Right ventricular involvement in Takotsubo cardiomyopathy

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Aims The aim of our study is to assess the incidence and clinical significance of right ventricular (RV) involvement in Takotsubo cardiomyopathy (TTC).

Methods and results Between February 2002 and December 2005, 47 patients with TTC underwent cardiovascular magnetic resonance (CMR) at our institutions. 13 patients with delayed initial CMR were excluded. In the remaining 34 patients (32 women), RV wall motion abnormalities (WMAs) were present in nine (26%). Left ventricular ejection fraction (LVEF) was significantly lower in patients with RV involvement (40 ± 6 vs. 48 ± 10%, P = 0.04). The most frequently affected RV segments were the apico-lateral (89%), the antero-lateral (67%), and the inferior segment (67%). All RV WMA improved or disappeared in eight of nine patients who underwent a follow-up CMR study. Pleural effusion was more common in patients with RV involvement (67 vs. 8%, P = 0.001) and was predictive of RV dysfunction (sensitivity 67% and specificity 92%). Significant or bilateral pleural effusions were seen exclusively in patients with RV involvement.

Conclusion RV involvement is common in TTC and seems to be associated with a more severe impairment in LV systolic function. It may be suspected by the presence of pleural effusion.

Keywords Takotsubo cardiomyopathy; Apical ballooning syndrome; Right ventricle

Introduction

Takotsubo cardiomyopathy (TTC) is characterized by the finding of transient wall motion abnormalities (WMAs) of the left ventricle (LV), without significant coronary artery stenosis, typically accompanied by chest pain, dynamic reversible ST-T segment abnormalities, and mild elevation of cardiac enzymes disproportionate to the extent of regional WMA.1 It has also been called acute LV apical ballooning syndrome, ampulla cardiomyopathy, broken heart syndrome, and stress cardiomyopathy. In its classical form, the LV apex is invariably affected, whereas in its variant form, the LV apex is spared.2–4

Despite sporadic reports on right ventricular (RV) involvement in this entity, research to date has mainly focused on LV pathology.5–7 Elesber et al.8 were the first to systematically evaluate RV involvement in TTC. In their recently published echocardiographic study of 25 patients, RV dysfunction was present in eight and associated with lower LVEFs, longer hospitalizations, and more complications such as severe congestive heart failure, intra-aortic balloon pump, and cardiopulmonary resuscitation. However, as recognized by the authors themselves, the study was somewhat limited due to the small number of patients as well as technical limitations of echocardiography for the assessment of RV function. Cardiovascular magnetic resonance (CMR) imaging does not have these technical limitations and is regarded as the gold standard for the assessment of RV function. Thus, the aim of our study was to determine the frequency and characterization of RV involvement in TTC using CMR imaging.

Methods

Patient population

Between February 2002 and December 2005, 2031 patients underwent left heart catheterization for suspected acute coronary syndrome at our two institutions. Among these, 51 patients were diagnosed with classical TTC and prospectively included in our database. The diagnosis of TTC was based on the following criteria: (i) reversible akinesia or dyskinesia of the LV apex and mid-segments beyond a single major coronary artery vascular distribution on left ventriculography; (ii) no coronary artery stenosis >50% of the luminal diameter on coronary angiography; (iii) dynamic ST-T segment abnormalities; and (iv) elevation of cardiac enzymes. Forty-seven of these patients also underwent gadolinium-enhanced CMR. CMR could not be performed in four patients because of claustrophobia (n = 2) or metal implants (n = 2). In 13 patients, LV WMA had already normalized (n = 8) or nearly normalized (n = 5) by the
time of the first CMR, because CMR had been performed relatively late after the onset of symptoms (median 9 days, interquartile range 8–14 days). These patients were excluded from further analysis. The remaining 34 patients comprised the final study group. In these patients, CMR studies were retrospectively reviewed for RV involvement.

The performance of this study was consistent with the standards of the local Ethics Committees at our institutions.

Cardiovascular magnetic resonance

CMR studies were independently reviewed by two experienced investigators (D.H. and T.P.) for the presence of RV WMA and pleural effusion. The investigators were blinded to clinical data. Any disagreements were resolved through consensus. All studies were performed using a 1.5 T whole body imaging system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany). A dedicated four-element, phased-array cardiac coil was used. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, ECG-gated cine images were then acquired using a segmented steady-state free-precession sequence (TE/TR 1.2/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4 × 1.8 mm, slice thickness 5 mm, and interslice gap 5 mm). Seven to 12 short-axis views covering the entire myocardium were obtained. After cine imaging in long-axis and short-axis views, an intravenous bolus of 0.2 mmol/kg gadolinium-diethylenetriaminepentaacetic acid (Magnevist, Schering AG, Berlin, Germany) was given and the same views were rescanned in identical orientation and slice position using a segmented inversion recovery gradient-echo sequence. Images were obtained 10 min after contrast administration. The inversion time was individually adjusted to optimally null myocardial signal (250–300 ms). Image analysis and quantitative analysis were performed off-line using a dedicated software (ARGUS, Siemens). Each study was examined for morphological abnormalities of both ventricles. Global and regional functions were studied on cine images. WMAs were classified as hypokinesia, akinesia, and dyskinesia. The LV chamber was assessed in the standard 17-segment model. The RV chamber was assessed in an eight-segment model (Figure 1). In the horizontal longitudinal plane, the RV was divided into three segments (apico-lateral, medio-lateral, and baso-lateral). In the short-axis plane, the RV chamber was divided into five segments (anterior, antero-lateral, lateral, infero-lateral, and inferior). Pleural effusion was visually estimated and classified as absent, mild (<2 cm), or significant (>2 cm) (Figure 2).

For volume analysis, the first phase was defined as end-diastole. The end-systolic image was defined visually as the frame revealing the smallest cavity area. End-diastolic and end-systolic volumes of the LV and RV were measured by volumetry. Stroke-volume and EF were calculated in the standard fashion.

Clinical assessment

Laboratory tests, serial electrocardiograms, and echocardiography were performed according to the standard protocol for the management of acute coronary syndromes at our institutions. All patients underwent left heart catheterization.
Statistics

Results are expressed as mean ± standard deviation or median (interquartile range) as appropriate. The Mann-Whitney test (SPSS software, version 13) was used to compare continuous variables between patients with and without RV involvement. The χ² test was used for categorical variables. The Wilcoxon signed-rank test was used to compare RV EFs at various times in patients with RV involvement. A two-sided P-value of less than 0.05 was considered significant. Sensitivity, specificity, and positive and negative predictive values were calculated in the standard fashion.

Results

Clinical characteristics

After exclusion of those 13 patients in whom LV WMA had already normalized or nearly normalized by the time of their first CMR study, 34 patients underwent further analysis. There were 32 women and two men. Prior cardiovascular history was unremarkable in all patients, with no history of angina, prior myocardial infarction, or heart failure. Nine patients (26%) had RV WMA on CMR imaging (Table 1). Relevant history in these patients included hypertension (n = 5), hypercholesterolaemia (n = 2), diabetes (n = 2), chronic obstructive pulmonary disease (n = 2), osteoporosis (n = 1), goiter (n = 1), Graves’ disease (n = 1), and paroxysmal atrial fibrillation (n = 1). Angina was the presenting symptom in five (56%) and dyspnoea in three (33%). One patient presented with nausea and vomiting. Antecedent physical or emotional stress could be identified in seven (n = 78%). Initial systolic blood pressure was $137 ± 30$ mmHg (range 90–197) and initial diastolic blood pressure was $77 ± 10$ mmHg (range 60–109). ST-T segment abnormalities upon admission consisted of ST segment elevation in three (33%), both ST-segment elevation and ST-segment depression in one (11%), and T-wave inversion in five (56%) patients. Clinical profiles did not differ between patients with and without RV involvement (Table 2).

Angiography

Left heart catheterization had been performed within 24 h of admission in seven patients. One patient underwent catheterization on day 3 (patient 1) and another patient on day 6 (patient 9). All patients had LV WMA consisting of akinesia, dyskinesia, or hypokinesia of the apical and mid-LV segments (Figure 3). None of the patients had significant coronary artery disease.

Right ventriculography had been performed in two patients (patients 8 and 9). WMAs affecting the apical and mid-RV segments were demonstrable in both the patients (Figure 3). RV function was severely reduced in patient 8 and mildly reduced in patient 9.

Cardiac magnetic resonance imaging

Patients underwent CMR at a median of 3 days (interquartile range 1–4 days) after admission. This time interval was 4 days (interquartile range 1–4 days) in patients without RV involvement vs. 2 days (interquartile range 1–3.5 days) in patients with RV involvement (P = 0.98). All patients had LV WMA consisting of akinesia, dyskinesia, or hypokinesia of the apical and mid-LV segments beyond a single coronary artery.
distribution (Figure 4). Systolic anterior motion of the mitral valve was present in three patients. LVEF was 48 ± 10% in patients without RV involvement and 40 ± 6% in patients with RV involvement (P = 0.04). Only one patient had a small area of LV subendocardial delayed hyperenhancement. RV WMAs consisting of akinesia, dyskinesia, or hypokinesia were present in nine patients (Figures 2 and 5). The most frequently affected segments were the apico-lateral segment (89%), the antero-lateral segment (67%), the inferior segment (67%), and the medio-lateral segment (56%). Follow-up CMR was performed in eight of nine patients 362 ± 429 days later (range 6–905 days). RV WMA had disappeared in five and significantly improved in three patients. In the latter three patients who did not have complete resolution of WMA, CMR had been performed relatively early after the onset of symptoms (days 6, 10, and 10, respectively).

Pleural effusion was more common in patients with RV involvement than in those without (67 vs. 8%, P < 0.01) (Table 2). Patients with pleural effusions had a lower mean EF (40 ± 8 vs. 47 ± 10%, P = 0.04). The sensitivity, specificity, and positive and negative predictive values of any pleural effusion for the detection of RV involvement were 67% (95% confidence interval 36–84%), 92% (95% confidence

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical profiles of patients with and without RV involvement</th>
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<tr>
<td></td>
<td>RV− (n = 25)</td>
</tr>
<tr>
<td>Age</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Female gender</td>
<td>24 (96%)</td>
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<tr>
<td>Preceding stressor</td>
<td>19 (76%)</td>
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<tr>
<td>Angina</td>
<td>18 (75%)</td>
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<tr>
<td>Blood pressure (mmHg)</td>
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<tr>
<td>Systolic</td>
<td>133 ± 21</td>
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<tr>
<td>Diastolic</td>
<td>68 ± 12</td>
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<tr>
<td>Peak CK (U/L) (normal range: 0–145)</td>
<td>177 ± 164</td>
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<tr>
<td>Peak troponin I (μg/L) (normal range: 0–0.4)</td>
<td>11.4 ± 9.2</td>
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<tr>
<td>CMR-derived EF (%)</td>
<td>47 ± 10</td>
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<tr>
<td>Any pleural effusion</td>
<td>2 (8%)</td>
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<tr>
<td>Bilateral pleural effusion</td>
<td>0</td>
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<td>Significant pleural effusion</td>
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RV−, patients without RV involvement; RV+, patients with RV involvement; CK, creatinine kinase.
interval 81–98%), 75% (95% confidence interval 40–94%), and 88% (95% confidence interval 78–95%), respectively. Significant or bilateral pleural effusions were only present in patients with RV involvement.

Discussion

We describe a retrospective clinical experience over a 4-year period in which 47 patients with TTC underwent gadolinium-enhanced CMR. We excluded those patients in whom LV WMA had already normalized by the time of CMR study and evaluated the remaining 34 patients for RV involvement. The vast majority of patients was elderly women and initial presentation mimicked acute coronary syndrome in most cases. All patients had dynamic reversible ST-T segment abnormalities and a preceding stressor could often be identified. Thus, clinical profiles of our patients were similar to those reported in other recently published series.1,12–17

Until the recently published report by Elesber et al.,8 RV involvement had not been systematically evaluated in TTC. This could partly be attributed to the well-known difficulties in echocardiographic assessment of RV morphology and function and to the often impressive LV dysfunction which might have diverted attention away from the RV. Another possible explanation could be the obscure clinical significance of RV pathology in TTC. However, RV involvement in TTC had not been completely unknown. In a small case series, Donohue et al.5 reported on marked biventricular apical akinesia in one of four patients with TTC. Single cases of biventricular TTC had also been reported by Nyui et al.,6 Nishikawa et al.,7 and Kurisu et al.18

In the recently published study by Elesber et al.8 from the Mayo Clinic, 25 of 30 consecutive patients with TTC underwent echocardiography in the acute setting. Of these, eight had apical RV involvement. RV dysfunction was associated with lower LVEFs, longer hospitalizations, and more complications such as severe congestive heart failure, intra-aortic balloon pump, and cardiopulmonary resuscitation. Assuming that those five patients who did not have echocardiography at initial evaluation did not have RV involvement, the estimated prevalence of RV dysfunction would be 27%, which is very similar to the observed prevalence of 26% in our study.

When using CMR to evaluate RV function, one must keep in mind that RV WMA can also be present in healthy subjects. In fact, Sievers et al.11 recently demonstrated regional RV hypokinesis, akinesia, or bulging in 13.8% of healthy subjects in the short-axis plane and in 41.4% of cases in a modified horizontal longitudinal plane. However, in our study, eight of nine patients with RV involvement had a follow-up study demonstrating complete recovery or significant improvement of the initial regional WMA. In the three

Figure 4 Distribution of LV WMA as assessed by tomographic CMR. (A) 17-segment model of the LV chamber, (B) distribution of LV WMA in all patients, and (C) distribution of LV WMA in patients with RV involvement.

Figure 5 Distribution of RV WMA as assessed by tomographic CMR in patients with RV involvement (n = 9).
patients who did not have complete recovery of their initial RV WMA, CMR had been performed relatively early after the onset of symptoms. Thus, regional RV WMAs unrelated to TTC do not seem to be responsible for our observations. The most severely affected RV segments were the apical-lateral segment (segment 1), the medio-lateral segment (segment 2), the anterolateral segment (segment 5), and the inferior segment (segment 8).

What is the clinical significance of our findings? The pathophysiological mechanism underlying TTC has not been clearly established. One hypothesis has suggested that in individuals with a sigmoid septum, small LV outflow tract and reduced LV volumes intense adrenergic stimulation or hypovolaemia may lead to significant LV outflow tract obstruction, which, in turn, may lead to secondary ischaemia in the LV apex and anterior wall due to increased anterior and apical wall stress. A similar hypothesis has recently proposed a combination of an induced severe transient mid-ventricular cavity dynamic gradient with catecholamine-induced reduction in subendocardial blood flow to be responsible for the findings in TTC. However, the observation of RV involvement in TTC argues against the above-mentioned sequence of events and hence against a dominant role of dynamic LV gradients in the development of TTC. A dynamic LV gradient seems to be an epiphenomenon rather than the cause of TTC. This view is further supported by other observations. (i) The reported incidence of dynamic LV gradient is low, even in series where patients underwent left heart catheterization within 24 h of admission (e.g. three of 16 patients in the study by Bybee et al. and five of 22 patients in the study by Sharkey et al.) and (ii) a variant form of TTC without apical involvement is now increasingly being recognized. Dynamic LV gradients cannot explain the occurrence of these variants of TTC.

Another significant finding of our study was the observation that the majority of patients with RV involvement had pleural effusions and that significant or bilateral effusions did not occur, unless TTC had affected both ventricles. This observation can easily be explained by the pathophysiological mechanisms, leading to the development of pleural effusion: LV dysfunction may lead to elevation of pulmonary venous pressure, which, in turn, may cause leakage of oedema fluid from the visceral pleural surface. However, an additional elevation in systemic venous pressure—as can be expected in acute severe RV dysfunction—will increase the filtration of fluid from parietal capillaries and simultaneously decrease lymphatic flow from the pleural cavity, leading to a more pronounced accumulation of fluid in the pleural cavity. The more pronounced reduction of systolic LV function in patients with RV involvement could be another explanation.

Why is the RV affected in some patients and not affected in others? Patients with RV involvement had a significantly lower LVEF than those without RV involvement. If TTC can be regarded as a myocardial stunning-like phenomenon, one can hypothesize that patients with more severely depressed LV functions must have had a more severe initial insult, which, in turn, could have affected both ventricles rather than the LV alone. However, three of nine patients (patients 1, 3, and 9) had only mild impairment of LV systolic function, hence casting doubts on this hypothesis. Although entirely speculative, differences in the distribution and/or density of RV adrenoceptors or differences in RV blood supply are other potential explanations for the variable occurrence of RV dysfunction.

Limitations

One limitation of our study is its retrospective assessment of RV morphology and function which did not allow us to tailor image acquisition to the RV. Another limitation is the time delay between presentation and CMR study. It cannot be excluded that we missed some early WMA. However, this time delay, if anything, means that the true prevalence of RV involvement in TTC is higher than observed.

In conclusion, reversible RV dysfunction is common in TTC and involves about one-quarter of patients. Its presence seems to be associated with a more severe impairment in LV function. Pleural effusion, especially when significant or bilateral, is a reliable clinical indicator of RV involvement.

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