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ORIGINAL ARTICLE

Relationship between electrical conduction and phasic left atrial function: P-wave signal-averaged electrocardiography and time-left atrial volume curve assessments using two-dimensional speckle-tracking echocardiography

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Abstract

P-wave signal-averaged electrocardiography (P-SAECG) can detect imperceptible conduction abnormalities, and volume analysis using two-dimensional speckle-tracking echocardiography (2-DSTE) allows us to easily measure the phasic function of the left atrium (LA). Both conduction abnormalities and functional deformation of the LA may be linked to the clinical outcome; however, the exact relationship is unclear. The aim of this study was to investigate the relationship between the phasic function of the LA and electrical conduction using P-SAECG and 2-DSTE. The subjects were 112 male volunteers (age 46.9 ± 13.2 years) with normal cardiac function who underwent P-SAECG and 2-DSTE. The filtered p-wave duration (FPD) and the root-mean-square voltage for the last 20 ms (RMS20) on P-SAECG wave were measured in ms and μV, respectively. Total emptying function (EF) (reservoir function), passive EF (conduit function), and active EF (booster pump function) of the LA were calculated as percentages to evaluate phasic LA function using 2DSTE. The mean FPD was 134.3 ± 11.7 ms and the mean RMS20 was 4.59 ± 2.39 μV. The mean total EF was 60.5 ± 13.1%, mean passive EF was 39.4 ± 13.9%, and mean active EF was 35.1 ± 13.9%. FPD had a negative correlation with passive EF ($r = -0.20$, $p = 0.039$). FPD showed no significant relationship with total EF ($r = -0.03$, $p = 0.78$) or active EF ($r = 0.13$, $p = 0.18$). There was a significant association between RMS20 and passive EF ($r = 0.19$, $p = 0.048$); however, no there was no correlation between RMS20 and total EF ($r = 0.12$, $p = 0.23$), or between RMS20 and passive EF ($r = -0.02$, $p = 0.86$). In multivariate regression analysis, passive EF was an independent factor that influenced FPD duration. This study indicated that FPD was associated with conduit function, which includes phasic LA function. Therefore, electrical conduction of the LA and left ventricular diastolic function are closely related. In the clinical setting, when conduction abnormalities are detected, lifestyle measures or interventions can be applied to reduce cardiovascular risk.

Keywords Left atrium · Signal-averaged electrocardiography · Speckle-tracking echocardiographic imaging

Introduction

Impaired arterial conduction or impaired left atrial (LA) function can preempt cardiovascular outcomes in the clinical setting. Consequently, many reports clarifying the significance of LA deformation and electrophysiological assessments have appeared in the literature. P-wave-triggered signal-averaged electrocardiography (P-SAECG) is a high-resolution technique used to detect impaired arterial conduction electronically [1–3]. P-wave prolongation and low energy parameters assessed by P-SAECG are associated with

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cardiovascular events such as atrial fibrillation or cardiac dysfunction [1, 2, 4–7]. Two-dimensional speckle-tracking echocardiography (2-DSTE) is a useful method for analyzing LA function during a cardiac phase [8]. Volume analysis using 2-DSTE allows us to easily measure the phasic function, which comprises reservoir, conduit, and atrial contraction components [8–11]. Deteriorations in each phase of LA function are also factors impacting cardiovascular events or function [10, 12–14]. Thus, both conduction abnormalities and functional deformation of the LA may be linked to the clinical outcome; however, the exact relationship is unclear. In this study, we used both P-SAECG and 2-DSTE to test the hypothesis that there is an association between the mechanical and electrophysiological function of the LA.

Materials and methods

Study design and eligibility

The present study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Gifu Prefectural General Medical Center. All study subjects gave informed consent to participate in the study.

This was a retrospective study. The subjects were 161 consecutive subjects who were received a digital-Holter ECG with P-SAECG. They underwent transthoracic echocardiography and a digital-Holter ECG with P-SAECG in our echocardiography and electrocardiography laboratory on the same day to screen for cardiac disease as part of a health check (110 subjects) or on the recommendation of their primary physician (51 subjects). We excluded five subjects without receiving echocardiographic study. Thirty-six subjects were excluded, because they had more than moderate valve disease, old myocardial infarction or cardiomyopathy. Three subjects were excluded from the study because the tracking quality on the echocardiographic recordings was poor, and two were eliminated because the noise level of the P-SAECG was excessive. Because there were only three females meeting inclusion criteria, this study was limited to men. Thus, 112 subjects comprised the final study population.

Hypertension was determined when patients had a previously documented diagnosis, or were already on antihypertensive therapy. Hyperlipidemia was defined as a total cholesterol level of > 220 mg/dL and LDL cholesterol level of > 140 mg/dL, as previously documented, or the use of anti-hyperlipidemia therapy. Diabetes mellitus was defined as a level of glycosylated hemoglobin (HbA1c) > 6.5%, use of any anti-hyperglycemic medication, or a previous diagnosis of diabetes mellitus. Smoking status was defined as positive if at baseline the patient was a smoker or had quit less than a year before the study.

P-wave-triggered signal-averaged electrocardiography

P-SAECG recordings were obtained from the Frank XYZ leads during sinus rhythm using a digital-Holter ECG (FM-180, Fukuda Denshi Co. Ltd. Tokyo, Japan) in all subjects. The signals were amplified and filtered with a low-cut filter of 40 Hz (slope − 18 dB/octave). The filtered p-wave duration (FPD) and the root-mean-square voltage for the last 20 ms (RMS20) of the signal-averaged p-wave were measured using SCM-6600 (Fukuda Denshi Co. Ltd. Tokyo, Japan). In this system, the p-waves are selected by matching an averaged template waveform [3, 5]. We set it to analyze FPD and RMS20 every 15 min over a maximum of 200 cardiac cycles. Detected waveforms were averaged by the p-wave triggering system to obtain a noise level of < 0.4 μV (Fig. 1). During the 24-h recording period, we obtained FPD and RMS20 when a minimum noise level was achieved and the numbers of averaging and observation waveforms were similar [3].

Echocardiography

Transthoracic echocardiography was performed using a Xario SSA-660A (TOSHIBA. Co. Ltd., Tokyo, Japan) ultrasound system with a PST-30BT (3 MHz) ultrasound transducer for conventional screening. Conventional echocardiographic parameters were measured according to standard echocardiographic methods.

Speckle-tracking analysis was performed using velocity vector imaging (VVI) software (Syngo Velocity Vector imaging, Siemens). The echocardiographic data were sent to the VVI software on a new off-line. A time-LA volume (LAV) was automatically provided (Fig. 2). With this method, the endocardial border of the LA is visually identified and manually outlined by the examiner. Manual placement of an endocardial tracing over one frame is then automatically tracked throughout the cardiac cycle. The examiner is able to assess the tracking quality and to edit the initial trace. If tracking is poor, the tracing can be readjusted. To avoid significant tracking errors, the sample speed is monitored and, if it is unnatural, the examiner readjusts the initial trace. VVI is an endocardial border tracking technique that can track the movement of a thin-walled structure such as the LA. Maximum LAV, minimum LAV, and LAV just before atrial contraction (pre-atrial contraction LAV, preAC LAV) were obtained from the apical four-chamber view using VVI. The total LA emptying function (EF) (reservoir function), passive EF (conduit function), and active EF (booster pump function) were calculated to evaluate

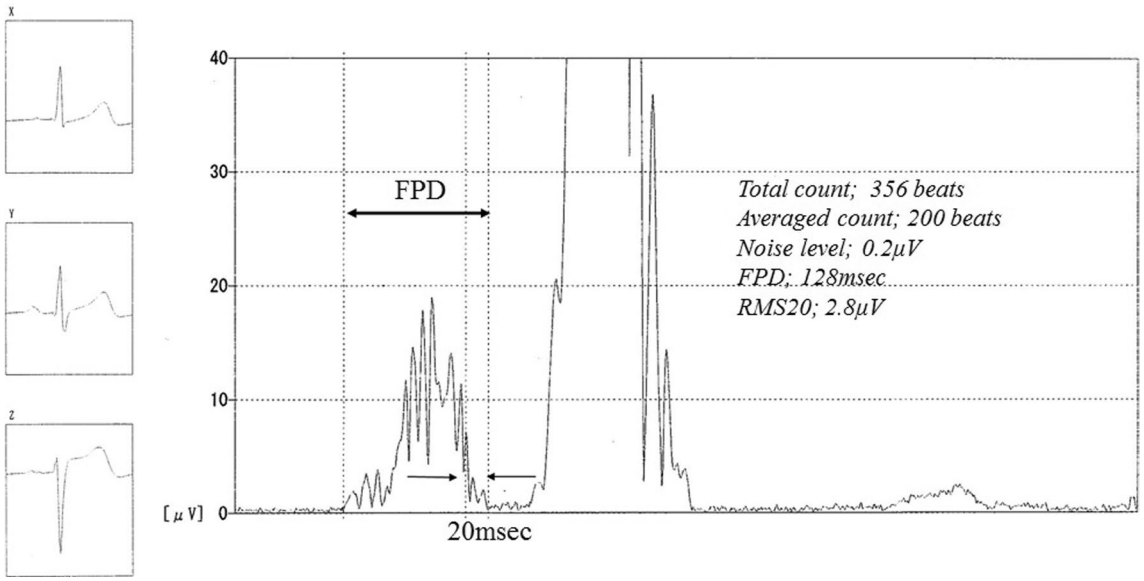

Fig. 1 Representative case of P-wave-triggered signal-averaged electrocardiography. *FPD* filtered P-wave duration, *RMS20* root-mean-square voltage for the last 20 ms

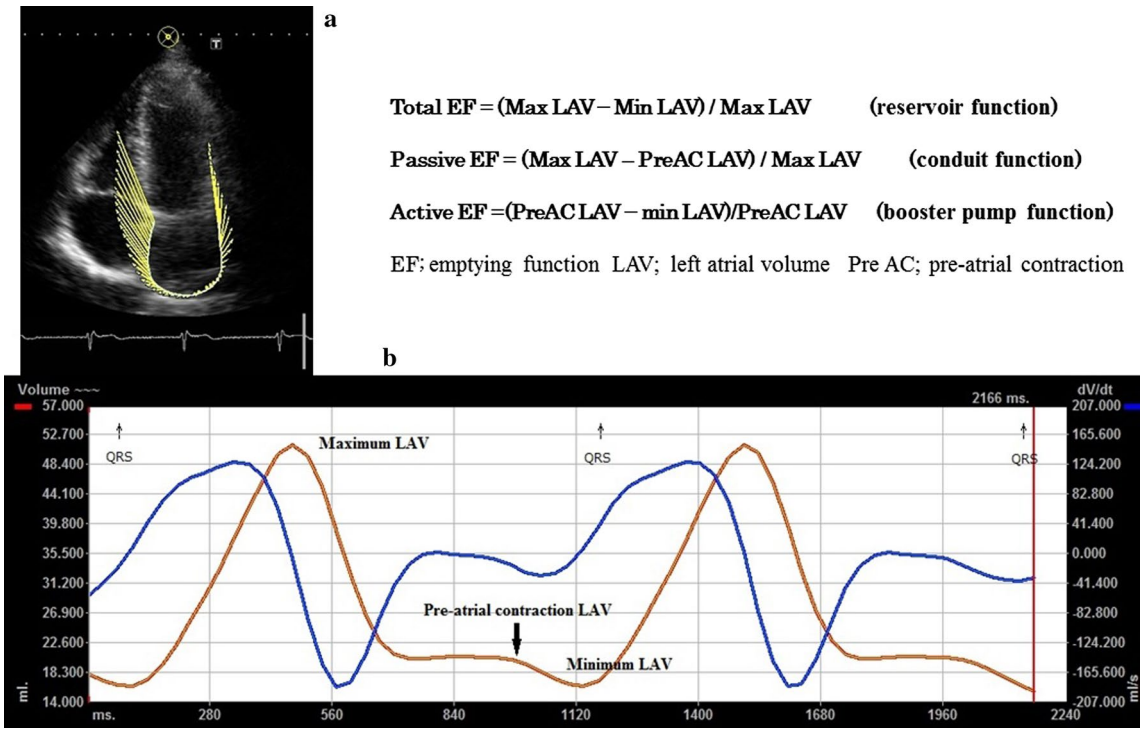

Fig. 2 Representative case—velocity vector imaging. Images derived from two-dimensional speckle-tracking echocardiography (**a**) and a time-LA volume curve (**b**). The time-LA volume curve is shown as an orange line and the time-d*V*/d*t* curve is shown as a blue line. The arrows represent QRS. This is the same case as shown in Fig. 1. *EF* emptying function, *LA*, left atrium, *LAV* left atrial volume, *PreAC* pre-atrial contraction

phasic LA function. LA total, passive, and active EF were defined as (maximum LAV − minimum LAV)/maximum LAV × 100% (maximum LAV − pre-atrial contraction LAV)/maximum LAV × 100%, and (pre-atrial contraction LAV—minimum LAV)/pre-atrial contraction LAV × 100%, respectively, during a cardiac cycle (Fig. 2). We assessed LA

function in the 4-chamber view based on a previous study that had predicted the clinical outcome from the phasic function of LA from the 4-chamber view assessment [10, 11]. Another reason was that much of the 4-chamber views were of a high quality for optimal speckle-tracking analysis in this retrospective study. Different from previous studies, devices from different vendors were used for data acquisition and speckle-tracking analysis. There was a lack for the reliability of not only strain and strain values, but also LAV. For the securement of reliability of the feature-tracking echocardiographic method, maximum LAV, minimum LAV, and pre-atrial contraction LAV, as measured by VVI, were compared with the values obtained by the manual tracing method for the same frame numbers in 20 randomly selected patients.

Statistical analysis

Continuous data were expressed as mean ± SD or as proportions, while categorical data were expressed as frequencies or percentages. Pearson's correlation and simple regression were used to assess the relationship between 2-DSTE and P-SAECG values. Multivariate regression analysis was performed to identify the independent predictors of FPD and RMS20 values. We performed multivariate analysis on factors including age, lifestyle-related disease (HT, HL, and DM), LA size, and left ventricular (LV) systolic/diastolic function. Values of $p < 0.05$ were considered significant. All analyzes were performed using Microsoft Excel version 2013 and SAS software version 5.0 (SAS Institute, Inc., Cary, NC).

Results

Validation of velocity vector imaging method by manual tracing, and reproducibility and reliability of left atria volume on each cardiac phase using the velocity vector imaging method.

There were significant correlations between the VVI method and manual tracing for the evaluation of maximum LAV ($r = 0.99$, $p < 0.001$), pre-AC LAV ($r = 0.99$, $p < 0.001$), and minimum LAV ($r = 0.98$, $p < 0.001$) (Fig. 3). The inter-observer differences for maximum LAV, pre-AC LAV, and minimum LAV, as measured by the VVI method, were 0.44 ± 3.01 mL, 0.73 ± 2.56 mL, and 0.40 ± 3.62 mL, respectively. The intra-observer differences for maximum LAV, pre-AC LAV, and minimum LAV, as measured by the VVI method, were 0.72 ± 1.99 mL, 0.57 ± 2.83 mL, and 0.67 ± 4.10 mL, respectively.

Characteristics of the study subjects

The clinical characteristics of the 112 study subjects are summarized in Table 1. All subjects in this study were men. The mean age was 47 years (range 18–65 years). Twenty-five had been visiting the clinic or hospital regularly. Twenty were smokers and 11 were habitual drinkers, 18 had hypertension, 8 had hyperlipidemia, and 7 had diabetes. The mean blood pressure on examination was 125.4/74.6 mmHg and the mean heart rate was 70.5 min^{-1}.

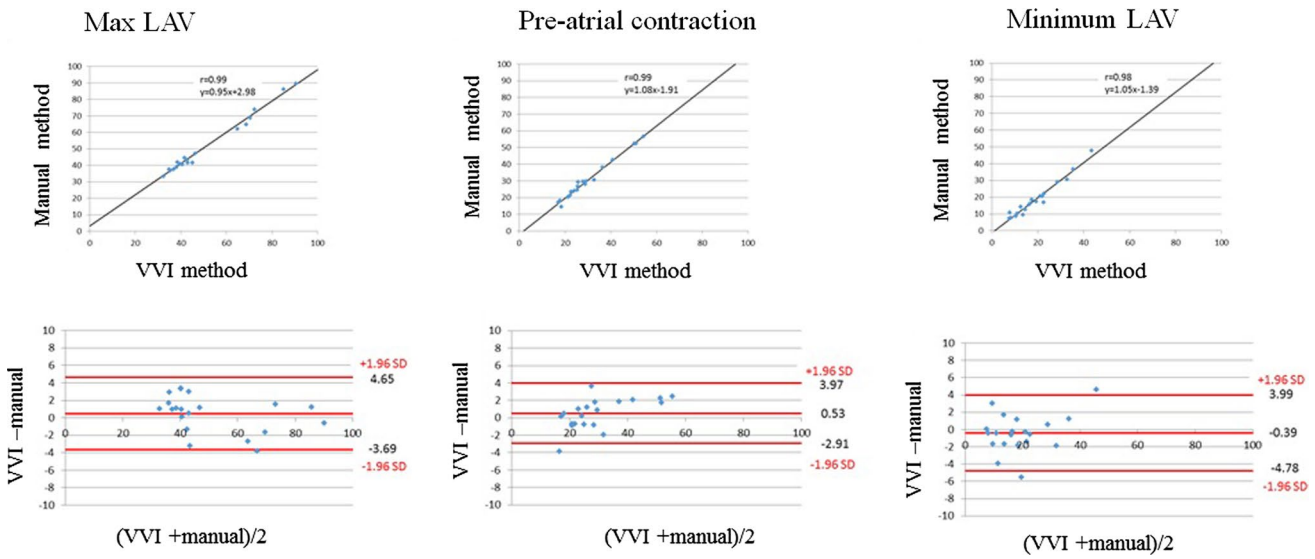

Fig. 3 Bland–Altman plots for determining the agreement between velocity vector imaging and manual tracing for the measurement of maximum LAV, LAV on atrial contraction, and minimum LAV. *LAV* left atrial volume, *VVI* velocity vector imaging

Table 1 Patient characteristics

n	112
Age (year-old)	46.9 ± 13.2 (18–65)
Male, *n* (%)	112 (100%)
SBP (mmHg)	125.4 ± 14.7
DBP (mmHg)	74.6 ± 13.3
Heart rate (/min)	70.5 ± 13.0
Smoker, *n* (%)	20 (21.2%)
Habitual drinking, *n* (%)	11 (8.8%)
Healthy object, *n* (%)	87 77.6%)
Primary illness, *n* (%)	25 (22.3%)
Hypertension, *n* (%)	19 (22.3%)
Hyperlipidemia, *n* (%)	8 (18.8%)
Diabetes mellitus, *n* (%)	7 (6.3%)
Others, *n* (%)	3 (3.8%)

Blood pressure and hear rate was at the time of echocardiographic study

Data are means ± SD

SBP sytolic blood pressure, *DBP* diastolic blood pressure

Blood examinations results

Blood examinations results are summarized in Table 2. The mean total cholesterol level was 197.0 mg/dL, mean low-density lipoprotein cholesterol was 115.4 mg/dL, and mean HbA1c level was 5.5%.

Echocardiographic features

The results of the conventional echocardiographic study are also summarized in Table 2. No abnormal left ventricular wall motion, such as asynergy, was observed, nor any diffuse hypokinesis. The mean LVEF was 71.4 ± 6.6%. The mean LAD was 31.9 mm. The mean LVMI was 78.7 ± 20.4 g/m^2, and mean E/e' was 7.7 ± 2.0.

Regarding LA phasic function derived from 2DSTE data, total EF, passive EF, and active EF were 60.5 ± 13.1%, 39.4 ± 13.9, and 35.1 ± 13.9, respectively (Table 3).

P-wave-triggered signal-averaged electrocardiography (P-SAECG).

The P-SAECG measurements are summarized in Table 3. The mean FPD was 134.3 ± 11.7 ms and mean RMS20 was 4.59 ± 2.39 μV (Table 3).

Associations between LA function and P-SAECG parameters.

On simple regression analysis (Table 4, Fig. 4), we found a significant correlation between FPD and age ($r = 0.29$, $p = 0.002$). There was also a significant relationship between FPD and prevalence of hypertension ($r = 0.21$, $p = 0.027$). On conventional echocardiographic

Table 2 Patients backgrounds

n	112
Total-cholesterol (mg/dL)	197.0 ± 34.1
LDL-cholesterol (mg/dL)	115.4 ± 29.8
HDL-cholesterol (mg/dL)	60.1 ± 14.8
Triglyceride (mg/dL)	107.9 ± 75.9
Plasma glucose (mg/dL)	94.2 ± 12.5
HbA1c (%)	5.5 ± 0.5
Uric acid (μg/dL)	6.0 ± 1.2
Creatinine (mg/dL)	0.89 ± 0.12
Conventional echocardiographic parameters	
LAD (mm)	31.9 ± 4.5
IVSd (mm)	8.2 ± 1.6
LVPWd (mm)	8.6 ± 1.8
LVDd (mm)	49.6 ± 4.2
LVDs (mm)	28.2 ± 4.8
FS (%)	43.6 ± 7.3
LVEF (%)	71.4 ± 6.6
LVMI (g/m^2)	78.7 ± 20.4
LAVI (mL/m^2)	28.4 ± 7.4
E/A	1.2 ± 0.4
E/e'	7.7 ± 2.0

Data are means ± SD

HDL high density lipoprotein, *LDL* low density lipoprotein, *LAD* Left atrial diameter, *IVSd* interventricular septal wall thickness in diastole, *LVPWd* left ventricular posterior wall thickness in diastole, *LVDd* left ventricular end-diastolic dimension, *LVDs* left ventricular end-systolic dimension, *FS* fractional shortening, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LAVI* Left atrial volume index, *E* mitral inflow velocity at early diastolic, *A* mitral inflow velocity at atrial contraction, *e'* mitral annular velocity at early diastolic

Table 3 Left atria phasic function derived 2DSTE and P-SAECG data

n	112
2DSTE	
Total EF (%)	60.5 ± 13.1
Passive EF (%)	39.4 ± 13.9
Active EF (%)	35.1 ± 13.9
P-SAECG	
Total cycle of sinal-averaged (beat)	232 ± 187
Template-matching cycle (beat)	127 ± 59
Percent of matching (%)	66.2 ± 22.3
Noise level (μV)	0.36 ± 0.07
FPD (ms)	134.3 ± 11.7
RMS20 (μV)	4.59 ± 2.39

EF emptying function, *PSAECG* P-wave-trigger signal averaged electrocardiography, *FPD* filtered P wave duration, *RMS20* root-mean-square voltage for the last 20 ms

Table 4 Pearson's correlation and simple regression in PSAECG

	FPD (ms)		RMS20 (μV)	
	r	*p* value	*r*	*p* value
Age	0.29	0.002	− 0.10	0.31
Hypertension	0.21	0.027	0.01	0.96
Hyperlipidemia	0.15	0.20	− 0.03	0.78
Diabetes	− 0.04	0.72	0.13	0.17
HbA1C (%)	0.12	0.20	0.06	0.52
LVEF (%)	0.06	0.51	− 0.10	0.29
LVMI (g/m^2)	0.07	0.45	− 0.07	0.44
LAD (mm)	0.18	0.065	− 0.06	0.55
LAVI (mL/m^2)	0.05	0.63	0.02	0.88
E/A	− 0.20	0.033	0.08	0.42
E/e'	− 0.08	0.390	0.07	0.44
Total EF (%)	− 0.03	0.78	0.12	0.23
Passive EF (%)	− 0.20	0.039	0.19	0.048
Active EF (%)	0.13	0.18	− 0.02	0.86

PD filtered P wave duration, *RMS20* root-mean-square voltage for the last 20 ms, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LAVI* left atrial volume index, *E* mitral inflow velocity at early diastolic, *A* mitral inflow velocity at atrial contraction, *e'* mitral annular velocity at early diastolic, *EF* emptying function

measurements, the ratio of mitral inflow velocity in early diastolic to atrial contraction (E/A) was associated with FPD ($r = -0.20$, $p = 0.033$).

Regarding LA function, we observed a significant negative correlation between FPD and passive EF ($r = -0.20$, $p = 0.039$). There was also a significant correlation between RMS20 and passive EF ($r = 0.19$, $p = 0.048$) (Table 4, Fig. 4).

In multivariate regression analysis, passive EF was an independent predictor of FPD (Table 5).

Discussion

The results of this study indicate that the values of P-SAECG (FPD and RMS20) are significantly related to passive EF and that FPD is significantly associated with age, prevalence of hypertension, and the E/A ratio on conventional echocardiography. We also demonstrated that passive EF was an independent predictor of FPD.

Studies have reported an association between decreased LA function and adverse cardiovascular events [10–14], or between atrial electrophysiological abnormalities and cardiovascular events [1, 2, 4, 7, 15, 16]. Given these reports, it is not surprising that there is a significant correlation between P-SAECG and LA deformation variables. Generally, LA function includes three components: reservoir function, conduit function, and booster pump function. Passive EF is closely associated with conduit function, which is related to LV relaxation or diastolic function. Furthermore, FPD is significantly correlated with E/A, age and prevalence of hypertension, which affect LV diastolic function. Our study found that intra-atrial conduction derived from P-SAECG could closely predict LV diastolic function. One previous study showed that FPD was significantly correlated with left ventricular end-diastolic pressure, but not with LAD

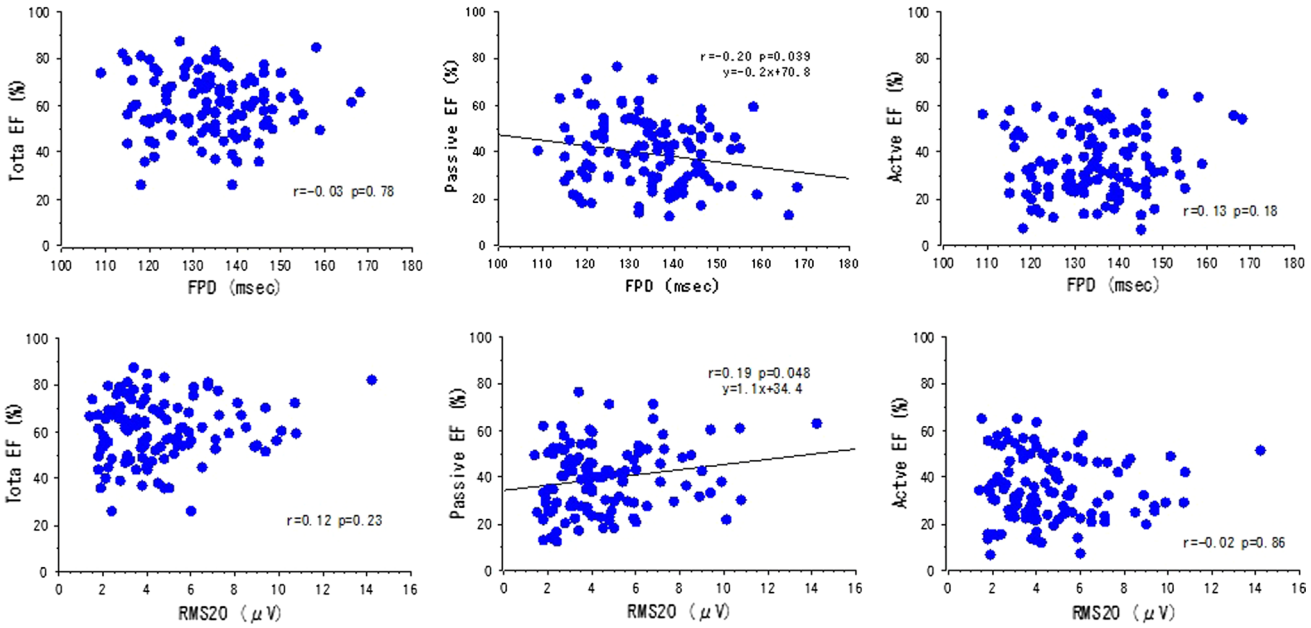

Fig. 4 Relationship between parameters measured by P-SAECG and LA phasic function. *P-SAECG* P-wave-triggered signal-averaged electrocardiography, *LA* left atrium, *FPD* filtered P-wave duration, *RMS20* root-mean-square voltage for the last 20 ms, *EF* emptying function

Table 5 Multiple regression analysis with FPD and RMS20

	β	*p*		*β*	*p*
FPD		0.026	RMS20		0.79
Age	0.17	0.21		− 0.10	0.47
Total EF	1.23	0.056		− 0.17	0.81
Passive EF	− 0.93	0.039		0.28	0.56
Active EF	− 0.67	0.12		0.09	0.84
Hypertension	0.10	0.34		0.04	0.72
Hyperlipidemia	0.11	0.32		− 0.01	0.96
Diabetes	− 0.20	0.081		0.10	0.41
HbA1c	0.07	0.59		0.04	0.77
LAD	0.49	0.24		0.03	0.80
LVEF	0.06	0.55		0.10	0.35
E/A	0.04	0.72		− 0.01	0.98

FPD filtered P wave duration, *RMS20* root-mean-square voltage for the last 20 ms, *β* standardized partial regression coefficient, *EF* emptying function, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *E* mitral inflow velocity at early diastolic, *A* mitral inflow velocity at atrial contraction

[1]. FPD prolongation has also been observed in patients with a pathophysiology of LV diastolic dysfunction such as hemodialysis [5] or obstructive sleep apnea syndrome [6]. Because our study population was younger than that of previous studies [mean age of our subjects was 47 years (oldest 65 years)] and included healthy subjects, slight intra-atrial abnormalities may have occurred at the early stage of LV diastolic dysfunction.

In the present study, P-SAECG values did not correlate with total EF (reservoir function) or active EF (booster pump function), and this finding is in contrast with previous reports. Each component of LA function during a cardiac cycle—reservoir, conduit, and booster pump—has been associated with cardiovascular outcomes [10–14]. The differences between our findings and those of previous reports may also reflect age differences in the study populations given that baseline left ventricular diastolic function or pathological degeneration are dependent on age [17]. Conflicting theories exist [18, 19] with regard to remodeling in that electrophysiological remodeling in the LA is thought to occur prior to tissue remodeling, and that LA mechanical remodeling may develop earlier than electrical remodeling. From our study findings, we speculate that inter-atrial conduction delay may potentially depend on LV diastolic function.

In our study, we found that RMS20 had no associations in the multiple regression analysis. Previous reports showed that p-wave energy parameters had significantly lower values to predict events related to cardiovascular outcomes [6–8]. We know that increasing fibrotic degeneration of the right atrial wall may cause low RMS20 values [20]. Another study showed that RMS20 was related to type III collagen-N-peptide, which is a fibrous marker for the recurrence of cardiovascular events [21]. A previous transesophageal echocardiographic study reported that pathological atrial degeneration predicted cardiovascular outcomes [22, 23]. In our study population, pathological degeneration was less advanced because of the low age range. However, according to previous reports, the energy parameters may reflect pathological changes in booster pump function; thus, further studies are needed.

Clinical implications

The findings of this study are in agreement with those of previous studies about the risk of cardiovascular events in relation to the electrophysiology or function of the LA. Intra-atrial conduction is associated with the diastolic function. When LV diastolic dysfunction is observed in clinical practice, the presence of electrophysiological abnormality should be recognized. Because LA conduit function is often regarded as a predictor of other cardiovascular diseases, such as heart failure with preserved ejection fraction, the combination of electrophysiological and functional assessment might assist risk stratification by allowing the early identification of cardiovascular risk. If the risk is verified, lifestyle measures or interventions can be applied to reduce the cardiovascular risk. Furthermore, because large proportion of worker men occupied participant in this study, assessment of conduction abnormalities by P-SAECG and the phasic function of the LA can be useful maintaining and promoting workers' health including changing the location of work, changing the work contents, shortening the working hours, reducing the frequency of night work and so on.

In this study, digital-Holter ECG only measured parameters of P-SAECG. The digital-Holter ECG can also measure digital late potential of the QRS-wave trigger or alternative T which can predict cardiovascular events [3, 24]. There is a possibility that the risk stratification for maintaining and promoting workers' health in further collaboration study with the digital-Holter ECG and 2DSTE.

Study limitations

This study had several important limitations. We evaluated only a small group of Japanese men, which limits the generalizability of the results. We performed echocardiography and P-SAECG at the same time, but at only one point in time, so it is possible that unknown or unmeasured factors may alter the responses at other points in time. This was a nonrandomized study, in which the study population was small, and the results reflect the experience of only a single center. Therefore, this study lacks the obvious advantages of a larger, multicenter, multinational randomized trial. P-SAECG data measured by Holter-ECG exhibited a

circadian rhythm, without premature atrial contractions, or unexpectedly noisy p-waves. However, it was necessary to exclude many waveforms that did not match the averaged template waveform [3]. To average the consecutive wave patterns, we obtained FPD and RMS20 when a minimum noise level was obtained and when the averaging and observation waveforms were close in number [3].

In conclusion, we investigated the relationship between the phasic function of the LA and electrical conduction using P-SAECG and 2-DSTE. Passive EF calculated from 2-DSTE was an independent predictor of FPD derived from P-SAECG. Our findings suggest that conduction abnormalities may lead to a deterioration of LV diastolic function. In the clinical setting, when conduction abnormalities are detected, lifestyle measures or interventions can be applied to reduce cardiovascular risk.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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