Pulmonary transit time as a marker of diastolic dysfunction in Takotsubo syndrome.

Keywords: Takotsubo; CMR; Pulmonary transit time; diastole; first-pass

Key points

- PTT was suggested as a feasible CMR tool to assess diastolic dysfunction.
- TS patients showed higher PTT, PTTI, and PBVI values in comparison with healthy controls.
- PTT and its derived parameters may be new tools in evaluating the diastolic function in TS patients.

Abbreviations

TS Takotsubo syndrome

LV left ventricle

RV right ventricle

CMR cardiac magnetic resonance

TTE transthoracic echocardiography

PTT Pulmonary transit time

PTTI Pulmonary transit time index

PBVI Pulmonary blood volume index

Introduction

Takotsubo syndrome (TS) is a well-recognized form of cardiomyopathy characterized by a specific pattern of left ventricular (LV) dysfunction, presenting as apical ballooning and hyperkinesis of basal segments the mostly. Less common variants of the disease can involve mid-ventricular, basal, and focal LV segments or the whole LV or both ventricles, or just the right ventricle (RV)[1–4]. Along with LV systolic impairment, diastolic dysfunction can arise in a significant number of TS patients during the transient course of the cardiomyopathy[5–7]. Not only, but the onset of diastolic dysfunction is known to have a prognostic negative impact on TS clinical outcome[6].

Pulmonary transit time (PTT) is a previously studied tool to evaluate cardiopulmonary function and provide information regarding an increase in LV filling pressure, a condition which has been termed diastolic dysfunction or "hemodynamic congestion"[8]. PPT can be measured either invasively, by using cardiac catheterization, or by means of non-invasive modalities, such as radionuclide imaging, computed tomography, echocardiography, and cardiac magnetic resonance imaging (CMR)[9]. Several recent studies have investigated the role of PTT using CMR[8,10–12] and noted prolonged PTT and derived parameters in patients with heart failure[6]. On the other hand, CMR is used in daily practice to evaluate TS[13]

The aim of this study was to evaluate PTT and its linked parameters in patients with TS as a marker of diastolic dysfunction and its association with echocardiography and CMR parameters.

Material and Method

Study population

In this retrospective single-center study, we searched in our database all the patients who underwent CMR between March 3rd, 2017, and February 7th, 2021, because of clinical suspicion of apical ballooning TS. We enrolled only TS patients with LV diastolic dysfunction assessed by Doppler echocardiography, as described previously [14]

A total of 42 subjects were finally included in the study cohort. Of those, 22 were TS and 20 were controls.

TS diagnosis was made using the current definition as reported in the Position Statement of the European Society of Cardiology Heart Failure Association[15]. The diagnostic criteria include regional wall motion abnormalities not limited to a single epicardial vascular distribution region, which are usually preceded by a stressful trigger, in the absence of culprit atherosclerotic disease as assessed by invasive catheterization; new ECG abnormalities; elevated serum natriuretic peptide and a small increase in cardiac troponin; and recovery of LV dysfunction at follow-up.

Exclusion criteria included: subjects < 18 years; contraindication to CMR (such as implantable devices, severe claustrophobia), or history of significant renal disease with a eGFR < 30 mL/min/1.73 m2; and coronary artery disease.

Controls were age-, sex- matched and underwent CMR to rule out scar-related ventricular tachycardia. Controls were included if CMR showed no signs of structural heart defects. The Institutional Review Board approval for this retrospective, cross-sectional study was obtained, and patient's consent was waived because of the retrospective nature.

A flowchart demonstrating the application of inclusion and exclusion criteria is provided in **Figure 1.**

CMR acquisition

All CMR scans were performed at 4.1±2.6 days (median = 1 day, range = 1-10 days) after admission to the hospital by using a Philips Achieva Stream 1.5 T scanner system (*Philips Healthcare, Best, The Netherlands*). Anterior coil arrays were used. Cine-CMR examinations were electrocardiogram triggered and performed during breath-holding. Thirty phases were derived for each cardiac cycle. The CMR protocol was based on functional sequences, such as cine white blood

steady-state free precession (SSFP) on the short and long axes (2 chambers, 3 chambers, and 4 chambers). CMR perfusion was performed with the first-pass perfusion technique, with a bolus of contrast media injection (Gadovist, Bayer Healthcare, Berlin, Germany) with a dose of 0.15 ml per kg body weight. Image acquisition was begun at the same time as the contrast media injection using a cardiac-gated saturation-recovery sequence. Perfusion imaging was acquired in three short-axis views (basal, middle, and apical). LGE imaging was performed 10-12 minutes after contrast media injection (Gadovist, Bayer Healthcare, Berlin, Germany) with a dose of 0.15 ml per kg body weight using phase-sensitive inversion recovery sequences acquired in both short and long axis. The correct inversion time was determined using the Look-Locker technique.

CMR image post-processing

The commercially available software system Circle CVI42 (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used for PTT and its related parameters analysis. First-pass images were obtained with a bolus of gadolinium-contrast agent, thus allowing to evaluate an image for each heartbeat. PTT represents the number of cardiac cycles required for a bolus to pass from the RV to the LV. Briefly, a region of interest (ROI) was placed in the basal slice of RV and automatically copied in the entire stack of images, with manual correction when required. The second region of interest was positioned in the basal slice of LV. The average signal intensity and a signal intensity/ time curve was obtained for both ROIs in every image. PTT was measured as the peak-to-peak time between the two curves. Conversely, pulmonary transit time index (PTTI) represents the PTT values corrected for heart rate, according to Bazett's Formula:

PPTI (s)/√ R-R interval (s)

Finally, PBVI was calculated as the product of RV stroke volume index (RVSVI) and PTTI **(Figure 2):**

PBVI (ml/m^2) = RVSVI x PPTI

CMR feature tracking analyses of atrial deformation was conducted offline. Left atrial (LA) and right atrial endocardial borders were manually traced on long axis view of the cine images when the atrium was at its minimum volume. In particular, the four-, three-, and two-chamber views were used to derive LA longitudinal strain. LA appendage and pulmonary veins were excluded from segmentation. The right atrial longitudinal strain was based on the four-chamber view only. After manual segmentation, the software automatically tracked the myocardial borders throughout the entire cardiac cycle. The quality of the tracking and contouring was visually validated and manually corrected by a radiologist with 3 years of experience in cardiac imaging. There are three peaks in the strain curve, including reservoir, conduit, and booster strain. Accordingly, their corresponding strain rate parameters were included. **Figure 3**.

Global and regional T2 mapping were assessed on the same commercial post-processing software (*CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada*) by manually tracing endocardial and epicardial contours. A 10% safety margin was automatically set for both borders to prevent contamination from the blood pool and neighboring tissues. Finally, the reference point was set at the right ventricle insertion to generate a 16-segment AHA model.

Transthoracic echocardiography

All patients underwent transthoracic echocardiography *(*TTE) before the CMR examination (the median time interval was 3 days, ranging from 1 to 8 days). TTE allowed assessing LV diastolic function in terms of traditional and Tissue Doppler-derived parameters, such as mitral valve E/A, deceleration time of E wave, E/e'. TTE was carried out in agreement with the current international guidelines [14].

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Kolmogorov-Smirnov tests were used to check continuous variables for normal distribution. Comparisons of continuous

data were performed using independent samples t test or Mann-Whitney U test analysis. Categorical variables were compared using chi-square or Fisher's exact test, according to the data distribution. A receiver-operating characteristic (ROC) analysis was performed to calculate optimal thresholds and areas under the curves (AUCs). The Youden index was used to depict optimal cut-off values from the ROC curves. Sensitivities and specificities were calculated for these cut-off values with 95% confidence intervals. Correlation was assessed using the Pearson r and Spearman rho coefficient according to data distribution. Binary logistic regression was used to assess the value of PTT parameters for identification of TTC patients. PTT values were incorporated into univariable analysis as continuous variables, and age, gender, and CMR significant parameters ($P < 0.05$) were then included into multivariable analysis.

A p-value <0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA).

Results

Patient demographics, clinical and echocardiography data.

Twenty-two TS patients (20 females, mean age 68,9 ± 9,2 years.), and 20 healthy subjects (17 females, mean age 67,3 ± 10,2 years) were identified. Comparison of patient's baseline characteristics, echocardiography, CMR, and PTT with its derived parameters between control and patients are summarized in **Table 1**.

Pulmonary transit time in TS patients

PTT and its derived parameters are reported in **Table 1.** PTT, PTTI, and PBVI were significantly higher in TS patients in comparison with the control group (p= 0.0001, p=0.0001, and p=0.002, respectively) (**Figure 4**). PTT (OR 0.38; 95% CI 0.20-0.72, p=0.003), PTTI (OR 0.41; 95% CI 0.22 -0.74, p=0.003), and PBVI (OR 0.98; 95% CI 0.96 - 0.99, p=0.009) were significantly associated with

the presence of TTC in univariable analysis. Using multivariable logistic regression analysis, PBVI was the only independent discriminator between TTC and ACS (OR 1.01; 95% CI 0.97-1.21, p=0.03; **Table 2**)

PTT in relation to echocardiography and CMR data.

PBVI was significantly associated with a well-established TTE index of diastolic dysfunction, in particular E/e' ratio, E/A, and E wave deceleration time at Tissue Doppler (r= 0.643, p =0.001; r= 0,443 p= 0,021 and r= 0,719 p= 0,001, respectively). **Figure 5** showed the relationship between pulmonary blood volume (PBVI) and echocardiography indices of diastolic dysfunction. In addition, PBVI demonstrated a significant correlation with global T2 mapping (r= 0,520, p=0,019).

The left atrial size was a mean of 13,2 cm^2/m^2 and showed no correlation with PBVI (r=0,220, p=0,310). Conversely, left atrial strain and strain rate parameters correlated significantly with PBVI (**Table 3**). There was no other statistically significant correlation between PTT and CMR parameters.

ROC analysis

PTT, PTTI, and PBVI proved to have good-to-excellent sensitivity in differentiating patients with TS from healthy controls (AUCs of 0.90, 0.91, and 0.84, respectively). For PBVI the optimal cut-off value to identify TS was > 332.76 with a sensitivity and specificity of 70% and 90% respectively. (**Figure 6**)

Discussion

This study was carried out to non-invasively assess with new CMR parameters the diastolic function in TS patients and give an insight into the pathophysiology of the disease. PTT has been widely recognized as an important tool capable of providing useful information regarding the presence and severity of diastolic dysfunction during other cardiac diseases[8–11].

The main findings can be summarized as follow: (1) TS patients have longer PTT/PTTI and higher PBVI values in comparison with controls; (2) PBVI is related to diastolic dysfunction at TTE; (3) PTT and its related parameters have good-to-excellent diagnostic accuracy in detecting a diastolic impairment in TS.

A prompt and non-invasive assessment and grading of LV congestion is highly desirable in clinical practice. This is primarily because a non-invasive evaluation has the potential to detect LV congestion before it become clinically evident[16]. Currently, invasive cardiac catheterization is considered the gold standard to measure intracardiac filling pressure, but it is not without any risk for the patient. For these reasons, several non-invasive methods have been proposed. Among them, echocardiography represents the reference standard in the evaluation of LV diastolic function[14] but, at the same time, its diagnostic value is limited in case of poor acoustic windows, such as in overweight/obese subjects or patients with respiratory diseases[17–19].

On the other hand, CMR is the reference technique in the non-invasive assessment of cardiac systolic function and volumes. It allows tissue characterization as well, unlike TTE[3,20,21]. In the setting of TS, CMR enables detection of typical regional wall motion abnormalities as well as the possible reversible and irreversible myocardial damage at late gadolinium enhancement, thus providing a precise characterization of TS[3].

Although the role of CMR in evaluating ventricular diastolic function has not been fully elucidated yet, it has been suggested that it may play a role in this scenario as well. Recently, Ricci et al proposed PBVI as a quantitative marker to detect and quantify diastolic dysfunction in heart failure due to different etiologies[8,10].

TS is an acute ventricular dysfunction characterized by a diverse spectrum of outcomes, ranging from favorable to life-threatening[22]. While it is well known that TS is characterized by a transient form of ventricular systolic dysfunction with different patterns, the most frequent of which is apical ballooning along with hyperkinesis of basal segments, several studies suggested a possible concomitant diastolic involvement[7]. In the setting of TS, diastolic dysfunction is generally considered

to occur in close temporal correlation with segmental wall motion abnormalities[23]. Ahtarovsky et al. reported that despite a rapid restoration of systolic function, there was a delayed recovery of diastolic function, suggesting that LV relaxation may be compromised for an extended period[7]. Similar results were obtained by Medeiros et al., who demonstrated LV inability to fill adequately at normal pressure due to myocardial stiffness[5]. Again, Sun et al. described an abnormal diastolic function in 53 % of the 205 enrolled TS patients. At multivariate analysis, both persistent diastolic and systolic dysfunction were independent predictors of a poor outcome[6]. The trigger of diastolic dysfunction is usually represented by an increase in LV stiffness with consequent inability to properly relax, which in turn increases LV filling pressure and left atrial contractility[4,24–28]. Consequently, it was not surprising a significant correlation was found between PBVI and atrial strain parameters.

Fibrosis may be the underlying cause of LV dysfunction in TS[29]. In this respect, an immunohistological study showed an increase in collagen-1 subfraction content in the myocardial areas with late gadolinium enhancement[30]. Our study demonstrated a significant correlation between PBVI and T2 mapping. It is well known that myocardial edema impairs myocyte function and is responsible for diastolic impairment with decreased LV chamber compliance[31,32]. Based on this finding, we can speculate on another theory that sees myocardial edema as one of the determining factors of diastolic impairment in TTC patients.

Nevertheless, further studies are needed to clarify the role of myocardial edema fat in the course of diastolic dysfunction in TTC.

PTT/PTTI and PBVI already showed their ability as markers of diastolic dysfunction in different cardiac insufficiency scenarios and correlated with many clinical parameters [6,8]. The results of this study suggest that PTT and its derived parameters may be useful CMR-related tools for diastolic dysfunction in TS patients and may be used to refine the diagnosis of the disease. To our knowledge, this is the first study examining these parameters in the TS setting.

A major limitation of this research is certainly the relatively small sample size and the retrospective selection of the patients. However, all patients were very homogeneous, as we enrolled

only subjects with the classic apical ballooning subtype. The promising results of the study need to be confirmed with larger cohorts of patients. Moreover, the predictive value of PTT in terms of adverse cardiovascular events has not been assessed.

Finally, the hemodynamic congestion parameters derived by CMR in TS patients would have been probably different if CMR had been performed within a shorter period compared to echocardiography, ideally on the same day of hospital admission.

Conclusion

In this study, TS patients showed significantly higher PTT and derived parameters values in comparison with control group owing to the onset of diastolic dysfunction. PTT and PBVI may be additional CMR tools in refining TS pathophysiology.

Disclosure

All authors agreed with the content and gave consent to submit.

All authors contributed equally as authors to this work.

The authors state that this work is not under consideration elsewhere and none of the paper's contents have been previously published.

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Figure legends

Figure 1 A flowchart demonstrating the application of inclusion and exclusion criteria.

Figure 2 An example of pulmonary transit time analysis (PPT) in Takotsubo (a) and control group (b). As reported in the Method section, PPT was measured as the peak-to-peak time between the two-signal intensity/time curves, obtained with a ROI in the left and right ventricle, respectively.

Figure 3: Representative image of the different phases of left atrial strain, including reservoir, conduit and booster phase from 2-chambers view using CMR in a TS patient.

Figure 4 Box-Whisker plots representing the difference in PPT, PPTI and PBVI between Takotsubo patients and controls.

Figure 5 Correlation analysis showed the relationship between pulmonary blood volume (PBVI) and echocardiography indices of diastolic dysfunction, in particular E^I/e^I, E/A and E wave deceleration time.

Figure 6 ROC Curves for PPT, PPTI, and PBVI to identify the patients with Takotsubo**.**

Tables

Table 1: Comparison of Demographic features, TTE and CMR characteristics.

	TS	Control	p
Age (years)	68,95 ± 9,2	67,33 ± 20,22	0,54
Gender (females)	20/22 (91%)	17/20 (85%)	0,32
Heart rate (bpm)	70,14 ± 11	66,7 ± 7,9	0,46
BSA (m^2)	1,65 ± 0,15	1,79 ± 0,23	0,095
EDV/BSA LV (mL/m^2)	73,9 ± 15,33	82,82 ± 16,6	0,15
ESV/BSA LV (mL/m^2)	30,68 ± 9,83	32,29 ± 8,27	0,56
SV/BSA LV (mL/m^2)	42,88 ± 10,36	50,29 ± 10,38	0,69
LVEF (%)	54,7 ± 8,33	61,2 ± 4,6	0,36

EDV/BSA RV (mL/m^2)	57,1 ± 12,43	75,8 ± 19,6	0,57
ESV/BSA RV (mL/m^2)	23,4 ± 6	33,9 ± 9,7	**0,039**
SV/BSA RV (mL/m^2)	35,3 ± 7,3	42,2 ± 11,3	0,068
RVEF (%)	59,4 ± 5,8	55,6 ± 2,9	0,58
E/A	0,90 ± 0,37	1,25 ± 0,43	**0,019**
E wave (cm/s)	237,66 ± 69,55	229,5 ± 56,52	0,91
E/e	15,67 ± 14,67	8,45 ± 2,33	**0,013**
PPT (s)	8,75 ± 2,22	5,16 ± 1,46	**0,0001**
PPTI (s)	10,1 ± 3,2	5,74 ± 1,77	**0,0001**
PBVI (ml/m^2)	404,34 ± 107,03	255,72 ± 70,84	**0,002**
Left atrial area (cm^2/m^2)	13,2 ± 1,3	12,8 ± 1,1	0,59
Resevoir	24,66 ± 6,16	35,9 ± 4,9	**0,0001**
Conduit	11,10 ± 4,93	22,5 ± 4,2	**0,0001**
Booster	13,93 ± 7,37	13,4 ± 2,1	0,78

TS tako-tsubo syndrome; TTE transthoracic echocardiography; CMR cardiac magnetic resonance; RV right ventricle; LV left ventricle; EDV end-diastolic volume; ESV end-sistolic volume; SV stroke volume; EF ejection fraction; BSA body surface area; E/A mitral valve E velocity divided by A-wave velocity; E/e mitral valve E velocity divided by mitral anular e velocity; PPT pulmonary transit time; PPTI pulmonary transit time index; PBVI pulmonary blood volume index. Mean +/- DS	

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Table 2: Univariable and multivariable logistic regression of CMR variables for discrimination TTC and control group.

CMR variables	**Univariable**		**Multivariable**	
	OR (95%)	P-value	OR (95%)	P-value
PPT	0,38 (0.20-0.72)	0,003	0,57 (0.11- 2.72)	0,48
PPTI	0,41 (0.22 -0.74)	0,003	0.99 (0.32 – 3.16)	0,66
PBVI	0,98 (0.96 - 0.99)	0,009	1.01 (0.97 – 1.21)	0,03

PPT pulmonary transit time; PPTI pulmonary transit time index; PBVI pulmonary blood volume index.

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Table 3: Correlation between Pulmonary transit parameters and echocardiography and CMR data in TS patients.	
	PBVI
CMR parameters	

EDV/BSA LV (mL/m^2)	r= 0,330, p=0,133
ESV/BSA LV (mL/m^2)	r=0,141, p=0,53
SV/BSA LV (mL/m^2)	r=0,270, p=0,224
LVEF (%)	r=083, p=0,713
Left atrial area (cm^2/m^2)	r=0,220, p=0,310
Resevoir	**r=0,488, p= 0,021**
Reservoir strain rate	**r= 0,532, p=0,011**
Conduit	**r=0,498, p=0,018**
Conduit strain rate	**r=0,447, p=0,037**
Booster	r=0,262, p=0,23
Booster strain rate	**r=0,426, p= 0,048**
Global T2 mapping	**r= 0,520, p=0,019**
Global T1 mapping	r=0,180, p=0,473
Echocardiography parameters	
E/A	**r=0,443, p= 0,021**
E wave (cm/s)	**r=0,719, p= 0,001**
E/e	**r=0,683, p= 0,001**
TS tako-tsubo syndrome; CMR cardiac magnetic resonance; LV left ventricle; EDV end-diastolic volume; ESV end-sistolic volume; SV stroke volume; EF ejection fraction; BSA body surface area; E/A mitral valve E velocity divided by A-wave velocity; E/e mitral valve E velocity divided by mitral anular e velocity; PPT pulmonary transit time; PPTI pulmonary transit time index; PBVI pulmonary blood volume index. Mean +/- DS	

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