Journal of Cardiology (2008) **51**, 121—130

JAPANESE CIRCULATION SOCIETY
CARDIOLOGY
Official Journal of the Japanese College of Cardiology
www.elsevier.com/locate/jjcc

Scintigraphic studies on the etiology of Ampulla Cardiomyopathy

Yasuto Uchida*, Shuji Nanjo, Shinichiro Fujimoto, Shohei Yamashina, Kenji Wagatsma, Hajime Nakano, Junichi Yamazaki

Division of Cardiovascular Medicine, Department of Internal Medicine, Ohmori Hospital, Toho University School of Medicine, Tokyo, Japan

Received 11 June 2007; received in revised form 25 January 2008; accepted 4 February 2008

KEYWORDS
Ampulla cardiomyopathy;
Myocardial scintigraphy;
Myocardial stunning;
Catecholamine

Summary
Background: Although there are many reports on Ampulla Cardiomyopathy, its etiologic mechanisms are not well known.
Aim: Etiology of Ampulla Cardiomyopathy was investigated by myocardial scintigraphy with various nuclear tracers.
Subjects and methods: In nine patients with Ampulla Cardiomyopathy, myocardial scintigraphy was performed at acute, subacute and chronic phases. Total defect score (TDS) of tallium-201 (Tl) or technetrium-99m sestamibi (MIBI) myocardial perfusion and iodine-123-beta-methyl-*p*-iodophenyl penta-decanoic acid (BMIPP) scintigraphies was calculated. Cardio-mediastinal ratio (H/M) and washout rate (WR) of early and delayed images of iodine-123-*meta*-iodobenzylguanidine (MIBG) scintigraphy were also calculated. The patients in whom TDS of myocardial perfusion scintigraphy at acute phase was 0, were classified into group N ($n=5$) and those with TDS ≥ 1 into group D ($n=4$).
Results: TDS of BMIPP at acute, subacute and chronic phases was higher in D than in N; 28.8 ± 10.3 vs. 7.2 ± 4.7 ($p=0.0039$), 15.5 ± 2.1 vs. 1.0 ± 0.8 ($p<0.0001$) and 2.7 ± 1.2 vs. 0 ($p=0.05$), respectively. WR of MIBG at acute phase was also higher in D ($50.3\pm5.7\%$ vs. $36.6\pm10.5\%$, $p=0.05$). H/M (dH/M) on the delayed images and WR at chronic phase were not different between the two groups. H/M (eH/M) on the early images was lower in D. Blood noradrenaline (ng/ml) at acute phase was higher in D than in N (1.21 ± 0.55 vs. 0.45 ± 0.33, $p<0.05$). Left ventricular ejection fraction (LVEF) was decreased in both at acute phase but it was lower in D than in N ($48.1\pm3.7\%$ vs. $69.9\pm9.7\%$, $p<0.05$) at subacute phase.
Conclusion: These findings suggest that the etiology of Ampulla Cardiomyopathy is neurologically stunned myocardium induced by coronary microcirculatory disorder.

* Corresponding author at: Division of Cardiovascular Medicine, Department of Internal Medicine, Ohmori Hospital, Toho University School of Medicine, 6-11-1 Ohmori-nishi, Ohta-ku, Tokyo 143-8541, Japan.
E-mail address: yasutoyasutouchida@s6.dion.ne.jp (Y. Uchida).

0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2008.02.002

Due to the significant amount of time that was necessary for normalization of wall motion in the D group, myocardial scintigraphy is believed to be also useful in assessment of severity.

Introduction

Ampulla Cardiomyopathy is accompanied by chest symptoms and ECG changes similar to acute myocardial infarction. This disorder, however, has no significant coronary artery stenosis but demonstrates a takotsubo shape with reduced contractions centering in the apex and compensatory basal hypercontraction [1—8]. Ampulla Cardiomyopathy is definitely not a rare disorder. It is revealed in approximately 2% of patients undergoing emergent cardiac catheterization in Japan. It is more commonly seen in women 60 years or older, and the association of some kind of emotional stress prior to onset has been indicated. The basis for this diagnosis is said to be apical wall motion abnormalities, which do not match up with coronary artery territories, and complete improvement over a few weeks course of time. Since reported by Satoh et al. [1] in 1990, similar cases have come to be reported outside of Japan as well.

Various theories on the etiology of Ampulla Cardiomyopathy have been reported including stunned myocardium resulting from myocardial ischemia due to multivessel epicardial coronary artery spasm or microvascular spasm, catecholamine-induced myocardial dysfunction, and myocarditis, but the cause has yet to be elucidated. Myocardial scintigraphy is utilized as a noninvasive tool to grasp the pathophysiology and evaluate the severity of cardiac disease. In Japan three isotopes are mainly used for imaging: myocardial perfusion scintigraphy (tallium-201 (Tl) or technetrium-99m sestamibi (MIBI)), iodine-123-beta-methyl-*p*-iodophenyl penta-decanoic acid (BMIPP) scintigraphy for imaging of fatty acid metabolism and iodine-123-*meta*-iodobenzylguanidine (MIBG) scintigraphy for imaging of the sympathetic nervous system. While we can find reports in recent years of studies conducted separately on Ampulla Cardiomyopathy, there are almost no reports of myocardial scintigraphy using three isotopes during the same interval and observed over a long period as well. In this study, triple isotope imagings — myocardial perfusion scintigraphy (with Tl or MIBI) and BMIPP and MIBG scintigraphy — were conducted in the acute, subacute, and chronic phases in nine consecutive patients diagnosed with Ampulla Cardiomyopathy. The findings were used to consider the pathophysiology of this disorder. We also studied the possibility of its usefulness in evaluating the severity of Ampulla Cardiomyopathy.

Subjects and methods

Subjects

Nine patients diagnosed as Ampulla Cardiomyopathy by left ventriculography and coronary angiography underwent MIBI, BMIPP and MIBG scintigraphies at acute (mean; 6.2 ± 3.4 days), subacute (mean; 46.6 ± 9.1 days), and chronic phases (mean; 171.4 ± 21.9 days) during January 2002 and December 2004. The time lag between the onset of symptoms and admission was 6.2 ± 5.5 h. The diagnostic criteria of Ampulla Cardiomyopathy were as follows: (1) elevated ST segment of electrocardiogram at the time of onset and large negative T wave appearing over time, (2) no significant organic stenoses of the coronary arteries by angiography despite ST elevation, (3) by ventriculography, reduced contraction of apical segment which does not correspond to the irrigating coronary artery and augmented contraction of mid- to basal segments showing octopus-trap-like configuration, (4) mildly elevated plasma enzymes eluted from the myocardium, and (5) complete disappearance of abnormal left ventricular contraction in later phase.

Blood examinations

Blood cell counts and biochemical examinations were performed on admission and they were repeated in later phase. Brain natriuretic peptide (BNP), noradrenaline, adrenaline and dopamine levels in the blood were also measured on days 1.3 ± 0.6 (acute phase), 63 ± 9.6 (subacute phase), and 175 ± 24 (chronic phase) after hospitalization.

Electrocardiography

Electrocardiography was conducted in all patients on days 2, 8.2 ± 2.4, 26 ± 6.4, 68 ± 8.8 and 142 ± 25.8 after hospitalization. The changes in ST

segments and T waves and QTc time were also examined repeatedly.

Echocardiography

Echocardiography was performed to examine left ventricular function on days 2.2 ± 1.4 and 8.8 ± 1.8 after hospitalization and it was repeated every week until left ventricular wall motion became normal. Normalization in echocardiography was defined to be when complete improvement of local wall motion is revealed.

Cardiac catheterization

Left ventriculography and coronary angiography with acetylcholine load were performed by inguinal or radial approach using a 6 Fr catheter on admission and were repeated in five patients 7.2 ± 2.2 days later. Acetylcholine was infused into the right coronary artery, starting with 25 μg to provoke spasm. When spasm was not induced, the dose was increased up to 50 μg. Acetylcholine was also infused into the left coronary artery with 25 μg as a starting dose. When no spasms were induced, the dose was increased up to 100 μg.

Myocardial scintigraphy

Myocardial scintigraphy using three nuclear types of myocardial perfusion tracers (Tl or MIBI), BMIPP, and MIBG were conducted in all nine patients. In six of them, Tl (111 MBq) was administered intravenously at rest and radiograms were taken 5 min later for assessment of myocardial blood flow. In three patients, MIBI (740 MBq) was administered at rest and early and delayed images were taken after 45 min and 4 h, respectively also for assessment of myocardial blood flow. MIBG (111 MBq) was administered intravenously at rest and early and delayed images were taken after 20 min and 4 h, respectively, for assessment of cardiac sympathetic nerve activity. BMIPP (111 MBq) was infused intravenously at rest and early and delayed images were taken after 20 min and 4 h, respectively for assessment of myocardial fatty acid metabolism.

Time lag between scintigraphy and the onset of symptoms was 6.8 ± 3.6 days at acute phase, 46 ± 9.6 days at subacute phase, and 171 ± 21.9 days at chronic phase in Tl or MIBI myocardial perfusion scintigraphy; 6.6 ± 3.3 days, 45 ± 9.7 days, and 171 ± 21.9 days, respectively in BMIPP myocardial scintigraphy; 9.4 ± 2.5 days, 47 ± 8.1 days, and 175 ± 21.9 days, respectively in MIBG scintigraphy.

Image analyses of myocardial scintigraphy

AHA classification [9] was used for myocardial perfusion scintigraphy and BMIPP scintigraphy. Namely, the shorter axial tomograms and vertical longer axial tomograms of the myocardial SPECT images were divided into 17 segments, and the degree of the defect was evaluated macroscopically at each segment using five steps (0: normal perfusion, 1: mild hypoperfusion, 2: moderate hypoperfusion, 3: severe hypoperfusion, 4: defect) (Fig. 1). The total sum of degree of the defect was called total defect score (TDS). The presence of a mismatch [10,11] was defined as the case in which the TDS of the BMIPP scintigraphy was three points or more higher than that of myocardial perfusion scintigraphy. Five patients without defects in Tl or MIBI myocardial perfusion scintigraphy at the acute phase were assigned to group N and four patients with defects were assigned to group D. TDS in BMIPP, and WR, eH/M and dH/M in MIBG were compared between the two groups. The presence or absence of a mismatch was also investigated.

Statistical analyses

Numerical values are expressed as the mean level ± standard deviation. To compare each parameter between groups N and D, the unpaired Student's *t*-test was used and a significant difference was evaluated with $p < 0.05$.

Results

Patient backgrounds

The patients were composed of seven females and two males, ages ranging from 55 to 90 years old with a mean of 73 ± 9.9 years old. Medical histories were hypertension in three, hyperlipidemia in four, diabetes in one and epilepsy in one. Symptoms at the first examination included chest pain in five, epigastralgia in two, syncopy in one and convulsion in one. Mental stresses were found in six before the onset (67%). The time required for improvement of left ventricular wall motion was 6.2 ± 2.8 days in group N and 45.3 ± 23.7 days in group D (Table 1). The mean age was 76 ± 9.4 in group N and 69 ± 10.4 years old in group D. Group N consisted of four females and one male and group D consisted of three females and one male. No differences in patient background were found between the two groups (Table 2).

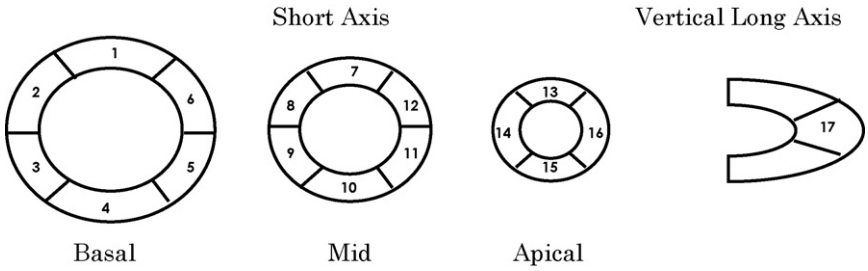

Figure 1 Myocardial perfusion spectrae. The myocardial perfusion spectra were divided into 17 segments on the long and short axial images and each segment was evaluated macroscopically with five steps.

Table 1 Backgrounds of nine patients with Ampulla Cardiomyopathy

Patient number	Age (years) and sex	Past history	Symptoms	Triggered event	Normalization of left ventricular contraction and mean days	
					Days later	Mean days
1	81F	Myoma uterus	Chest pain	Human relations	7	
2	68F	Hypertension, epilepsy	Convulsion	Hospitalization	10	6.2 ± 2.8
3	74F	Diabetes mellitus	Epigastralgia	None	4	
4	68F	Hyperlipidemia	Syncope	None	7	
5	90M	Hyperlipidemia	Chest pain	None	3	
6	74M	Lung cancer	Chest pain	Human relations	30	
7	79F	Hyperlipidemia	Chest pain	Death of spouse	80	45.3 ± 23.7
8	55F	Hypertension	Epigastralgia	External injury	30	
9	68F	Hypertension, hyperlipidemia	Chest pain	Death of spouse	41	

Serological and biochemical examinations

Peak CK level (normal: 49—159 IU/l) was 588 ± 853 IU/l in group N and 184 ± 53 IU/l in group D, and the peak CK-MB (normal: 1—20 IU/l) was 28.6 ± 12.0 IU/l in group N and 31.8 ± 14.2 IU/l in group D with no significant difference between them. Troponin-I (normal: <0.09 ng/ml) was 0.82 IU/l ± 0.37 ng/ml in group N and 2.54 ± 3.72 ng/ml in group D with no significant difference. BNP (normal: <20.0 pg/ml) was 187.0 ± 90.4 pg/ml in group N

Table 2 Backgrounds of patients in groups N and D

	Group N ($n = 5$)	Group D ($n = 4$)	p value
Age (years)	76.2 ± 9.4	69.4 ± 10.4	n.s.*
Female gender	4 (80%)	3 (75%)	n.s.
Risk factors			
Diabetes mellitus	1 (20%)	0	n.s.
Hypertension	1 (20%)	2 (40%)	n.s.
Hyperlipidemia	2 (40%)	2 (40%)	n.s.
Rise in viral antibody titers	0	0	n.s.

Data are presented as the mean value ± S.D. or number (%) of patients or control subjects. The unpaired Student's t-test or Fisher exact test was used.

* n.s. = not significant.

Table 3 Blood cell count and biochemical examinations at admission

Patient number	CK (IU/l)	CK-MB (IU/l)	Troponin-I (ng/ml)	NE (ng/ml)	BNP (pg/ml)	Peak cardiac enzymes	
						CK (IU/l)	CK-MB (IU/l)
1	348	34	0.70	0.21	80	421	37
2	1221	21	0.34	0.29	112	2096	21
3	169	45	1.12	0.67	194	203	45
4	76	17	1.27	0.69	263	152	24
5	67	16	0.69	0.39	286	67	16
6	89	15	0.17	1.60	39	238	28
7	92	14	0.81	1.20	17	112	14
8	200	47	8.09	1.60	2260	200	47
9	187	38	1.07	0.44	486	187	38

CK = creatinine kinase, CK-MB = MB isoenzyme of creatinine kinase, NE = plasma norepinephrine, BNP = brain natriuretic peptide, IU = international units.

and 700.5 ± 1061.9 pg/ml in group D with no significant difference. No differences were found in all data between the two groups at the subacute and chronic phases (Table 3). No significant differences in the blood adrenaline and dopamine levels were found during the entire periods, whereas blood noradrenaline (normal: 0.06—0.50 ng/dl) in group D at the acute phase was significantly ($p < 0.05$) higher than that in group N (1.21 ± 0.55 ng/dl vs. 0.45 ± 0.22 ng/dl). However, noradrenaline was not different between the two groups at subacute and chronic phases (0.64 ± 0.11 ng/dl vs. 0.71 ± 0.34 ng/dl and 0.69 ± 0.14 ng/dl vs. 0.72 ± 0.26 ng/dl, respectively) (Fig. 2). The viral antibody titer measured with a pair sera was negative in all patients (data are not shown).

Electrocardiographic findings

Elevated ST segment electrocardiogram taken at the first visit was found in six and an abnormal Q wave was found in two of these nine patients. A large negative T wave of electrocardiogram was found on mean day 3 ± 4 (1—9 days) after symptom onset in all patients. QTc time on the first disease day (normal level < 480 ms) was 460 ± 45 ms and the time on the second disease day was 520 ± 71 ms (447—622 ms), showing markedly prolonged QTc levels on both days. Electrocardiographic abnormalities such as ST-T change were normalized 91 ± 40 days after symptom onset. QTc time on the first disease day was 454 ± 34 ms in group N and 467 ± 64 ms in group D, showing no significant difference between them. QTc time on the second disease day was 522 ± 72 ms in group N and 515 ± 84 ms in group D. Although QTc was thus prolonged in both groups, no significant differences were found between them. The time required for normalization of electrocardiographic changes was 74 ± 49.9 days in group N and 107 ± 20.1 days in group D, showing no significant difference.

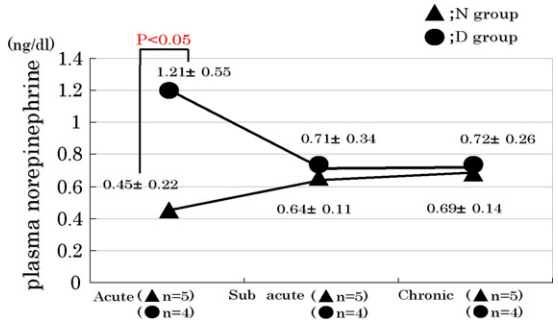

Figure 2 Blood noradrenaline levels in groups N and D. Data are presented as the mean value ± S.D. Acute: acute phase, subacute: subacute phase, chronic: chronic phase.

Echocardiographic findings

Echocardiography of the left ventricle conducted on day 2.2 ± 1.4 after symptom onset revealed reduced contraction of the apical segment and augmented contraction of the basal segments showing octopus-trap-like configuration. Left ventricular ejection fraction (LVEF) was 58.2 ± 18.8% in group N and 53.2 ± 3.6% in group D, showing no significant difference between them. LVEF was improved in both groups 8.8 ± 1.8 days after the onset of symptoms, however, the magnitude of improvement in group D was smaller than group N (48.1 ± 3.7% vs. 69.9 ± 9.7%, $p < 0.05$). The time required for normalization of the left ventricular contraction was longer in group D than group N (45 ± 2.3 days vs. 6.2 ± 2.8 days, $p < 0.05$).

Cardiac catheterization

Coronary angiography revealed no significant stenotic lesions in the coronary arteries, nor slow

Table 4 The total defect scores in MPS and ^{123}I-BMIPP

Patient number	Acute		Subacute		Chronic	
	MPS	^{123}I-BMIPP	MPS	^{123}I-BMIPP	MPS	^{123}I-BMIPP
Group N						
1	0	4	0	2	0	0
2	0	4	0	1	0	0
3	0	6	0	1	—	—
4	0	15	0	0	—	—
5	0	7	0	1	—	—
Group D						
6	9	19	0	14	0	2
7	11	21	—	—	0	2
8	20	35	0	17	0	4
9	27	40	—	—	—	—

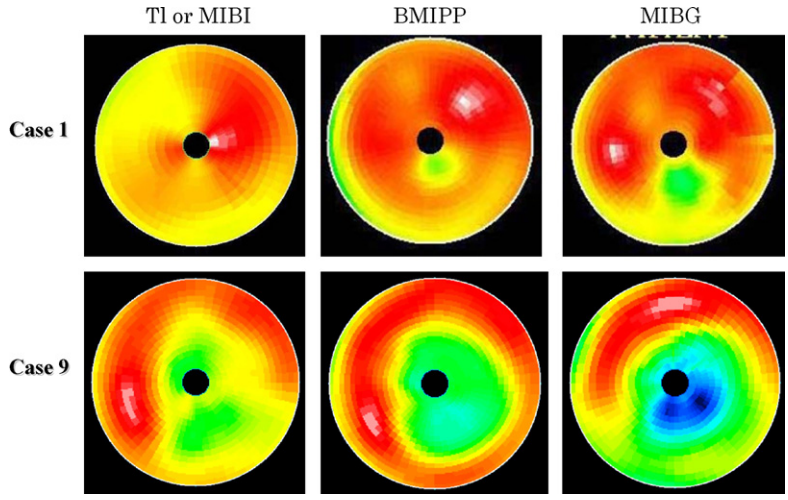

Figure 3 Typical myocardial scintigraphies at acute phase in groups N and D.

coronary blood flow in any patients. Spasm provocation test by intracoronary acetylcholine was performed on day 7.2 ± 2.2 after hospitalization and it was provoked in the large epicardial coronary artery in two of five patients. In one patient, diffuse coronary spasm was induced in the left anterior descending artery (middle to distal segments) which was accompanied by ST elevation. Similarly, spasm of the right coronary artery (distal segment) accompanied by ST elevation was provoked in another patient.

Myocardial scintigraphy

The myocardial perfusion scintigraphy at the acute phase revealed no defect of the TDS in group N while defect was observed in all four of group D. TDS of these four patients was 9, 11, 20, and 27. However, these defects disappeared at subacute and chronic phases (Table 4). Typical myocardial

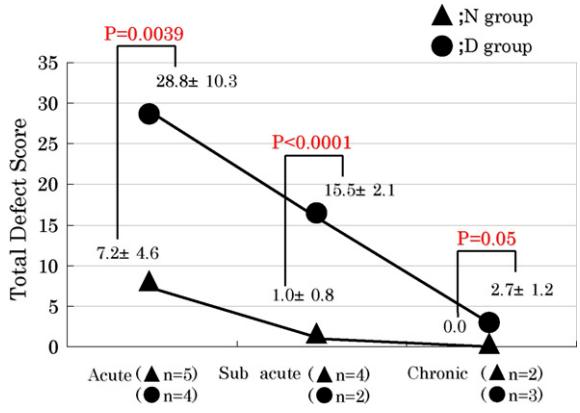

Figure 4 The total defect scores in ^{123}I-BMIPP in groups N and D. The scores at the acute ^{123}I-BMIPP; iodine-123-beta-methyl-*p*-iodophenyl penta-decanoic acid.

Table 5 WR and H/Ms with ^{123}I-MIBG

Group	WR (acute) (%)	H/M ratio (acute)	WR (subacute) (%)	H/M ratio (subacute)	WR (chronic) (%)	H/M ratio (chronic)
Group N						
Early	36.6 ± 10.5	2.05 ± 0.19	36.8 ± 9.9	2.07 ± 0.25	35.7 ± 6.5	2.39 ± 0.22
Delayed		1.93 ± 0.15		2.02 ± 0.27		2.31 ± 0.28
Group D						
Early	50.3 ± 5.7	1.82 ± 0.30	39.7 ± 7.0	1.91 ± 0.17	37.0 ± 9.8	1.99 ± 0.13
Delayed		1.62 ± 0.29		1.78 ± 0.32		1.94 ± 0.32

WR: washout rate, H/M: heart/mediastinum ratio; acute: acute phase; subacute: subacute phase; chronic: chronic phase.

scintigraphies at acute phase are shown in Fig. 3. In BMIPP scintigraphy, TDS at acute phase was 7.2 ± 4.6 in group N and 28.8 ± 10.3 in group D, showing a significant difference between them ($p = 0.0039$). TDS at subacute phase was 1.6 ± 1.5 in group N and 15.5 ± 2.1 in group D, showing a significantly higher level in group D ($p < 0.0001$). TDS at chronic phase was 0 in group N and 2.7 ± 1.2 in group D, showing a higher level in group D ($p = 0.05$) (Fig. 4). Mismatch was found between the myocardial perfusion scintigraphy and BMIPP scintigraphy at acute phase in all patients. In the results of MIBG scintigraphy (Table 5), the WRs at the acute phase were 36.6 ± 10.5% in group N and 50.3 ± 5.7% in group D, showing a higher level in group D ($p = 0.05$). However, no significant differences were found at subacute and chronic phases between the two groups (Fig. 5).

eH/M at acute and subacute phases in groups N and D was 2.05 ± 0.19 vs. 1.82 ± 0.30 and 2.07 ± 0.25 vs. 1.91 ± 0.17, showing no significant difference between them. At chronic phase, however, it was 2.39 ± 0.22 in group N and 1.99 ± 0.13 in group D ($p < 0.05$), exhibiting a significantly lower level in group D. dH/M level at acute phase was 1.93 ± 0.15 in group N and 1.62 ± 0.29 in group D, showing a lower tendency in group D. However, no

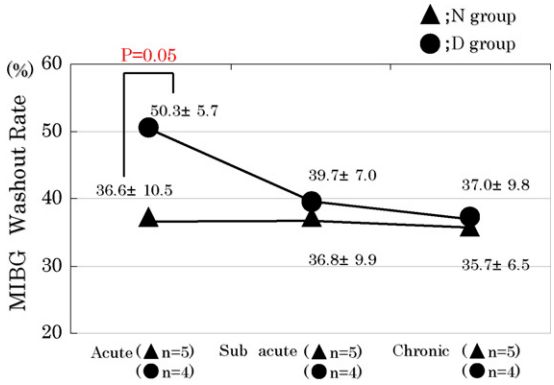

Figure 5 The washout rates of ^{123}I-MIBG in groups N and D. ^{123}I-MIBG: iodine-123-*meta*-iodobenzylguanidine.

Table 6 H/Ms and LVEF and MIBG between groups N and D

	Group N ($n = 5$)	Group D ($n = 4$)	p value
MIBG early H/M			
Acute	2.05 ± 0.19	1.82 ± 0.30	n.s.
Subacute	2.07 ± 0.25	1.91 ± 0.17	n.s.
Chronic	2.39 ± 0.22	1.99 ± 0.13	$p < 0.05$
MIBG delay H/M			
Acute	1.93 ± 0.15	1.62 ± 0.29	$p = 0.07$
Subacute	2.02 ± 0.27	1.78 ± 0.32	n.s.
Chronic	2.31 ± 0.28	1.94 ± 0.32	n.s.
Ejection fraction (%)			
Acute	58.2 ± 18.8	53.2 ± 3.6	n.s
Subacute	69.9 ± 9.7	48.1 ± 3.7	$p < 0.05$
Chronic	68.4 ± 4.2	76.0 ± 3.3	n.s.

Data are presented as the mean value ± S.D. n.s. = not significant.

significant difference was found in it between them at subacute and chronic phases (Table 6).

Discussion

In this present study, we attempted to elucidate the etiology of Ampulla Cardiomyopathy through the different myocardial scintigraphies taken in the acute, subacute, and chronic phases. The following summarizes the results of cardiac nuclear medicine studies on nine patients with Ampulla Cardiomyopathy. (1) Mismatch between myocardial perfusion scintigraphy and BMIPP scintigraphy conducted in the acute period was seen in all subjects. MIGB scintigraphy in the acute period also revealed defects in the same site in all patients. Normalization of uptake was seen in the order of myocardial perfusion scintigraphy, BMIPP and MIBG. (2) Between the N group, which was found to be normal in myocardial perfusion scintigraphy in the acute phase, and the D group, which revealed defects, significant differences were revealed in the degree of BMIPP and MIBG defects, plasma noradrenaline levels, and period until resolution of left wall motion abnormalities.

In this study, a mismatch was revealed between myocardial perfusion scintigraphy and BMIPP in all nine patients with Ampulla Cardiomyopathy. According to Tamaki et al. [10] cases of acute myocardial infarction successfully achieving reperfusion revealed a strong mismatch with greater BMIPP defects compared to myocardial perfusion tracer defects. They report that this reflects the salvage area [12]. It is also said that when a mismatch between T1 and BMIPP is revealed in patients with chronic ischemic heart disease, this demonstrates the presence of myocardial ischemia [13]. Hashimoto et al. [14] report that the presence of mismatch demonstrates myocardial stunning or hibernation. Additionally, according to Bax et al. [15] among patients with stunned myocardium, approximately 61% improve within 3 months. It is said that in patients with MIBG mismatch, defects are generally revealed at the same site as that of BMIPP.

In patients with stunned myocardium, myocardial scintigraphy also improves in line with recovery of wall motion, and this recovery is said to occur in the order of myocardial perfusion scintigraphy, BMIPP, and MIBG. This is extremely similar to the changes we were able to observe in the different myocardial scintigraphies of this present study of Ampulla Cardiomyopathy. The only dissimilar point was that the defect site in Ampulla Cardiomyopathy did not match any clear coronary artery territory. Meanwhile, it has also been pointed out that noradrenaline is associated with the etiology of Ampulla Cardiomyopathy. In neurological stunned myocardium [16] associated with cerebral vascular disorders or pheochromocytoma-induced catecholamine cardiomyopathy, along with the increase of endogenous catecholamines, mediation by alpha 2 receptors induces coronary microvascular spasm. It is believed that because of this, platelet aggregation is accelerated, cell membrane permeation increases, and due to this, calcium load occurs in the myocardial cells followed by cell death, resulting in myocardial dysfunction [17]. Simons and Downing [18] report that in animal tests an increase in coronary vessel resistance and diminished flow was manifested through continuous administration of noradrenaline. Regarding why reduction in wall motion occurs mainly in the apex, when considering reports noting a density of stellate ganglia of the cardiac sympathetic nerves centering in the apex, and that noradrenaline is released from the stellate ganglion, there is the possibility that noradrenaline is associated with this mechanism. Based on MIBG findings, Akashi et al. [8] are looking at the neurological stunned myocardium as the etiology of this disorder. But because MIBG defects are also noted at times of functional disorders in the sympathetic nervous system [19] or when denervation of the sympathetic nerves in the myocardium occurs due to severe ischemia such as acute myocardial infarction, it would be difficult to pin the cause of Ampulla Cardiomyopathy on the neurological stunned myocardium based on MIBG findings alone. Our observations in this present study, though, also showed levels of plasma noradrenaline rising in association with the increasing severity of cases, namely cases revealing slow recovery of wall motion and even defects in the perfusion scintigram as well. From these observations, we believe it highly possible that the mechanism for the onset of neurological Ampulla Cardiomyopathy is neurological stunned myocardium, in which an acceleration of cardiac sympathetic nerve activity causes the release of noradrenaline that induces coronary microvascular ischemia, which in turn results in reduced wall motion due to stunned myocardium.

While the prognosis of Ampulla Cardiomyopathy is generally viewed to be good, cases complicated by heart failure and arrhythmia have been noted at times, making evaluation of severity important. Myocardial perfusion scintigraphy is used to assess myocardial perfusion and viability [20]. When exposed to severe ischemia such as acute myocardial infarction or unstable angina, defects in myocardial perfusion scintigraphy are revealed,

matching the reduction of wall motion and the site of ischemia [21,22]. On the other hand, when the degree of ischemia is moderate, we often experience cases that do not show defects in myocardial perfusion scintigraphy. Watanabe et al. [23] have reported that in stunned myocardium induced by frequent onsets of vasospastic angina (VSA), transient reduction of wall motion and BMIPP defects were revealed, but the T1 myocardial scintigram was normal. Because of this, in this present study we classified the patients into the group with normal perfusion scintigraphy in the acute phase (N group) and the group revealing defects (D group), and examined the two groups for differences. Both groups showed BMIPP defects in the acute phase, but the D group had significantly higher TDS. While a tendency for improvement in the subacute and chronic phases was seen in both groups, the TDS of the D group was significantly higher than the N group even in the subacute phase. It has been reported that in ischemic heart disease, patients with strong BMIPP defects have delayed improvement of wall motion [14,24]. In addition, in a canine study by Hosokawa et al. [25], BMIPP defects did not appear in moderate ischemia as that caused by blockage of coronary flow for 10 min, but clear BMIPP defects appeared in severe ischemic conditions similar to 30 min of occlusion. Regarding MIBG, both groups revealed eH/M and dH/M decrease and WR increase in the acute phase, but compared to the N group, the D group showed a tendency for lower dH/M and a tendency for higher WR. In the subacute phase, both groups showed a tendency for gradual improvement, with no significant difference revealed.

In the chronic phase, eH/M and dH/M were normalized in the N group, but was low in the D group, with eH/M significantly lower in the D group. Due to the fact that WR remained high in both D and N groups without achieving a normal rate, it became clear that damage to the sympathetic nervous system and its increased activity are prolonged in Ampulla Cardiomyopathy. This tendency was distinctly seen in the D group, which had defects in myocardial perfusion tracers in the acute phase. In cardiac ultrasound, the N and D groups revealed no significant difference in cardiac functions at the time of hospital admission. But while wall motion of the N group normalized within 1 week, wall motion in the D group showed no improvement. It is believed that the D group manifested more severe ischemia compared to the N group due the large degree of defects in both myocardial perfusion tracers and BMIPP, and the delay in their improvement. From these findings, it was believed that the longer duration of spasms in the D group compared to the N group may have led to a higher degree of myocardial ischemia. In addition, from the fact that plasma noradrenaline levels were higher in the D group, it was suggested that similar to neurological stunned myocardium associated with cerebral vascular disorders, myocardial ischemia could have been induced by coronary microvascular spasm due to plasma noradrenaline. From our observations in this study, myocardial scintigraphy was believed to be also useful in assessing the severity of Ampulla Cardiomyopathy.

Study limitations

Different to myocardial infarction caused by organic coronary disease, Ampulla Cardiomyopathy is rare disease. Therefore, only nine patients could be investigated in this study. Therefore, studies using larger number of patients should be carried out to clarify the etiology of this disease.

In this study, the reasons are still unknown as to why the reduction of the wall movement occurs mainly at the apex. Mori et al. [26] reported that the density of astrocytic ganglions of the cardiac sympathetic nerve is specifically high at the apex. Therefore, in addition to the difference in coronary anatomy between apical and basal areas, it should be clarified whether or not noradrenaline is secreted from the astrocytic ganglions and is accumulated in the apical area. In this study, it was not clarified whether or not noradrenaline increased primarily due to stresses or secondary to ischemia of the microvasculature circulation through reflex excitation of sympathetic efferent nerves due to excitation of sympathetic afferent nerves.

Conclusion

From the findings of triple isotope myocardial scintigraphy and the changes in plasma noradrenaline, it was inferred that the etiology of Ampulla Cardiomyopathy is neurological stunned myocardium on the coronary microvascular level. Myocardial scintigraphy was also extremely useful in assessing the severity of Ampulla Cardiomyopathy.

References

[1] Satoh H, Tateishi H, Uchida T. Stunned myocardium with specific (tsubo-type) left ventriculographic configuration due to multivessel spasm. In: Kodama K, Haze K, Hori M, editors. Clinical aspects of myocardial injury: from ischemia to

heart failure. Tokyo: Kagakuhyouronsya; 1990. p. 56—64 [in Japan].
[2] Pavin D, Breton H, Daubert C. Human stress cardiomyopathy mimicking acute myocardial infarction. Heart 1997;38:41—6.
[3] Tsuchihashi K, Ueshima K, Uchida T, Ohmura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol 2001;38:11—8.
[4] Abe Y, Kondoh M, Matsuoka R, Araki M, Dohyama K, Tanio H, et al. Apical defect of Tc-99m tetrofosmin SPECT in Ampulla (Takotsubo) cardiomyopathy may not imply the disturbance of myocardial blood flow. Jpn Circ J 2001;65(Suppl. A):420.
[5] Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I, et al. 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—3.
[6] Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. J Am Coll Cardiol 2003;41:743—8.
[7] Kume T, Akasaka T, Kawamoto T, Watanabe N, Yoshitani H, Akiyama M, et al. Relationship between coronary flow reserve and recovery of regional left ventricular function in patients with tako-tsubo-like transient left ventricular dysfunction. J Cardiol 2004;43:123—9.
[8] Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K, et al. ^{123}I-MIBG myocardial scintigraphy in patients with ''takotsubo'' cardiomyopathy. J Nucl Med 2004;45:1121—7.
[9] Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539—42.
[10] Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid analog. J Nucl Med 1992;33:659—67.
[11] Marwick TH, MacIntyre WJ, Lafont A, Nemec JJ, Salcedo EE. Metabolic responses of hibernating and infarcted myocardium to revascularization. A follow-up study of regional perfusion, function, and metabolism. Circulation 1992;85:1347—53.
[12] Nishimura T, Nishimura S, Kajiya T, Sugihara H, Kitahara K, Imai K, et al. Prediction of functional recovery and prognosis in patients with acute myocardial infarction by ^{123}I-BMIPP and ^{201}TI myocardial single photon emission computed tomography: a multicenter trial. Ann Nucl Med 1998;12(5):237—48.
[13] Tamaki N, Tadamura E, Kudoh T, Hattori N, Yonekura Y, Nohara R, et al. Prognostic value of iodine-123 labelled BMIPP fatty acid analogue imaging in patients with myocardial infarction. Eur J Nucl Med 1996;23:272—9.
[14] Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Iimura O, et al. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. Am J Cardiol 1996;77:25—30.
[15] Bax JJ, Visser FC, Poldermans D, Elhendy A, Cornel JH, Boersma E, et al. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. Circulation 2001;104(12 Suppl. 1):1314—8.
[16] Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A, et al. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. J Am Coll Cardiol 1994;24:636—40.
[17] Heusch G, Baumgart D, Camici P, Chilian W, Gregorini L, Hess O, et al. α-Adrenergic coronary vasoconstriction and myocardial ischemia in humans. Circulation 2000;101:689—94.
[18] Simons M, Downing SE. Coronary vasoconstriction and catecholamine cardiomyopathy. Am Heart J 1985;109:297—304.
[19] Takano H, Nakamura T, Satou T, Umetani K, Watanabe A, Ishihara T, et al. Regional myocardial sympathetic dysinnervation in patients with coronary vasospasm. Am J Cardiol 1995;75:324—9.
[20] Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. Circulation 1993;87:1—20.
[21] Wackers FJ. Thrombolytic therapy for myocardial infarction: assessment of efficacy by myocardial perfusion imaging with technetrium-99m sestamibi. Am J Cardiol 1990;66:36E—41E.
[22] Noriyasu K, Mabuchi M, Kuge Y, Morita K, Tsukamoto T, Kohya T, et al. Serial changes in BMIPP uptake in relation to thallium uptake in the rat myocardium after ischaemia. Eur J Nucl Med Mol Imaging 2003;30:1644—50.
[23] Watanabe K, Takahashi T, Miyajima S, Hirokawa Y, Tanabe N, Kato K, et al. Myocardial sympathetic denervation, fatty acid metabolism, and left ventricular wall motion in vasospastic angina. J Nucl Med 2002;43:1476—81.
[24] Nishimura T, Sago M, Kihara K, Oka H, Shimonagata T, Katabuchi T, et al. Fatty acid myocardial imaging using ^{123}I-beta-methyl-iodophenyl pentadecanoic acid (BMIPP): comparison of myocardial perfusion and fatty acid utilization in canine myocardial infarction (occlusion and reperfusion model). Eur J Nucl Med 1989;15:341—5.
[25] Hosokawa R, Nohara R, Fujibayashi Y, Okuda K, Ogino M, Hata T, et al. Myocardial kinetics of iodine-123-BMIPP in canine myocardium after regional ischemia and reperfusion: implications for clinical SPECT. J Nucl Med 1997;38:1857—63.
[26] Mori H, Ishikawa S, Kojima S, Hayashi J, Watanabe Y, Hoffman JI, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res 1993;27:192—8.