Prevalence and clinical features of focal takotsubo cardiomyopathy
（限局型たこつぼ心筋症の頻度及び臨床的特徴）

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Prevalence and clinical features of focal takotsubo cardiomyopathy

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Short title: Focal Takotsubo Cardiomyopathy

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Abstract

Background: Because it is difficult to distinguish between focal takotsubo cardiomyopathy and aborted myocardial infarction, there is little information about the prevalence and clinical features of focal takotsubo cardiomyopathy.

Methods and Results: Our cardiac catheterization databases were queried to identify patients with focal takotsubo cardiomyopathy and other types of takotsubo cardiomyopathy. In this time, we defined focal takotsubo cardiomyopathy as hypo-, a- or dyskinesis in both anterolateral and septal segments without obstructive coronary artery disease explaining the wall motion abnormality. A total of 10 patients were diagnosed with focal takotsubo cardiomyopathy. The control group was comprised of patients with takotsubo cardiomyopathy with apical, mid-ventricular, or basal ballooning. Clinical features and in-hospital outcomes were compared between patients with focal takotsubo cardiomyopathy and those with other types of takotsubo cardiomyopathy. Of 144 patients with takotsubo cardiomyopathy, apical, mid-ventricular, basal, and focal types were observed in 85 (59.0%), 49 (34.0%), 0 (0%), and 10 patients (6.9%), respectively. The left ventricular ejection fraction was significantly higher in the focal group compared to the apical and mid-ventricular group (56 ± 13 vs. 45 ± 13 vs. 46 ± 12%, $p = 0.03$). In-hospital outcome was not significantly different among the 3 groups.

Conclusions: Focal takotsubo cardiomyopathy is not rare. Biplane left ventriculography is useful for its diagnosis.

Key Words: Takotsubo cardiomyopathy・Apical ballooning syndrome・Acute coronary syndrome・Left ventriculography

Introduction

Takotsubo cardiomyopathy is classically described as apical ballooning.[1] However, other types of takotsubo cardiomyopathy, such as mid-ventricular[2] and basal ballooning,[3] have been demonstrated. Several case reports have shown focal takotsubo cardiomyopathy.[4-9] Recently, the International Takotsubo Registry has demonstrated that focal takotsubo cardiomyopathy was identified in 1.5% of patients with takotsubo cardiomyopathy.[10] The transient nature of left ventricular dysfunction is one of the most important characteristics of takotsubo cardiomyopathy. However, aborted myocardial infarction may exhibit transient left ventricular dysfunction. It may be difficult to distinguish between focal takotsubo cardiomyopathy and aborted myocardial infarction in the absence of obstructive stenosis or clear thrombus in the corresponding artery. Thus the prevalence of focal takotsubo cardiomyopathy may be underestimated. It is important to distinguish focal takotsubo cardiomyopathy from aborted myocardial infarction because patient follow-up and medical management are different. Therefore, it is imperative to establish a method to distinguish focal takotsubo cardiomyopathy from aborted myocardial infarction. In the present study, we propose a method to diagnose focal takotsubo cardiomyopathy using biplane left ventriculography, and evaluated its prevalence and clinical features.

Methods

Patients and Inclusion Criteria

The International Takotsubo Registry showed that, in most cases, an anterolateral segment was involved in patients with focal takotsubo cardiomyopathy.[10] As a result, the cardiac

catheterization databases of Chiba University Hospital, Chiba Emergency Medical Center, and Kimitsu Chuo Hospital from June 2007 to May 2015 were queried to identify consecutive patients with hypo-, a- or dyskinesis in the anterolateral segment and basal, mid-inferior, and apical sparing in the right anterior oblique (RAO) projection of left ventriculography (Figure 1A, B). Patients excluded were those with the presence of obstructive coronary artery disease or acute plaque rupture in the diagonal branch, because myocardial infarction in the diagonal branch area shows left ventricular wall motion abnormality in the anterolateral segment and apical sparing. Patients with pheochromocytoma or myocarditis were also excluded, leaving a total of 20 patients fulfilling the criteria. However, patients with aborted myocardial infarction in the diagonal branch area might be included. To exclude patients with aborted myocardial infarction in the diagonal branch area certainly, we also evaluated left ventricular wall motion in the septal segment using the left anterior oblique (LAO) projection of left ventriculography, because myocardial infarction in the diagonal branch area does not show wall motion abnormality in the septal segment. Three patients were excluded due to absence of the LAO views, and 7 patients were also excluded because of normal contraction of the septal segment. A total of 10 patients were diagnosed with focal takotsubo cardiomyopathy with left ventricular wall motion abnormality in both anterolateral and septal segments.

The control group was comprised of patients with takotsubo cardiomyopathy with apical, mid-ventricular, or basal ballooning in the same period according to the following criteria[11]: 1) transient hypo-, a- or dyskinesis of the left ventricle; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; 2) absence of obstructive

coronary artery disease or angiographic evidence of acute plaque rupture; 3) new electrocardiographic abnormalities or modest elevation in cardiac troponin; and 4) absence of pheochromocytoma or myocarditis. Resolution of left ventricular wall motion abnormality was confirmed by echocardiography. Apical type was defined as apical wall motion abnormalities with or without mid-ventricular involvement and basal hyperkinesis. Mid-ventricular type was defined as bilateral mid-ventricular wall motion abnormalities with basal and apical sparing. Basal type was defined as bilateral basal with or without mid-ventricular involvement with apical sparing. Clinical and laboratory information as well as in-hospital outcome data were obtained from hospital charts that were reviewed by independent research personnel who were unaware of the objectives of the study. The ethics committee of Chiba University approved the study.

Statistical Analysis

Continuous variables are presented as mean ± SD and were compared with 1-way analysis of variance and Welch's test with the post-hoc test. Categorical variables are presented as counts and percentages and were compared by Fisher's exact test. Statistical analysis was performed using JMP 11 (SAS Institute, Cary, NC). A P value of <0.05 was considered statistically significant.

Results

A total of 144 patients received the diagnosis of takotsubo cardiomyopathy. Apical and

mid-ventricular ballooning were observed in 85 (59.0%) and 49 (34.0%) patients, respectively. None of the patients had basal ballooning. Focal type was observed in 6.9% of patients with takotsubo cardiomyopathy (Figure 2). All patients with focal type had wall motion abnormality in the basal-septal segment in the LAO projection of left ventriculography (Figure 1C, D). There was no significant difference in baseline clinical characteristics among the 3 groups (Table 1). Figure 3 shows the incidence of ST segment elevation and/or T wave inversion in each lead in patients with focal takotsubo cardiomyopathy. In leads V_2 to V_4, they were observed in most of the patients. Around half of the patients had electrocardiographic changes in leads I, aV_L, V_5, and V_6. There was a trend toward lower left ventricular end-diastolic pressure and significantly higher left ventricular ejection fraction in the focal group compared to the apical and mid-ventricular group (Table 2). In-hospital outcomes were not significantly different among the 3 groups (Table 3).

Discussion

The main results of this study were: 1) focal takotsubo cardiomyopathy was observed in 6.9% of patients with takotsubo cardiomyopathy; 2) biplane left ventriculography was useful to diagnose focal takotsubo cardiomyopathy; and 3) left ventricular ejection fraction was higher in patients with focal takotsubo cardiomyopathy compared to those with apical and mid-ventricular takotsubo cardiomyopathy.

Takotsubo cardiomyopathy was named after noticing the resemblance of the left ventricle to a Japanese octopus pot (takotsubo) that has a round bottom and narrow neck.[12]

Although apical ballooning is the most common, variant forms such as mid-ventricular[2] and basal type[3] have been demonstrated. The mid-ventricular type has been present in approximately 4% to 40% of patients with takotsubo cardiomyopahy.[13-18] The basal type is rare and seen in only 1% to 3%.[14-16] There does not appear to be a difference in patient clinical characteristics among the apical, mid-ventricular and basal types.[17] Segmental wall motion abnormalities involving the apical right ventricle may be observed in patients with takotsubo cardiomyopathy. Right ventricular dysfunction is a marker for severity of takotsubo cardiomyopathy and associated with lower left ventricular ejection fraction and a higher incidence of severe heart failure.[19] In contrast, the higher left ventricular ejection fraction and lower left ventricular end-diastolic pressure in patients with focal takotsubo cardiomyopathy may be associated with smaller left ventricular area with wall motion abnormality. The exact pathophysiology of takotsubo cardiomyopathy is still uncertain, although several hypotheses, such as sympathetic excitation, multivessel coronary spasm, and microvascular impairment, have been postulated.[20] Thus the difference in pathophysiology among the types of takotsubo cardiomyopathy is also unknown.

Several case reports have demonstrated focal takotsubo cardiomyopathy, especially using cardiovascular magnetic resonance imaging.[7,9] Eshtehardi et al. showed that focal type was observed in 3 (7%) of 41 patients with takotsubo cardiomyopathy.[21] Recently, the International Takotsubo Registry reported clinical features and outcomes of 1,750 patients with takotsubo cardiomyopathy.[10] Focal type was observed in 1.5% of the patients, which is lower than that in the present study (6.9%). However, neither studies showed how they were distinguished from aborted myocardial infarction. The difference in prevalence of focal takotsubo cardiomyopathy

between the present study and other studies may be because of misdiagnosis of focal takotsubo cardiomyopathy as acute coronary syndrome due to transient thrombotic occlusion or severe coronary artery spasm. It is important to distinguish focal takotsubo cardiomyopathy from acute coronary syndrome, because patient follow-up and medical management such as antiplatelet agents, β-blockers, and angiotensin converting enzyme inhibitors are different.

Cardiovascular magnetic resonance imaging (CMR) may be useful to distinguish between focal takotsubo cardiomyopathy and acute coronary syndrome. However, it may not be routinely performed in patients with focal ballooning. Patel et al. have shown that the presence of systolic dysfunction in the posterolateral segment in the LAO projection of left ventriculography most accurately distinguishes the apical type of takotsubo cardiomyopathy from aborted anterior myocardial infarction.[22] The posterolateral segment represents the territory that is generally perfused by the circumflex artery, and occasionally by a large dominant right coronary artery, which accounts for the lack of regional wall motion abnormality in anterior myocardial infarction. In the present study, focal takotsubo cardiomyopathy was diagnosed in patients with regional wall motion abnormality in both the anterolateral and basal-septal segments and apical sparing. Apical sparing means that the left anterior descending coronary artery is not the culprit vessel. The anterolateral segment is perfused by the diagonal branch and the basal-septal segment by a septal branch, which means that the regional wall motion abnormality in both the anterolateral and basal-septal segments and apical sparing extends beyond a single epicardial vascular distribution. Because regional wall motion abnormalities extending beyond a single epicardial coronary artery distribution represents one of the most important features to distinguish takotsubo

cardiomyopathy from coronary artery disease, biplane left ventriculography should be routinely performed in patients with suspected takotsubo cardiomyopathy. However, CMR or single-photon emission computed tomography (SPECT) using 123I-metaiodobenzylguanidine (MIBG) or 123I-beta-methyl iodophenyl pentadecanoic acid (BMIPP) may be considered to distinguish patients with focal takotsubo cardiomyopathy from those with acute coronary syndrome, if biplane LVG is not available in catheterization laboratory. CMR may show left ventricular wall motion abnormality beyond a single epicardial vascular distribution in patients with focal takotsubo cardiomyopathy. SPECT may demonstrate reduced uptake of 123I- MIBG or 123I- BMIPP beyond a single epicardial vascular distribution.[23,24]

In the present study, in-hospital outcomes were not significantly different among the 3 groups. It is consistent with the result in a previous study that showed no significant difference in long-term outcomes between apical and non-apical type.[16]

Study Limitations

There are some limitations in the present study. The number of patients was relatively small. Focal takotsubo cardiomyopathy was diagnosed in patients with regional wall motion abnormality in both the anterolateral and basal-septal segments. There may be patients with focal takotsubo cardiomyopathy who have regional wall motion abnormality only in the anterolateral segment or the basal-septal segment. Furthermore, focal takotsubo cardiomyopathy might be observed in other segments. The prevalence of focal takotsubo cardiomyopathy might be underestimated. However, the International Takotsubo Registry showed that most cases with

focal takotsubo cardiomyopathy had left ventricular wall motion abnormality in the anterolateral segment.

Conclusions

Focal takotsubo cardiomyopathy is not rare. Biplane left ventriculography is useful for its diagnosis, affecting medical management of these patients.

Conflict of Interest: none declared.

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Table 1. Baseline Clinical Characteristics

	Apical (n=85)	Mid-ventricular (n=49)	Focal (n=10)	P value
Age (years)	71 ± 12	70 ± 9	69 ± 18	0.88
Female	72 (85%)	41 (84%)	10 (100%)	0.56
BMI (kg/m^2)	21.6 ± 3.8	20.8 ± 3.5	21.5 ± 3.0	0.58
Hypertension	43 (51%)	24 (49%)	6 (60%)	0.90
Dyslipidemia	32 (38%)	18 (37%)	4 (40%)	>0.99
Diabetes mellitus	22 (26%)	9 (18%)	2 (20%)	0.47
Smoking	10 (12%)	8 (16%)	2 (20%)	0.59
Symptoms				
Chest pain	36 (42%)	27 (55%)	7 (70%)	0.15
Dyspnea	18 (21%)	13 (27%)	1 (10%)	0.53
Triggers				
Emotional stress	12 (14%)	9 (18%)	2 (20%)	0.71
Physical stress	41 (48%)	26 (53%)	3 (30%)	0.45
No apparent trigger	33 (39%)	14 (29%)	5 (50%)	0.32
ECG findings				
ST elevation	61 (72%)	37 (76%)	4 (40%)	0.10
T wave inversion	53 (62%)	31 (65%)	7 (70%)	0.89
QTc (msec)	489 ± 66	478 ± 50	503 ± 64	0.37
Troponin elevation*	67 (84%)	44 (92%)	8 (87%)	0.42

*Troponin was measured in 137 patients. BMI = body mass index; ECG = electrocardiography. There was no significant difference in baseline clinical characteristics between 3 types of takotsubo cardiomyopathy.

Table 2. Cardiac Catheterization Results

	Apical (n=85)	Mid-ventricular (n=49)	Focal (n=10)	P value
Heart rate (bpm)	92 ± 20	94 ± 20	90 ± 20	0.87
Systolic blood pressure (mm Hg)	122 ± 30	123 ± 28	140 ± 35	0.30
Diastolic blood pressure (mm Hg)	66 ± 15	70 ± 15	71 ± 19	0.40
LVEDP (mm Hg)	22 ± 8	21 ± 9	17 ± 6	0.09
Left ventricular ejection fraction (%)	45 ± 13	46 ± 12	56 ± 13	0.03
LVOT gradient ≥15 mm Hg*	18 (22%)	8 (17%)	2 (20%)	0.84
Mitral regurgitation grade 3 or 4	6 (7%)	4 (8%)	1 (10%)	0.89

*LVOT gradient was measured in 139 patients. LVEDP = left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract.

There was significantly higher left ventricular ejection fraction in the focal group compared to the apical and mid-ventricular group.

Table 3. In-hospital Outcomes

	Apical (n=85)	Mid-ventricular (n=49)	Focal (n=10)	P value
Congestive heart failure	21 (25%)	17 (35%)	3 (30%)	0.45
Cardiogenic shock	13 (15%)	11 (22%)	1 (10%)	0.59
Ventricular tachycardia or fibrillation	7 (8%)	2 (4%)	1 (10%)	0.48
Complete atrioventricular block	3 (4%)	1 (2%)	0 (0%)	>0.99
Thromboembolism	4 (5%)	0 (0%)	0 (0%)	0.47
Cardiac rupture	1 (1%)	0 (0%)	0 (0%)	>0.99
Cardiac death	2 (2%)	2 (4%)	0 (0%)	0.72
Total in-hospital cardiac complication	33 (39%)	21 (43%)	4 (40%)	0.93

In-hospital outcomes were not significantly different between 3 types of takotsubo cardiomyopathy.

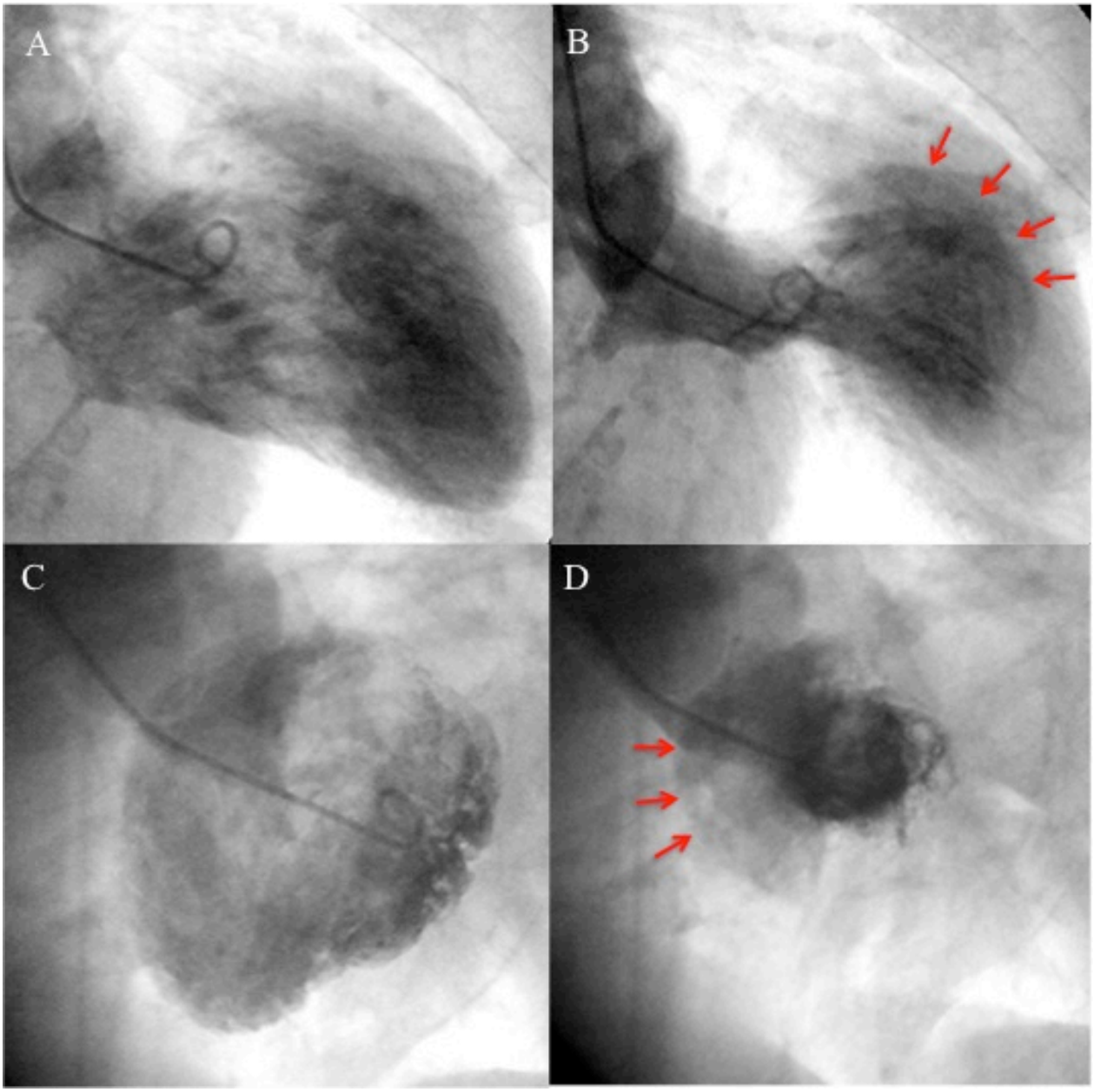

Figure 1. Focal takotsubo cardiomyopathy.

Left ventriculography in the right anterior oblique projection during diastole (A) and systole (B) shows dyskinesis in the anterolateral segment (arrows) and basal, mid-inferior, and apical sparing. Left ventriculography in the left anterior oblique projection during diastole (C) and systole (D) demonstrates akinesis in the basal-septal segment (arrows).

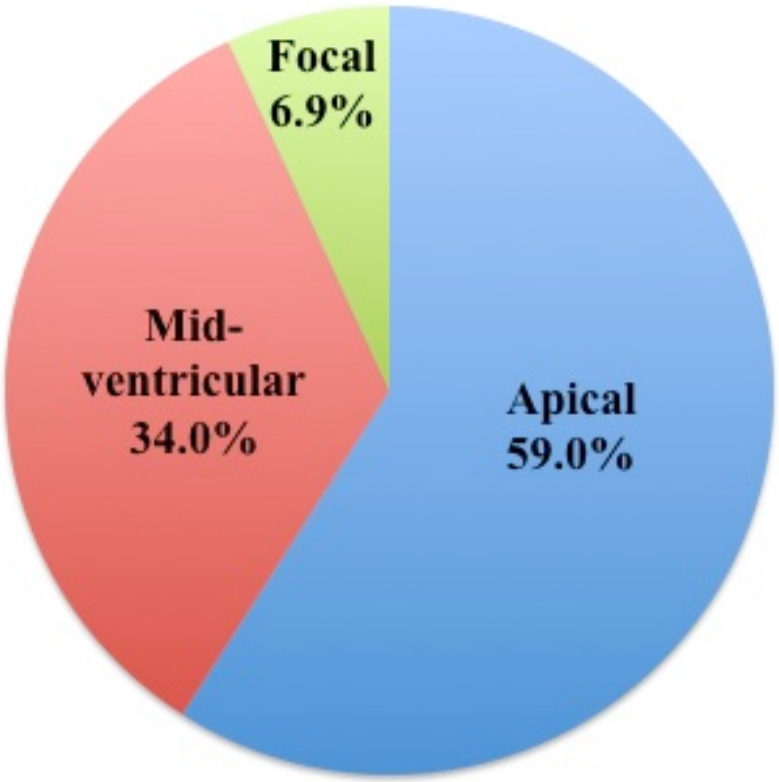

Figure 2. Prevalence of the types of takotsubo cardiomyopathy.

Of 144 patients with takotsubo cardiomyopathy, apical, mid-ventricular, basal, and focal types are observed in 85 (59.0%), 49 (34.0%), 0 (0%), and 10 patients (6.9%), respectively.

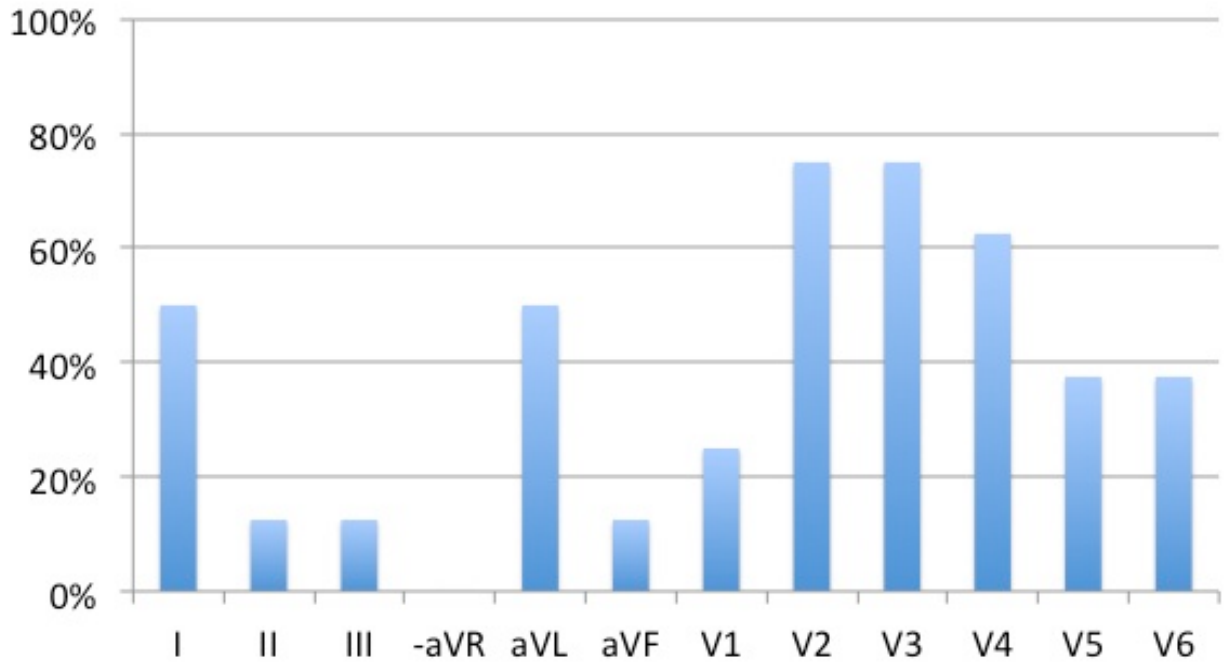

Figure 3. The incidence of ST segment elevation and/or T wave inversion in each lead in patients with focal takotsubo cardiomyopathy.

In leads V_2 to V_4, ST segment elevation and/or T wave inversion are observed in most of the patients. Around half of the patients had electrocardiographic changes in leads I, aV_L, V_5, and V_6.

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