**VIA MEDICA**

ORIGINAL ARTICLE

# Left ventricular function after takotsubo is not fully recovered in long-term follow-up: A speckle tracking echocardiography study

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**Abstract**

**Background:** *Complete improvement of left ventricle (LV) systolic function is an essential feature of takotsubo cardiomyopathy (TTC). It is suggested that 2-dimensional speckle tracking echocardiography (2D STE) can evaluate LV dysfunction more accurately than conventional echocardiography. Thus, the purpose of this research was to assertain whether LV function recovery is complete after the acute phase of TTC using 2D STE commencing 6 to 9 months after discharge.*

**Methods:** *Thirty patients (29 females, 67 ± 11 years) with an apical ballooning TTC pattern 225.5 ± ± 27.4 days after their index event were enrolled. The control group consisted of 20 (19 females, 64 ± ± 9 years) age- and sex-matched volunteers without structural heart disease. Classic echocardiographic parameters, longitudinal strain and LV twist parameters were assessed and compared between the groups.*

**Results:** *There were no differences in traditional LV systolic, diastolic parameters and in global peak longitudinal strain. In comparison to controls, patients with TTC had lower mean apical rotation (14.4° ± ± 6.5° vs. 18.3° ± 6.7°; p = 0.048), slower mean peak early diastolic apical rotation rate (–85.1–°/s ± 40.9–°/s vs –119.4–°/s ± 41.9–°/s; p = 0.006) and higher pre-stretch index in the apex (2.16, IQR 0.33–5.50 vs. 0.00, IQR 0.00–2.95, p = 0.008).*

**Conclusions:** *The improvement of LV function in patients with TTC as assessed by 2D STE may not always be complete. Some residual abnormalities in LV apex function were observed in long-term recovery following TTC episodes.* (Cardiol J 2017; 24, 1: 57–64)

**Key words: takotsubo cardiomyopathy, echocardiography, 2-dimensional-speckle tracking echocardiography, rotation, left ventricular twist**

## Introduction

Takotsubo cardiomyopathy (TTC) is an acute syndrome that is characterized by transient left ventricle (LV) wall motion abnormalities. Several studies have reported complete recovery of LV systolic function in patients with TTC as analyzed by the LV ejection fraction (LVEF) during follow-up [1–3]. Two-dimensional speckle tracking echocardiography (2D STE) is a valuable tool to evaluate global and regional LV function and appears to be more precise and distinctive than traditional echocardiography for detecting subtle myocardial abnormalities [4–6]. Apical and basal LV rotation

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have been described as an important part of LV twist, which plays a key role in maintaining both systolic and diastolic function [5–8]. LV untwisting parameters have been used to quantify LV diastolic function by 2D STE [5, 8]. Parameters of rotational mechanic of the LV have been used in many studies in hypertensive heart disease, coronary artery disease, valvular heart diseases and cardiomyopathies [5]. Pre stretch phenomenon is mainly caused by electrical dyssynchrony and leads to ineffective LV systolic function, a decrease in cardiac output and worsening of prognosis [9]. Although persistent LV impairment in TTC patients has been documented shortly after discharge [4], there are no studies showing LV function as assessed by 2D STE over an extended time period.

Herein, we sought to investigate whether LV function recovery is complete after the acute phase of TTC using 2D STE, LV rotation, twist, untwist and longitudinal strain commencing at least 6 months after discharge.

## Methods

Eighty-three patients were enrolled and admitted to the documented institution which meets currently acceptable diagnostic criteria for TTC: 1) transient regional wall motion abnormalities extending beyond a single epicardial vascular distribution, 2) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin, 3) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture [10].

Apical ballooning was observed in 67 patients. Follow-up echocardiography was performed on 55 patients 225.5 ± 27.4 days (minimum 180, maximum 270 days) post discharge (8 patients were lost to follow-up, 4 died). From these examinations 17 were excluded due to poor or non-optimal visualization, and 8 were excluded due to rhythm and conduction disturbances (left bundle branch block, pacemakers, atrial fibrillation or premature ventricular contractions). Thirty echocardiographic examinations of excellent quality were analyzed by speckle tracking (29 females, 67 ± 11 years) (Fig. 1). The control group consisted of 20 age and sex-matched subjects without structural heart disease as evaluated by thorough medical history records, physical examination, electrocardiogram (ECG) and echocardiogram. The study protocol was approved by the Local Ethics Committee, and all patients provided written informed consent.

A comprehensive transthoracic echocardiography was performed using commercially available
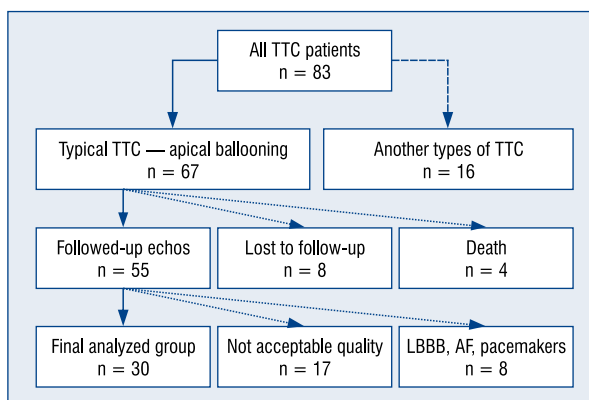


**Figure 1.** Flow-chart of patients with takotsubo cardiomyopathy (TTC) enrolled in the study; LBBB — left bundle branch block; AF — atrial fibrillation.

VIVID E9 GE with a M5s probe (GE Ultrasound, Horten, Norway). All echocardiograms were stored digitally, and further offline analysis was performed using a dedicated 2D strain imaging software package (EchoPac workstation, GE Healthcare). Traditional echocardiographic measurements were obtained according to the principles described in Recommendations for Chamber Quantification [11]. LVEF measurements were based on Biplane Simpson's method. Pulsed-wave Doppler examination of mitral and pulmonary venous inflow as well as Doppler tissue imaging of the mitral annulus was performed to evaluate diastolic function. To quantify apical (Ar) and basal (Br) rotation, parasternal and apical short-axis planes were scanned at a frame rate of 60–80 fps at the end of an expiratory breath hold. The basal plane was defined as showing the tips of the mitral leaflets and the apical plane was defined as the level just above the end-systolic LV luminal obliteration. All efforts were made to obtain cross-sections that were as circular as possible. The LV endocardial border was manually traced, and the reliability of the tracking was confirmed and visually checked and readjusted when necessary. Counter-clockwise rotations viewed from the LV apex were expressed as a positive value, clockwise rotations as a negative value. LV twist was defined as the highest net difference in degrees between the Ar and Br. LV torsion was defined as LV twist indexed by LV diastolic longitudinal length (the distance between mitral annulus and the apex in end-diastole). Peak systolic and early diastolic apical (As, Ad) and basal (Bs, Bd) rotation rates were derived from rotation rate curves. The peaks of the LV twist rates (TR) and untwist rates (UR) were derived from LV TR curves. UR begins after the peak LV twist and

**Table 1.** Demographic characteristics and clinical features of patients with takotsubo cardiomyopathy (TTC) and controls.

| Variable | TTC (n = 30) | Controls (n = 20) | P |
|---|---|---|---|
| Age [years] | 67 ± 11 | 66 ± 9 | 0.58 |
| Female | 29 (96%) | 19 (95%) | 0.92 |
| Body mass index [kg/m$^2$] | 23.6 ± 4.9 | 25.3 ± 5.6 | .3 |
| Hypertension | 18 (60%) | 11 (55%) | 0.74 |
| Diabetes | 2 (6%) | 1 (5%) | 0.83 |
| Current smokers | 4 (13%) | 2 (10%) | 0.74 |
| Hypercholesterolemia | 11 (36.6%) | 7 (35%) | 0.92 |
| On beta-blockers | 16 (53%) | 9 (45%) | 0.77 |
| On ACEI/ARB | 13 (43%) | 8 (20%) | 0.83 |

Data are mean ± standard deviation for continuous variables; n (%) for categorical variables; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blockers

**Table 2.** Traditional echocardiographic parameters in patients with takotsubo cardiomyopathy (TTC) during initial event and follow up examination.

| Variable | TTC | Follow-up | P |
|---|---|---|---|
| IVSD [mm] | 10.10 ± 1.16 | 9.87 ± 1.63 | 0.070 |
| LVEDD [mm] | 44.13 ± 5.59 | 44.20 ± 4.57 | 0.919 |
| PWD [mm] | 9.97 ± 2.01 | 9.83 ± 1.29 | 0.677 |
| LVESD [mm] | 26.83 ± 5.57 | 27.03 ± 5.26 | 0.825 |
| LA [mm] | 35.23 ± 3.85 | 34.83 ± 4.15 | 0.419 |
| LVEF [%] | 38.27 ± 6.08 | 63.63 ± 5.40 | < 0.001 |

Data are mean ± standard deviation. IVSD — intraventricular diastolic septum diameter; LVEDD — left ventricular end diastolic diameter; PWD — posterior wall diastolic diameter; LVESD — left ventricular end systolic diameter; LA — left atrium anterior posterior diameter; LVEF — left ventricular ejection fraction

reaches its highest value after the opening of the mitral valve. The first negative peak in early diastole was used for evaluation of the LV peak UR. The systolic duration was defined as the period from QRS onset on the ECG to the aortic valve closure (AVC) determined manually from the Continuous Wave Doppler aortic flow spectrum images. The pre-stretching index (PSTRI) was also calculated using 2D speckle-tracking analysis for apical segments. From apical long-axis, 4- and 2-chamber images, global LV longitudinal peak systolic strain (GLPS) and post systolic index (PSI) were quantified by automated functional imaging.

### Statistical analysis

Continuous data are presented as means ± ± standard deviation (SD) or medians and their interquartile ranges (IQR) while categorical data are expressed in proportion. Comparison between groups was performed with Student's t-test or U Mann-Whitney test for continuous variables and the Pearson's $\chi^2$ test for categorical variables

when appropriate. P-values of less than 0.05 were considered significant. SPSS software was used (version 21, SPSS Inc, Chicago, Illinois, USA) for all analysis.

### Results

Patients with TTC did not differ from controls on their baseline or clinical characteristics (Table 1). Mean LVEF in the TTC group improved during follow-up (38.3 ± 6.08% vs. 63.6 ± 5.4%; p < < 0.001) (Table 2, Fig. 2). Patients with TTC had lower heart rates and AVC was noted earlier in the control group. There were no significant differences in the traditional echocardiographic parameters for the LV diameters and both systolic and diastolic LV functions (Table 3). None of the patients or controls had concomitant valvular heart disease. In a comparison with control patients, mean apical rotation (Ar) was significantly reduced in patients with TTC (14.4 ± 6.5 vs. 18.3 ± 6.7; p = 0.048) (Fig. 3), and mean peak early diastolic apical rota-
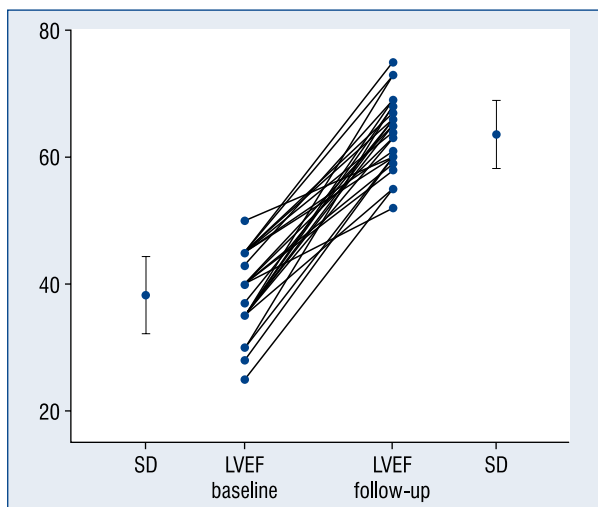
**Figure 2.** Left ventricular ejection fraction (LVEF) of patients with takotsubo cardiomyopathy at admission and at follow-up.

tion rate (Ad) was significantly slower in patients with TTC (–85.1/s ± 40.9/s vs. –119.4/s ± 41.9/s; p = 0.006). Additionally, in TTC patients, prestretch in apex portion of LV was observed significantly more often (23 vs. 6 patients; p = 0.001), involved significantly more segments (70 vs. 28; p = 0.035), and PSTRI calculated as a median value for all apical segments was significantly higher (2.16, IQR 0.33–5.50 vs. 0.00, IQR 0.00–2.95, p = 0.008) than in controls. Patients with TTC and controls did not differ in GLPS or post systolic shortening expressed as PSI (Table 4).

## Discussion

This study suggests that the improvement of LV function in patients with TTC as assessed by 2D STE may be incomplete. Interestingly, although standard 2D TTE showed LVEF improvement, there are some

**Table 3.** Traditional echocardiographic parameters in patients with takotsubo cardiomyopathy (TTC) and controls.

| Variable | TTC (n = 30) | Controls (n = 20) | P |
|---|---|---|---|
| IVSD [mm] | 9.9 ± 1.6 | 9.7 ± 2.3 | 0.75 |
| LVEDD [mm] | 44.2 ± 4.6 | 44.1 ± 6.3 | 0.98 |
| PWD [mm] | 9.8 ± 1.3 | 9.1 ± 3.8 | 0.33 |
| LVESD [mm] | 27 ± 5.6 | 27 ± 7.3 | 0.99 |
| LA [mm] | 34.8 ± 4.1 | 36.2 ± 4.6 | 0.29 |
| Left atrium volume [mL] | 54 ± 19.6 | 58.7 ± 16.3 | 0.41 |
| Asc Ao [mm] | 30.4 ± 4.3 | 30.9 ± 3.8 | 0.7 |
| LVEDV [mL] | 69 ± 23 | 74 ± 16 | 0.33 |
| LVESV [mL] | 26 ± 9 | 30 ± 9 | 0.1 |
| LVEF [%] | 63.6 ± 5.4 | 62 ± 4.9 | 0.29 |
| E [cm/s] | 0.69 ± 0.2 | 0.69 ± 0.2 | 0.89 |
| A [cm/s] | 0.89 ± 0.2 | 0.86 ± 0.16 | 0.66 |
| E/A | 0.81 ± 0.27 | 0.83 ± 0.25 | 0.87 |
| Dec T [ms] | 258 ± 55 | 268 ± 82) | 0.61 |
| S [cm/s] | 0.63 ± 0.14 | 0.62 ± 0.12) | 0.89 |
| D [cm/s] | 0.4 ± 0.09 | 0.41 ± 0.09 | 0.66 |
| S/D | 1.63 ± 0.4 | 1.56 ± 0.3 | 0.56 |
| E' [m/s] | 0.079 ± 0.02 | 0.08 ± 0.02 | 0.8 |
| E/E' | 9.6 ± 4.8 | 8.7 ± 2.4 | 0.49 |
| HR [bpm] | 67 ± 7.5 | 73 ± 11 | 0.009 |
| SBP during examination [mm Hg] | 128.5 ± 13.7 | 125.5 ± 15.4 | 0.47 |
| DBP during examination [mm Hg] | 77.6 ± 7.6 | 75 ± 8.7 | 0.26 |

Data are mean ± standard deviation. A — peak velocity of the late filling wave; Asc Ao — diameter of ascending aorta; D — peak velocity of diastolic pulmonary vein flow; DBP — diastolic blood pressure, Dec T — deceleration time of the E wave velocity; E — peak velocity of the early rapid filling wave; E' — peak velocity of mitral annulus coded by tissue Doppler; HR — heart rate; IVSD — intraventricular diastolic septum diameter; LA — left atrium anterior posterior diameter; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEDD — left ventricular end diastolic diameter; LVESD — left ventricular end systolic diameter; LVEF — left ventricular ejection fraction; PWD — posterior wall diastolic diameter; S — peak velocity of systolic pulmonary vein flow; SBP — systolic blood pressure
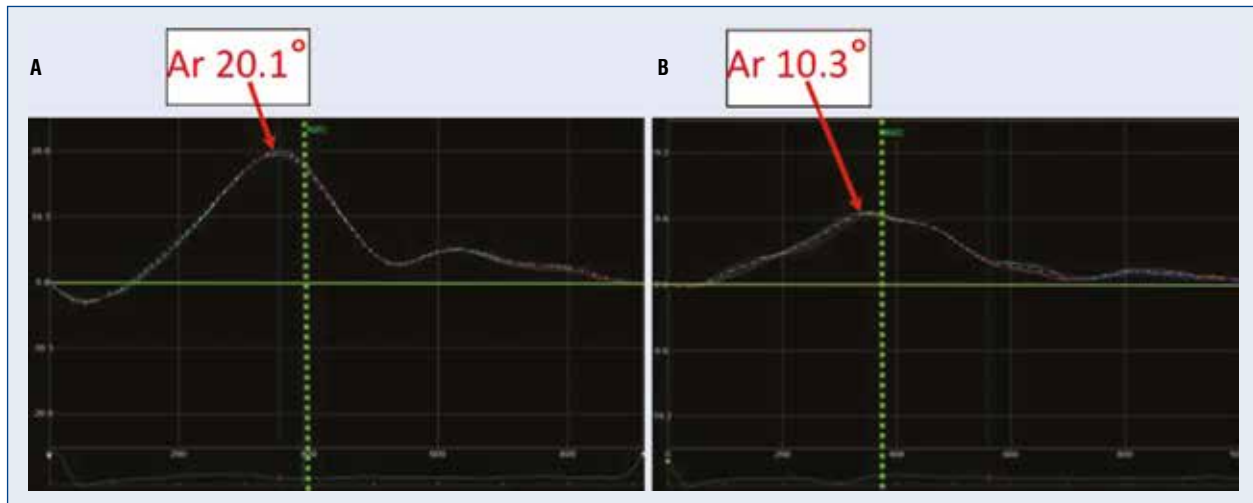
**Figure 3.** Example of left ventricular apex rotation curves (Ar) determined for a control group patient (**A**) and patient with takotsubo cardiomyopathy (**B**).

**Table 4.** Speckle tracking echocardiography parameters of patients with takotsubo cardiomyopathy (TTC) and controls.

| Variable | TTC (n = 30) | Controls (n = 20) | P |
|---|---|---|---|
| AVC [ms] | 384 ± 30 | 360 ± 27 | 0.007 |
| Ar [°] | 14.4 ± 6.5 | 18.3 ± 6.7 | 0.048 |
| Br [°] | –8.05 ± 5.1 | –6.3 ± 3.8 | 0.20 |
| LV twist [°] | 21.7 ± 9.5 | 24.2 ± 10.9 | 0.39 |
| LV torsion [°/cm] | 2.9 ± 1.3 | 3.4 ± 1.7 | 0.34 |
| TR [°/s] | 120.9 ± 46.9 | 135 ± 48.9 | 0.30 |
| As [°/s] | 85.9 ± 30.9 | 93.7 ± 38.7 | 0.43 |
| Bs [–°/s] | –65.5 ± 28.4 | –55.8 ± 24.8 | 0.21 |
| UR [–°/s] | –126.7 ± 61.1 | –96.56 ± 48.9 | 0.37 |
| Ad [–°/s] | –85.1 ± 40.9 | –119.4 ± 41.9 | 0.006 |
| Bd [°/s] | 60.03 ± 42.1 | 60.4 ± 31 | 0.21 |
| PSTRI | 2.16 (0.33–5.50) | 0.00 (0.00–2.95) | 0.008 |
| Pre-stretch — patients | 23 (76.66%) | 6 (20%) | 0.001 |
| Pre-stretch — segments | 70 (38.8%) | 28 (23.3%) | 0.035 |
| GLPS [%] | –20.4 ± 1.7 | –20.0 ± 2.8 | 0.49 |
| PSI [%] | 1.33 ± 1.799 | 1.62 ± 1.719 | 0.6 |
| PSS — patients | 16 (53%) | 17 (82%) | 0.058 |
| PSS — segments | 59 (39%) | 54 (54%) | 0.2 |

Data are mean ± standard deviation for continuous variables; n (%) for categorical variables. Ad — peak early diastolic apical rotation rate; Ar — mean apical rotation; As — peak systolic apical rotation rate; AVC — aortic valve closure time; Bd — peak early diastolic basal rotation rate; Br — mean basal rotation; Bs — peak systolic basal rotation rate; GLPS — global longitudinal peak systolic strain; LV — left ventricle; PSI — post systolic index; PSS — post systolic shortening; PSTRI — pre-stretch index; TR — twist rate; UR — untwist rate

subclinical abnormalities of LV apex function that may still be observed several months after discharge.

The acute phase of TTC is characterized by factors suggestive of substantial heart muscle injury [12]. Nearly all patients have elevated biomarkers of cardiac myonecrosis [13–19] and the ECG findings are typical of acute ischemia [15, 16, 20, 21]. Akinesis or dyskinesis (ballooning) of segments affected by TTC observed during the initial examination may lead to high intraventricular pressure and increased

LV wall stress, which may cause perfusion disturbances [22, 23]. Focal late gadolinium enhancement in cardiac magnetic resonance, which is believed to be evidence of irreversible fibrosis, is observed in 9–40% of patients with TTC [24–27]. Cardiac rupture is the most severe and oftentimes fatal complication of TTC, which supports the transmyocardial damage [28, 29]. Histopathological findings at the rupture site include myocardial necrosis with hemorrhaging, fused foci of coagulation necrosis and contraction band necrosis, as well as diffuse patchy infarction of myocardial in the surrounding tear area [30–33]. In myocardial biopsies, intestinal fibrosis, contraction band necrosis and mild cell infiltration have been described [13, 32]. Several studies have reported complete recovery of LV systolic function in patients with TTC as analyzed by the LVEF during follow-up [2, 34, 35]. However, Heggemann et al. [4] recently proposed that subtle abnormalities of LV mechanical function could persist into the early recovery period of TTC.

The complex mechanism of myocardial function in human heart during systole and diastole is related to intricate myofiber architecture and intracellular matrix. Deformation of myocardium runs in three directions — longitudinal, radial and circumferential. During the cardiac cycle, there is also a systolic twist and diastolic untwist. When viewed from the apex, LV rotation at the base is clockwise. At the apical level, counterclockwise rotation takes place. The potential energy stored in cardiac extracellular matrix proteins (collagen and fibronectin) during the active systole phase is released back during the onset of relaxation, which generates both untwist and suction [5, 7, 9].

Volumetric measurement using the Biplane method of disks (modified Simpson's rule) is the method of choice for assessing LV systolic function, but it has some limitations [11]. In 2- and 4-chamber views the apex is frequently foreshortened and the precise border of the endocardium for measurements of LV end-diastolic and end-systolic volume is hard to define. This method relies only on two planes and is based on mathematical assumption. Furthermore, it does not yield the complexity of LV mechanics even when supported by 3D acquisition [6, 36–38]. In our study, no significant differences in traditional echocardiographic parameters of a systolic and diastolic function of LV were observed.

2D STE is a relatively new echocardiographic method. This method analyzes myocardial velocities and deformations and is, therefore, useful in assessing LV systolic and diastolic function [5, 6, 39–42]. 2D STE has, in previous studies, been used to assess the functional recovery of LV systolic function after the acute phase of TTC. Mansencal et al. [43] observed no significant differences between the TTC and control group of healthy volunteers in mean values of segmental systolic peak velocity, strain and strain rate, but this measurement was only taken during early follow-up (1 month). Meimoun et al. [44] assessed the LV rotation in patients with typical TTC during the acute phase and during early follow-up, comparing both samples in patients with anterior wall ST-segment elevation acute myocardial infarction and control group. They observed complete recovery of previously impaired LV function. As mentioned previously, Heggemann et al. [4] measured longitudinal and radial strain and calculated PSI in patients with TTC on admission and then in one subsequent month. Abnormal global and regional strain patterns during the acute phase also improved significantly during follow-up. However, subtle regional abnormalities remained. During follow-up of the TTC group, more than half of the LV segments showed post systolic shortening which is known, but is not a specific marker of regional dysfunction and could be an indicator that dysfunction and LV is prolonged [4]. In this paper, LV longitudinal strain and twist mechanics assessed by 2D STE in longer term follow-up have been evaluated. LV rotation parameters were preserved in basal segments while rotation of the apex during systole and diastole was significantly reduced in the TTC group in comparison to age and gender-matched volunteers without any known structural cardiac disease.

The elastic solid body returns to its original shape after deformation. According to Hook's law, an elastic force is directly proportional to the value of deformation. All biological tissues are viscoelastic and have the property of both viscous and elastic materials [45]. The elasticity of the heart is provided mainly by its elastic extracellular matrix, especially the extensive collagen network. Torsional deformation of the LV causes elastic potential energy storage, which is released and converted to kinetic energy during untwist in the early diastolic phase. As the mathematical equation states, elastic energy is proportional to the square of deformation: $Ep = 1/2kx2$, where k is the elasticity constant (N·m−1), and x is the deformation from the equilibrium position (in m).

In our study deformation has the value of variable Ar, the mean angular deformation of the apex mass in a counterclockwise direction during the systolic phase. The lower value of Ar as in our TTC group, the less elastic force and elastic potential

energy absorbed by the cardiac interstitium. This causes motion in a clockwise direction of the apex with a smaller angular velocity during diastole and is displayed as a lower value of Ad in our TTC group.

### Limitations of the study

Our study has some limitations. First, the study is limited by the relatively low number of patients, which is a result of the highly selective enrollment process to achieve the best quality of images. Thus, further reports with bigger sample size are strongly needed. Secondly, we did not confirm our results by another imaging technique such as LV tagging imaging by use of cardiac magnetic resonance. Last but not least, since this was not a protocol-based study, extensive evaluation of LV function was not performed during the bedside TTE at baseline.

### Conclusions

The results of the present study showed that improvement of the LV systolic and diastolic function in TTC assessed by use of 2D STE may not be optimally substantial, and some subclinical residual abnormalities in LV apex functioning may be still observed several months after discharge. TTC could permanently impair the LV regions affected by this disease during its acute phase, so the question as to whether a "broken heart" can be completely mended remains unresolved. Moreover, whether these findings have potential implications for treatment (e.g., long-term use of beta-blockers or angiotensin-converting enzyme inhibitors) and the prognosis remains unknown.

**Conflicts of interest:** None declared

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