ORIGINAL ARTICLE

Prolonged total atrial conduction time evaluated with tissue Doppler imaging predicts poor cardiac prognosis in patients with heart failure

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Abstract

Prolonged total atrial conduction time is caused by atrial remodeling. Left atrial remodeling is associated with poor outcome in patients with heart failure (HF). This study aimed to investigate whether prolonged total atrial conduction time predicts poor prognosis in patients with HF. We performed transthoracic echocardiography in 100 patients (65 men; mean age 68 ± 13 years) who were hospitalized for HF. Total atrial conduction time was defined as the duration from P wave onset on electrocardiography to peak A' wave on tissue Doppler imaging (TDI) echocardiography (PA-TDI duration). There were 37 cardiac events (37%) during a median follow-up period of 414 days. The PATDI duration was significantly longer in patients with cardiac events than in those without (150 ± 18 ms vs 133 ± 19 ms; $P < 0.05$). There were no significant differences in left ventricular end-diastolic dimensions and ejection fractions between patients with and without cardiac events. Patients with HF were divided into 3 groups according to tertiles of the PA-TDI duration. Kaplan–Meier analysis showed that the highest tertile of PA-TDI duration was associated with the greatest risk among patients with HF. Multivariate Cox proportional hazard analysis showed that the PA-TDI duration was an independent predictor of cardiac events, leading to the conclusion that prolonged PA-TDI duration was a feasible predictor of cardiac prognosis in patients with HF.

Keywords Heart failure · Atrial conduction time · Tissue Doppler imaging · Prognostic factor

Introduction

Heart failure (HF) is a major and growing health problem in developed countries. Despite advances in medical treatment, the annual mortality and morbidity rates for HF are still high [1–3]. Several studies have shown that increased left atrial (LA) remodeling predicts a poor prognosis in patients with HF [4]. Since the LA is directly exposed to left ventricular (LV) filling pressure during the diastolic phase, an increase in LA filling pressure leads to dilatation of the chamber in patients with HF. Therefore, LA pressure and size can be a marker of the burden of LV diastolic dysfunction [5].

Atrial size is most commonly used as a marker of structural atrial remodeling [6]. By contrast, prolonged total atrial conduction time is a sign of electrical and structural remodeling of the atria [7]. Several studies have suggested that atrial conduction time evaluated through signal-averaged electrocardiography (ECG) was associated with poor cardiac prognosis in patients with HF [8]. However, it takes a long time to evaluate atrial conduction time with signal-averaged ECG. Recently, an easy method for evaluating atrial conduction time by means of tissue Doppler imaging (TDI) echocardiography was reported [7]. The present study aimed to examine whether the total atrial conduction time as evaluated by TDI echocardiography can risk-stratify patients with HF and predict cardiac prognosis.

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Methods

Patients

One hundred patients (65 men and 35 women; mean age 68 ± 13 years) who were admitted to Yamagata University Hospital for the treatment of worsening HF or therapeutic evaluation of HF were enrolled in the study. The diagnosis of HF was made by two senior cardiologists using the generally accepted Framingham criteria and other relevant information, including a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion or peripheral edema, the presence of moist rales on auscultation, or the documentation of LV enlargement or dysfunction by chest radiography or echocardiography [9, 10]. The functional severity of HF at admission was assessed by the New York Heart Association (NYHA) functional class. Diagnoses of hypertension, diabetes, and hyperlipidemia were obtained from medical records or patient histories of current or previous medical therapy.

All patients were evaluated clinically through ECG, echocardiography, and routine biochemical tests. Echocardiography recordings were obtained when patients had a normal sinus rhythm with a heart rate of 50–100 beats/min. The exclusion criteria were as follows: advanced malignant tumors, renal insufficiency characterized by a serum creatinine concentration > 2.0 mg/dL, severe valvular heart disease, atrial flutter, chronic atrial fibrillation (AF), and permanent pacemaker implantation. Informed consent was given by each patient before participation in the study, and the protocol was approved by the institution's Human Investigations Committee.

Blood samples were obtained for the measurement of plasma B-type natriuretic peptide (BNP) upon admission and discharge and for the measurement of estimated glomerular filtration rate (eGFR) upon discharge. Plasma BNP levels were measured using a commercially available specific radio-immunoassay (SHIONORIA BNP assay kit; Shionogi & Co. Ltd., Osaka, Japan) [10]. Clinical data, including age, sex, and NYHA functional class upon admission, were obtained from hospital medical records and patient interviews. The time of discharge was decided by two senior cardiologists.

Echocardiography

Transthoracic echocardiography (TTE) was performed on a Vivid E9 ultrasound instrument (GE Healthcare, Chicago, IL USA), equipped with a sector transducer (carrier frequency of 2.5 or 3.75 MHz). During echocardiography, single-lead ECG was simultaneously recorded. TTE was performed while the patient was in a stable condition with HF before discharge. The following parameters were assessed using standard views and techniques: left atrial dimension (LAD) was measured at end-systole in the 2-dimensional parasternal long-axis view. LA volume was assessed at LV end-systole using the biplanar area-length method from the 4- and 2-chamber views [11]. Measurements of LA volume were indexed by body surface area (LA volume index, LAVI). LV internal diameter was measured at end-diastole and end-systole in the 2-dimensional parasternal long-axis view. LV ejection fraction (LVEF) was calculated using the biplanar method of disks (modified Simpson's rule) [12]. All patients underwent pulsed-wave Doppler examination of mitral inflow. Peak transmitral flow E wave and A wave velocities, E wave deceleration time (DCT), and ratio of E wave to A wave were measured from the apical 4-chamber view. The apical 4-chamber view was used to obtain the TDI of the mitral annulus. A sample volume of pulsed-wave Doppler was positioned at the septal and lateral side of the mitral annulus, and the spectral signal of the mitral annular velocity was recorded. The peak early (E') mitral annular velocity was measured, and the ratio of the E wave to E' (E/E') was calculated. Total atrial conduction time was assessed by measuring the time interval between the onset of the P wave on the surface ECG and the point of the peak A wave on TDI echocardiography from the LA lateral wall just over the mitral annulus (PA-TDI duration) [7]. All valves were evaluated using continuous Doppler color flow and Doppler imaging for stenosis and regurgitation. Patients with severe stenosis and regurgitation were excluded, and those with less than moderate stenosis and regurgitation were included in the present study. All echocardiographic measurements were calculated as mean values from three consecutive cardiac cycles and evaluated by two independent experienced echocardiologists who were blinded to the clinical status of patients.

The reproducibility of the PA-TDI duration measurement was assessed in 20 randomly selected subjects. Interobserver variability presented by interclass correlation coefficient (ICC) was calculated using images independently recorded on two different occasions by two different observers. Interobserver ICC of the PA-TDI duration was 0.85, indicating that the reproducibility was good.

Endpoints and follow-up of patients

Patients were prospectively followed until the occurrence of cardiac events, and no patients were lost to follow-up after discharge (median follow-up period of 414 days, interquartile range 192–730 days). The endpoints were the following: (1) cardiac death, defined as death due to worsening HF or sudden cardiac death, and (2) worsening HF requiring

rehospitalization. Sudden cardiac death was defined as death without definite preceding symptoms or signs and was confirmed by the attending physician.

Statistical analysis

Results are expressed as means ± standard deviation (SD) for continuous variables and as percentages of the total number of patients for categorical variables. Data for skewed variables are presented as medians with interquartile ranges. Independent *t*-tests and chi-squared tests were used for comparison of continuous and categorical variables, respectively. If data were not normally distributed, the Mann–Whitney *U* test was used. Cox proportional hazard analysis was performed to determine independent predictors of cardiac events for the entire population. Variables that were significant in the univariate analysis were entered into the multivariate model. The cardiac event-free curve was analyzed using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was defined as *P* values < 0.05. Statistical analyses were performed using a standard statistical program (JMP software, version 11.2, SAS Institute Inc., Cary, NC USA).

Results

Clinical characteristics of the study subjects

There were 13 patients (13%) in NYHA functional class II, 47 patients (47%) in class III, and 40 patients (40%) in class IV. The etiology of HF was dilated cardiomyopathy in 24 patients (24%), ischemic heart disease in 31 (31%), valvular heart disease in 10 (10%), hypertensive heart disease in 19 (19%), and other causes in 16 (16%). During the median follow-up of 414 days, there were 37 cardiac events (37%) including 6 cardiac deaths and 31 rehospitalizations due to worsening HF. The clinical characteristics of patients with or without cardiac events are shown in Table 1. Patients with cardiac events were significantly older than those without. There were no significant differences identified in sex; NYHA functional class; prevalence of hypertension, diabetes mellitus, dyslipidemia, and paroxysmal AF; and the etiology of HF between patients with and without cardiac events.

Echocardiographic parameters

Patients with cardiac events had a significantly greater LAVI, *E* wave, *E/E′* ratios, and a longer PA-TDI duration than did those without (Table 1). There were no significant differences in LVDd, LVEF, and *E/A* ratios between patients with and without cardiac events. There was a weak correlation between the PA-TDI duration and the LAVI (*r* = 0.232;

P = 0.023) (Fig. 1a). However, simple linear regression analysis showed no correlation between the PA-TDI duration and age (*P* = 0.599) (Fig. 1b), *E/E′* (*P* = 0.709) (Fig. 1c), and BNP (*P* = 0.565) (Fig. 1d).

Blood markers and medication use

Although there was no significant difference in plasma BNP levels at admission between patients with and without cardiac events, plasma BNP levels at discharge were significantly higher in patients with cardiac events than in those without. eGFR was significantly lower in patients with cardiac events than in those without. There were no significant differences in medication use between patients with and without cardiac events.

Risk stratification by PA-TDI duration and clinical outcome

The univariate Cox proportional hazard analysis revealed that the PA-TDI duration was associated with cardiac events (Table 2). LAVI, *E* wave, *E/E′*, BNP, and eGFR were related to cardiac events. In a multivariable Cox analysis adjusted for age, LAVI, and *E/E′*, the PA-TDI duration was independently associated with cardiac events [hazard ratio (HR) 2.498; 95% confidence interval (CI) 1.684–3.714; *P* < 0.001; Table 3, model 1]. The PA-TDI duration remained independently associated with cardiac events with the adjustment for BNP instead of *E/E′* (HR 2.542; 95% CI 1.727–3.745; *P* < 0.001; Table 3, model 2). The results were similar after the adjustment for eGFR instead of *E/E′* (HR 2.476; 95% CI 1.726–3.582; *P* < 0.001; Table 3, model 3).

Supplemental Figure 1 is the scatter plot of the PA-TDI duration in patients with HF with and without cardiac events. There was a slight overlap in the distribution between the 2 groups. All patients were divided into tertiles according to the PA-TDI duration: first tertile (< 131 ms, *n* = 33), second tertile (131–147 ms, *n* = 34), and third tertile (> 147 ms, *n* = 33). Kaplan–Meier analysis demonstrated that the risk of cardiac events was significantly higher in patients in the third tertile than in the other groups (Fig. 2). We then categorized patients into four groups according to the median LAVI (51.3 mL/m²) and median PA-TDI duration (140 ms): low LAVI and short PA-TDI duration, low LAVI and long PA-TDI duration, high LAVI and short PA-TDI duration, and high LAVI and long PA-TDI duration. Figure 3 shows hazard ratios for cardiac events in patients stratified by LAVI and PA-TDI duration categories compared to those with low LAVI and short PA-TDI duration. Patients with high LAVI and long PA-TDI duration had the highest risk for cardiac events among patients with HF (HR 5.270; 95% CI 1.979–18.187; *P* = 0.005).

Table 1 Comparison of clinical characteristics between patients with and without cardiac events

	Event free n=63	Cardiac event n=37	P value
Age (years)	65 ± 14	73 ± 10	.0060
Gender (M/F)	42/21	23/14	.6492
NYHA functional class I–II/III–IV (at admission)	9/54	4/33	.6138
NYHA functional class I–II/III–IV (at discharge)	61/2	36/1	.8930
Heart rate (beats/min)	66 ± 11	63 ± 11	.2418
Hypertension	41 (65%)	23 (62%)	.7695
Diabetes mellitus	27 (43%)	13 (35%)	.4450
Dyslipidemia	30 (48%)	14 (38%)	.3399
Current smoker	21 (33%)	13 (35%)	.8544
Paroxysmal atrial fibrillation	11 (17%)	10 (27%)	.2620
Etiology of heart failure			.2439
DCM	18 (29%)	6 (16%)	
IHD	20 (32%)	11 (30%)	
VHD	5 (8%)	5 (14%)	
HHD	13 (21%)	6 (16%)	
Others	7 (11%)	9 (24%)	
Echocardiography			
LAVI (mL/m^2)	49 ± 14	64 ± 30	.0006
LVDd (mm)	58 ± 8	55 ± 11	.2107
LVEF (%)	43 ± 13	45 ± 14	.3388
E wave (cm/s)	56 ± 30	76 ± 38	.0056
Deceleration time (ms)	196 ± 58	185 ± 49	.3163
E/A	1.22 ± 0.96	1.46 ± 1.19	.3043
E/E'	14.1 ± 5.7	17.9 ± 8.3	.0088
PA-TDI duration (ms)	133 ± 19	150 ± 18	< .0001
Blood marker			
BNP at admission (pg/mL)	703 (454–1513)	821 (568–1529)	.9713
BNP at discharge (pg/mL)	165 (107–398)	399 (187–587)	.0282
eGFR (mL/min/1.73 m^2)	64 ± 19	50 ± 21	.0010
Medication			
ACE inhibitors or ARBs	57 (90%)	30 (81%)	.2341
β-blockers	51 (81%)	31 (84%)	.7204
Ca-channel blockers	14 (22%)	8 (22%)	.9441
Diuretics	40 (63%)	27 (73%)	.3265

Results are presented as mean ± SD, n (%), or median (interquartile range)

DCM dilated cardiomyopathy, *IHD* ischemic heart disease, *VHD* valvular heart disease, *HHD* hypertensive heart disease, *LAD* left atrial dimension, *LAVI* left atrial volume index, *LVDd* left ventricular end diastolic dimension, *LVEF* left ventricular ejection fraction, *E wave* the early transmitral flow velocity, *E/A* the ratio of peak early to late filling velocity, *E/E'* the ratio of the early transmitral flow velocity and the early mitral annular velocity, *BNP* B-type natriuretic peptide, *eGFR* estimated glomerular filtration rate, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

Discussion

The new findings from this study are as follows: (1) PA-TDI duration was associated with poor cardiac prognosis in patients with HF. (2) PA-TDI duration showed weak or no correlation to conventional echocardiographic parameters and BNP, suggesting that these parameters may have different prognostic significance. (3) The combined assessment of the PA-TDI duration and LAVI appeared to be clinically relevant to the risk stratification of adverse outcome in patients with HF.

Van Beeumen et al. [13] reported that atrial conduction delay is independent of the atrial tissue mass or the surface area in patients with HF. Atrial conduction disturbance results from the structural remodeling of the atria, characterized by the occurrence of fragmented atrial activity,
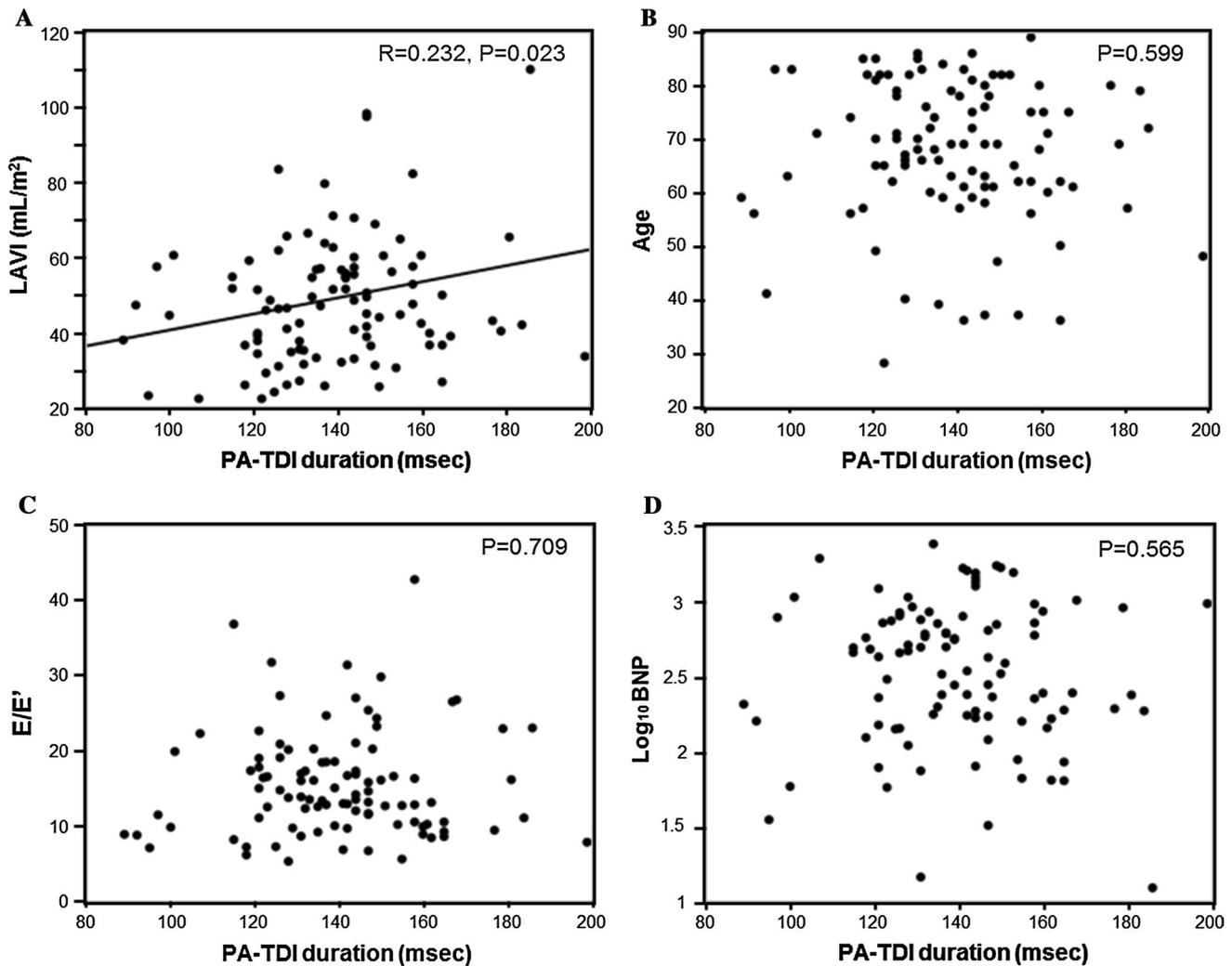
Fig. 1 The relationship between the PA-TDI duration and LAVI. The PA-TDI duration has a weak correlation with LAVI ($r = 0.232$; $P = 0.023$) (**a**). The relationship between the PA-TDI duration and age. The PA-TDI duration has no correlation with age ($P = 0.599$) (**b**). Relationship between the PA-TDI duration and E/E'. The PA-TDI duration has no correlation with E/E' ($P = 0.709$) (**c**). The relationship between the PA-TDI duration and BNP. The PA-TDI duration has no correlation with BNP ($P = 0.565$) (**d**). *LAVI* left atrial volume index, *PA-TDI* prolonged total atrial conduction time on tissue Doppler imaging echocardiography, *E/E'* the peak early (E') mitral annular velocity was measured, and the ratio of the E wave to E' (E/E') was calculated, *BNP* plasma B-type natriuretic peptide

regions of low voltage, and interstitial atrial fibrosis [14]. These findings demonstrate that this functional physiological parameter, atrial conduction time, is a surrogate marker of atrial remodeling. Ozer et al. [15] showed that the total atrial conduction time was longer in patients with mitral stenosis than in control subjects and that atrial conduction delay was related with LA size. Similarly, Caglar et al. [16] showed that the right atrial conduction time is longer in patients with chronic obstructive pulmonary disease than in control subjects, and they observed a positive correlation between the right atrial area and atrial conduction time. These indicate atrial size as being an important factor for determining the atrial conduction time.

Signal-averaged ECG is a noninvasive method for measuring the cardiac conduction time and has been used as the gold standard for determining the atrial conduction time. Atrial conduction time has been evaluated for atrial remodeling in some cardiac disorders such as paroxysmal AF, acute myocardial infarction, and congestive HF [8, 17, 18]. However, signal-averaged ECG is not routinely used in every hospital because of the requirement for special hardware and the time-consuming nature of the technique. On the contrary, atrial conduction time evaluated by TDI echocardiography is easy to assess in clinical practice. Merckx et al. [7] demonstrated that the PA-TDI duration showed a significant correlation with the signal-averaged P wave duration.

Table 2 Results of univariate Cox proportional hazard analysis for cardiac events

Variable	Hazard ratio	95% CI	*P* value
Age (per 1 increase)	1.034	1.007–1.065	.0124
Gender (female)	1.108	0.556–2.130	.7631
NYHA functional class III–IV (at admission)	1.208	0.480–4.056	.7145
Paroxysmal atrial fibrillation	1.641	0.755–3.289	.1996
LAVI (per 1SD increase)	1.745	1.296–2.264	.0005
LVDd (per 1SD increase)	0.785	0.549–1.111	.1738
LVEF (per 1SD increase)	1.179	0.855–1.615	.3128
E wave (per 1SD increase)	1.677	1.158–2.379	.0065
E/E' (per 1SD increase)	1.380	1.047–1.758	.0239
PA-TDI duration (per 1SD increase)	2.150	1.534–2.995	<.0001
Log_{10} BNP at admission (per 1SD increase)	1.134	0.825–1.565	.4387
Log_{10} BNP at discharge (per 1SD increase)	1.581	1.114–2.294	.0097
eGFR (per 1SD increase)	0.585	0.428–0.803	.0010

Abbreviations as in Table 1

CI confidence interval

Table 3 Results of multivariate Cox proportional hazard analysis for cardiac events

Analysis	Hazard ratio	95% CI	*P* value
Unadjusted	2.150	1.534–2.995	<.0001
Model #1: adjusted for age, LAVI and *E/E'*	2.498	1.684–3.714	<.0001
Model #2: adjusted for age, LAVI and BNP	2.542	1.727–3.745	<.0001
Model #3: adjusted for age, LAVI and eGFR	2.476	1.726–3.582	<.0001

Abbreviations as in Table 1

CI confidence interval

Fig. 2 Kaplan–Meier analysis showed that there was an increase in risk of cardiac events with each incremental category of the PA-TDI duration. *PA-TDI* prolonged total atrial conduction time on tissue Doppler imaging echocardiography
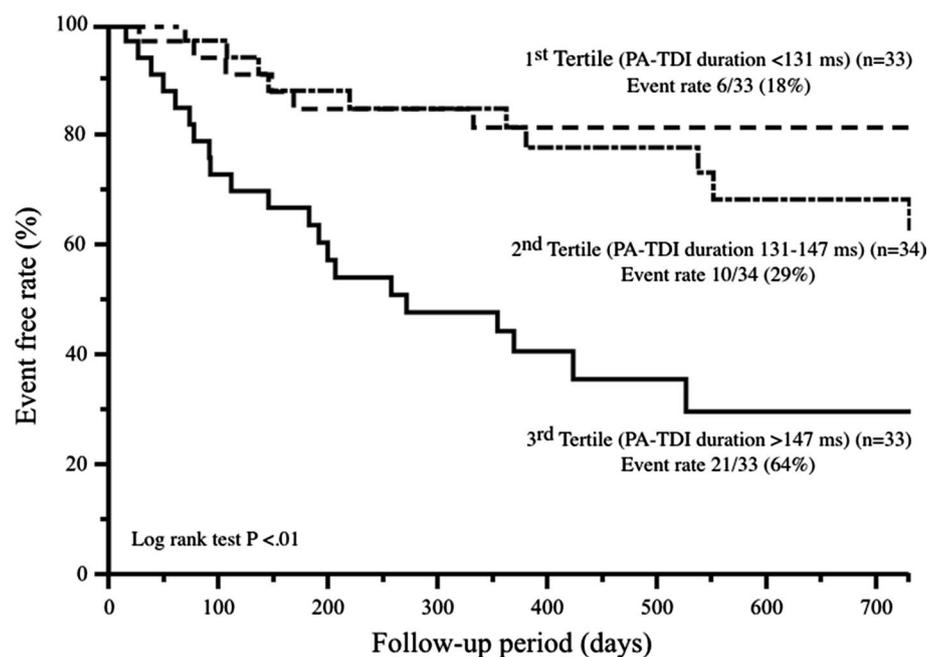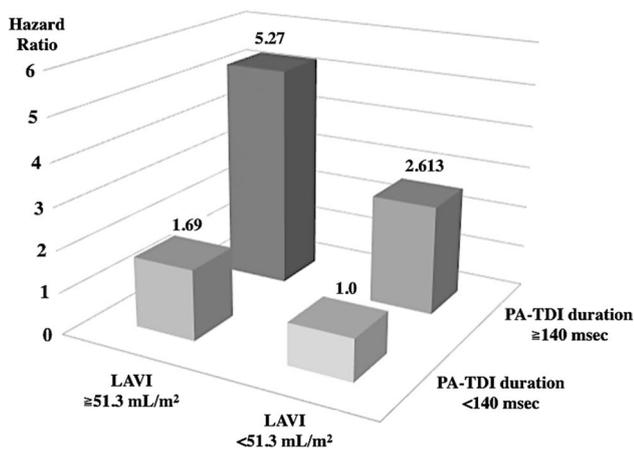
Fig. 3 Cox proportional hazard regression for cardiac events in patients stratified by the PA-TDI duration and LAVI categories. *LAVI* left atrial volume index, *PA-TDI* prolonged total atrial conduction time on tissue Doppler imaging echocardiography

Furthermore, Deniz et al. [19] demonstrated that the PA-TDI duration showed a fair correlation with the atrial conduction time as evaluated by an electrophysiological study. These findings support the finding that the PA-TDI duration is a feasible marker for total atrial conduction time.

Several studies have identified the PA-TDI duration as an independent predictor of new-onset AF, postoperative AF after cardiac surgery, and recurrent AF after catheter ablation and electrical cardioversion [20, 21]. These suggested that a prolonged PA-TDI duration is considered to be a predictor of the development of AF and a useful parameter of atrial remodeling. Waggoner et al. showed that the atrial conduction time is increased in patients with severe left ventricular systolic dysfunction and wide QRS interval [22].

However, the prognostic value of the PA-TDI duration in patients with HF has not been fully determined. For the first time, we demonstrated that the PA-TDI duration was an independent predictor of adverse cardiac events in patients with HF. Similarly, Bilgin et al. showed that atrial conduction delay is frequently observed in patients with systolic HF and is associated with mortality [23]. In their study, patients with systolic HF had prolonged PA-TDI duration (139 ms) compared with patients without HF (109 ms). PA-TDI duration in patients with systolic HF [ejection fraction (EF) < 50%] was 138 ± 20 ms in the present study which was equal to the results from the previous report.

In the present study, the PA-TDI duration did not correlate with *E/E′* and plasma BNP levels at discharge. *E/E′* and the plasma BNP level are established markers associated with LV end-diastolic pressure (LVEDP) [24, 25]. However, Doppler variables and plasma BNP levels are affected by hemodynamic changes and are easily altered. We suggest that the PA-TDI duration is less influenced by acute hemodynamic changes and reflects the atrial structural and the electrical remodeling more than other markers.

Our results are consistent with those in these earlier reports. In the present study, since there were 35 patients with a preserved EF, LVEF was not a significant predictor of cardiac events. By contrast, Hosseinsabet [26] showed that there was no significant difference in the atrial conduction time between patients with mild LV diastolic dysfunction and normal LA volume who showed normal LV filling pressure and healthy subjects. Kishima et al. [27] reported that atrial conduction delay was significantly associated with high LA pressure in patients with AF who have normal LA size. These findings suggested that the atrial conduction time can better reflect atrial pressure than atrial size. Atrial conduction time correlates to the severity of atrial remodeling rather than the atrial size itself in HF. Further, combined assessment of LAVI and the PA-TDI duration stratified patients with HF well.

Many previous studies have reported that AF is an independent risk factor for a deteriorating clinical prognosis in patients with HF. Finding a feasible prognostic predictor is still important even for patients without AF. The PA-TDI duration provides new insight into the evaluation of atrial remodeling.

The present study has several limitations. First, this study population was relatively small and from a single institution. The present findings should be validated in a larger prospective study. Second, the PA-TDI duration can be measured only in patients with sinus rhythm. Third, because echocardiography was not performed during follow-up, it remains unclear whether the long-term prognosis was affected by improvement in the PA-TDI duration. Fourth, since we included patients admitted for HF into this study, the characteristics of patients were heterogenous, including patients with different etiologies and varied EFs. Therefore, the study patients included both those with a preserved EF and a reduced EF. We could not perform a subanalysis to clarify the predictive value of the PA-TDI duration for HF patients with a preserved EF and a reduced EF because of the small number of patients in each subgroup. Further study with a large study population is needed for an adequate subanalysis.

Conclusion

The PA-TDI duration may be a feasible noninvasive parameter for predicting poor cardiac prognosis in patients with HF. It is important to evaluate not only structural LA remodeling but also functional LA remodeling.

Compliance with ethical standards

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

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