Q J Med 2004; **97**:599–607
doi:10.1093/qjmed/hch094

Plasma brain natriuretic peptide in *takotsubo* cardiomyopathy

Y.J. AKASHI[1,2], H. MUSHA[1], K. NAKAZAWA[2] and F. MIYAKE[2]

From the [1]Department of Cardiology, St Marianna University, Yokohama-city Seibu Hospital, Yokohama, and [2]Division of Cardiology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki, Japan

Received 23 December 2003 and in revised form 31 March 2004

Summary

Background: *Takotsubo* cardiomyopathy is a reversible left ventricular dysfunction with symptoms resembling acute myocardial infarction, but without coronary lesions. Patients have wall motion abnormalities (apical akinesis and basal hyperkinesis), and characteristic left ventricular morphology.

Aim: To investigate plasma brain natriuretic peptide (BNP) concentrations in *takotsubo* cardiomyopathy.

Methods: Ten consecutive patients with *takotsubo* cardiomyopathy underwent cardiac catheterization on their first hospital day, and blood was collected to measure BNP. To evaluate acute basal hyperkinesis, the difference in diameter between systole and diastole was measured at 10 mm below the aortic valve (the δBase value).

Results: Coronary angiography revealed no significant stenosis in any patient. Initial ejection fraction was 42.2 ± 7.3%, cardiac index was 1.90 ± 0.39 l/min/m^2, and plasma BNP was 522.5 ± 632.9 pg/ml. Ventricular contraction and the ejection fraction were normalized on echocardiography after 17.9 ± 6.3 days. BNP was significantly correlated with δBase, but not with other cardiac parameters.

Discussion: Initial δBase value seems to be a good indicator of the severity of basal hyperkinesis in patients with *takotsubo* cardiomyopathy. In contrast to other diagnoses, a high BNP concentration is not associated with a poor prognosis in this condition.

Introduction

Recent reports have described a rare type of left ventricular (LV) dysfunction that clinically resembles acute myocardial infarction, but is associated with normal coronary arteries and a left ventricle shaped like a *takotsubo* (the Japanese name for an octopus fishing pot) on left ventriculography (LVG).[1–17] This type of reversible LV dysfunction has been called '*takotsubo* cardiomyopathy' (TC), or 'left ventricular apical ballooning', especially in Japan.[6–17] Plasma brain natriuretic peptide (BNP) concentration is known to be related to LV systolic and diastolic dysfunction,[18–21] and BNP may also be an indicator of long-term survival in cardiac patients.[22–24] BNP has never been studied in patients with TC, because of the rarity of this disease. To assess the significance of BNP in TC, we analysed data from 10 TC patients who were admitted to our institution from 1998 to 2002.

Address correspondence to Dr Y.J. Akashi, Division of Cardiology, Dept. of Internal Medicine, St Marianna University School of Medicine, 2–16–1 Sugao Miyamae-ku, Kawasaki-city, Kanagawa-pref., 216-8511, Japan. e-mail: johnny@marianna-u.ac.jp

Methods

Patients

A total of 653 patients with the sudden onset of heart failure, acute myocardial infarction-like abnormal Q waves, and ST-T changes on the electrocardiogram (ECG) were admitted to our institution (St Marianna University, Kawasaki, Japan) from January 1998 to December 2002. Of these, 637 had acute myocardial infarction, 13 (1.9 %) had TC, and three had acute viral myocarditis. The subjects of the present study consisted of 10 of these 13 patients, with TC defined by the following features: (i) heart failure similar to that observed with acute myocardial infarction, (ii) a *takotsubo*-shaped hypokinetic left ventricle on echocardiography and LVG, (iii) normal coronary angiography findings despite persistent ST-segment abnormalities, and (iv) complete resolution of LV dysfunction within a few weeks.

ECG and echocardiography

A standard 12-lead ECG (25 mm/s paper speed, with calibration of 10 mm = 1.0 mV) was recorded at hospital admission, and at 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, and 4 weeks after admission. The sites of the precordial leads were marked on the patient's chest wall with an indelible marker.

Two-dimensional echocardiography (SSH-140A, Toshiba) was performed 2–3 times during the first week of hospitalization. The LV ejection fraction (EF) was calculated by the single-plane-area-length method in the apical two-chamber view, and was expressed as a percentage.

Cardiac catheterization

Cardiac catheterization was performed within 1 h of admission in all 10 patients, and was repeated after LV dysfunction had normalized on echocardiography. Coronary angiography and left ventriculography were performed with six French catheters. The LVEF was calculated by Simpson's method.[25] To evaluate basal hyperkinesis during the acute phase, the left ventricular end-systolic and end-diastolic basal diameters were measured at a site 1 cm below the aortic valve, and the difference between these diameters was calculated in mm and defined as the δBase value.

After the initial cardiac catheterization, a Swan-Ganz catheter was placed at a suitable position in each patient, and haemodynamics were continuously monitored throughout the time in the coronary care unit. For the purpose of ruling out any relation to coronary vasospasm, coronary angiography with acetylcholine provocation was performed during follow-up cardiac catheterization in all patients. Acetylcholine chloride was injected within 30 s at a dose of 50 μg for the right coronary artery and 100 μg for the left coronary artery.

Measurement of plasma BNP and other parameters

For measurement of the plasma BNP concentration, 5 ml of venous blood was drawn from the femoral vein just before cardiac catheterization, and was immediately placed in a polypropylene tube containing 4.5 mg EDTA-2Na and 150 μl tradirol. The blood was immediately cooled on ice and centrifuged at 3000 rpm for 10 min at 4°C to separate the plasma, which was stored frozen at –70°C until analysis. The plasma BNP concentration was measured by an immunoradiometric assay (Shionoria BNP) using two monoclonal antibodies.

Routine laboratory tests were performed on admission, as well as after 1 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 1 week, 2 weeks and 4 weeks. Results were expressed as the mean ± SD.

Statistical analysis

All data were expressed as means ± SD. Comparisons of parameters between BNP and LV functional parameters were made using analysis of variance (ANOVA). A p value <0.05 was considered significant.

Ethics

The retrospective study protocol was approved by the Human Investigation Committee of St Marianna University School of Medicine. The nature and purpose of the study and risks involved were explained, and written informed consent to participation in the study was obtained at the initial cardiac catheterization from all subjects prior to their enrolment.

Results

Clinical profile

Table 1 shows the clinical characteristics of the patients. Nine of the 10 patients were women and one was a man. Mean age was 72.9 years. Seven patients had a history of hypertension, four had hyperlipidaemia, three had previous cerebral infarction, one had diabetes mellitus, one asthma, and one breast cancer. One patient had no past history of relevance. One had a past history of paroxysmal atrial fibrillation, but there was no family history or past history of structural

Table 1 Patients characteristics, past histories, trigger events, and symptoms on admission

Patient	Age (years)	Sex (M/F)	Height (cm)	BW (kg)	BMI (kg/m^2)	BSA (m^2)	Past history	Trigger event	Symptom
1	63	F	160.0	61.4	24.0	1.77	H/T, H/L, PAF	None	Dyspnoea
2	80	F	145.0	34.4	16.4	1.22	H/T, H/L, CI, BA	None	Loss of consciousness
3	83	F	148.0	30.0	13.7	1.17	H/T	Pneumothorax	Chest pain
4	66	F	155.0	47.5	19.8	1.44	None	None	None
5	85	M	160.0	50.6	19.8	1.56	H/T, H/L, CI, BPH	None	None
6	57	F	150.0	52.0	23.1	1.49	H/T	None	Dyspnoea
7	67	F	155.0	48.0	20.0	1.51	Ovarian cystectomy, H/L	Ventricular tachycardia	Syncope
8	77	F	145.0	35.0	16.6	1.23	H/T, CI, Left mamma ca	Intestinal perforation	Abdominal pain
9	81	F	148.0	43.0	19.6	1.36	H/T, Knee OA	Severe knee pain	Chest oppression
10	70	F	154.0	40.0	16.9	1.36	DM	Left facial pain	General fatigue
Mean	72.9		152.0	44.2	19.0	1.41			
SD	11.0		6.9	10.7	3.6	0.20			

BW, body weight; BMI, body mass index; BSA, body surface area; H/T, hypertension; H/L, hyperlipidaemia; PAF, paroxysmal artrial fibrillation; CI, cerebral infarction; BA, bronchial asthma; BPH, benign prostata hypertrophy; ca, carcinoma; OA, osteoarthrosis; DM, diabetes mellitus.

heart disease. Table 1 shows the symptoms at admission and the trigger events that caused admission. Two patients were admitted with chest symptoms and one was admitted with loss of consciousness. Two patients were referred after ECG abnormalities were found at a routine health check. We were able to identify possible triggers of LV dysfunction in five patients, including pneumothorax in one, ventricular tachycardia in one, intestinal perforation in one, severe knee pain in one, and left facial pain with common cold-like symptoms in one. There were no obvious trigger events in the other five cases, although patient 7 had a physically handicapped husband, and the burden of home care caused her severe physical and emotional stress.

Electrocardiography

All 10 patients exhibited acute myocardial infarction-like changes on the ECG, such as ST segment deviation and Q waves, as well as inverted T waves during the chronic phase. The ECG changes were not specific to any lead. ST segment depression was observed in patient 1, while ST segment elevation persisted for one week or more in the remaining 9 patients. Ultimately, inverted T waves were observed in the leads that showed ST segment changes and abnormal Q waves, but the Q waves did not persist in all cases.

Laboratory data

Table 2 shows the results of laboratory tests performed on admission, and the maximum values of the cardiac enzymes. The white blood cell count was increased on admission (>8000/μl) in six cases. Cardiac enzymes, including creatinine kinase (CK) and its MB isoenzyme, showed no significant increase (MB/total CK<10%) during the entire period of hospitalization, and laboratory findings were normalized within 1 week in 9/10 patients. Only patient 8 had high peak levels of CK and its MB isoenzyme, because of undergoing closure of a perforated small bowel. In patient 10, C-reactive protein (CRP) was significantly elevated, but the reason was probably a urinary tract infection. The plasma norepinephrine concentration was increased in five cases (normal 0.24–0.57 ng/ml), and a marked increase of BNP to a mean value of 522.5 pg/ml (normal <18.4 pg/ml) was observed. Tests of paired sera for viral infection were negative in all cases.

Cardiac catheterization

Cardiac catheterization was performed within 30 min of admission to the coronary care unit of our Heart Center in all 10 patients. Coronary angiography revealed normal coronary arteries without any stenosis or obstruction. LVG showed akinesis of the apical, diaphragmatic and/or anterolateral segments, and hyperkinesis of the basal segments. Figure 1 shows representative ventriculography findings. Table 3 shows the acute haemodynamic data: the mean values of LVEF, pulmonary artery wedge pressure, cardiac output, and cardiac index were $42.2 \pm 7.3\%$, 8.0 ± 3.9 mmHg, 2.66 ± 0.78 l/min, and 1.90 ± 0.39 l/min/m^2, respectively.

Table 2 Laboratory findings on admission and peak cardiac enzyme

Patient	WBC (/μl)	Hb (g/dl)	GOT (IU/l)	LDH (IU/l)	CK (IU/l)	CK-MB (IU/l)	BUN (IU/l)	Cr (IU/l)	UA (mg/dl)	Glu (mg/dl)	CRP (mg/dl)	NE (ng/ml)	BNP (pg/ml)	Trop. T (ng/ml)	Peak cardiac enzyme	
															CK (IU/l)	CK-MB (IU/l)
1	11600	14.1	45	449	93	0	19.0	0.80	7.3	317	0.3	0.50	180.0	0.22	93	0
2	15500	14.2	24	550	308	35	13.0	0.80	8.3	155	0.3	2.90	906.0	0.91	376	35
3	17700	13.1	71	563	377	34	29.0	1.20	5.6	130	0.6	1.20	1330.0	1.14	433	38
4	7800	12.8	38	383	231	21	12.0	0.70	3.8	92	0.3	0.58	36.7	0.75	367	34
5	9600	10.3	42	390	210	13	27.0	1.10	4.7	122	1.2	1.10	1460.0	1.07	210	13
6	13500	15.6	24	528	163	0	17.0	0.60	5.5	177	0.3	0.35	14.0	NM	325	19
7	5300	12.7	42	221	65	0	18.6	0.64	3.2	140	0.3	0.24	150.0	0.19	113	7
8	5400	10.2	55	208	176	16	29.3	0.65	3.0	159	3.6	7.40	891.0	1.74	2972	212
9	10100	12.3	33	210	179	20	14.2	0.47	3.2	100	0.3	0.19	39.8	0.28	267	22
10	12000	11.9	67	375	604	41	24.9	0.65	6.7	424	20.5	0.46	217.0	1.03	604	41
Mean	10850.0	12.7	44.1	387.7	240.6	18.0	20.4	0.76	5.13	181.6	2.77	1.49	522.5	0.81	576.0	42.1
SD	4361.8	1.7	15.8	121.6	111.6	15.7	6.5	0.23	1.82	73.4	0.34	0.92	632.9	0.42	135.2	15.0

WBC, white blood cells; Hb, haemoglobin; CK, creatinine kinase; CK-MB, the MB isoenzyme of creatinine kinase; Cr, creatinine; UA, uric acid; Glu, glucose; CRP, C-reactive protein; NE, plasma norepinephrine; BNP, brain natriuretic peptide; Trop. T, troponin T; NM, not measured.

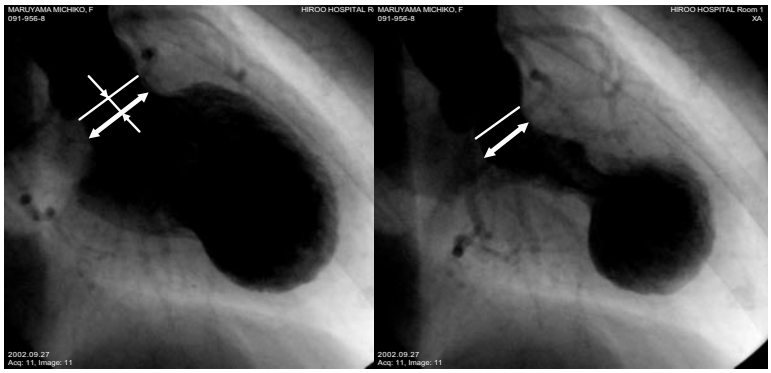

Figure 1. Typical left ventriculography features of '*takotsubo* cardiomyopathy', showing akinesis of the apical, diaphragmatic, and anterolateral segments, and hyperkinesis of the basal segments. In order to evaluate basal hyperkinesis in the acute phase, the left ventricular end-systolic and end-diastolic basal diameters were measured at a site 10 mm below the aortic valve, as shown in the figure.

The initial Swan-Ganz data indicated a mean Forrester class of III for the patients. The LV basal diameter was measured during end-diastole (35.5 ± 6.4 mm) and end-systole (18.8 ± 4.6 mm), and the mean δBase value was calculated to be 16.7 ± 7.8 mm.

All 10 patients underwent repeat cardiac catheterization after improvement of LV wall motion on echocardiography, revealing normal coronary arteries and normal wall motion. When acetylcholine provocation was done during the follow-up catheterization study, none of the patients showed vasospasm.

Clinical course

None of the patients received oral medications such as digitalis, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, or beta-blockers during the hospital stay. Complete normalization of LV contraction was confirmed after 17.9 ± 7.3 days in hospital and the LVEF was 64.4 ± 7.3 % (Table 3). While in hospital, paroxysmal atrial fibrillation occurred in patients 1 and 6, non-sustained ventricular tachycardia occurred in patients 2 and 7, and patient 3 suffered from recurrent pneumothorax. In patient 2, the only patient requiring medication, intravenous administration of magnesium sulphate (2 mg) was effective in suppressing frequent episodes of non-sustained ventricular tachycardia. The pneumothorax in patient 3 was spontaneous, and insertion of a chest tube resulted in complete healing within one week. Patient 7 was diagnosed with the short-coupled variant of idiopathic ventricular tachycardia. Syncope occurred at 6 h after admission, and polymorphic ventricular tachycardia with short-coupled premature ventricular beats was observed for 90 s. After the event, we diagnosed TC echocardiographically, and an implantable cardioverter defibrillator was inserted to prevent lethal arrhythmias.

During an observation period of 1–5 years after discharge, none of the patients had a recurrence of TC and there were no deaths from cardiac events.

BNP and cardiac catheterization parameters

Figure 2 shows the relationships between plasma BNP levels and the parameters obtained by left ventriculography. There was a positive correlation between the plasma BNP concentration and δBase ($r = 0.67$, $p < 0.05$). There was also a positive correlation between BNP and LVEDP ($r = 0.65$, $p < 0.05$). However, there was no correlation between BNP and LVEF, LVEDV, or LVESV.

Discussion

BNP in *takotsubo* cardiomyopathy

Given the considerable rarity of TC, it is not surprising that no previous study has investigated the potential associations between BNP and cardiac parameters in patients with TC. Throughout our investigation, however, we noted an association between BNP and basal hyperkinesis, a characteristic LV wall motion abnormality in the acute phase of TC. Based on the results of our study, we hypothesized that the BNP production in TC patients may be accelerated by excessive basal contraction itself, as well as by sudden changes in the LV systolic and diastolic function. Yasue *et al.* reported that increased regional LV wall stress might promote the secretion of BNP.[18] Moreover, transient abnormal wall stress might increase the BNP in patients

Table 3 Data obtained from cardiac catheterization

Patient	LVEF (%)	EDV (ml)	ESV (ml)	LVEDP (mmHg)	LVDd (mm)	LVDs (mm)	Basal Dd (mm)	Basal Ds (mm)	δBase (mm)	RA (mmHg)	mean PA (mmHg)	PAWP (mmHg)	CO (ml/min)	CI (ml/min/m^2)	Normalization of LV (days)	Normalized LVEF (%)
1	35	91	59	14	56.6	42.9	28.8	22.1	6.7	3	16	6	3.1	1.8	8	50
2	32	75	51	25	40.7	35.1	36.4	15.6	20.8	2	10	15	2.0	1.7	24	61
3	37	74	46	18	33.2	33.1	36.6	14.2	22.4	4	23	8	1.7	1.5	20	70
4	35	74	48	6	43.5	27.0	27.9	12.9	15.0	5	20	7	2.8	1.9	22	64
5	48	101	57	15	46.3	44.2	42.4	13.9	28.5	3	22	8	2.9	1.8	17	63
6	44	85	48	14	55.7	55.3	42.5	24.4	18.1	9	22	13	2.5	1.7	10	74
7	51	86	42	10	48.1	40.0	28.6	20.4	8.2	0	8	3	4.1	2.7	14	64
8	48	87	45	18	35.4	35.2	39.7	23.5	16.2	5	27	5	2.1	1.7	22	58
9	61	73	28	9	42.7	34.4	38.8	17.5	21.3	7	18	11	2.4	1.8	13	75
10	31	88	60	5	43.5	41.5	33.5	23.6	9.9	1	9	5	3.0	2.4	29	65
Mean	42.2	83.4	48.4	13.4	44.6	38.9	35.5	18.8	16.7	3.9	17.5	8.1	2.66	1.90	17.9	64.4
SD	7.3	10.2	6.0	6.0	8.3	9.1	6.4	4.6	7.8	2.8	6.1	4.1	0.78	0.39	6.3	7.3

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDP, left ventricular endodiastolic pressure; LVEF, left ventricular ejection fraction; EDV, endodiastolic volume; ESV, endosystolic volume; SV, systolic volume; LVDd, left ventricular endodiastolic diameter; LVDs, left ventricular endosystolic diameter; Basal Dd, left ventricular basal endodiastolic diameter; Basal Ds, left ventricular basal endosystolic diameter; δBase, basal (Dd-Ds) value; RA, right atrium; PA pulmonary artery; PAWP, pulmonary artery wedge pressure; CO, cardiac output; CI, cardiac index; LV, left ventricle.

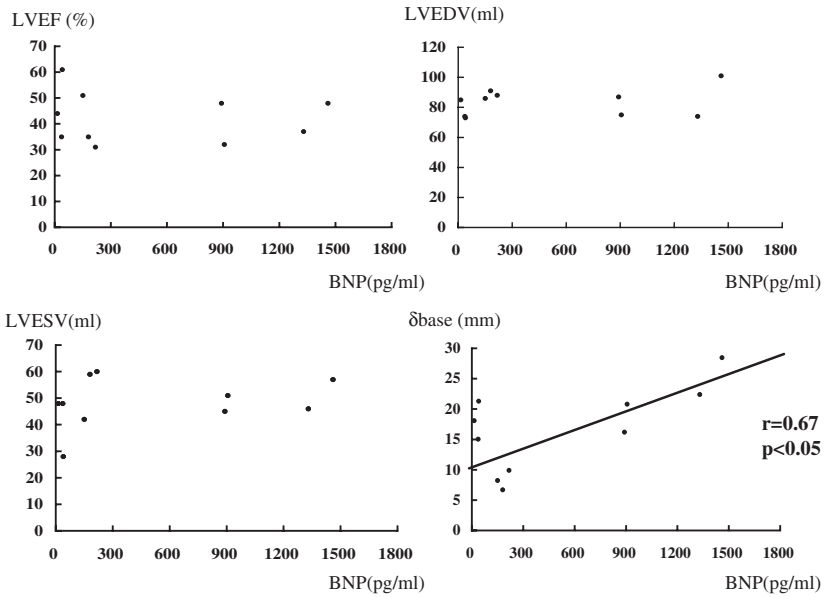

Figure 2. Association between plasma BNP concentration and catheterization parameters obtained during left ventriculography. There was a positive correlation between the plasma BNP level and δBase. In contrast, there was no correlation between BNP and LVEF, LVEDV, or LVESV.

with TC, as well as those with other cardiac diseases. Excessive hypercontractility of the LV base could conceivably lead to a pressure overload in the LV similar to the overloads observed in patients with aortic stenosis and hypertrophic obstructive cardiomyopathy. As previously experienced in these latter patients, the initial Swan-Ganz data on our patients revealed low output due to the basal hypercontraction and apical akinesis. Unable to find a remarkable pressure gradient between the LV apex and base in our subjects, we assumed that LV regional wall stress might be present, based solely on the shape of the LVG in the acute phase. Combined with the correlations between BNP and LVEDP, this raised the possibility that pressure overload in the LV promoted the BNP production.

The BNP level was markedly elevated during the acute phase in most of our TC patients, but not in three of them. We surmise that the BNP sampling may have been too early to indicate a high level. As some of our subjects were asymptomatic, we could not determine when their TC actually developed, and the sampling time of each BNP was different. We tried to measure BNP as soon as possible after symptoms or clinical abnormalities were found in the hospital. In one study on the time course of BNP, Morita *et al.* found that BNP peaked within 24 h of admission in patients with acute myocardial infarction.[21] BNP levels in our patients rose to their peaks within a week, then normalized within the next few months. We were unable to measure the BNP concentrations of all of our cases throughout the entire clinical period in this study. The actual time of peak BNP production and the clinical course of TC patients need to be investigated more extensively in the future.

A high serum level of BNP is a well-known marker of poor prognosis.[22–24] Although very high plasma BNP levels were observed in our subjects in the acute phase, their prognosis was good, and cardiac death did not occur during the follow-up period. This is the first description of high BNP levels associated with a good prognosis, and the paradox may relate to the cause of BNP production. In patients with myocardial infarction, increased regional wall stress is believed to be associated with adverse ventricular remodelling and a poor prognosis.[18] In contrast, BNP production in patients with TC may be promoted by LV basal hyperkinesis. We found that after wall motion was normalized, BNP production decreased to a normal level, and remained at that level throughout the rest of the study period. We did not observe our subjects for long enough to reach a definitive conclusion, and the chronic phase was not evaluated. Thus, more investigations on this point will also be needed in the future.

Catecholamine in *takotsubo* cardiomyopathy

An increase in the plasma norepinephrine concentration was observed on admission in about half of our subjects. The catecholamine increase in our initial findings may have been due to the heart failure. However, a catecholamine increase could

not be ruled out completely as one of the origins of the cardiomyopathy, as there was no relationship between the plasma norepinephrine value and the markers of cardiac function. After confirming an absence of catecholamine-related disease, we suspected this cardiomyopathy might be a myocardial response to the excessive catecholamine. The very high serum catecholamine concentration observed in some of our cases supports this hypothesis. Owa *et al*. reported that the recovery in I^{123}-metaiodobenzyl-guanidine (^{123}I-MIBG) myocardial uptake was most delayed in some tracers, and they suggested that the origin of TC was related to a disturbance of cardiac sympathetic innervation.[7] We have observed the same ^{123}I-MIBG findings in some of our patients with *takotsubo* cardiomyopathy.[11,12,17] The systematic catecholamine increase may have been one of the primary results of this heart failure.

On the other hand, there is evidence that circulating plasma norepinephrine concentration is almost normal in some patients with TC.[10] We hypothesized that excessive activation of cardiac catecholamine receptors may have been another results of this heart failure, but it may also have been the origin of TC.[16] Experimentally, Ueyama *et al*. developed an animal model of transient left ventricular hypocontraction via excessive activation of cardiac adrenoceptors.[9] The same authors have reported that LV dysfunction induced by emotional stress could be normalized by pretreatment with an α- and β-adrenoceptor blocker in the rat.[26] Moreover, they demonstrated that α- and β-adrenoceptor activation was the trigger for emotional stress-induced molecular changes in the heart.[27] We greatly support their hypothesis for the models of *takotsubo* cardiomyopathy. A *takotsubo*-like LV asynergy due to the regional differences in cardiac sympathetic nerve endings, has been seen in the dog.[28]

Limitations

This could not be a large-scale prospective study because of the rarity of the disease, so further studies involving a larger number of institutions will be needed.

Our BNP data were obtained in the acute phase soon after the onset of TC. However, some patients had no symptoms on admission, so it is possible that their TC had occurred some time previously. A high level of circulating catecholamines or activation of cardiac catecholamine receptors was suspected to be one of the factors related to the development of TC. Because we failed to elucidate why the asynergy was regional, the distribution of catecholamine receptors in the myocardium should be examined to determine the mechanism of regional dysfunction.

Conclusions

From its clinical features, '*takotsubo* cardiomyopathy' is a distinct type of heart failure. Its origin remains unclear, but coronary vasospasm, acute myocarditis, and other diseases that have been previously suggested can be ruled out as the cause of this cardiomyopathy. Heart failure in TC patients can resolve completely without any treatment, and has a good prognosis after the acute stage. TC may be a cause of sudden cardiac death in individuals without obvious heart disease. Although catecholaminergic or adrenoceptor-based cardiomyopathy was suspected as an instigating factor for TC, further investigations are needed to confirm this. Compared with LV function parameters, the initial δBase value seems to be a more accurate indicator of the severity of basal hyperkinesis in patients with TC. Basal hyperkinesis is the main characteristic of TC, and may lead to production of BNP, explaining why BNP is not correlated with parameters of LV function in these patients.

References

1. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982; **66**:1146–9.
2. Pollick C, Cujec B, Parker S, Tator C. Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. *J Am Coll Cardiol* 1988; **12**:600–5.
3. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasm: a review of 5 cases. *J Cardiol* 1991; **21**:203–14 (in Japanese).
4. Salathe M, Weiss P, Ritz R. Rapid reversal of heart failure in a patient with phaeochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril. *Br Heart J* 1992; **68**:527–8.
5. Iga K, Himura Y, Izumi C, Miyamoto T, Kijima K, Gen H, Konishi T. Reversible left ventricular dysfunction associated with Guillain-Barré syndrome: An expression of catecholamine cardiotoxicity? *Jpn Circ J* 1995; **59**:236–40.
6. Kawai S, Suzuki H, Yamaguchi H, Tanaka K, Sawada H, Aizawa T, Watanabe M, Tamura T, Umawatari K, Kawata M, Nakamura T, Yamanaka O, Okada R, Kawada M. Ampulla cardiomyopathy ('Takotusbo' cardiomyopathy) -reversible left ventricular dysfunction: with ST segment elevation. *Jpn Circ J* 2000; **64**:156–9.
7. Owa M, Aizawa K, Urasawa N, Ichinose H, Yamamoto K, Karasawa K, Kagoshima M, Koyama J, Ikeda S. Emotional stress-induced 'ampulla cardiomyopathy': discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. *Jpn Circ J* 2001; **65**:349–52.

8. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, Yoshiyama M, Miyazaki S, Haze K, Ogawa H, Honda T, Hase M, Kai R, Morii I. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol* 2001; **38**:11–18.
9. Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of 'tako-tsubo' cardiomyopathy. *Circ J* 2002; **66**:712–13.
10. Kurisu S. Transient left ventricular hypocontraction induced by emotional stress with immobilization: an animal model of tako-tsubo cardiomyopathy in humans? *Circ J* 2002; **66**:985–6.
11. Akashi YJ, Sakakibara M, Miyake F. Reversible left ventricular dysfunction: 'takotsubo' cardiomyopathy associated with pneumothorax. *Heart* 2002; **87**:E1.
12. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Sasaka K. Reversible left ventricular dysfunction: 'takotsubo' cardiomyopathy related to catecholamine cardiotoxicity. *J Electrocardiol* 2002; **35**:351–6.
13. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol* 2003; **41**:737–42.
14. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Umemura T, Nakamura S, Yoshida M, Sato H. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* 2003; **41**:743–8.
15. Akashi YJ, Nakazawa K, Kida K, Ryu S, Takagi A, Kishi R, Kunishima T, Sakakibara M, Miyake F. Reversible ventricular dysfunction (takotsubo cardiomyopathy) following polymorphic ventricular tachycardia. Can. J. Cardiol. 2003; **19**:449–51.
16. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. *Q J Med* 2003; **96**:563–73.
17. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Sasaka K, Musha H. ^{123}I-MIBG myocardial scintigraphy in patients with takotsubo cardiomyopathy. *J Nucl Med* 2004; **45**:1121–7.
18. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994; **90**:195–203.
19. Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 1996; **28**:988–94.
20. Omland T, Aakvaag A, Bonarjee VVS, Caidahl K, Lie RT, Nilse DWT, Sndsfjord JA, Dickstein K. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: Comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. *Circulation* 1996; **93**:1963–9.
21. Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsmura T, Mukoyama M, Nakano K. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. *Circulation* 1993; **88**:82–91.
22. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide: a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; **135**:825–32.
23. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, Sugimoto Y, Kinoshita M. Attenuation of compensation of endogeneous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; **96**:509–16.
24. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, Ohnishi M, Sawaki M, Fujii M, Hiroe H, Sugimoto Y, Kinoshita M. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with symptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. *Eur Heart J* 1999; **20**:1799–807.
25. Chapman CB, Baker O, Raynolds J, Bonte FJ. Use of biplane cineangiography for measurement of ventricular volume. *Circulation* 1958; **18**:1105–17.
26. Ueyama T, Yoshida K, Senba E. Emotional stress induces immediate-early gene expression in rat heart via activation of α- and β-adrenoceptors. *Am J Physiol* 1999; **277**:H1553–61.
27. Ueyama T, Senba E, Kasamatsu K, Hano T, Yamamoto K, Nishio I, Tsuruo Y, Yoshida K. Molecular mechanism of emotional stress-induced and catecholamine-induced heart attack. *J Cardiovasc Pharmacol* 2003; **41 (Suppl. 1)**:S115–18.
28. Murphree SS, Saffits JE. Quantiive autoradiographic delineation of the distribution of beta-adrenergic receptors in canine and feline left ventricular myocardium. *Circ Res* 1987; **60**:568–79.