ORIGINAL ARTICLE

The relationship between T-wave peak-to-end interval and hemodynamic parameters in patients with pulmonary arterial hypertension

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Abstract

Background: T-wave peak-to-end interval (TPEI) is a measure of repolarization dispersion on surface electrocardiogram (ECG). TPEI has been reported as a prognostic parameter with heart disorders. In this study, we aimed to evaluate the relationship between echocardiogram-derived right heart parameters, right heart catheterization (RHC) measurements, and TPEI in patients with precapillary pulmonary arterial hypertension (PAH).

Methods: Thirty-eight patients (29 females and 9 males, mean age of 54.9 ± 10.9 years) who had undergone RHC for a preliminary diagnosis of pulmonary hypertension (PH) were included in the study. We performed transthoracic echocardiography (TTE), and resting 12-lead ECG was recorded before RHC. TPEI was measured from leads of V1-V6, DII, DIII, and aVF, and these values are averaged to obtain the global TPEI.

Results: Duration of TPEI was significantly correlated with mean PAP, pulmonary vascular resistance (PVR), and cardiac index (CI). Longer TPEI was associated with higher N terminal probrain natriuretic peptide (NT pro-BNP) level, lower 6-min walk distance (6MWD), and lower tricuspid annular plane systolic excursion (TAPSE).

Conclusion: Prolongation of TPEI could be a new predictor of adverse outcome in PAH and may provide additional prognostic information for patients with PAH.

KEYWORDS
ECG, pulmonary arterial hypertension, right heart catheterization, T-wave peak-to-end interval

1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a hemodynamic and pathophysiological condition resulting from restricted flow through the pulmonary arterial circulation, leading to increased pulmonary vascular resistance (PVR) and, finally, right-sided heart failure (HF) (Farber

& Loscalzo, 2004). Precapillary PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg and PVR > 3.0 Wood units (WU) without significant elevation of the pulmonary capillary wedge pressure (PCWP) (i.e., PCWP ≤ 15 mmHg) at rest as assessed by right heart catheterization (RHC) (Galiè, Humbert, & Vachiery, 2016). Right ventricular (RV) function is the major determinant of

functional capacity and prognosis in PAH (Voelkel et al., 2006). The assessment of a patient with suspected PH requires a series of investigations necessary to confirm the diagnosis (Galiè et al., 2016). The diagnostic tools involve electrocardiogram (ECG), chest radiograph, transthoracic echocardiography (TTE), pulmonary function tests and arterial blood gases, ventilation/perfusion lung scan, computed tomography (high-resolution and contrast-enhanced), and RHC.

Recent studies of experimental PAH demonstrate that there are additional electrophysiologic changes in the RV such as prolongation of the QRS duration and the corrected QT (QTc) interval on the surface ECG (Piao, Fang, & Cadete, 2010). T-wave peak-to-end interval (TPEI) has been used to evaluate ventricular repolarization in several studies (Antzelevitch, 2007; Yan, Lankipalli, & Burke, 2003). TPEI is more representative of transmural dispersion of repolarization than QTc (Antzelevitch, 2001). TPEI may be a more accurate marker of electrical dispersion than QTc because it focuses on repolarization rather than depolarization. Few studies have reviewed whether patients with PAH manifest prolongation of the QTc interval or increased QRS duration (Rich et al., 2013; Sun, Jiang, & Gomberg-Maitland, 2012).

Transthoracic echocardiography (TTE) is the most useful and readily available noninvasive tool to evaluate right ventricular function in patients with PAH (Rudski et al., 2010). Depending on the severity of disease, patients with significant PAH exhibit varying degrees of right heart chamber enlargement and reduced systolic function. Objective measures of RV systolic function include tricuspid plane annular excursion (TAPSE), right ventricular fractional area change (RVFAC), and RV ejection fraction (RVEF) (Lang et al., 2015; Rudski et al., 2010). The measurements of RVFAC and RVEF are more accurate with cardiac magnetic resonance imaging (MRI) than TTE (Peacock & Vonk, 2013). Paradoxical ventricular septal flattening is an indication of RV pressure overload, and it is a common finding in patients with significant PH. The pulmonary artery systolic pressure (PASP) can be estimated by using Doppler to measure the peak tricuspid regurgitant jet velocity (Lang et al., 2015). However, echo-Doppler estimates of PASP in PH patients can lead to both an underestimation and overestimation of the true PAP when compared with catheterization (Fisher, Forfia, & Chamera, 2009). Echocardiographic predictors of poor prognosis in patients with PAH include a right atrial enlargement, reduced TAPSE, interventricular septal flattening, and the presence of a pericardial effusion (Lang et al., 2015).

RHC is widely used in clinical practice for hemodynamic evaluation in patients with PAH. Measurements for evaluating PAH are mean right atrial pressure (mRAP), PAP, PCWP, cardiac output (CO), cardiac index (CI), mixed venous O_2 saturation, and pulmonary and systemic vascular resistance calculations (Davidson & Bonow, 2015).

The mean RAP, mean PAP, and CI are very important parameters to assess during RHC, as markedly elevated mean RAP, mean PAP, and reduced CI are indicative of right ventricular failure and poor survival in patients with PAH (D'Alonzo, Barst, & Ayres, 1991).

No studies have assessed whether TPEI prolongation in patients with PAH was associated with echocardiographic indices of RV and RHC. We performed the current study to determine whether TPEI prolongation was correlated with the measurements of RHC and the echocardiographic parameters of RV.

2 | METHODS

We enrolled 38 patients (29 females and 9 males, mean age of 54.9 ± 10.9 years), in whom PAH was diagnosed according to the ESC/ERS guidelines for the diagnosis of pulmonary hypertension. Informed consent was obtained from each enrolled patient. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee of Istanbul University. Patients with PAH associated with pulmonary hypertension due to left-sided heart disease and chronic obstructive pulmonary disease (COPD) were excluded. We also excluded patients with coincident cardiac diseases; left bundle branch block, significant arrhythmias, including atrial fibrillation, Wolff–Parkinson–White syndrome, supraventricular tachycardia, atrioventricular block, a pacemaker rhythm. In addition, patients with serum electrolyte imbalances and receiving antiarrhythmic drugs were also excluded from the study because of their possible effects on ECG measurements (Meierhenrich, Helguera, Kidwell, & Tebbe, 1997). Details of these patients at the time of diagnosis were analyzed, including sex, age, history of any other concomitant disease, physical examination, echocardiography, 6-min walk test distance (6MWD), hemodynamic parameters, and blood tests for biochemical markers that are correlated with clinical severity.

2.1 | ECG Analysis

All standard 12-lead ECGs were recorded with a speed of 25 mm/s and a 10 mm/mV gain on the same day before RHC. The QRS duration and the QT interval were measured from leads of V1-V6, DII, DIII, and aVF with an electronic caliper. The QT duration was determined as the interval from the beginning of the QRS wave to the point at which the T wave joined the isoelectric line. The corrected QT (QTc) duration was calculated using Bazett's formula (Bazett, 1920). TPEI was measured using the "Tangent Method" (Antzelevitch et al., 2007) from all leads, and these values are averaged to obtain the global TPEI. The time in milliseconds from the peak of the T wave in the presence of a negative or biphasic T wave) to the intersection between the tangent at the steepest point of the T-wave downslope and the isoelectric line was measured on digitized 12 lead ECG recordings using the on-screen digital caliper software Cardio Calipers version 3.3 (Iconico, Inc). Results were taken as the average of two readings. The same cardiologist who was blinded to the clinical characteristics of the patients interpreted the patients' ECGs.

2.2 | Transthoracic echocardiography

TTE was performed on a Vivid 7 (GE) system with transducer frequencies appropriate for patient size. The same cardiologist performed all

quantitative measures. All measurements were done in accordance with the current guidelines (Lang et al., 2015; Rudski et al., 2010). RV and RA end-diastolic transverse dimensions were recorded from the apical four-chamber view. Systolic pulmonary artery pressure was calculated from the tricuspid regurgitation Doppler by the modified Bernoulli equation. Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode from the lateral tricuspid annulus.

2.3 | Right heart catheterization

RHC was performed for patients thought to have PAH according to echocardiography. All patients were diagnosed by right-sided heart catheterization according to standard criteria: a mean pulmonary artery pressure (mPAP) ≥25 mmHg and PVR > 3 Wood units at rest in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg). Heart rate and systemic blood pressure were measured just before RHC. RA, RV, PA, and PCW pressures were measured via a catheter passed through a sheath placed in the femoral vein. Cardiac output (CO) was determined by the Fick method, using oxygen consumption. Cardiac index (CI) was calculated with the formula: CI $(\mathrm{L\,min^{-1}\,m^{-2}})$ = CO (L/min)/body surface $(\mathrm{m^2})$ and pulmonary vascular resistance (PVR) was calculated as: PVR (Wood units) = mPAP (mmHg)/CO (L/min). All the parameters were calculated as the mean value of three different measurements, according to current recommendations (Davidson & Bonow, 2015). After baseline hemodynamics were obtained, vasoreactivity was assessed with either inhaled nitric oxide or inhaled iloprost.

2.4 | Statistical analysis

Continuous variables with parametric distribution were expressed as mean ± standard deviation. Categorical data were expressed as frequencies, and their differences were analyzed using the chi-square test. Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they were normally distributed. Parameters which were normally distributed, the correlation coefficients, and their significance were calculated by Pearson's test. A multiple forward linear regression model was used to identify independent predictors of T-wave peak-to-end interval of pulmonary arterial hypertension patients. A 5% type I error level was used to infer statistical significance. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.). Statistical significance was taken as $p < .05$.

3 | RESULTS

3.1 | Study population, baseline clinical, laboratory, hemodynamic, and echocardiographic findings

A total of 38 patients were enrolled in the study. The baseline clinical, hemodynamic, echocardiographic, and electrocardiographic

TABLE 1 Baseline demographic, hemodynamic, echocardiographic, and electrocardiographic parameters of patients

Variables (n = 38)	Mean ± Std. Deviation
Cath meanPre (mmHg)	50.87 ± 23.05
CathSysPre (mmHg)	79.47 ± 31.89
CathdiastPre (mmHg)	29.16 ± 15.2
6MWD (m)	341.45 ± 99.36
PAPEcho (mmHg)	81.7 ± 23.08
Tapse (mm)	16.03 ± 1.83
Pro-BNP (pg/ml)	742.9 ± 746.1
PVR (Wood)	10.31 ± 5.43
CI (L min^{-1} m^{-2})	2.14 ± 0.25
RA (cm)	3.85 ± 0.63
RV (cm)	3.26 ± 0.5
TpeakTend (ms)	67.81 ± 9.68
QTc (ms)	415.63 ± 24.66
QRS (ms)	95.53 ± 7.18
LVEDD (cm)	4.8 ± 0.44
LVESD (cm)	2.9 ± 0.38
LV Mass (gram)	144.6 ± 16.65

Note: Cath meanPre denotes mean catheter pressure of pulmonary artery; CathSysPre denotes systolic catheter pressure of pulmonary artery; CathdiastPre denotes diastolic catheter pressure of pulmonary artery; 6MWD denotes 6-min walk distance; PAPEcho denotes pulmonary arterial pressure measured with echocardiography; Tapse denotes tricuspid annular plane systolic excursion; Pro-BNP denotes N terminal brain natriuretic peptide; PVR denotes pulmonary vascular resistance; CI denotes cardiac index; RA denotes right atria size; RV denotes right ventricle size; TpeakTend denotes T-wave peak-to-end duration; QTc denotes corrected QT distance; QRS denotes QRS duration; LVEDD denotes left ventricle end-diastolic diameter; LVESD denotes left ventricle end-systolic diameter; and LV Mass denotes left ventricle mass.

parameters of patients are shown in Table 1. The mean age was 54.9 ± 10.9 years, and female gender was dominant. Pulmonary artery pressure found by echocardiography was 81.7 ± 23.08 mmHg, while mean pulmonary artery pressure found by right heart catheterization was 50.87 ± 23.05 mmHg. T-wave peak-to-end interval calculated by surface electrocardiogram was 67.81 ± 9.68 ms, while the corrected QT distance was 415.63 ± 24.66 ms. QRS duration was 95.53 ± 7.18 ms.

3.2 | Correlations between T peak T end duration, mean catheter pressure of pulmonary artery, other hemodynamic and echocardiographic parameters

There was a strong negative correlation between T-wave peak-to-end interval and 6-min walk distance ($r = -0.60$, $p < .001$) (Table 2). Also, there was a positive correlation between T-wave peak-to-end interval and mean pulmonary artery pressure calculated by right

heart catheterization ($r = 0.90$, $p < .001$) (Table 2). There were also strong correlations between T-wave peak-to-end interval and other hemodynamic and echocardiographic parameters (Table 2).

3.3 | Independent predictors for T-wave peak-to-end interval of pulmonary artery hypertension patients

In the multiple linear regression analysis, mean pulmonary artery pressure found by right heart catheterization was independently related to T-wave peak-to-end interval (Table 3).

The multiple linear regression analysis gave us the formula to predict the T-wave peak-to-end interval.

T-wave peak-to-end interval = 48.16 (as a constant) + 0.38x (mean pulmonary artery pressure found by right heart catheterization)

4 | DISCUSSION

In this study, we investigated the relationship between the measurements of RHC, echocardiographic parameters of RV, and an ECG parameter of ventricular repolarization, namely TPEI in patients with precapillary PAH. We have demonstrated that TPEI is correlated with mean PAP, CI, PVR, and TAPSE.

TPEI is a reflection of transmural dispersion of repolarization (Yan & Antzelevitch, 1998). Few studies have examined whether TPEI prolongation occurs in cardiac diseases. In patients undergoing percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction, a longer pre-PCI TPEI predicted all-cause 1-year mortality (Haarmark et al., 2009). Daniel PM et al. found that a longer TPEI predicted overall mortality in patients with established cardiomyopathy even after correction for other predictors of mortality (Morin et al., 2012).

Acute and chronic right-sided heart failure occurs in patients with PAH and RV function is very essential for prognosis (Voelkel et al., 2006). Pei-Yu Sun et al. found that QRS prolongation had an independent association with cardiopulmonary mortality and could be a predictor of adverse outcomes in patients with IPAH (Sun et al., 2012). In this study, prolongation of the QRS duration was positively correlated with the diameter of the RA and RV. Patients with prolonged QRS duration had a reduced 6MWD and higher BNP levels. BNP/NT-pro-BNP levels associate with myocardial dysfunction and provide prognostic information at the time of diagnosis (Warwick, Thomas, & Yates, 2008). Similarly, in our study prolonged TPEI was positively correlated with the diameter of the RV, higher NT pro-BNP levels, and reduced 6MWD.

Another aspect of the present study involved the investigation of newer echo parameters of RV function in relation to RHC-derived hemodynamics and TPEI. Tricuspid annular plane systolic excursion (TAPSE) represents a simple method that quantifies the distance of RV systolic annular apical displacement using M-mode and represents longitudinal RV systolic function. TAPSE is validated against RV ejection fraction and fractional area shortening and recommended as a routine measure for the assessment of RV function (Rudski et al., 2010). In our study, we demonstrated significant negative correlations between TAPSE and RHC measurements of mPAP and PVR. There was a positive correlation between TAPSE and CI. In addition, TPEI was negatively correlated with TAPSE.

Previous studies have shown that the mortality in IPAH correlates RV hemodynamic variables such as mRAP, PVR, and CO (D'Alonzo et al., 1991; Humbert, Sitbon, & Chaouat, 2006). In patient with systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH), a high mRAP and low cardiac index were the strongest hemodynamic predictor of mortality (Mukerjee et al., 2003). Weatherald J. et al. showed that the 6 MWD, functional class, cardiac index, pulmonary arterial compliance, and pulmonary vascular resistance were independently associated with transplant-free survival at follow-up in patients with SSc-PAH (Weatherald et al., 2018). In our study, prolongation of TPEI was associated with mean PAP, PVR, and CI. Longer TPEI was correlated with higher mean PAP, higher PVR, and lower CI. These results proposed that prolongation of TPEI could be a new predictor of adverse outcome in PAH and may provide additional prognostic information for patients with PAH.

To the best of our knowledge, the current study is the first to demonstrate the relation between TPEI and RHC measurements in patients with PAH. The limitation of our study includes the small number of patients enrolled and lack of a follow-up period in terms of morbidity and mortality. Larger trials are needed to correlate our findings with long-term outcomes.

TABLE 2 Correlations between T peak T end duration, mean catheter pressure of pulmonary artery, and other hemodynamic and echocardiographic parameters

Correlations									
		Cath meanPre	Tapse	Pro-BNP	PVR	RV	CI	6mWD	PAPEcho
T peak T end	r	0.90	−0.70	0.58	0.85	0.44	−0.84	−0.60	0.66
	p	<.001	<.001	<.001	<.001	.005	<.001	<.001	<.001

Note: T peak T end denotes T-wave peak-to-end interval; Cath meanPre denates mean catheter pressure of pulmonary artery; 6MWD denotes 6-min walk distance; Tapse denotes tricuspid annular plane systolic excursion; Pro-BNP denotes *N* terminal brain natriuretic peptide; PVR denates pulmonary vascular resistance; RV denotes right ventricle size; CI denotes cardiac index; and PAPEcho denotes pulmonary arterial pressure measured with echocardiography.

TABLE 3 Multiple forward linear regression model to identify independent predictors of T-wave peak-to-end interval of pulmonary arterial hypertension patients

Coefficients[a]					
		Unstandardized Coefficients		**Standardized Coefficients**	
Model		**B**	**Std. Error**	**Beta**	**p Value**
1	(Constant)	48.16	1.75		.001
	MeanPAPcath	0.38	0.03	0.89	.001

Excluded Variables[a]					
				Collinearity Statistics	
Model		**Beta**	**Partial Correlation**	**Tolerance**	**p Value**
1	CathDiasPre	−0.09[b]	−0.07	0.66	.11
	Pro-BNP	−0.01[b]	−0.02	0.89	.41
	CathSysPre	0.27[b]	0.19	0.26	.09
	6MWD	0.04[b]	0.06	0.69	.52
	PAPEcho	−0.20[b]	−0.27	0.10	.33
	TAPSE	0.16[b]	0.21	0.21	.30
	QTc	0.10[b]	0.21	0.21	.87
	QRS	−0.02[b]	−0.04	0.80	.46
	PVR	−0.17[b]	−0.12	0.46	.10
	CI	−0.27[b]	−0.32	0.05	.27
	RAcm	−0.08[b]	−0.18	0.29	.91
	RVcm	−0.06[b]	−0.11	0.50	.69
	Age	−0.06[b]	−0.14	0.41	.87
	LVEDD	0.03[b]	0.07	1.0	.65
	LVESD	0.08[b]	0.17	0.97	.29
	LV Mass	0.01[b]	0.02	0.99	.87

Note: Cath meanPre denotes mean catheter pressure of pulmonary artery; CathSysPre denotes systolic catheter pressure of pulmonary artery; CathdiastPre denotes diastolic catheter pressure of pulmonary artery; 6MWD denotes 6-min walk distance; PAPEcho denotes pulmonary arterial pressure measured with echocardiography; Tapse denotes tricuspid annular plane systolic excursion; Pro-BNP denotes *N* terminal brain natriuretic peptide; PVR denotes pulmonary vascular resistance; CI denotes cardiac index; RA denotes right atria size; RV denotes right ventricle size; TpeakTend denotes T-wave peak-to-end duration; QTc denotes corrected QT distance; QRS denotes QRS duration; LVEDD denotes left ventricle end-diastolic diameter; LVESD denotes left ventricle end-systolic diameter; and LV Mass denotes left ventricle mass.

[a]Dependent variable: **TpeakTend.**

[b]Predictors in the Model: (Constant), **MeanPAPcath.**

5 | CONCLUSION

TPEI measured from surface ECG recordings is significantly correlated with mean PAP, PVR, and CI in patients with precapillary PAH. Additionally, TPEI was associated with the RV enlargement and TAPSE. The relevance of these findings to clinical outcomes and the clinical usefulness of this simple parameter remain to be determined with further studies.

CONFLICT OF INTEREST

None declared.

AUTHOR'S CONTRIBUTION

Designed research: A.E., S.E., A.K.B.; Performed research: O.E., A.E., G.O.; Collected data: O.E., E.B.K., S.E.; Analyzed data: A.E., A.K.B., A.O., K.A.; Wrote the paper: A.E., S.E.

ETHICS

The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee of Istanbul University.

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