Cardiac autonomic imbalance in patients with reversible ventricular dysfunction takotsubo cardiomyopathy

Y.J. AKASHI, G. BARBARO, T. SAKURAI, K. NAKAZAWA and F. MIYAKE

From the 1 Division of Cardiology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki, Japan, 2 Division of Applied Cachexia Research, Center for Cardiovascular Research, Charité Campus Mitte, Berlin, Germany, 3 Cardiology Unit, Department of Medical Pathophysiology, University ‘La Sapienza’, Rome, Italy and 4 Division of Laboratory Medicine, St Marianna University School of Medicine, Kawasaki, Japan

Summary

Background: Although in reversible takotsubo cardiomyopathy (TC), wall motion generally recovers dramatically within a few weeks, there are few data on changes in autonomic function in this condition.

Aim: To investigate cardiac autonomic function in the acute and chronic phases of TC.

Methods: Ten patients with TC (mean age 70.1 ± 13.7 years) underwent cardiac catheterization on the first hospital day, when left ventricular (LV) ejection fraction (EF) was calculated. A Holter electrocardiographic study was performed within 3 days after the onset of symptoms (0 months) and 3 months after discharge (3 months). The standard deviation of the mean cycle length of normal–normal R–R (NN) intervals over 24 h (SDNN), and the 24-h standard deviation of the mean value of the difference between the NN intervals for each 5-min segment (SDANN), were calculated according to time-area analysis of heart rate variability over 24 h. Frequency domain analysis was also done.

Results: Coronary angiography in the acute and chronic phases revealed no significant stenosis in any TC patient. LV wall motion returned to normal in 17.6 ± 6.4 days. LVEF was 45.7 ± 8.8% in the acute phase and 69.8 ± 6.8% after the improvement of wall motion (p < 0.001). Between 0 months and 3 months, SDNN and SDANN improved significantly, from 88.8 ± 35.5 to 109.5 ± 33.4 ms (p = 0.01) and from 79.9 ± 34.7 to 99.3 ± 40.3 ms (p = 0.03), respectively. No significant changes were observed in frequency domain parameters.

Discussion: These results support our previous hypothesis that TC might be caused by neurogenic stunning of the myocardium, due to acute autonomic dysfunction.

Introduction

Stress cardiomyopathy has been described as a left ventricular (LV) dysfunction whose symptoms resemble those of an acute myocardial infarction, but with normal coronary arteries and LV apical ballooning on left ventriculography (LVG). This disease is also known as ‘takotsubo cardiomyopathy (TC)’ and usually resolves within a few weeks.1–4 We have previously hypothesized that it might be caused by neurogenic myocardial stunning due to autonomic imbalance,5–7 but data are lacking on autonomic nervous function in TC patients. We therefore sought to assess autonomic nervous function in the acute and chronic phases of TC, comparing TC patients with healthy controls.
Methods

Patients

A total of 775 patients with sudden-onset heart failure, acute myocardial infarction-like ST-T changes and Q-wave formation on the electrocardiogram (ECG), have been admitted to our institution in the last 6 years. Of these, only 17 (2.2%) suffered from TC, as diagnosed by cardiac catheterization. Diagnostic criteria for TC consisted of the following: (i) a sudden occurrence of heart failure, accompanied by acute myocardial infarction-like symptoms (chest pain, chest discomfort, dyspnoea, and loss of consciousness), (ii) takotsubo-shaped hypokinetic LV on echocardiography and LVG, (iii) absence of coronary artery disease on coronary angiography, despite the presence of acute myocardial infarction-like ST segment elevation or T wave inversion on ECG, (iv) complete normalization of left ventricular dysfunction within a few weeks. Two patients with TC were excluded from this study because one suffered from uncontrolled diabetes mellitus, which is known to influence the autonomic nervous system, and another had chronic atrial fibrillation. Four patients dropped out of the study because they could not undergo the second Holter ECG monitoring. Hence, the present study finally included 10 patients who agreed to 24-h Holter ECG monitoring in the acute and chronic phases of TC.

A group of 10 healthy individuals of similar age to the patients was recruited in our institutions (mean age 70.0 ± 6.1 years). They underwent a normal echocardiogram, normal resting ECG, and normal maximal exercise testing to participate in this study as controls. None had a history of previous angina pectoris, myocardial infarction, or any other disease. All of them complained of mental stress, as assessed using a documented and validated questionnaire (PR-STRESS, IML).

Cardiac catheterization and blood tests

Cardiac catheterization was performed twice in all patients: within 1 h after admission and then after normalization of LV dysfunction, confirmed on echocardiography. Coronary angiography and left ventriculography were performed using six French catheters; LV ejection fraction (EF) was calculated using Simpson’s method. Before cardiac catheterization, venous blood was collected from the cubital vein to measure plasma norepinephrine and brain natriuretic peptide concentrations. Venous blood was also collected every 3 h to measure cardiac enzyme concentration in the acute phase, and this continued until a peak value was observed.

Coronary angiography with acetylcholine provocation was done to rule out any relation of coronary vasospasm during follow-up cardiac catheterization. Except for one case, the provocation test was performed at the initial catheterization. Acetylcholine chloride was injected within 30 s at a dose of 50 μg to the right coronary artery and 100 μg to the left coronary artery.

Holter monitoring

Patients underwent Holter monitoring for a mean of 23 ± 1 h, 2 ± 1 days after admission (0 months) and 3.0 ± 0.2 months after discharge (3 months). Controls underwent the same monitoring during their daily lives. Monitoring used a frequency-modulated, reel-to-reel two-channel SM-50 Holter recorder (Fukuda Denshi). All technical specifications were as recommended by the American Heart Association.5,9 24-h Holter ECG tapes were digitized, using a SCM-6000 scanner (Fukuda Denshi) with two observers, and subjected to standard methods for QRS labelling and editing. To be eligible for this study, a tape was required to have >22 h analysable data. Time duration between two consecutive R waves of the ECG (RR) was exported to a text file, which was further analysed using SCM-6000 software (Fukuda Denshi). The frequency histogram for the normal RR intervals was displayed, and electrocardiographic strips of the intervals in both tails of RR distribution were visually checked. Moreover, the histogram of the consecutive RR ratio was analysed using only 80–120% cycles preceding RR intervals. This analysis allowed the exclusion of noise, artifacts, premature beats, or postextrasystolic pauses from further analysis.

All tapes were subsequently analysed to measure HRV using a validated HRV program (HSP-RRLOP, Fukuda Denshi).

Time and frequency domain analysis of RR intervals

Time and frequency domain heart rate variability (HRV) parameters were all measured according to the recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.10 The following time domain measures were obtained from the time series of normal RR intervals after editing: mean normal RR intervals, variances, the standard deviation of normal RR intervals in the entire 24-h ECG recording (SDNN), the standard deviation of the average normal RR intervals for every 5-min segment of a 24-h ECG recording (SDANN), the percentage differences between adjacent normal RR intervals exceeding 50 ms (pNN50),
and the root-mean-square successive difference between adjacent normal NN intervals (r-MSSD).

A fast Fourier transformation was computed, and the resulting 24-h RR interval power spectrum was corrected for the attenuating effects of both the filtering and sampling.11 Frequency domain measure of RR variability was computed by integrating over their frequency intervals in two frequency bands: 0.04–<0.15 Hz (low frequency, LF) and 0.15–0.4 Hz (high frequency, HF). In addition, the total power (total frequency, TF) was calculated in the ≤0.4 Hz range.

Statistical analysis

Values are presented as means±SD. Between TC and control subjects, variables were compared using the Mann-Whitney U test. The Wilcoxon signed rank test was used to analyse continuous variables in TC. A two-tailed significance level of p<0.05 was used for all analyses.

Ethics

The study protocol was approved by the Committee on Human Investigation at St Marianna University School of Medicine. The nature, purpose, and risks of the study were fully explained, and written informed consent for participation was obtained from every subject prior to enrolment.

Results

Patient characteristics

The mean ±SD age of the patients was 70.1 ±13.7 years (Table 1). None of them received any oral medications such as digitalis, angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor antagonists, or β-blockers during the study period.

Laboratory data

Table 2 shows laboratory findings on admission and peak cardiac enzymes. The first blood sample was taken 15.1 ±16.5 h after the onset of clinical symptoms. The peak cardiac enzyme level was observed 19.3 ±13.6 h after admission. The peak value of creatinine kinase (CK) was slightly greater than the initial value (p=0.03), but the MB isoenzyme in the peak CK value showed no significant increase compared with the initial value (p=0.09). These laboratory findings normalized within 1 week in all cases. Of these, five cases revealed increased plasma norepinephrine (NE) concentration (normal 0.24–0.57 μg/l), and in each case, the plasma NE concentration was highest in the first blood sample. Plasma brain natriuretic peptide (BNP) concentration was also significantly elevated (mean 496.3 ±478.6 pg/ml, normal range <18.4 pg/ml).

Cardiac catheterization

Coronary angiography revealed normal arteries with no stenosis or obstruction in any TC patients. Left ventriculography showed akinesis in the apical, diaphragmatic and/or anterolateral segments. The initial LVEF was 45.7 ±8.8%. LV wall motion returned to normal within 17.6 ±6.4 days, and LVEF increased to 69.8 ±6.8% (p<0.001). Acetylcholine provocation for coronary spasm was negative in all patients, according to the catheterization study. No patient received oral medications during their hospitalization.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
<th>Trigger event</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>Female</td>
<td>148.0</td>
<td>43.0</td>
<td>19.6</td>
<td>Knee joint pain</td>
<td>Chest pain</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>Female</td>
<td>148.0</td>
<td>30.0</td>
<td>13.7</td>
<td>Pneumothorax</td>
<td>Chest pain, dyspnoea</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>Female</td>
<td>145.0</td>
<td>34.4</td>
<td>16.4</td>
<td>None</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>Female</td>
<td>148.9</td>
<td>51.0</td>
<td>22.8</td>
<td>Travel</td>
<td>Chest pain</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>Female</td>
<td>155.0</td>
<td>48.0</td>
<td>20.0</td>
<td>Ventricular fibrillation</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>Female</td>
<td>162.0</td>
<td>55.0</td>
<td>21.0</td>
<td>Change of job</td>
<td>Chest pain</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>Female</td>
<td>173.0</td>
<td>56.7</td>
<td>18.9</td>
<td>Lots of swimming</td>
<td>Chest pain</td>
</tr>
<tr>
<td>8</td>
<td>87</td>
<td>Male</td>
<td>162.0</td>
<td>48.0</td>
<td>18.3</td>
<td>None</td>
<td>Chest pain</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>Male</td>
<td>175.0</td>
<td>70.0</td>
<td>22.9</td>
<td>Viral infection</td>
<td>Chest pain</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>Female</td>
<td>147.3</td>
<td>43.0</td>
<td>19.8</td>
<td>Suicide attempt</td>
<td>Loss of consciousness</td>
</tr>
</tbody>
</table>

Mean: 70.1, SD: 13.7
Heart rate variability

Table 3 shows HRV data from the 24-h Holter monitoring. An interval was required that included at least 96% of the QRS complexes, which was classified as normal by the system and then accepted for further analysis. In TC patients, both SDNN (88.8 ± 35.5 to 109.5 ± 33.4 ms, *p* = 0.01) and SDANN (79.9 ± 34.7 to 99.3 ± 40.3 ms, *p* = 0.03) improved significantly between 0 months and 3 months. At 0 months, both SDNN (88.8 ± 35.5 vs. 139.7 ± 43.4 ms, *p* = 0.007) and SDANN (79.9 ± 34.7 vs. 133.5 ± 44.4 ms, *p* = 0.01) were significantly lower in TC patients than in controls.
controls. However, no significant differences in r-MSSD and pNN50 were observed between TC patients and controls (both $p > 0.2$) (Figure 1). TF at 0 months was significantly lower in TC patients than in controls ($1001.7 \pm 676.3$ vs. $2313.2 \pm 1120.1$ ms$^2$, $p = 0.005$) according to frequency domain analysis. This decrease in TF was no longer significant at 3 months ($p = 0.06$). LF was significantly lower in TC patients than in controls ($209.5 \pm 113.6$ ms$^2$), both at 0 months ($98.1 \pm 49.8$ ms$^2$, $p = 0.01$) and 3 months ($95.5 \pm 88.2$ ms$^2$, $p = 0.02$). At 3 months LF/HF was also significantly lower in TC patients ($1.1 \pm 0.3$) than in controls ($1.7 \pm 0.5$) ($p = 0.006$) (Figure 2).

**Discussion**

**Autonomic function in TC**

HRV is widely used to assess cardiac autonomic function, and is influenced by several factors, such as age,$^{12}$ time of day$^{13}$ and gender,$^{14}$ in healthy subjects. Although parasympathetic activity in pre-menopausal women is greater than that of men of the same age, no significant HRV difference is seen between healthy people of either sex after that time.$^{14}$ There are a handful of reports about HRV in TC, but no study has reported a transformation of autonomic nervous function in TC patients. Although SDNN and SDANN in TC patients were acute-phase predictors of relatively poor prognosis, these parameters normalized within a few months in our patients, as in previous reports.$^{15}$ We presumed that diminished vagal tone and increased sympathetic modulation of the sinus node affected the reduction of SDNN. Moreover, renin-angiotensin activities, abnormal chemoreceptor function, changes in respiratory pattern and physical inactivity contribute to the revealed SDNN value. The improvement in HRV, especially time-domain parameters, appears to at least contribute to the recovery of cardiac autonomic function in TC patients. No change in heart rate was observed.
between 0 months and 3 months, suggesting that time domain analyses were correctly conducted. r-MSSD and pNN50 indicate and evaluate parasympathetic activity; no significant changes were observed in either during the study period in our TC patients. The results of HRV time domain analysis suggest that parasympathetic nervous function is not related to the cause of this syndrome. LF is a marker of sympathetic activity, but HF is a marker of parasympathetic activity. In addition, the ratio of LF/HF is a marker of sympathovagal balance, a high level indicating sympathetic predominance. In our TC patients, LF was prominently decreased in the acute phase and was not improved at 3 months. Accordingly, we believe that a continuous LF decrease and a remarkable improvement of time domain parameters are specific characteristics of cardiac autonomic function in TC patients. This supports our previous investigation using 123I-metaiodobenzylguanidine (123I-MIBG) myocardial scintigraphy, which revealed remarkably improved catecholamine dynamics in the myocardium, although they were not fully improved within 3 months. Clearly, a sudden impairment of cardiac sympathetic nervous function has occurred in these patients. There is a discrepancy between the value of time domain analyses and frequency domain analyses in TC patients. The decrease in LF might be associated with abnormalities in central autonomic regulation and impairment of β-adrenergic receptor sensitivity in spite of high levels of sympathetic activation. Loss of modulation of autonomic outflow is consistent with the concept of reduced autonomic modulation with near-maximal stimulation. Sino-atrial node responsiveness to neurotransmitters is diminished as ventricular dysfunction progresses. This fact supports the idea that a state of functional sympathetic denervation exists in class III and IV heart failure as a result of persistent neurohormonal sympathetic stimulation. When muscarinic receptors appear to be intact and possibly up-regulated, parasympathetic ganglionic transmission

![Figure 2. Frequency domain analysis of heart rate variability. LF was significantly lower in TC patients vs. controls (209.5 ± 113.6 ms²), both at 0 months (98.1 ± 49.8 ms², p = 0.01) and 3 months (95.5 ± 88.2 ms², p = 0.02). LF at 0 months was also significantly lower in TC patients than in controls (1001.7 ± 676.3 vs. 2313.2 ± 1120.1 ms², p = 0.005), but not at 3 months (p = 0.06). At 3 months, LF/HF was significantly lower in TC patients (1.1 ± 0.3) than in controls (1.7 ± 0.5) (p = 0.006). *p < 0.05 vs. controls; †p < 0.01 vs. controls; ‡p < 0.1 vs. controls.](https://academic.oup.com/qjmed/article-abstract/100/6/335/2261030)
is impaired.17 Each of these mechanisms is likely to lead to a LF reduction in HRV in TC patients. If TC were caused by the impairment of coronary blood flow, as reported by Ibanez et al.18 HRV data in this study would be completely different from those previously reported. Petretta et al.19 investigated HRV before and after coronary intervention for single-vessel disease with left ventricular dysfunction, and reported the improvement of left ventricular wall motion and HRV parameters, especially LF power, within several weeks after the intervention. Patients with acute myocardial infarction generally have decreased parasympathetic nervous function and increased sympathetic outflow to the heart.20–22 Lombardi et al.20 reported that LF power in patients with myocardial infarction is greater (compared with controls) at 2 weeks after the onset of myocardial infarction. Thus the autonomic alterations in our TC patients were completely different from those in patients with coronary heart disease.

The prognostic value of LF is uncertain and still controversial; reduced LF15,21 or increased LF power might be associated with an increased risk of cardiac events.24 Since it was not possible to use spectral HRV analysis to measure cardiac sympathetic activity,25 the HRV value obtained from TC patients may be open to interpretation. For instance, in TC, the low HRV value does not mean an unfavourable prognosis; our TC patients suffered no further cardiac events in the 3-year follow-up. Larger studies are needed to discover whether LF data are useful for determining prognosis in TC patients.

**Underlying mechanism in TC**

The reason why the wall motion abnormality in TC is limited especially in the apical area may relate to differences of regional sympathetic innervations and catecholamine receptor density in each patient, as described in a canine model.26 Ueyama et al.27 demonstrated in rats that an administration of adrenergic receptor blocker could prevent stress-induced left ventricular dysfunction. They also reported that adrenoceptor blocker administration could also prevent ECG changes in rats under stress.28 Furthermore, in the apical region of the heart, a higher adrenergic receptor density and myocardial responsiveness to adrenergic stimulation has been demonstrated in a canine model.29 We previously reported that a remarkable decrease of 123I-MIBG uptake into myocardium during the acute phase of TC had a relationship with cardiac sympathetic nervous dysfunction, and the accelerated 123I-MIBG myocardial washout rate related to increased plasma norepinephrine concentration.5 When the level of circulating plasma norepinephrine in some patients were close to normal, it meant the presence of over-activated cardiac catecholamine receptors.5 The internal and external catecholamine dynamics of the heart may be a crucial mechanism for the onset of TC.

The onset mechanism of TC is still controversial. Studies have demonstrated the existence of intracoronary vulnerable plaque in TC patients using intravenous ultrasound, and a mechanism was suggested based on `intermittent coronary occlusion and spontaneous repertusion’.18 However, reviewing these reports, we believe that an impairment of coronary blood flow is not the cause of TC, for the following reasons. (i) Lack of coronary luminal narrowing due to spasm or sclerotic change during coronary angiogram even in persistent ST elevation on ECG, reported in several TC case studies. (ii) A significant discrepancy exists between the ventricular dysfunction areas and slightly increased cardiac enzyme once plaque rupture has occurred. (iii) The area of abnormal left ventricular wall motion is beyond the normal perfusion territory supplied by a single coronary artery.1 (iv) A significant difference is observed on ECG between patients with acute coronary syndrome and TC, and no reciprocal change is revealed in TC patients.31 (v) Ischaemic myocardial stun does not produce histological changes,32 which are often observed in TC.31,34 Accordingly, difficult to support myocardial stunning due to epicardial coronary insufficiency as a main cause of this cardiomyopathy.34,35 Since abnormal left ventricular wall motion in a large area and its dynamic changes have been already observed, it seems that coronary microcirculation disturbance might be occurring.26 We suggest that this finding is not the cause, but the result of apical ballooning induced by an autonomic imbalance. This concept might be helpful in understanding the pathogenesis of this disease.

**Limitations**

Evaluation of HRV, especially frequency domain analyses, might be useful to indicate strength of the modulation in autonomic nervous system rather than intensity of the regional or global cardiac sympathetic outflow. Thus, HRV is the only choice to assess cardiac sympathetic function and its role in the pathogenesis of TC. Unfortunately, we could not conduct a large-scale study because of the rarity of this disease; further studies will need to involve a...
larger number of institutions. It would have been better to have had healthy controls who were hospitalized at initial evaluation and treated at the same situation as the patients with TC.

Conclusions

Decreased HRV in TC patients suggests damage to the cardiac autonomic nervous system. These results support the hypothesis that TC is caused by neurogenic stunned myocardium due to acute cardiac autonomic dysfunction. Physicians should be aware of this cardiomyopathy as a possible cause of acute heart failure in individuals without definite heart disease. An international approach is needed for future studies, to maximize the number of cases studied.

References


24. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA, Crijns HJ. Prognostic value of heart rate...


Autonomic imbalance in takotsubo cardiomyopathy 343