Noninvasive Assessment of Left Ventricular Diastolic Electromechanical Coupling in Hypertensive Heart Disease

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Running title: Electromechanical Coupling in HHD

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Key Words: Tpeak-Tend interval, E/e', hypertension, diastolic electromechanical coupling

Word counts: 2823

Abstract

Background: There is a need to stratify patients who may develop heart failure because of the current "heart failure pandemic". We hypothesized that noninvasive assessment of diastolic electromechanical coupling by electrocardiography and Doppler echocardiography may be clinically useful for risk stratification of hypertensive patients who may develop heart failure.

Methods: We measured the time from the peak to end of the T-wave (TpTe) as an electrophysiological parameter, and peak early-diastolic mitral flow (E) and lateral annular (e') velocities as mechanical parameters in 109 patients with hypertension. Relationships between these parameters and their association with the prognosis was evaluated.

Results: The e' was inversely correlated with TpTe ($p<0.001$) and QTc ($p < 0.014$), whereas E/e' was positively correlated with TpTe ($p<0.001$) and QTc ($p<0.001$). The TpTe predicted patients with E/e' > 12. There were 24 cardiovascular events during follow-up (57 ± 20 months), and Kaplan-Meir analysis showed that outcome was worse ($p=0.003$) in patients with higher E/e' than lower E/e', however, there was no difference between patients with longer TpTe (≧72 msec) and shorter TpTe (<72 msec).

Conclusions: The correlation of TpTe with e' and E/e' in hypertensive patients suggests that these parameters reflect diastolic ventricular electromechanical coupling. The E/e' predicted outcome, and an elevated E/e' should be suspected when TpTe is prolonged (> 72 msec).

Noninvasive evaluation of diastolic electromechanical coupling is clinically useful in patients with hypertension.

Introduction

The number of patients suffering from heart failure and the number deaths from heart failure are increasing worldwide, and this has been called a "heart failure pandemic".[1] In advanced countries, the prevalence of heart failure is increasing despite the declining population, and the medical expenses in this population are also increasing.[2] Until around 1980, heart failure with reduced left ventricular ejection fraction (HFrEF) was dominant, but in recent years heart failure with preserved left ventricular ejection fraction (HFpEF) has increased, and more than half of all cases of heart failure are currently due to HFpEF, especially in advanced countries.[3] Typical features of patients with HFpEF are older age, female gender and the presence of hypertensive heart disease. The prognosis of HFpEF is the same as that of HFrEF.[4] Thus, early identification of patients at risk of HFpEF and early intervention to improve prognosis are important issues.

Currently, the diagnosis of the HFpEF generally requires 1) signs of heart failure, 2) normal ejection fraction (>40-50%) and 3) proof of left ventricular diastolic dysfunction[5]. In order to prove left ventricular diastolic dysfunction, Doppler echocardiography is used in the clinical setting to obtain left atrial size and other Doppler echocardiographic parameters, such as transmitral flow velocity profile, mitral annular velocity and tricuspid regurgitant flow velocity[6]. Furthermore, the interval from T-peak to T-end (TpTe) in the electrocardiogram

(ECG) has been suggested as an index of transmural dispersion of repolarization and as a marker of left ventricular relaxation.[7] Combining the two modalities, which can be obtained in routine clinical practice, allows noninvasive evaluation of “diastolic electromechanical coupling”.[8] We hypothesized that the pathophysiological evaluation of diastolic ventricular electromechanical coupling may provide clinically useful information for the risk stratification of patients who are at risk of developing heart failure.

To verify this hypothesis, we evaluated diastolic electromechanical coupling using electrocardiography and echocardiography in patients with hypertensive heart disease, which is a typical background disease of HFpEF, and assessed the relationship between impaired diastolic electromechanical coupling and prognosis. The purpose of this prospective study was to establish the clinical usefulness of noninvasive evaluation of diastolic electromechanical coupling in hypertensive patients who are at risk of developing heart failure.

Methods

Study population

The study population included consecutive 120 patients with hypertension who underwent electrocardiography and echocardiography in Tokushima University Hospital from January 2010 to October 2012 and had follow-up by December 2016. All subjects had antihypertensive drugs prescribed. A few subjects had anti-arrhythmic drugs such as pilsicainide (n=1), mexiletine hydrochloride (n=1). Eleven patients were excluded due to moderate or severe valvular disease (n=3), atrial fibrillation/flutter (n=3), congenital heart disease (n=1), significant interstitial lung disease (percent forced vital capacity <70%, n=2) and significant chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m^2, n=2). No patient had malignant tumor with a poor prognosis. There were no patients with bundle-branch block, atrioventricular block, conduction disturbances such as WPW syndrome and pacemaker implantation due to intraventricular conduction delay. Patients with atrial flutter and multiple premature contractions were not included in our study. Demographic and clinical characteristics of the study subjects were obtained from our electronic medical records. The protocol of this study was approved by the Institutional Review of Tokushima University Hospital (no.2537), and written informed consent was obtained from each patient.

Electrocardiography

All subjects underwent standard 12-lead electrocardiography and transthoracic echocardiography on the same day. We performed a manual analysis of the standard 12-lead ECG at a speed of 50 mm/s and an amplitude of 10 mm/mV. ECGs were analyzed by a single trained reader blinded to the echocardiographic findings. Each ECG was analyzed according to a systematic protocol, which included measurement of ventricular activation time (VAT), QRS duration and QTc interval. The amplitudes of the R wave or R + S waves in several ECG leads (SV1+RV5, RV5, RI+SIII, RaVL) were used as parameters of left ventricular hypertrophy. VAT was measured in milliseconds in lead V5 or V6 from the onset of the QRS complex to the peak of the R-wave. We also measured the time from the peak of the T-wave to the end of the T-wave (TpTe) in lead V5 (Online figure 1). In cases in which V5 was not suitable for analysis, leads V4 or V6 were used for the measurement. The offset of the descending limb of the T-wave was defined as the intersection of a tangent to the terminal downslope of the T-wave and the isoelectric line. We used the QRS duration and VAT as ventricular depolarization and TpTe as ventricular repolarization.

Echocardiography

Routine transthoracic echocardiography was performed including 2-dimensional, M-mode, pulsed/continuous Doppler, color Doppler, and tissue Doppler imaging, according to guidelines of the American Society of Echocardiography[6, 9] and Japanese Society of Echocardiography.[10] Echocardiography was performed using commercially available ultrasound diagnostic machines (iE 33, Philips Medical Systems, Andover, MA, USA; Vivid E9, GE Healthcare, Milwaukee, WI, USA; Aplio 500, Toshiba Medical Systems, Tochigi, Japan). Digital echocardiographic data containing a minimum of 3 consecutive beats were acquired and transferred to a server for storage and archiving. Left ventricular ejection fraction (EF) was measured by the 2-dimensional biplane method of disks from the 4- and 2-chamber views. Left ventricular end-diastolic diameter, and interventricular septal and posterior wall thickness were measured at end diastole by M-mode or 2-dimensional echocardiography from the parasternal view as recommended by the American Society of Echocardiography. These parameters were used to calculate relative wall thickness and left ventricular mass, which was indexed to body surface area (LVMI). Left atrial and LV volumes were also measured at end-systole by the biplane method of discs, and left atrial volume was indexed to body surface area (LAVI). Left ventricular diastolic function was assessed according to the guidelines of the American Society of Echocardiography and included the following parameters: peak early-diastolic transmitral flow velocity (E), peak atrial-systolic transmitral flow velocity (A), E-wave deceleration time (E-DcT), E/A ratio, early-diastolic mitral annular velocity (e'), E/e' ratio, and atrial-systolic mitral annular velocity (a'). We measured e' and a' on the lateral side of the annulus, which usually shows greater values compared with the velocities on the septal side of the annulus.

Clinical Outcomes

Cardiac death, hospitalization due to acute heart failure, lethal arrhythmia, acute myocardial infarction, aortic dissection and stroke were considered major cardiac events. In addition, new onset atrial fibrillation, loss of consciousness, hypertensive crisis and symptoms of angina pectoris were considered minor cardiac events. If a patient died during follow-up, the cause of death was identified by medical record review or telephone contact. Cardiac death was defined as either a death directly related to cardiac disease (mainly congestive heart failure), stroke or sudden death.

Statistical Analysis

All data are expressed as mean ± SD. Statistical analyses were carried out with MedCalc Software 12.7.5.0 (Ghent, Belgium). A p-value < 0.05 was considered significant. To determine if two variables (electrocardiography and echocardiography) were associated, we used linear regression analysis. If one variable increased when the second one increased, then a positive correlation was present. In this case, the correlation coefficient would be close to 1. If one variable decreased when the other variable increased, then there was a negative correlation, and the correlation coefficient would be close to -1. The P-value is the probability that we would have found the current result if the correlation coefficient were in fact zero. To determine the electrocardiographic index that was the best predictor of an elevated E/e', we created receiver operating characteristics (ROC) curves, and tested the statistical significance of the difference between the areas under the ROC curves using the Z-test. The cutoff value of abnormal E/e' was determined as >12.[11] In Kaplan-Meier survival analysis, we used the log-rank test to compare event-free survival between patients stratified into two groups based on the median value of TpTe or E/ e'.

Results

Subject characteristics

The baseline characteristics of the 109 subjects are summarized in Table 1. The mean age was 64 ± 13 years, 64% were male, the mean blood pressure was 148 ± 24 / 81 ± 17 mmHg and the mean heart rate was 69 ± 12 beats/minute. As comorbidities, 69 (63%) patients had obesity, 38 (34%) had diabetes mellitus and 29 (26%) had hyperlipidemia. During the follow-up period, there were 24 cardiovascular events that included 5 percutaneous interventions (21%), 5 deaths (21%), 5 cerebral infarctions (21%), 3 cases of heart failure (13%), 3 supraventricular arrhythmias (12%), 1 case of syncope (4%), 1 myocardial infarction (4%) and 1 hypertensive crisis (4%).

Electrocardiographic and echocardiographic parameters

Baseline electrocardiographic and echocardiographic data are summarized in Table 1. The mean TpTe was 71.4 ± 11.9 msec, the mean VAT was 39.2 ± 6.1 msec, the mean QRS duration was 92.6 ± 9.5 msec and the mean QTc duration was 433.5 ± 24.9 msec. The mean left ventricular ejection fraction and the mean % fractional shortening were both in the normal range. The mean E-wave velocity was 66 ± 20 cm/sec, the mean A-wave velocity was 84 ± 22 cm/sec, the mean e' velocity was 7.8 ± 2.5 cm/sec, the mean a' velocity was 10.8 ± 3.1 cm/s and the mean E/e' was 9.2 ± 3.5.

Correlations between echocardiographic and electrocardiographic parameters

Figure 1 demonstrates correlations between the electrocardiographic parameters and the diastolic function (mechanical) parameters. The e' was inversely correlated with TpTe ($r = -0.49$, $p < 0.001$, Figure 1A) and QTc ($r = -0.23$, $p < 0.014$, Figure 1B), whereas E/e' was positively correlated with TpTe ($r = 0.42$, $p < 0.001$, Figure 1C) and QTc ($r = 0.41$, $p < 0.001$, Figure 1D). The correlations between TpTe and the diastolic function parameters were much stronger than the correlations between QTc and the diastolic function parameters. The relationship between TpTe and E was not significant ($p = 0.899$), whereas there was a correlation between QTc and E ($p = 0.009$). VAT was correlated with e' ($r = 0.21$, $p = 0.023$) and E/e' ($r = 0.31$, $p = 0.001$). Correlations between each diastolic echocardiographic and electrocardiographic parameter were shown in online table 1.

Comparison of ROC curves for predicting an elevated E/e'

Figure 2 shows ROC curves to discriminate an elevated E/e' (>12) based on the electrocardiographic indexes (TpTe, QTc and VAT). Cut off value for TpTe was 76 msec (sensitivity 69.6%, specificity 75.6%). The AUCs for TpTe, QTc and VAT were 0.722, 0.686 and 0.667, respectively, and the AUC for TpTe was the greatest.

Kaplan-Meier analysis for predicting clinical outcomes

Figure 3 displays Kaplan-Meier curves for survival free from cardiac events. Subjects were divided into two groups according to the median TpTe (Group 1: ≧ 72.0 msec, Group 2: < 72.0 msec) and median E/e' (Group 3: ≧ 9.07, Group 4: < 9.07). The higher E/e' group had a worse outcome compared with the lower E/e' group (p = 0.0033, Figure 3B); however, there was no difference in outcome between Group 1 and Group 2 (p = 0.701, Figure 3A).

Discussion

We attempted to evaluate diastolic electromechanical coupling in 120 hypertensive patients by comprehensive comparisons of diastolic parameters obtained by electrocardiography (QRS, VAT, QTc and TpTe), and Doppler echocardiography (E/A, E, A, E-DcT, e', a' and E/e'). Our key findings were as follows: 1) the TpTe and QTc intervals were negatively correlated with e' velocity, and the correlation between TpTe and e' velocity was much stronger than the correlation between QTc and e' velocity; 2) the TpTe and QTc intervals were positively correlated with E/e', and the correlation between TpTe and E/e' was much stronger than the correlation between QTc and E/e'; and 3) VAT was correlated weakly with the various Doppler parameters, but TpTe was strongly and specifically correlated with e’ and E/e’. Furthermore, we showed that TpTe can predict an elevated E/e’, which has been established as a prognostic marker in various cardiac diseases.

Diastolic electromechanical coupling

Left ventricular electromechanical coupling in systole has been widely examined by many investigators, and impaired left ventricular electromechanical coupling is a well-known phenomenon in various cardiac diseases, especially in patients with reduced ejection fraction.[12, 13] On the other hand, diastolic electromechanical coupling has not been extensively studied, although it has been evaluated in some patients with a long QT syndrome.[13, 14] Wilcox et al. demonstrated a good relationship between QTc interval and the diastolic dysfunction grade determined by Doppler echocardiography in unselected patients and suggested that QTc prolongation was the best electrocardiographic parameter to predict diastolic dysfunction.[15] However, the QTc interval encompasses both depolarization (systole) and repolarization (diastole). An animal study demonstrated that the T-peak to T-end (TpTe) interval in the ECG is more representative of transmural dispersion of repolarization than QTc.[7] Subsequently, Sauer et al.[8] demonstrated an inverse relationship between TpTe and tissue Doppler e' in unselected patients without long QT syndrome. In our study, both QTc and

TpTe were correlated with e' velocity and E/e', and TpTe had a stronger correlation with these echocardiographic parameters than QTc, which is consistent with previous reports. We confirmed a link between transmural electrical dispersion of repolarization and abnormal myocardial relaxation. Although VAT has attracted attention as a useful index for the electrocardiographic diagnosis of left ventricular hypertrophy, it has also been reported to be useful for detecting early diastolic dysfunction in patients with hypertension in recent years.[16] In the present study, VAT showed only a weak correlation with the diastolic parameters (e', E/e'), and there was a much stronger correlation of VAT with some of the other echocardiographic indices, such as LVMI.

Prediction of outcomes

The progression of diastolic dysfunction has been associated with adverse outcomes, including progression to overt heart failure.[17] E/e', which reflects left ventricular filling pressure, has been reported to predict prognosis in various heart diseases.[18, 19] Furthermore, TpTe prolongation has been shown to be associated with an increased risk of ventricular arrhythmias and mortality.[20] The TpTe interval, rather than the corrected QT interval (QTc), was reported to be a better predictor of arrhythmogenic risk in various pathological conditions.[21-25] In our study on cardiovascular outcome, an elevated E/e’ was strongly associated with adverse outcomes. Although there were slightly more events in the group with a higher TpTe than in the group with a lower TpTe, the difference was not significant. This result may have been because of the small number of subjects and the limited number of events due to ventricular arrhythmias. However, the fact that TpTe obtained from the ECG is related to E/e', which strongly reflects prognosis, may be clinically useful.

Clinical implications

The correlation between TpTe and E/e’ in patients with hypertension suggests a possible contribution of impaired ventricular diastolic electromechanical coupling as a mechanism of diastolic dysfunction. E/e’ is consistently a good parameter for predicting cardiac events, and a prolonged TpTe was associated with elevated E/e’ in the present study. Doppler echocardiography should be performed in patients with a prolonged TpTe (>72 msec). In asymptomatic patients with untreated hypertension, the progression of the disease may lead to heart failure. It is useful that electrocardiography, which is the simplest test of cardiac function, provides an index (TpTe) that reflects prognosis. The TpTe may correlated with LV diastolic mechanical dyssynchrony, which seems to be interesting topics for future investigation. Impaired diastolic electromechanical coupling may be a new target for the treatment of heart failure, and further research is necessary to clarify the mechanism.

Limitations

This was a single center study, the sample size was small and there were relatively few events, which poses a potential risk for model overfitting. We excluded patients with atrial fibrillation, although many patients with HFpEF due to hypertension or valvular heat disease have this arrhythmia. The difficulty in determining T-end when the T-wave morphology is flat or multiphasic may have affected the measurement of TpTe. However, the ECG reader was blinded, so that any such errors would be unrelated to the values of the other electrocardiographic or echocardiographic parameters. Therefore, any bias introduced by this error would be unlikely to affect the validity of the findings. Invasive diastolic parameters such as tau and –dP/dt were not able to be evaluated in this study. According to these limitations, the present study should be considered proof of concept, and we believe that larger prospective multicenter studies that include various etiologies of heart failure are warranted.

Conclusions

The electrocardiographic parameter, TpTe, was correlated with e’ and E/e’ determined by echocardiography in patients with hypertension, and this suggests that these parameters reflect diastolic ventricular electromechanical coupling. E/e’ was a predictor of outcome but

TpTe was not. Noninvasive evaluation of diastolic electromechanical coupling was clinically useful in patients with hypertension and should be performed in various cardiac diseases, since impaired diastolic electromechanical coupling may become a new target for heart failure management.

Funding

This work was partially supported by JSPS Kakenhi Grants (No. 16H05299 and 26248050 to M. Sata) and a grants-in-aid from the Takeda Science Foundation (to M.S.), the Fugaku Trust for Medical Research (to M.S.) and the Vehicle Racing Commemorative Foundation (to M.S.).

Disclosure

The authors declare that there is no conflict of interest.

Figure legends

Figure 1. Relationships between the diastolic electrocardiographic and Doppler echocardiographic parameters.

e', early-diastolic mitral annular velocity; QTc, corrected QT interval.

Figure 2. Comparisons of ROC curves of the electrocardiographic parameters to predict an E/e' > 12.

Figure 3. Kaplan-Meier survival curves comparing the cumulative freedom from clinical events between TpTe < 72 and ≧ 72 (A), and E/e' ≧ 9.07 and E/e' < 9.07(B).

Online figure 1. Measurement of TpTe. Time from the peak of the T-wave to the end of the T-wave (TpTe) in the 12-lead ECG was measured in lead V5. If this could not be measured in lead V5, then we used other leads.

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*Highlights

・Diastolic electromechanical coupling can be evaluated by electrocardiography and Doppler echocardiography

・The e’ inversely correlates with TpTe and QTc, whereas E/e’ positively correlates with TpTe and QTc

・The E/e’ predictes outcome, and an elevated E/e’ should be suspected when TpTe is prolonged

Figure 1A
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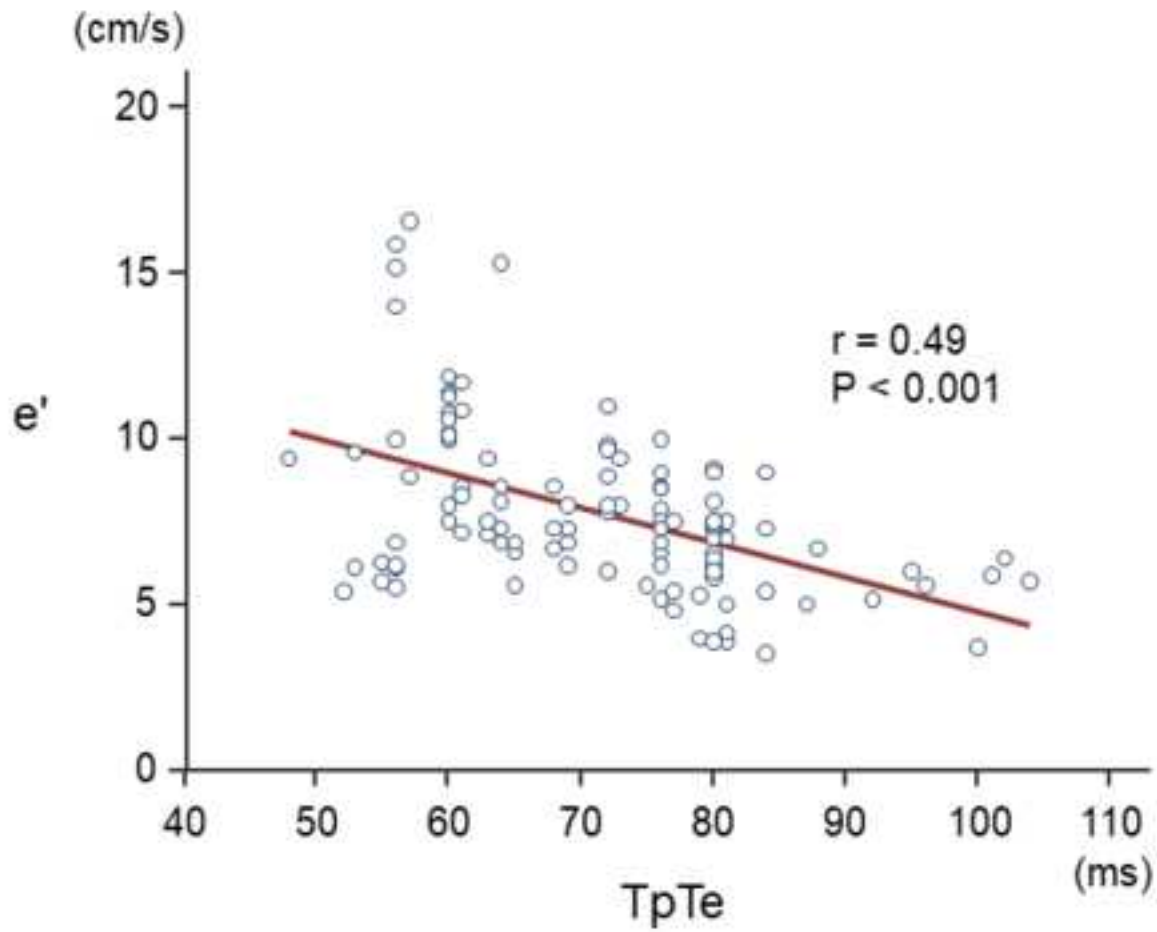
Figure 1A



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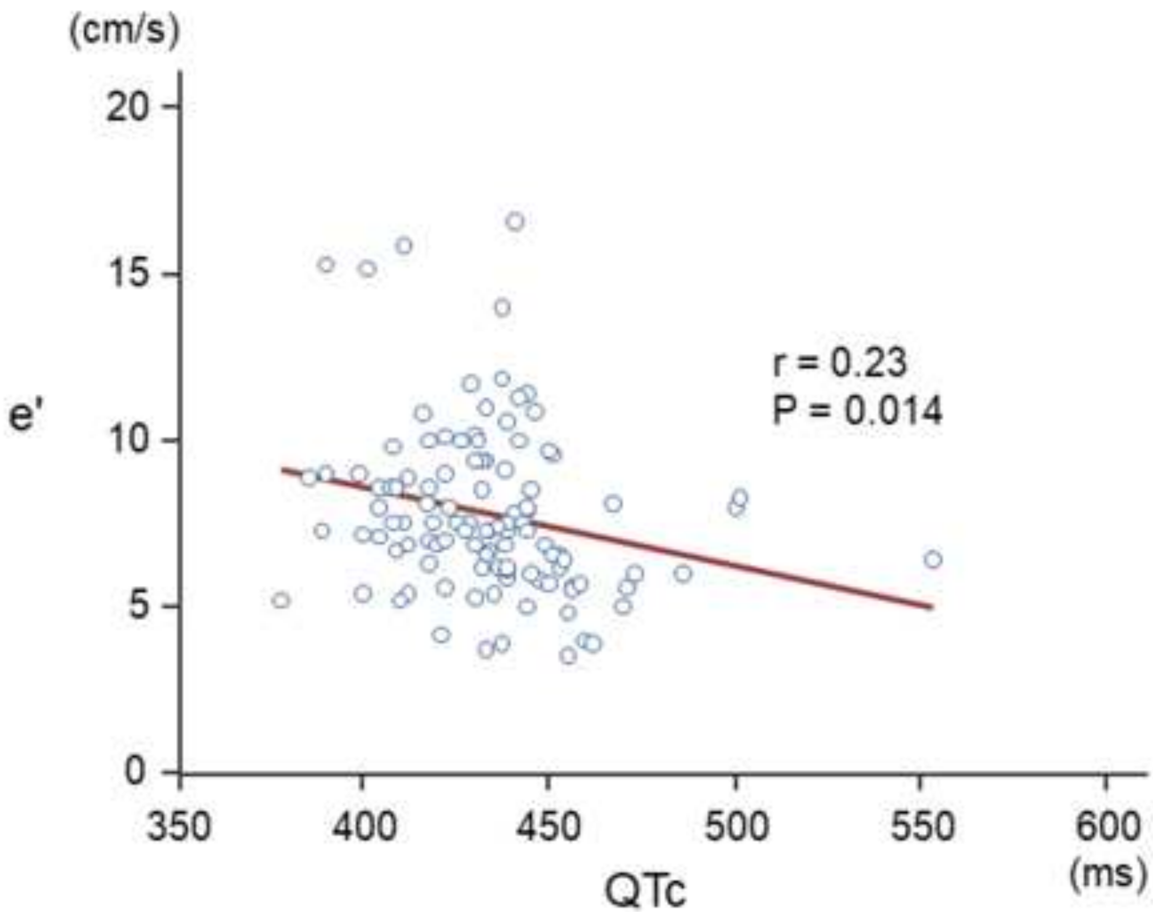

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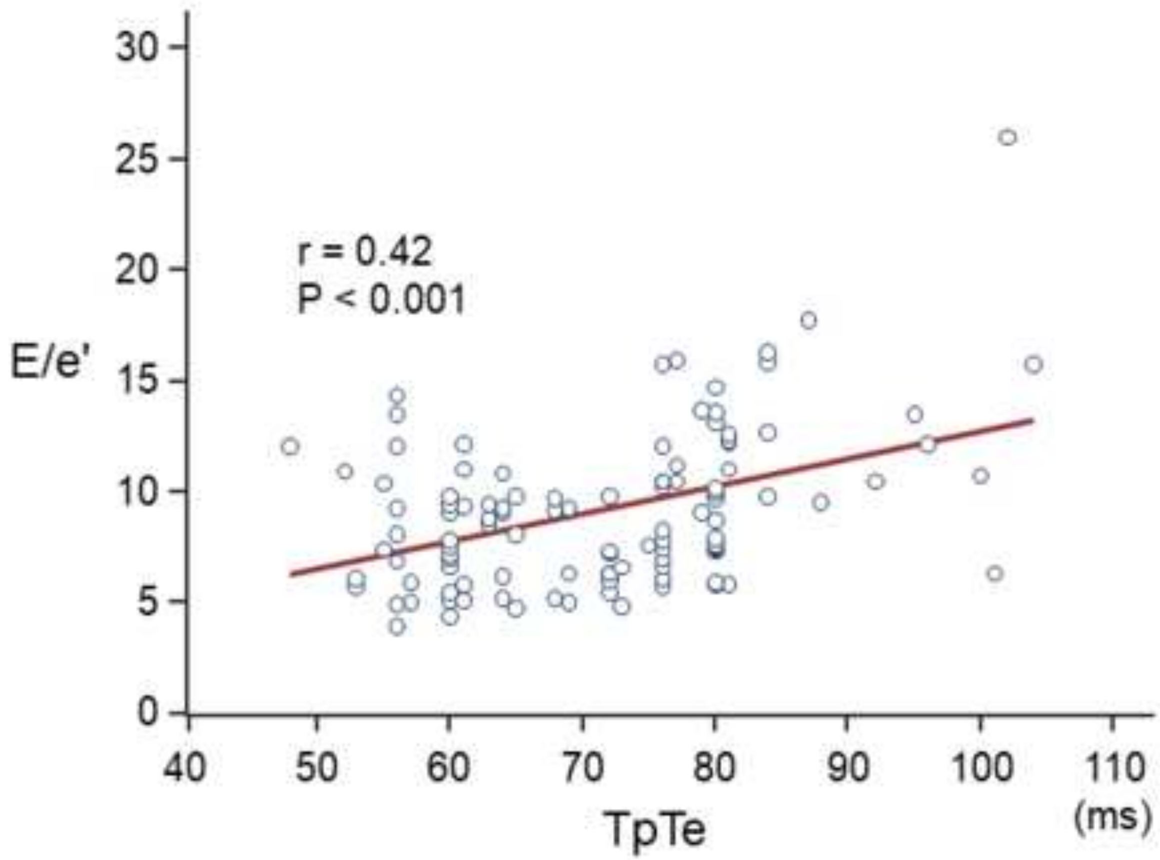

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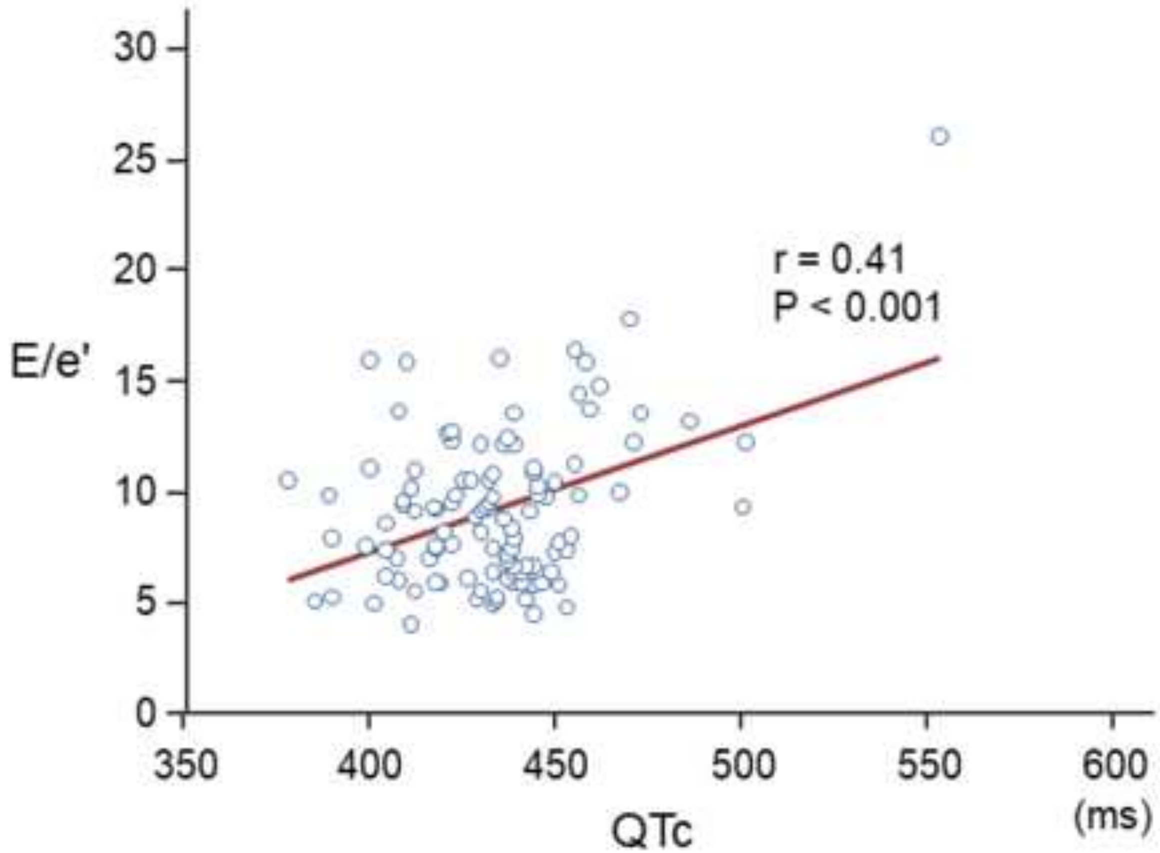

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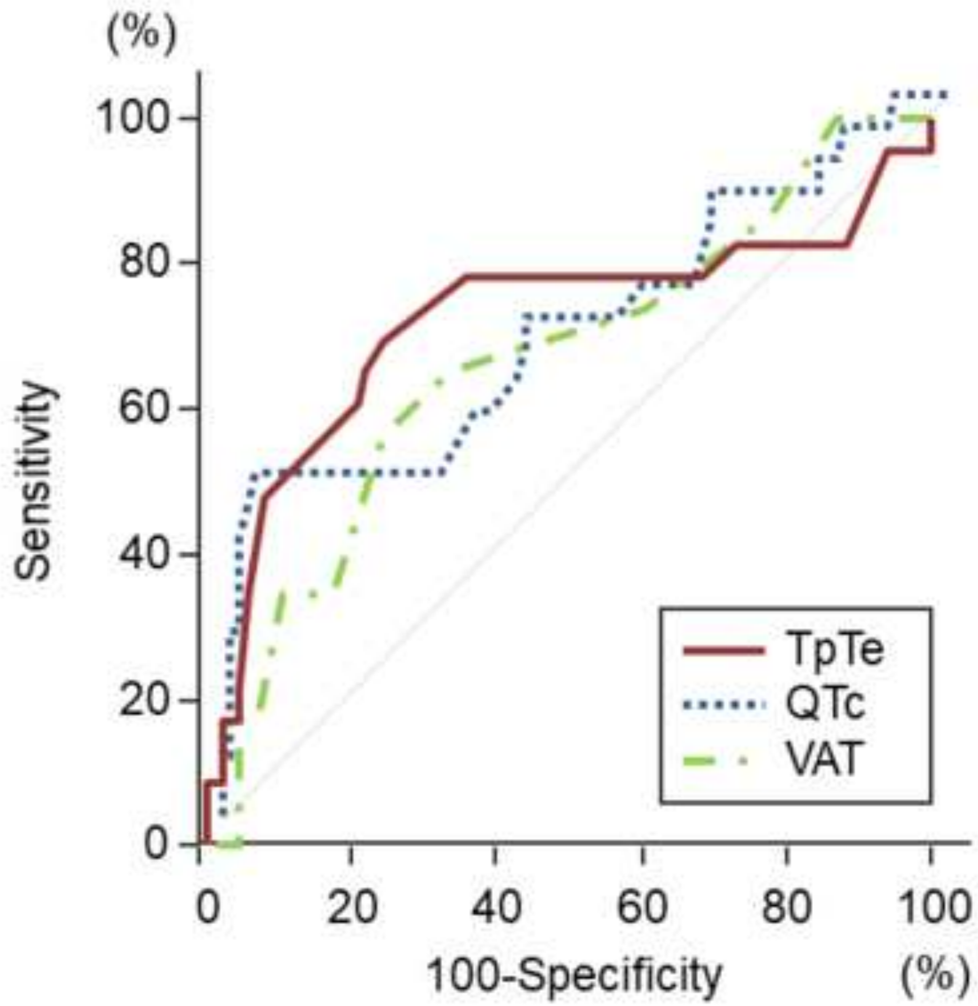
Figure 2



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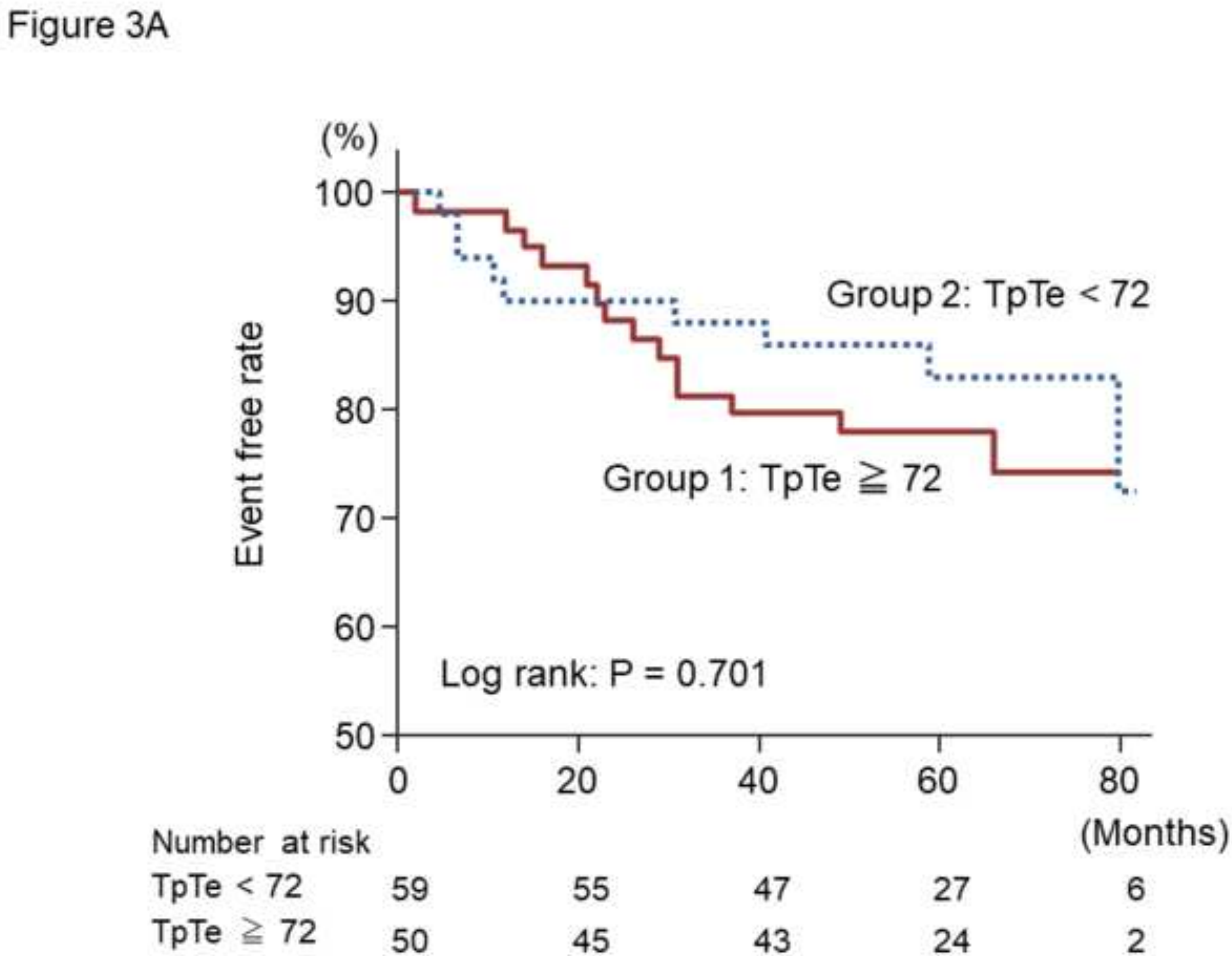

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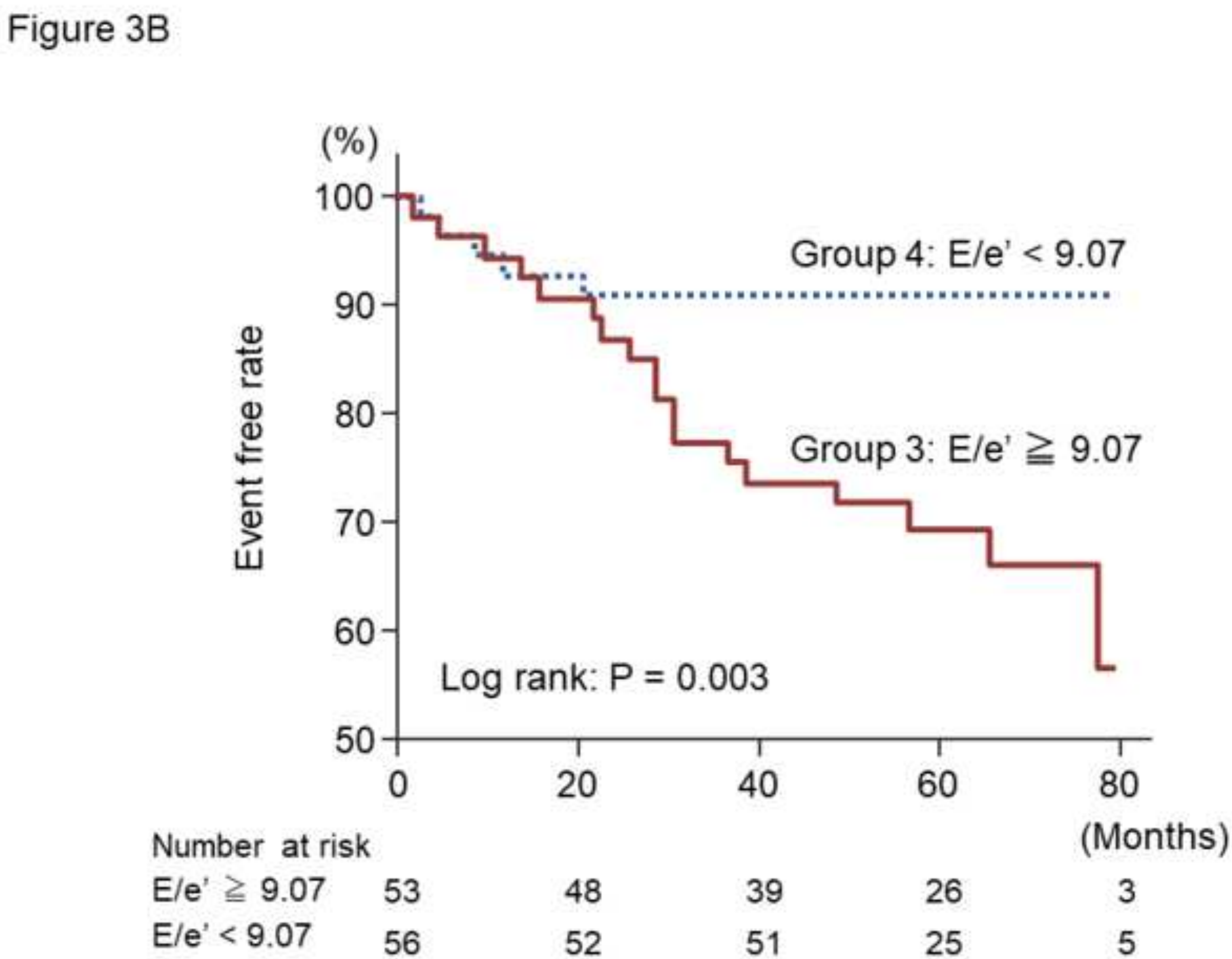

Table 1

Table 1. Baseline patients' characteristics

Clinical characteristics	n=109
Age, years	64 ± 13
Sex, M/F	70 / 39
Height, cm	160 ± 9
Body weight, kg	66 ± 14
Body surface area, m^2	1.7 ± 0.2
BMI, kg/m^2	25±4
Obese (BMI≧25%), n (%)	69 (63)
Systolic blood pressure, mmHg	148 ± 24
Diastolic blood pressure, mmHg	81 ± 17
Heart rate, beats /minute	69 ± 12
Diabetes mellitus, n (%)	38 (34)
Hyperlipidemia, n (%)	29 (26)
Electrocardiographic parameters	
VAT, ms	39.2 ± 6.12
QRS, ms	92.6 ± 9.5
QTc, ms	433.5 ± 24.9
TpTe, ms	71.4 ± 11.9
SV1 + RV5, mV	3.39 ± 1.19
RV5, mV	2.18 ± 0.87
RI + SIII, mV	1.16 ± 0.56
RaVL, mV	0.49 ± 0.31
Echocardiographic parameters	
Left atrial dimension, mm	41 ± 6
Aortic diameter, mm	32 ± 5
Left ventricular end-diastolic dimension, mm	48 ± 7
Left ventricular end-systolic dimension, mm	30 ± 6
Left ventricular end-diastolic volume, ml	94 ± 37
Left ventricular end-systolic volume, ml	34 ± 20
Ejection fraction, %	65 ± 6
% fractional shortening, %	37 ± 7
Relative wall thickness	0.43 ± 0.07
Left atrial volume, ml/m^2	31.3 ± 11.2
Left ventricle mass index, g/m^2	126.4 ± 43.5

E, cm/s	66 ± 20
A, cm/s	84 ± 22
E-deceleration time, ms	232 ± 54
E/A	0.819 ± 0.278
e', cm/s	7.8 ± 2.5
a', cm/s	10.8 ± 3.1
E/e'	9.2 ± 3.5

Values are median (interquartile range), n (%) or mean ± SD. BMI: body mass index, VAT: ventricular activation time, E: early-diastolic transmitral flow velocity, A: atrial-systolic transmitral flow velocity, E/A: ratio of early-diastolic to atrial-systolic transmitral flow velocity, e’: peak early-diastolic mitral annular velocity, a’: peak atrial-systolic mitral annular velocity