertension, n	129 (66.5%)
Systolic hypertension, n	67 (34.5%)
Diabetes, n	65 (33.5%)
Dyslipidemia, n	107 (55.2%)
Smoking, n	47 (24.2%)
Pulmonary artery and aorta parameters (mean±SD)	
PAD (cm)	2.6±0.4
AAD (cm)	3.4±0.4
PAD/AAD	0.76±0.12
Echocardiography data and CT angiography data	
LVM, median (0.25-0.75) (g)	144.5 (113.3-173.5)
RWT (mean±SD)	0.42±0.09
LVEF, median (0.25-0.75), %	65 (60-71)
LAV, median (0.25-0.75) (mL)	38 (29-51.8)
E/e' (mean±SD)	12.1±4.1

BSA: body surface area, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, PAD: pulmonary artery diameter, AAD: ascending aorta diameter, PAD/AAD: pulmonary artery to aorta ratio, LVM: left ventricular mass, RWT: relative wall thickness ratio, LVEF: left ventricular ejection fraction, LAV: left atrial volume, E/e': early mitral inflow velocity to mitral annular early diastolic velocity ratio

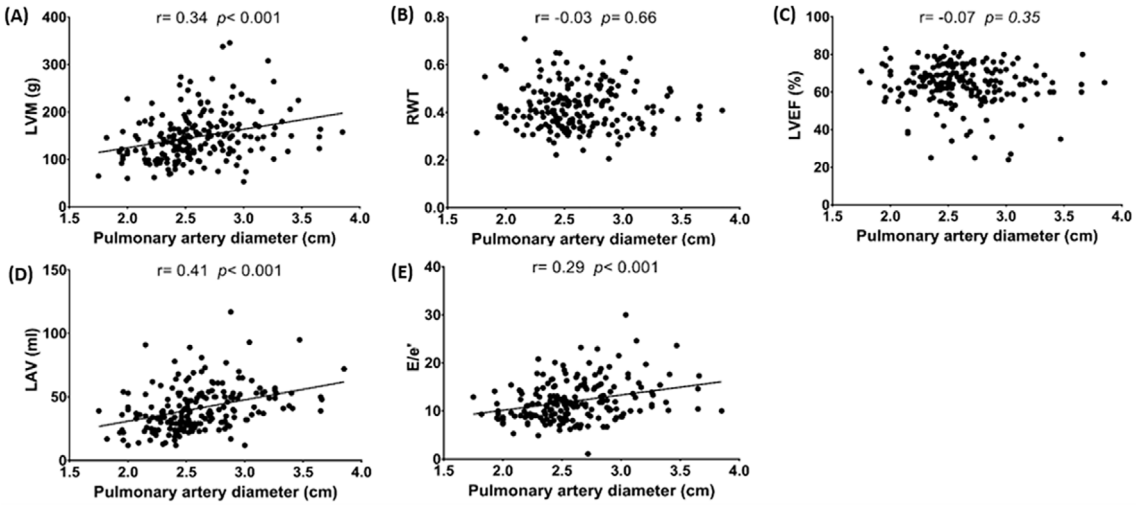

Figure 2. The correlations of PAD with (A) LVM, (B) RWT, (C) LVEF, (D) LAV, and (E) E/e'. PAD had positive linear correlations with LVM, LAV and E/e'.

stolic function with higher LAV and E/e'. Our study is the first study which documents the associations between the pulmonary artery parameters simply derived from non-contrast CT and the cardiac parameters, particularly the left ventricular parameters, in detail. Our results demonstrated that the PAD and PAD/AAD ratio may be used as simple and straight-forward indicators of cardiac remodeling and function, and thus potentially have some prognostic value for CVD events.

Previous studies demonstrated that PA enlargement among HF patients or COPD patients reflects increased pulmonary artery pressure (6, 14). PAD can be measured easily by non-

Table 2. Association of PAD and PAD/AAD with Echocardiography Parameters.

	Univariate linear regression			Multivariate linear regression			
PAD (cm)	**β coefficient**	**Std. error**	**p value**	**β coefficient**	**Std. error**	**p value**	**r value**
LVM (g)	39.44	9.43	<0.001	22.49	8.87	0.01	0.2
RWT	-0.0075	0.017	0.66	-	-	-	-
LVEF (%)	-2.72	2.14	0.20	-	-	-	-
LAV (mL)	16.72	3.13	<0.001	11.26	3.10	<0.001	0.23
E/e'	0.76	0.20	<0.001	2.59	0.79	<0.01	0.22
PAD/AAD	**β coefficient**	**Std. error**	**p value**	**β coefficient**	**Std. error**	**p value**	**r value**
LVM (g)	67.27	30.534	0.03	32.02	29.19	0.27	0.25
RWT	-0.018	0.05	0.73	-	-	-	-
LVEF (%)	-5.4	6.7	0.42	-	-	-	-
LAV (mL)	34.23	10.23	<0.001	32.05	10.26	0.002	0.28
E/e'	5.08	2.47	0.04	6.04	2.64	0.02	0.26

PAD: pulmonary artery diameter, PAD/AAD: pulmonary artery to aorta ratio, LVM: left ventricular mass, RWT: relative wall thickness ratio, LVEF: left ventricular ejection fraction, LAV: left atrial volume, E/e': early mitral inflow velocity to mitral annular early diastolic velocity ratio. Coefficients were measured using linear regression models to assess the association of AAW with LV structural and functional measures as dependent variables. Multiple regression analysis adjusted with following covariates: age, gender, BSA, HR, CKD, hypertension, diabetes mellitus, dyslipidemia, smoking, chronic obstructive pulmonary disease and coronary heart disease.

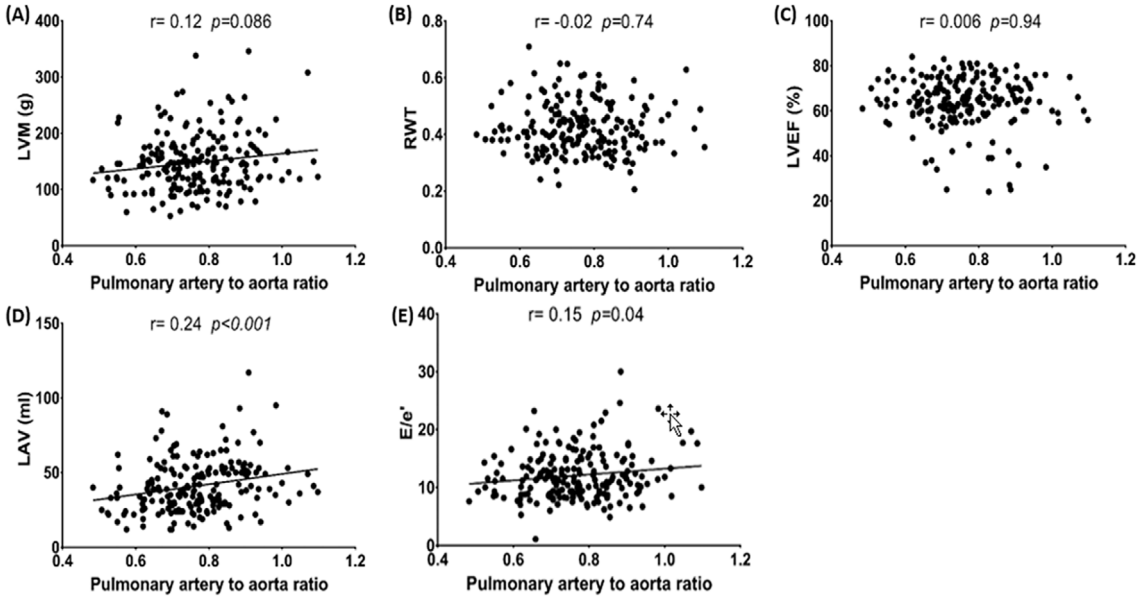

Figure 3. The correlations of PAD/AAD with (A) LVM, (B) RWT, (C) LVEF, (D) LAV, and (E) E/e'. PAD/AAD had positive linear correlations with LVM, LAV and E/e'.

invasive imaging methods such as MRI and CT. In our study, we could measure both PAD and AAD on just one axial slice at the site of pulmonary artery bifurcation. Measurements of PAD and AAD are also reproducible and accurate and do not require dedicated software or advanced expertise. Our inter-observer agreement was excellent and consistent with previous studies (6, 15).

There are few studies that explore the relationship between PAD or PAD/AD and the LV structural measures such as LVM. Our results showed significant positive correlations of PAD or PAD/AAD with LVM, and these correlations persisted after adjusting for demographic parameters and cardiovascular risk factors. These findings seem reasonable because both a higher LVM and increased pulmonary pressure are closely associated with an adverse outcome among patients with left heart disease (7). The present study also showed that a greater PAD and PAD/AAD were not associated with RWT. This result might indicate that PA enlargement develops not with the concentric, but with the eccentric hypertrophy of LV. We also found that a larger PAD and PAD/AAD ratio was related to a higher LAV. An enlarged LA serves as a marker of morbidity and mortality in HF patients and it is a consequence of LV remodeling and dysfunction (16, 17). LA remodeling is an important factor in

pathogenic alterations in the pulmonary circulation (3). Contributing to the complex alterations of cardiopulmonary interaction, LAV remodeling affects cardiac filling and output, and the backward transmission of elevated left-sided filling pressure leads to an increase of the pulmonary pressure, thus resulting in an increase of pulmonary vascular remodeling (18, 19) presenting as PA enlargement.

The gold standard for the assessment of LV diastolic function is invasive assessment of the pressure volume relationship which requires LV volume estimation using the conductance method (3, 20). It has been reported that E/e' assessed by echocardiography can be an alternative to invasive assessments of the hemodynamics and it is useful for evaluating diastolic dysfunction (21, 22). We found significant positive correlations of PAD and PAD/AAD ratio with E/e'. This result might be a clue to the pathophysiology of cardiopulmonary interaction in LV dysfunction. In contrast, the PAD and PAD/AAD ratio did not reveal any association with LVEF, a surrogate for the systolic dysfunction. Although LVEF is the most representative measure for systolic function, LVEF could not detect LV systolic dysfunction in its early stages. Myocardial deformation measurements that are useful for detecting an early stage LV functional impairment may potentially correlate with PAD, but we did not conduct any deformation measurements in this study.

It should be noted that PAD indexed to BSA or height also showed significant positive correlations with LVM, LAV and E/e'. Our indexed value findings further emphasized that PAD may have some demographic-independent prognostic value and it may be reliably widely applied. An additional finding of note was that both PAD and PAD/AAD were associated with LVM, LAV and E/e' independently with demographic and other vascular cardiac risk factors. Our results suggest that PA enlargement and its ratio to the aorta may have potential as predictors for cardiovascular diseases.

This study is associated with some limitations. Although we found statistically positive associations of PAD with LVM, LAV, and E/e', these associations were mild (r is about 0.3 to 0.4). However, these associations were maintained even after adjusting for CVD risk factors. We did not analyze the RV parameters, which may have allowed us to further evaluate the potential of PAD or PAD/AAD ratio as prognostic predictors. We did not include the estimated right ventricular systolic pressure (eRVSP), which is routinely measured and calculated as 4×peak tricuspid regurgitation (TR) velocity^2+estimated right atrial pressure, because TR velocity could not be obtained in many cases (n=81) in this study. We confirmed that PAD was associated with eRVSP ($r=0.31$, $p<0.001$) in the analysis using participants with TR velocity (n=113, data not shown). The systolic excursion of the tricuspid annular plane (TAPSE) was not measured in this study cases. However, the purpose of this study was to assess the association of PAD with LV measures that are easy to measure on CT and echocardiography. In addition, Echocardiography and CCTA scans were performed on a mean of 4.8 days apart. However, no eligible patients had any clinical events during the time between the two examinations. Our study population consisted of patients who underwent CCTA, as opposed to patients who underwent thoracic CT. This may have led to a smaller study cohort. We used the Teichholz method to calculate EF instead of the modified Simpson's method, which is the preferred method according to the current guidelines. In some cases, we could not use Simpson's method due to a poor image quality, especially in the lateral wall. In addition, the population of this study included Japanese patients with suspected CVD in a single institution. Further investigation should be done on other study populations with different ethnicities or risk factors (e.g. oncology patients or screening patients), to reveal whether detecting a larger PAD by CT may potentially help to identify the presence of cardiac remodeling, even in patients without any known cardiac disease.

Conclusion

PAD and PAD/AAD derived from non-contrast CT are simple-to-measure parameters. A greater PAD and PAD/AAD ratio are significantly and independently correlated with LV remodeling and function. These parameters should be assessed further to investigate their relationships with cardiac events.

The authors state that they have no Conflict of Interest (COI).

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