Noninvasive Measurement of Pulmonary Capillary Wedge Pressure by Speckle Tracking Echocardiography

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Abstract

The severity of left-sided heart failure can be evaluated by pulmonary capillary wedge pressure (PCWP) because PCWP reflects left ventricular (LV) filling pressure. Owing to developments in echocardiographic technology, speckle tracking echocardiography (STE) has allowed automatic construction of time-left atrial (LA) volume (LAV) curves. Thus, we developed a novel index based on a combination of LAV and LA function that would estimate PCWP using STE. The following regression equation described the relationship between PCWP that was obtained by right-heart catheterization and active LAEF/minimum LAV index (volume was indexed to body surface area: LAVI) in the patients with sinus rhythm: PCWP = 10.8–12.4 [$\log_{10}$ (active LAEF/minimum LAVI)] (r = −0.86, p <0.001) (measurements from the apical 4-chamber view). We defined this index [$\log_{10}$ (active LAEF/minimum LAVI)] as the kinetics-tracking index (KT index). The PCWP estimated by the KT index (ePCWP) had a strong correlation with PCWP obtained by right-heart catheterization (r = 0.92, p <0.001). The ePCWP measured by STE could be a useful parameter to improve clinical outcomes in patients with heart failure.

Keywords: speckle tracking echocardiography, heart failure, pulmonary capillary wedge pressure

1. Noninvasive assessment of PCWP

1.1. Introduction

Regardless of the presence of abnormal left ventricular (LV) systolic fraction, chronic heart failure (HF) causes cardiac disease or cardiac death. The physiological cause in patients with

HF with preserved ejection fraction (HFPEF) is a diastolic dysfunction [1]. Evaluation of left atrial (LA) pressure is a useful parameter for the diagnosis and treatment of HF. However, measurement of pulmonary capillary wedge pressure (PCWP) or LV filling pressure is an invasive method, and there have been few noninvasive indices that can precisely estimate PCWP or LV filling pressure. Therefore, the establishment of a noninvasive parameter to easily and accurately predict PCWP is important for the clinical diagnosis of HF.

LA volume (LAV) has been thought to reflect elevated LV filling pressure and serves as a parameter to evaluate prognosis of cardiac disease [2–4]. LV filling pressure and LV diastolic function can be estimated by the regional tissue velocity of the mitral annulus measured during early filling (e′) or the ratio of peak early transmitral flow velocity (E) to regional tissue velocity of the mitral annulus measured during early filling (E/e′) [5–8]. However, these parameters do not necessarily reflect the conditions of myocardial expansion during mid and late diastole [8].

Speckle tracking echocardiography (STE) has allowed the automatic construction of time-left atrial (LA) volume curves due to developments in echocardiographic technology [9]. STE has also permitted the evaluation of phasic LA function and volume [10, 11]. LA function and volume are directly influenced by LV diastolic function. Therefore, the combined parameter of LA function and volume would be useful to estimate PCWP. A novel index based on the combination of LA function and volume evaluated by the time-LA volume curve using STE would be more accurate to evaluate PCWP than conventional parameters such as E/e′ and LAV.

1.2. Methods

1.2.1. Subjects and study protocol

The study group consisted of a training study and a testing study. Patients in normal sinus rhythm (NSR), patients with chronic atrial fibrillation (AF) and patients with moderate-to-severe mitral valve regurgitation (MR), who were referred for clinically-indicated right-heart catheterization, were evaluated. In the training study, we measured LAV and LA emptying function (LAEF) in patients in sinus rhythm without chronic AF or moderate-to-severe MR to derive a novel index that gave the best estimate of PCWP. Four parameters based on various combinations of active or total LAEF and minimum or maximum LAV were used to estimate PCWP. In the testing study, we evaluated the reliability and accuracy of the novel index in patients in sinus rhythm, patients with chronic AF and patients with moderate-to-severe MR. Volume was indexed to body surface area (LAV index: LAVI). Transthoracic echocardiography was performed in the left lateral decubitus position by two experienced sonographers just before right-heart catheterization (within 1 hour). As recommended by the American Society of Echocardiography, measurements of phasic LAV were made from the apical 2- and 4-chamber views [12].

1.2.2. Echocardiographic studies and invasive measurements of PCWP

Total LAEF (reservoir function), active LAEF (booster pump function) and passive LAEF (conduit function) were measured to estimate phasic LA function (**Figure 1**). Total, active and

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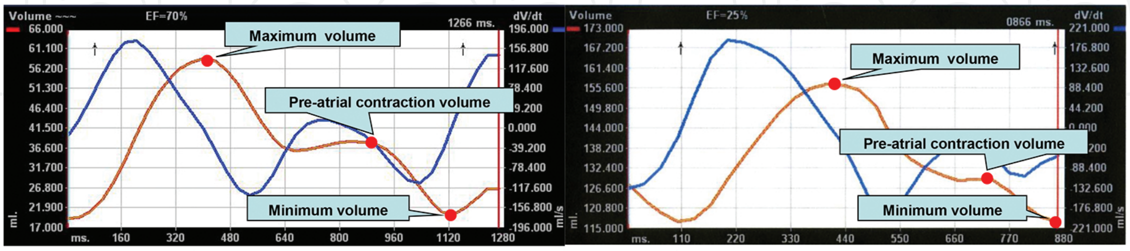
passive LAEF were defined as (maximum LAV – minimum LAV)/maximum LAV × 100%, (pre-atrial contraction LAV – minimum LAV)/pre-atrial contraction LAV × 100% and (maximum LAV – pre-atrial contraction LAV)/maximum LAV × 100%, respectively. The measurements of LAV and LA function were averaged from three consecutive beats. The reliability of the quantification of phasic LAV and LA function by STE has been established in previous studies [10, 11].



PCWP = 5 mmHg
Estimated PCWP = 6 mmHg
LVEF = 65%

PCWP = 20 mmHg
Estimated PCWP = 21 mmHg
LVEF = 64%

Figure 1. Representative time-left atrial volume curves in two patients. The patient on the left had a PCWP measured by right-heart catheterization of 5 mmHg, whereas the one on the right had a PCWP of 20 mmHg. Red lines are the time-left atrial volume curves, and blue lines are the d*V*/d*t* curves. PCWP: pulmonary capillary wedge pressure; LVEF: left ventricular ejection fraction.

A pulmonary artery balloon-occlusion catheter was connected to a fluid-filled transducer that was balanced before the study with the transducer located at the mid-axillary line. By the use of fluoroscopy, the wedge position was verified and the mean PCWP was measured.

1.3. Results

1.3.1. Association between PCWP and echocardiographic parameters in the training and testing studies

From the combination of LV function and volume, the following four parameters were calculated in the training study to predict PCWP:

1. Total LAEF/minimum LAVI
2. Total LAEF/maximum LAVI
3. Active LAEF/minimum LAVI
4. Active LAEF/maximum LAVI.

In the training study, all of these indices were found to be logarithmically correlated with PCWP obtained by right-heart catheterization (**Figure 2**). Therefore, we used the logarithm of these parameters in linear regression analyses. E/e′ and the logarithm of these four indices along with phasic LAVI and phasic LA function were linearly correlated with PCWP measured by right-heart catheterization (**Figure 3**). The logarithm of active LAEF/minimum LAVI had the strongest correlation with PCWP obtained by right-heart catheterization among all of the echocardiographic parameters (**Figure 3**). We defined this novel index [$\log_{10}$ (active LAEF/minimum LAVI)] as the kinetics-tracking index (KT index).

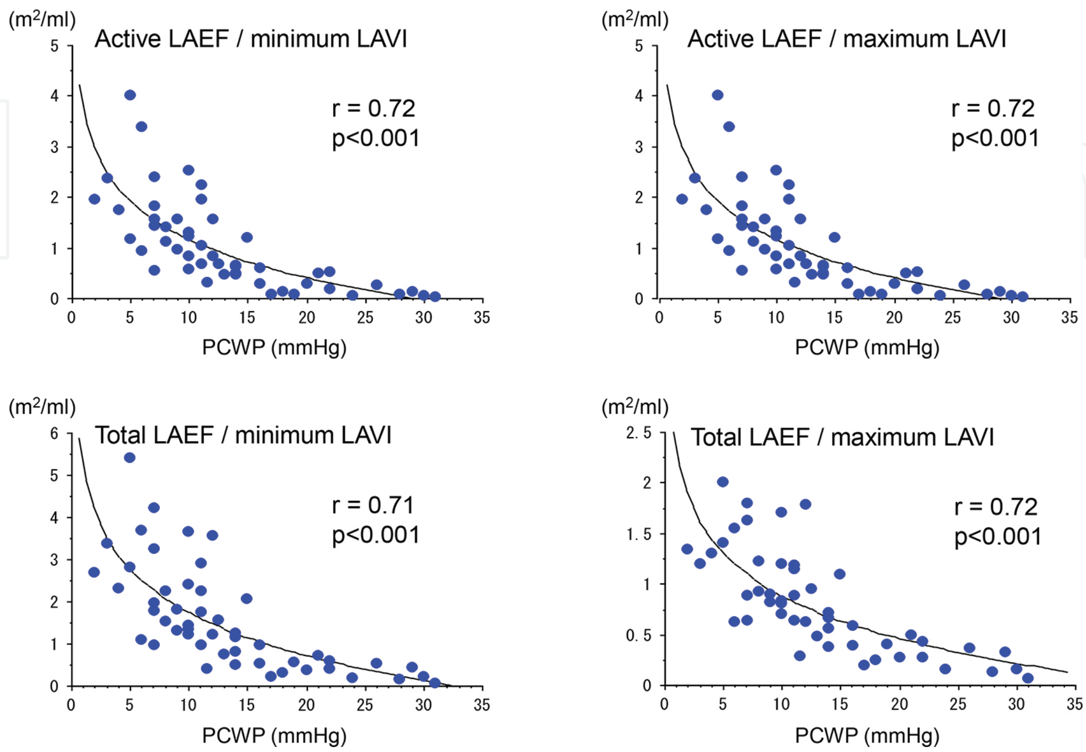


Figure 2. Relationship between pulmonary capillary wedge pressure measured by right-heart catheterization and the combined parameters of left atrial function and volume in the training study (n=50). The logarithm of each index was used in linear regression analysis. PCWP: pulmonary capillary wedge pressure; LAEF: left atrial emptying function; LAVI: left atrial volume index.

The following regression equation described the relationship between PCWP and active LAEF/minimum LAVI in patients with sinus rhythm:

PCWP = 10.8–12.4 [$\log_{10}$ (active LAEF/minimum LAVI)] ($r = -0.86$, $p < 0.001$) (measurements from the apical four-chamber view);

PCWP = 11.5–12.1 [$\log_{10}$ (active LAEF/minimum LAVI)] ($r = -0.87$, $p < 0.001$) (measurements from the apical two- and four-chamber view).

In patients with chronic AF, total LAEF was substituted for active LAEF because pre-atrial contraction LAV was not present during AF. Only the KT index was found to be an independent predictor of PCWP among the various echocardiographic parameters by multiple regression analysis.

There was a strong correlation between the PCWP estimated by the KT index and PCWP obtained by right-heart catheterization ($r = 0.92$, $p < 0.001$). **Figure 4** showed the relationship between PCWP estimated by the KT index and PCWP obtained by right-heart catheterization in the testing study.

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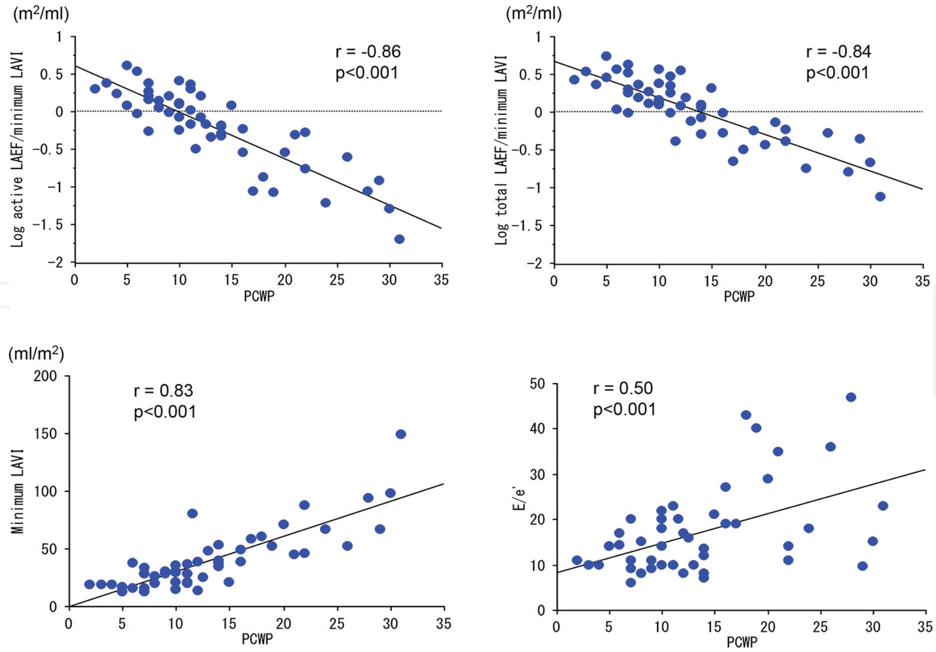

Figure 3. Relationship between pulmonary capillary wedge pressure measured by right-heart catheterization and echocardiographic parameters in the training study (n=50). PCWP: pulmonary capillary wedge pressure; LAEF: left atrial emptying function; LAVI: left atrial volume index. Note that the KT index was better than LAV alone and E/e′ for estimation of PCWP.

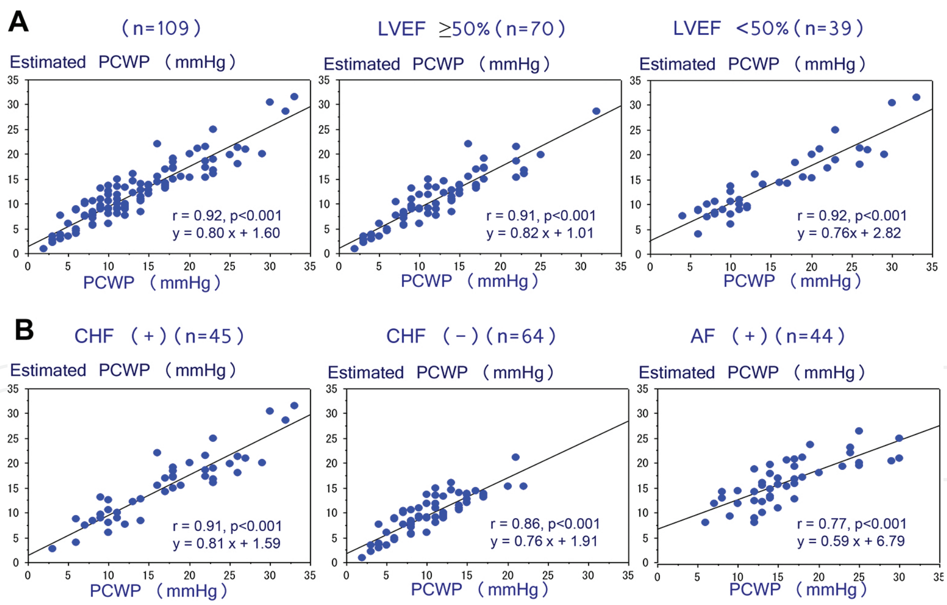

Figure 4. (**A**) Relationship between pulmonary capillary wedge pressure measured by right-heart catheterization and estimated by the KT index in patients in the testing study and in the subgroups with left ventricular ejection fraction (LVEF) ≥50% and LVEF <50%. The relationships were evaluated by simple linear regression analysis. (**B**) Relationship between pulmonary capillary wedge pressure measured by right-heart catheterization and estimated by the KT index in patients in the testing study, in the subgroups with (CHF+) or without (CHF−) symptoms of congestive heart failure and in the subgroup with chronic atrial fibrillation (AF+). The relationships were evaluated by simple linear regression analysis.

1.4 Discussion

1.4.1. Establishment of the KT index

A previous experimental study reported that the LA pressure-volume relationship consists of two loops arranged in a horizontal figure-of-eight pattern that incorporates both the active (A loop) and passive (V loop) components of LA function [13]. Dernellis et al. [14] reported that there was a linear correlation between minimum LAVI and LA pressure in subjects with normal atrial function, patients with acute myocardial infarction and patients with chronic HF. LA volume increases in proportion to the deterioration of LV diastolic function [15, 16]. Therefore, we employed LAV as the denominator in the KT index to evaluate PCWP. Likewise, active LAEF decreases in proportion to the deterioration of LV diastolic function [17]. Therefore, we employed active LAEF as the numerator in the KT index to evaluate PCWP. Moreover, the logarithmic correlation between LV filling pressure and LA distensibility [(max LAVI – min LAVI)/min LAVI] that is similar to the total LAEF [(max LAVI –min LAVI)/max LAVI] is reported [16]. Therefore, we determined the logarithmic association between ePCWP and LA function. Based on our equation, the KT index decreased in proportion to the increase of PCWP.

In the patients with chronic AF, we calculated the regression equation using the data in the testing study and obtained the following regression equation: PCWP (measured by catheterization) = 10.5–12.5 KT index ($r = 0.76$). Intriguingly, PCWP obtained by the KT index in patients with chronic AF had good agreement with PCWP obtained by right-heart catheterization, even using the same regression equation as in patients in NSR. A possible explanation that the ratio of pre-AC LAVI to min LAVI (1.191) (similar ratio to active LAEF) in patients in NSR was similar to the ratio of max LAVI to min LAVI (1.213) (similar ratio to total LAEF) in the patients with chronic AF.

1.4.2. Diagnostic accuracy of KT index and E/e′ for the prediction of PCWP

It was reported that e′ represents regional tissue velocity and e′ reflects LV relaxation and has a good correlation with PCWP [7, 18]. However, e′ is associated not only with active relaxation but also with lengthening load and elastic recoil of left ventricle [19]. Thus, e′ does not directly reflect intrinsic LV relaxation. The E wave is also associated with loading conditions (afterload and preload) [20, 21]. Therefore, E/e′ does not directly reflect atrial active function that is associated with LV stiffness or the condition of diastasis that occurs during mid and late diastole. Therefore, E/e′ is an index that evaluates only early diastole. In the present study, there was a significant but moderate correlation between E/e′ and PCWP obtained by right-heart catheterization ($r = 0.50$), as well as in a previous study ($r = 0.47$) [17]. Several parameters (LAEF [17] and isovolumetric myocardial acceleration obtained by tissue Doppler imaging [22]) were reported to predict LV filling pressure or PCWP. However, the correlation coefficient ($r = -0.63$ and $r = 0.74$) between LV filling pressure and PCWP was less than that in the present study ($r = -0.87$). In addition, the prediction by isovolumetric myocardial acceleration was limited to patients with left ventricular ejection fraction (LVEF) <55% and E/e′ <8 or >15 [22]. In healthy subjects or in patients with acute decompensated HF, the correlation between E/e′

and LV filling pressure was not significant [23, 24]. We proposed a combination of minimum LAVI and active LAEF (KT index) that evaluates LA features throughout diastole to estimate LV filling pressure to overcome the limitations of E/e′.

2. Impacts of gender and healthy aging on PCWP

2.1. Introduction

Measurement of intracardiac pressure such as PCWP or LV filling pressure is useful for the stratification of LV diastolic dysfunction that can lead to HF due to hypertension and aging [25, 26]. However, measurement of PCWP or LV filling pressure is an invasive method, and there have been few noninvasive indices that can precisely estimate PCWP or LV filling pressure. The KT index was a more accurate and useful predictor of PCWP than E/e′ [27].

There have been no previous reports that evaluated PCWP in healthy subjects in a relatively large population because there has been no noninvasive method to measure PCWP in healthy subjects. Therefore, the aim of the present study was to evaluate the impact of gender and healthy aging without hypertension on ePCWP and other echocardiographic parameters.

2.2. Methods

2.2.1. Subjects and study protocol

Healthy subjects, who were free of cardiovascular or other systemic disease and not taking any medications, were included in the study. All the subjects had to have normal findings based on a physical checkup once every year or school physical checkup once every 3 years. We included subjects who were more than 40 years old with a normal electrocardiogram (ECG), but with chest discomfort or pain and shown to be free from cardiovascular disease evaluated by multidetector computed tomography, myocardial scintigraphy or left heart catheterization. We also included subjects more than 40 years old with a normal ECG, but with chest discomfort or pain and shown to be free from cardiovascular disease evaluated by exercise stress ECG. Although we included subjects who had a normal chest x-ray and echocardiographic findings according to the recommendations of the American Society of Echocardiography [12], we also included patients who had trivial valvular regurgitation and those with abnormal values of diastolic function parameters such as E/A and E/e′. Measurements of echocardiography were made according to the criteria of the American Society of Echocardiography [12]. Doppler measurements of mitral inflow E-wave and A-wave velocity were obtained, and tissue Doppler measurements of mitral e′ wave velocity were made at the septal annulus. Total, passive, active LAEF and KT index were also measured.

2.3. Results

2.3.1. Impacts of healthy aging and gender on echocardiographic parameters

The LVEF was not significantly different among the eight age groups of both males and females. The minimum, maximum and pre-atrial contraction LAVI significantly increased with advancing age, resulting in a deterioration of passive and total LAEF. E/e′ and E/A (indicators of LV diastolic function) with advancing age. However, ePCWP was maintained due to compensation by an increase in active LAEF. As shown in **Figure 5**, maximum and minimum LAVI in octogenarians were greater than those in subjects in their thirties, forties and fifties in both males and females.

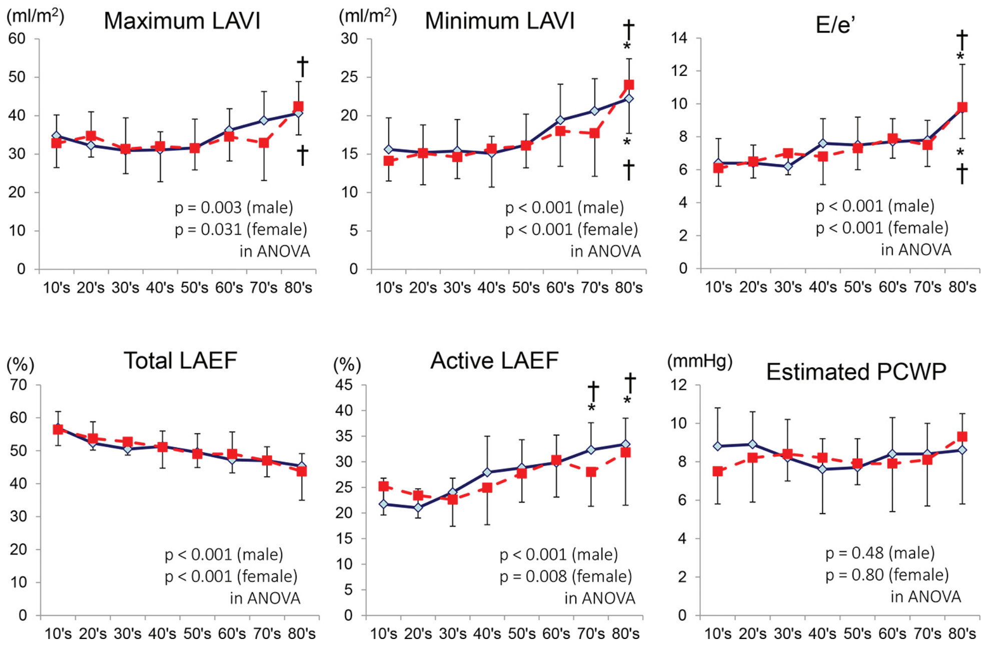

Figure 5. Left atrial volume and function in each decade. Solid blue line: male; broken red line: female. LAVI: left atrial volume index, LAEF: left atrial emptying function, PCWP: pulmonary capillary wedge pressure, ANOVA: one-way analysis of variance. *p<0.05 vs. twenties; †p<0.05 vs. thirties, forties and fifties;

2.3.2. Relationship between age and LV diastolic dysfunction

The relationships between age and the echocardiographic parameters that indicated LV diastolic dysfunction are shown in **Figure 6**. As age increased, the echocardiographic parameters, such as E/A and E/e′ (indicators of LV diastolic function) deteriorated to the same extent in males and females (slope of E/A: −0.021 in females and −0.021 in males) (slope of E/e′: 0.039 in females and 0.041 in males). However, there was no significant relationship between age and ePCWP. This suggested that ePCWP was maintained around 8 mmHg due to compensation by an increase in active LAEF in subjects without cardiovascular disease. Contrary, the compensation for LV diastolic dysfunction by an increase in active LAEF was more efficient in males than in females (slope=0.11) (slope=0.18, p=0.060 vs. females).

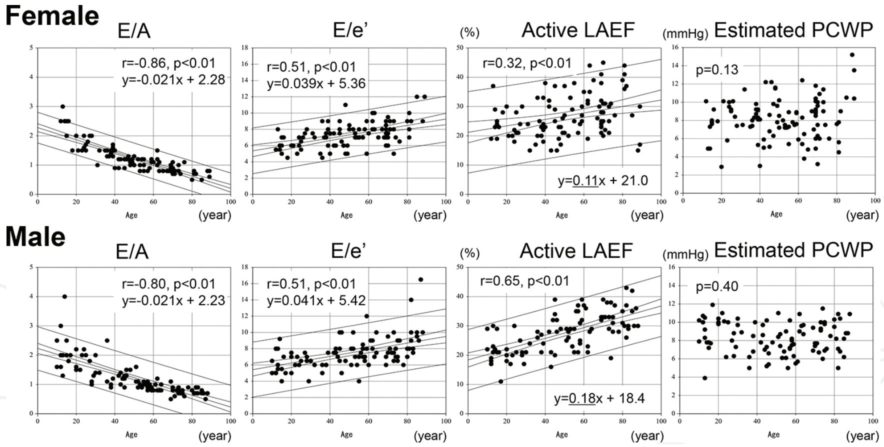

Figure 6. Relationships between age and the echocardiographic parameters. LAEF: left atrial emptying function, PCWP: pulmonary capillary wedge pressure. Center line indicates regression line. Inner lines indicate 95% confidence interval of the regression line. Outer lines indicate 95% confidence interval of the raw data.

2.4. Discussion

2.4.1. The clinical value of estimated PCWP in healthy subjects

HF affects many conditions of LV fluid volume and pressure status. The noninvasive measurement of PCWP in healthy subjects as well as patients with HF is useful for the quantitative stratification of intravascular fluid pressure and volume status to predict prognosis of HF. However, there have been few studies that evaluated PCWP in healthy subjects in a relatively large population because the measurement of PCWP requires an invasive method such as right-heart catheterization. PCWP in healthy subjects was maintained regardless of deterioration of LV diastolic function due to compensation by an increase in active LAEF in the present study. A previous study demonstrated that LV diastolic dysfunction, evaluated by E/A and E/e′, deteriorated with advancing age in healthy subjects [28]. However, that report did not evaluate PCWP. Another study also demonstrated echocardiographic parameters using three-dimensional echocardiography in healthy subjects [29]. That study focused only on volumetric parameters in the left atrium. However, the present study focused on ePCWP and LA function as well as LAV and demonstrated that the deterioration of LV diastolic function due to aging was compensated by LA function; thus, PCWP was maintained.

2.4.2. Estimated PCWP in healthy subjects

A few studies that elucidated PCWP in the healthy subjects in small populations have been performed. In a previous study, PCWP was evaluated by right-heart catheterization in 70 healthy volunteers. The PCWP in these healthy volunteers was around 12 mmHg and did not differ among seniors (50% men, 70 ± 3 years old), late middle age (48% men, 57 ± 4 years old), early middle age (32% men, 42 ± 5 years old) and young (57% men, 28 ± 4 years old) [30], whereas E/A deteriorated from 1.9 to 0.8. PCWP measured by right-heart catheterization (12 mmHg) was slightly higher than that in the present study (8 mmHg), whereas this finding that did not differ with advancing age reinforced the present results. This discrepancy of PCWP (12 and 8 mmHg) may be due to the fact that evaluation of PCWP measured by right-heart catheterization was performed by an invasive method that imposed a physical burden on the healthy volunteers, whereas ePCWP measurement by STE did not impose a physical burden on the healthy subjects. Previous study reported PCWP that was measured by right-heart catheterization in 50 healthy, elderly, nonsedentary volunteers who had a normal echocardiographic and ECG findings and was free of pulmonary, cardiovascular, systemic disease, shortness of breath and chest pain. The PCWP in these subjects was around 9 mmHg (65 ± 10 years old, 74% men) [31]. This value was similar to ePCWP in the present study.

2.4.3. Atrial function of males and females

The maximum LAVI in octogenarians was greater than the values in subjects in their thirties, forties and fifties regardless of gender, whereas deterioration of passive LAEF developed almost two decades earlier in both males and females. These results were the same as the results of a previous study [32]. In the present study, however, there was compensation by an increase of active LAEF only in male septuagenarians and octogenarians. Another intriguing finding in the present study was that as age increases, the echocardiographic parameters that reflect LV diastolic dysfunction deteriorated to the same extent in both males and females. However, compensation for deterioration of LV diastolic function by an increase in active LAEF was more pronounced in males (slope = 0.18) than females (slope = 0.11). In males, there was a stronger correlation between E/A and active LAEF, and between E/e′ and active LAEF than in females. The slopes of these two regression lines indicate that the strength of the compensation for deterioration of LV diastolic function was also lesser in females than males. Compensation by an increase in active LAEF was less prominent in females than males. The Framingham Heart Study demonstrated that the prevalence of congestive HF in septuagenarians was higher in males than females [33]. However, the prevalence of congestive HF in octogenarians was lower in males than in females. The 11-year follow-up study reported that female gender was associated with new onset of HFPEF, whereas male gender was associated with new onset of HFPEF, after adjusting for age [34]. In the present study, compensation for deterioration of LV diastolic function by an increase in active LAEF was more increased only in male octogenarians than female octogenarians. This may explain why HFPEF occurs more frequently in females than in males.

2.4.4. Clinical implications

The potential clinical application of the present methods and findings is broad. Noninvasive measurement of ePCWP is useful for the evaluation for intravascular fluid volume and pressure status to identify the onset of HF. Stratification of the risk of HF in patients as well as healthy subjects using PCWP is important for understanding when and why HF develops. The ePCWP that is measured by KT index also may be applicable for the determination of appropriate dry weight during dialysis and prediction of the onset of AF.

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