Functional recovery of regional myocardial deformation in patients with takotsubo cardiomyopathy

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**A B S T R A C T**

**Background:** Takotsubo cardiomyopathy (TC) is acute, but completely reversible in the absence of significant coronary artery disease. This study aims to assess the functional recovery of regional myocardial deformation in patients with TC using 2-dimensional (2D) speckle tracking echocardiography.

**Methods:** Thirty-three patients diagnosed with TC (mean age 63 years, 26 female) prospectively underwent serial 2D echocardiography on day 1 (initial presentation), day 4 (the middle, interquartile range [IQR] 2–5 days), and day 21 (recovery, IQR 13–32 days). Twenty-one (64%) patients showed classical type of TC with akinesis of mid-left ventricular (LV) and apical segments and 12 (36%) of patients presented with mid-LV variant with apical sparing. Myocardial deformations were serially assessed using 2D strain analysis. All echocardiographic values on day 21 were compared with the corresponding values from 30 controls of similar age and gender.

**Results:** LV ejection fraction (EF) gradually improved at follow-up (32 ± 8% on day 1 vs. 62 ± 4% on day 21, p < 0.001). Despite no difference in LVEF between the patients with complete recovery (LVEF >60% on day 21) and controls, the patients showed significantly lower global longitudinal strain than controls. On regional analysis of the mid-LV segments, both longitudinal and circumferential strains of patients with TC were similarly diminished on day 1. During recovery, longitudinal strain showed more delayed recovery than circumferential strain compared to the values of controls.

In LV apex of controls, circumferential strain normally presented higher value than longitudinal strain. In LV apex of patients with classical TC, the reduced circumferential strain on day 1 rapidly increased with a wide variation to maintain augmented circumferential shortening.

**Conclusions:** Quantifying LV myocardial deformation in patients with TC is informative in the detection of persistent subtle LV dysfunction and improves our understanding of regional myocardial mechanics during recovery.

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**Introduction**

Takotsubo cardiomyopathy (TC) is a cardiac condition characterized by acute, but completely reversible, left ventricular (LV) dysfunction in the absence of significant coronary artery disease. Although the exact pathophysiologic mechanism of TC has not been fully elucidated, catecholamine-mediated myocardial stunning is the most favored explanation for the development of TC [1]. Excessive catecholamine leads to microvascular dysfunction and can directly affect the cardiac myocyte, leading to structural alteration of calcium handling protein that may contribute to the LV contractile dysfunction in patients with TC [2–4]. Additionally, the wall motion abnormality of TC characteristically shows rapid recovery, occurring within a few days to weeks. However, more detailed evaluations revealed that subtle LV dysfunction in TC persists for weeks or months even after the normalization of LV ejection fraction (LVEF) [5–7]. Two-dimensional (2D) strain imaging has been proposed as a reliable means to define regional LV systolic function and has facilitated the early detection of subtle changes in LV myocardial
deformation during the earlier stage of hypertension, diabetes, aortic stenosis, and various cardiovascular (CV) risk factors with preserved LVEF [8–12].

Although there are a few longitudinal data on myocardial deformation of the longitudinal and/or radial directions or LV torsion in patients with TC [5,13,14], we prospectively assessed the serial changes of regional myocardial deformations and investigated the characteristics of functional recovery of LV dysfunction in patients with TC.

Methods

Study population

A total of 33 consecutive patients diagnosed with TC were prospectively identified. Patients with significant arrhythmia and valvular heart disease were excluded. Thirty subjects of similar age and gender who had a normal echocardiography were recruited as controls. The diagnosis of TC was based on the modified Mayo clinic criteria [1]: (1) transient akinesia/hypokinesia of mid-left ventricular (LV) segments with or without apical involvement beyond single major coronary artery distribution, (2) absence of obstructive coronary artery disease or acute plaque rupture on the coronary angiogram, (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or biomarker elevation, and (4) no pheochromocytoma or myocarditis. Patients with TC had at least three serial echocardiographic examinations; after the initial presentation (day 1), follow-up examinations were performed every 2 days to capture the intermediate stage of recovery and final examination to identify whether full recovery was performed before or after discharge. The study protocol was approved by the local ethics committee of the Hallym University College of Medicine and informed consent was obtained from all individual participants of the study.

Echocardiography

Comprehensive echocardiographic images were obtained using commercially available Vivid 7 machine (GE-Vingmed, Horten, Norway) or Vivid 1 machine (GE-Vingmed) echocardiographic system. Echocardiography was performed according to American Society of Echocardiography recommendations [15]. The LV volumes and LVEF were obtained by the modified biplane Simpson’s method from the apical 4- and 2-chamber views.

Two-dimensional speckle tracking

All echocardiographic data were digitally recorded in cine loop format and 2D strain analysis was performed offline using custom 2D strain imaging software (EchoPac, Version 11.0, GE-Vingmed) by one investigator who was blinded to the clinical data. Frame rates of 60–90 Hz were used because they are considered optimal for 2D speckle tracking.

The endocardial borders were traced at the end-systolic frame and an automated tracking algorithm outlined the myocardial motion. The width of the region of interest (ROI) was adjusted to include the entire thickness of the LV myocardium. The software automatically divided the cross-sectional images into six standard segments of inferoseptal, anteroseptal, anterior, anterolateral, posterior, and inferior. The circumferential peak systolic strain of the six segments was determined in the short-axis view of the LV base, mid-LV (papillary muscle level), and apex.

The longitudinal peak systolic strain of the six segments were determined in the apical two-, three- and four-chamber views of the LV base, mid-LV, and apex. LV global performance was measured by assessing the averaged global longitudinal strain and a bull’s eye plot of peak systolic strain using the automated functional imaging technique based on 2D longitudinal strain imaging in the apical two-, three- and four-chamber views [16,17]. The software automatically checked the tracking quality within the ROI and the tracking quality was verified for each segment. The ROI was manually adjusted if necessary and the segments with poor tracking despite manual readjustments were excluded from analysis. Echocardiographic data on day 21 obtained from the patients with TC were compared with the corresponding values of the controls.

Statistical analysis

Continuous variables are expressed as mean ± SD and were compared using Student t test. Categorical data are presented as percentages and were compared using the $\chi^2$ test.

Repeated measures analysis of variance with the Bonferroni post hoc test was used to compare the serial changes in the heart rate, EF, LV volumes, and regional myocardial deformations during recovery. The strain measurements were repeated by the same observer >3 weeks later to verify the intraobserver variability and strain measurements were performed by two independent blinded observers on the same echocardiographic images to verify the interobserver variability. The reproducibility of strain measurements was determined as intraclass correlation coefficient (ICC) with 95% confidence interval (CI) and mean absolute difference with 95% limits of agreement (LOA) using Bland–Altman analysis [18]. An ICC value >0.75 was interpreted as excellent, 0.4–0.75 as fair-to-good, and <0.4 as poor. The significance level was set at $p < 0.05$. Statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY, USA).

Results

Twenty-one (64%) patients showed the classic type of TC with akinesia of the mid-LV and apical segments, while 12 (36%) patients presented with mid-LV variant with apical sparing. Follow-up echocardiography after the initial presentation (day 1) was performed on day 4 [intermediate, interquartile range (IQR) 2–5 days] and on day 21 (recovery, IQR 13–32 days). The baseline characteristics of the study population are summarized in Table 1. The mean age of the patients with TC was 63 ± 15 years (range 35–82 years), and they were predominantly women (79%). The serial echocardiographic measurements during recovery in patients with TC were shown in Table 2.

Fig. 1 indicates an example of bull’s eye plot of peak systolic strain in a patient recovering from TC in which the global longitudinal strain value gradually improved over time. In Fig. 2, the serial changes of the circumferential and longitudinal myocardial deformations were presented from LV base to apex in patients recovering from TC. Although the LV base showed normal or hyperkinetic wall motion in 2D echocardiography, 2D strain analysis revealed reduced values on day 1 and only the circumferential strain on day 21 caught up with the value of the controls. In the mid-LV level, both longitudinal and circumferential strain were similarly diminished on day 1 and significantly improved in stages. However, longitudinal strain showed slower improvement than the circumferential strain on day 21 compared to the values of controls. In LV apex of the controls, the absolute value of circumferential strain was significantly higher than that of longitudinal strain in contrast with the similar values of those strains in LV base and mid-LV. In LV apex of patients with classical TC, both strains were significantly diminished on day 1, circumferential strain rapidly increased with a wide variation to catch up the value of controls. On the other hand, LV apex of
patients with mid-LV variant showed preserved strain values in a similar fashion to controls.

Table 3 dichotomizes the patients according to the recovery status of LVEF on day 21 (LVEF >60% on day 21, complete recovery). Although there was no difference in LVEF between the patients with complete recovery and controls, the patients showed a significantly lower global LV strain than controls. In segmental analysis, circumferential strain of the patients caught up with the value of controls, whereas, longitudinal strain was still inferior to those of controls \((p < 0.001)\). When we compared the clinical and echocardiographic data according to the type of TC (classical TC vs. mid-LV variant) (Table 4), patients with mid-LV variant TC were younger and showed lower B-type natriuretic peptide at admission than patients with classical TC. However, they revealed no significant difference in functional recovery of myocardial deformations of mid-LV segments in 2D strain analysis.

The intra- and interobserver reliability of 2D strain analysis showed that the 2D strains showed good intra- and interobserver agreements measured as the ICC values with 95% CI and the mean difference with 95% LOA (Supplement file).

Discussion

The principal findings of this study were: (1) even though LV systolic function appears to have completely resolved in 2D echocardiography, it does not mean a full recovery of myocardial contractility and subtle LV dysfunction may persist even after LVEF normalization; (2) In regional analysis, longitudinal strain showed more delayed recovery than circumferential strain and the circumferential augmentation of LV apex made a different feature in functional recovery of myocardial deformations between base to mid-LV and LV apex.

Despite the rapid resolution of wall motion abnormality, 2D strains on day 21 were still inferior to the values of the controls, suggesting that LVEF as a global estimate of LV systolic function is
The presence of subtle LV dysfunction even after normalization of LVEF in patients with TC may be associated with earlier reports that impaired myocardial metabolism and disturbed repolarizations were sustained even after resolution of wall motion abnormality in patients with TC [6,7]. It underscores the clinical importance of 2D strains to assess full recovery of myocardial deformation even after normalization of LVEF and to determine the follow-up duration in recovering patients with TC.

In mid-LV, the longitudinal strain showed slower recovery than circumferential strain compared to each value of the controls. Longitudinal myocardial fibers have a larger radius of curvature and are located in the subendocardium; therefore, they are insufficient in quantifying intrinsic myocardial contractility. The presence of subtle LV dysfunction even after normalization of LVEF in patients with TC may be associated with earlier reports that impaired myocardial metabolism and disturbed repolarizations were sustained even after resolution of wall motion abnormality in patients with TC [6,7]. It underscores the clinical importance of 2D strains to assess full recovery of myocardial deformation even after normalization of LVEF and to determine the follow-up duration in recovering patients with TC.

The LV base in classical TC shows normo- or hyperkinesia on 2D echocardiography [19]. In this study, 2D strain analysis revealed diminished strains of the LV base on initial presentation. This finding is in line with the observation of previous studies that showed reduced longitudinal strain [5,20] and systolic myocardial velocities [13] at the LV base in patients with classic TC. It might be anticipated that hemodynamic loading and geometric changes caused by a dysfunctional segment increase wall stress on the surrounding myocardium as seen in myocardial infarction [21].

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### Table 3
Clinical and echocardiographic characteristics according to the recovery status of the patients with takotsubo cardiomyopathy and comparisons with controls.

<table>
<thead>
<tr>
<th></th>
<th>TC (Incomplete recovery n=11)</th>
<th>Complete recovery (n=22)</th>
<th>Controls</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 13</td>
<td>62 ± 16</td>
<td>61 ± 14</td>
<td>0.860</td>
</tr>
<tr>
<td>Female (%)</td>
<td>64</td>
<td>86</td>
<td>67</td>
<td>0.105</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>55</td>
<td>46</td>
<td>46</td>
<td>0.931</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>18</td>
<td>14</td>
<td>14</td>
<td>0.765</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>36</td>
<td>14</td>
<td>37</td>
<td>0.064</td>
</tr>
<tr>
<td>Classical type (%)</td>
<td>82</td>
<td>55</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>Mental stress (%)</td>
<td>9</td>
<td>14</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>ST segment elevation (%)</td>
<td>36</td>
<td>41</td>
<td>0.801</td>
<td>–</td>
</tr>
<tr>
<td>BNP at admission (pg/ml)</td>
<td>2729 (750–3686)</td>
<td>1136 (553–2241)</td>
<td>0.089</td>
<td>–</td>
</tr>
<tr>
<td>Echocardiography (day 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>57 ± 3</td>
<td>64 ± 3</td>
<td>0.001</td>
<td>64 ± 3 ± 4</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>71 ± 29</td>
<td>70 ± 19</td>
<td>0.611</td>
<td>75 ± 17 ± 6</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>30 ± 12</td>
<td>25 ± 7</td>
<td>0.440</td>
<td>26 ± 6 ± 6</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>41 ± 17</td>
<td>45 ± 12</td>
<td>0.154</td>
<td>49 ± 12 ± 6</td>
</tr>
<tr>
<td>Global LV strain (%)</td>
<td>-13.5 ± 3.2</td>
<td>-16.1 ± 3.4</td>
<td>0.036</td>
<td>-19.6 ± 2.8</td>
</tr>
<tr>
<td>Segmental strain (mid-LV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>17.7 ± 3.9</td>
<td>19.8 ± 2.9</td>
<td>0.335</td>
<td>21.4 ± 3.1</td>
</tr>
<tr>
<td>Longitudinal strain (%)</td>
<td>10.5 ± 2.5</td>
<td>15.0 ± 3.6</td>
<td>0.101</td>
<td>20.5 ± 2.1</td>
</tr>
</tbody>
</table>

TC, takotsubo cardiomyopathy; BNP, B-type natriuretic peptide; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular.

* Complete recovery vs. controls.
Table 4
Comparisons of clinical and echocardiographic data during recovery between the classical type of takotsubo cardiomyopathy and mid-ventricular variant.

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Classical TC (n=21)</th>
<th>Mid-ventricular variant (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 12</td>
<td>53 ± 16</td>
<td>0.020</td>
</tr>
<tr>
<td>Female (%)</td>
<td>81</td>
<td>73</td>
<td>0.667</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>57</td>
<td>36</td>
<td>0.264</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>24</td>
<td>0</td>
<td>0.078</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>15</td>
<td>27</td>
<td>0.667</td>
</tr>
<tr>
<td>Mental stress (%)</td>
<td>10</td>
<td>18</td>
<td>0.593</td>
</tr>
<tr>
<td>ST segment elevation (%)</td>
<td>38</td>
<td>46</td>
<td>0.687</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>2147 (1030–3371)</td>
<td>578 (142–1826)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

TC, Takotsubo cardiomyopathy; BNP, B-type natriuretic peptide; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular.

* Day 21 of classical TC vs. day 21 of mid-LV variant.

Exposed to higher wall stress than the circumferential fibers of the mid-wall having a shorter radius [22–25], Donal et al. reported earlier impairment of longitudinal function with relatively preserved radial function in a pig model of acute pressure overload [26]. In an animal model with tagged magnetic resonance imaging, the longitudinal strain was lost first with decreasing perfusion (48%), followed by circumferential (40%) and finally radial strain (35%) during graded myocardial ischemia [27]. These properties of longitudinal strain as an earlier impairment and a delayed recovery during stress verify that longitudinal fibers are more susceptible to the hemodynamic stress than circumferential fibers. Inversely, the earlier recovery of myocardial dysfunction in the mid-wall (circumferential or radial) fibers with less wall stress might be a compensatory response to the delayed recovery of the longitudinal myocardial strain in these patients with TC. It has been reported that the radial or circumferential strain was augmented to compensate for the decreased longitudinal myocardial strain in patients in the earlier stage of hypertension, diabetes, and patients with CV risk factors [8,9,11].

In LV apex, apical strain differed substantially from base to mid-LV strain.

In controls, both longitudinal and circumferential strains of LV base and mid-LV showed similar values, whereas in LV apex, circumferential strain maintained higher value than longitudinal strain, consistent with those of controls in previous reports [28,29].

It suggests that circumferential shortening is normally augmented rather than longitudinal shortening in LV apex. Thus, in patients with classical TC, the reduced circumferential strain in LV apex showed a rapid increment to maintain augmented circumferential shortening.

LV stroke volume is produced by radial thickening determined by both circumferential and longitudinal fiber shortening. Particularly, in LV apex with shorter radius, circumferential shortening contributes more to LV systolic function than longitudinal shortening. Considering that LV wall stress is determined by the curvature and increases as the radius of curvature increases according to the law of Laplace, both myofiber architecture and local geometry result in a non-uniform wall stress distribution from the LV base to the apex [22–25]. Regarding the different response of LV regional mechanics to hemodynamic alteration, Akagawa reported the differences in responses of radial strain between the LV base and apex with incremental doses of dobutamine [30], while Carasso et al. reported the changes in circumferential strain at the apex differed from that of the mid-LV after aortic valve replacement [28]. In these patients with TC, although the mechanism is not clear, circumferential augmentation in LV apex made a different feature in functional recovery of myocardial deformations between base to mid-LV and LV apex.

In comparisons of patients with classical TC and mid-LV variant, patients with mid-LV variant were younger and showed milder clinical presentation, which is consistent with the previous reports [31,32]. However, there was no difference in functional recovery of myocardial deformations of mid-LV segments between the groups in 2D strain analysis. It implies that the two types of TC share similar pathophysiological basis of reversible cardiomyopathy, although the regional preponderance of ballooning is not clearly understood.

Study limitations

Several limitations of this study require consideration. Although we assessed the functional recovery in the classical subset and mid-LV variant of TC, these results do not reflect what occurs in the reverse type of TC, which may show different myocardial mechanics during recovery.

Although the ages and gender of the controls were similar to those of the study patients, they were not randomly sampled; thus, selection bias is possible. The CV medications used might affect the functional recovery of myocardial deformation in these patients with TC. It is difficult to evaluate the effect of medications on myocardial deformation because of the wide variations in the medication administration between and within patients due to the fluctuating blood pressure and heart rate in the acute stage of TC. This study presented relatively short-term data of the recovery process of TC. More longitudinal data are necessary to fully follow the recovery and better understand the myocardial mechanics in recovering patients with TC.

Conclusion

Quantifying LV myocardial deformation is informative for the detection of persistent subtle LV dysfunction in patients with TC and improves our understanding of regional myocardial mechanics during recovery. Clinically, 2D strain analysis is valuable to determine the follow-up until the full recovery of myocardial deformations in patients with TC.
Conflicts of interest
None.

Disclosures
None.

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Appendix A. Supplementary data

References