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Letter to the Editor

Presence of ventricular aneurysm predicts poor clinical outcomes in patients with cardiac sarcoidosis☆

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Sarcoidosis is a granulomatous disorder characterized by multisystem involvement. Although cardiac involvement is common in patients with systemic sarcoidosis, cardiac sarcoidosis with no known systemic organ involvement is not rare [1]. Atrioventricular block (AVB), ventricular arrhythmias, congestive heart failure (CHF), and sudden death are well-known manifestation of cardiac sarcoidosis. On the contrary, some patients exhibit ventricular aneurysm, which is commonly observed in the anterolateral and septal walls [2]. However, little is known about the clinical course in patients with cardiac sarcoidosis who had ventricular aneurysm. To characterize the clinical feature in patients with cardiac sarcoidosis who had ventricular aneurysm, we investigated the long-term clinical outcome in patients with cardiac sarcoidosis who were complicated by ventricular aneurysm.

Patients with sarcoidosis, who were diagnosed in the Sakakibara Heart Institute from 1986 to 2012 according to the "Diagnostic Standard and Guideline for Sarcoidosis-2006" [3], were retrospectively analyzed. The study included 50 patients with sarcoidosis who met the clinical criteria suggesting the cardiac involvement. Study subjects were divided into 2 groups according to the presence (aneurysm group) or absence (non-aneurysm group) of ventricular aneurysms at the time of diagnosis. Ventricular aneurysm was defined as a bulging of ventricular wall at end-diastole [4] in one of the imaging tests including transthoracic echocardiography, contrast left ventriculography, and magnetic resonance imaging. Composite cardiac event was defined as hospitalization for CHF, advanced AVB, sustained ventricular tachycardia or fibrillation (SVT/VF), and all-cause death. Major cardiac event was defined as SVT/VF and all-cause death. Data were expressed as mean ± SD. Comparison between aneurysm and non-aneurysm groups was performed using nonpaired t-test. Kaplan–Meier survival curves were depicted, and differences were assessed by log-rank test. Multivariate analysis was performed to determine the significance of the presence of aneurysm in the clinical outcomes. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee, and an informed consent was obtained from each patient.

Mean age was 63.6 ± 12.5, and there were 24 males and 26 females. There were 20 patients in the aneurysm group and 30 patients with non-aneurysm group. Table 1 showed baseline characteristics at the time to start observation, comparing aneurysm group and non-aneurysm group. Female patients were more common in the aneurysm group than non-aneurysm group. Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists were less commonly prescribed in patients with aneurysm. However, there were no differences between the 2 groups in terms of age, other medication, or device therapies. Cardiac biomarkers including brain natriuretic peptide (BNP) and N-terminal pro-natriuretic peptide (NT-proBNP) levels tended to be higher in the aneurysm group, but there was no statistical significance between the 2 groups. Echocardiographic findings showed that chamber size was larger in the aneurysm group than the non-aneurysm group, as reflected by left ventricular end-diastolic and end-systolic dimensions and volumes. Left ventricular ejection fraction (LVEF) was also lower in the aneurysm group. There was no difference in left atrial size between the 2 groups.

Mean follow-up period was 59.0 ± 69.2 months. Composite cardiac events were more common in the aneurysm group than the non-aneurysm group ($p = 0.04$). Major events were also more common in the aneurysm group ($p = 0.03$). Cardiac death including sudden death and heart failure death was more commonly observed in the aneurysm group ($p = 0.03$). Kaplan–Meier survival curves showed that composite event-free survival was significantly lower in the aneurysm group than the non-aneurysm group. Major event-free survival was

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Table 1
Patient characteristics.

	Aneurysm	Non-aneurysm	P value
Age (years)	63.6 ± 10.7	63.7 ± 13.8	0.95
Female	70% (14)	40% (12)	0.04
Medications (n)			
ACE-I/ARB	40% (8)	70% (21)	0.04
β-blocker	25% (5)	30% (9)	0.70
Antiarrhythmics	20% (4)	20% (6)	1.00
Diuretics	5% (1)	30% (9)	0.15
Device therapy (n)			
PM implantation	30% (6)	37% (11)	0.63
ICD implantation	5% (1)	7% (2)	0.84
Biomarker			
BNP (pg/ml)	544 ± 512	251 ± 238	0.08
NT-proBNP (pg/ml)	5297 ± 7704	1542 ± 1399	0.21
Echocardiography			
LVDd (mm)	63 ± 9	54 ± 8	0.001
LVDs (mm)	52 ± 12	41 ± 9	0.004
LAD (mm)	40 ± 8	40 ± 9	0.70
LVEF (%)	30 ± 10	49 ± 13	<0.001
EDV (ml)	181 ± 52	116 ± 28	<0.001
ESV (ml)	122 ± 49	64 ± 28	<0.001

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PM, pacemaker; ICD, implantable cardioverter-defibrillator; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LAD, left atrial dimension; EDV, end-diastolic volume; ESV, end-systolic volume.

also lower in the aneurysm group. Overall survival was not different between the 2 groups (Fig. 1).

Since there was a difference in baseline cardiac function between the 2 groups, we divided the study population into 2 groups according the median baseline LVEF measured by echocardiography. We defined patients with reduced LVEF as baseline LVEF < 42%, and those with preserved LVEF as baseline LVEF > 42% according to the baseline median value. Hospitalization for CHF tended to be higher in the aneurysm group than the non-aneurysm group for patients with reduced EF ($p = 0.06$), while advanced AVB was more common in the aneurysm group than the non-aneurysm group for those with preserved EF ($p = 0.02$). Multivariate analysis showed that the presence of aneurysm was not associated with composite cardiac events or major events, as well as BNP, NT-proBNP, and left ventricular volumes.

Although there are many case reports that showed cardiac sarcoidosis was complicated by ventricular aneurysm [5–7], its incidence has been uncertain. Autopsy findings showed that frequency of aneurysm formation was approximately 8% of patients with cardiac involvement of sarcoidosis [8]. In the present study, incidence of ventricular aneurysm was 40%, which was unexpectedly high. Almost all patients were referred to our hospital because of refractory CHF or life threatening arrhythmias. Predominance of advanced cases appears to be one of the major reasons why the incidence of aneurysm was so higher than previous reports. One more reason is that our hospital handles only

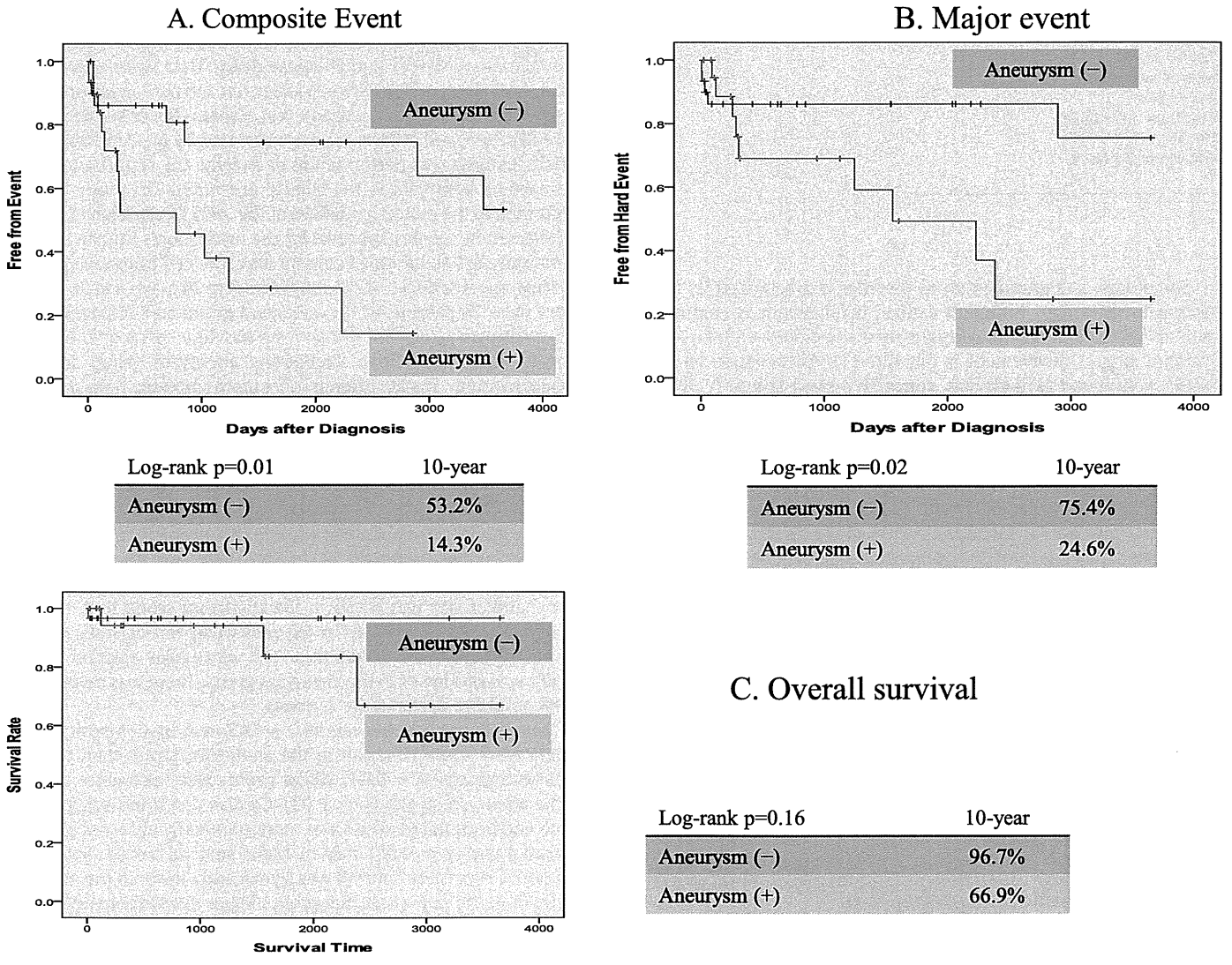

Fig. 1. Kaplan–Meier survival curves depicting event-free survival from composite cardiac events (A), major event (B), and overall death (C).

patients with cardiovascular diseases, where patients with systemic sarcoidosis with only minor cardiac involvement are excluded. These reasons may account for the discrepancy of the incidence of aneurysm formation.

Since there was a difference in terms of left ventricular end-diastolic and end-systolic volumes, LVEF between patients with aneurysm and those without aneurysm, we attempted to identify the significance of the presence of aneurysm independently from cardiac function. Unfortunately, we failed to demonstrate the prognostic significance of ventricular aneurysm for both composite cardiac event and major event independently from cardiac function. Sub-group analysis according to the baseline LVEF has shown that some of the adverse clinical outcomes tended to be more common in the aneurysm group than those in the non-aneurysm group for individual categories stratified by LVEF.

In conclusion, the presence of ventricular aneurysm in patients with cardiac sarcoidosis was associated with increased risk of cardiac events. This study suggests that the presence of ventricular aneurysm portends high risk for cardiac events during the clinical course, as well as impaired ventricular function. In this regard, early intervention should be considered to prevent such fatal sequelae.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Review

Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology

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ABSTRACT

Takotsubo cardiomyopathy, a new concept of cardiomyopathy, is characterized by transient cardiac dysfunction, commonly triggered by physical or emotional stress. Differential diagnosis is important, since takotsubo cardiomyopathy presents similar images to those shown in acute coronary syndrome, with ST-segment elevation, T-wave inversion, QT-prolongation, and others on electrocardiogram. Typically, apical involvement with hypercontraction of basal left ventricle (apical type) is predominant, but atypical types involving basal, mid-ventricular, and right ventricular myocardium are also described. In-hospital death occurs at similar level with patients with acute coronary syndrome, but it is significantly affected by underlying diseases. This disease presents diverse cardiac complications in acute phase, such as life-threatening ventricular arrhythmias, pump failure, cardiac rupture, and systemic embolism. The pathogenic mechanism of this disease is still unclear but sympathetic hyperactivity, as well as coronary vasospasm, microcirculatory disorder, and estrogen deficiency, have been considered as one of the most likely pathogenic mechanism. Long-term prognosis is also largely unknown. Issues such as establishment of acute phase treatment, prediction of cardiac complications, and prophylactic measures against recurrence need to be further explored.

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Transient cardiac dysfunction with characteristic morphology has been termed as "takotsubo cardiomyopathy", a new concept of cardiomyopathy, commonly induced by emotional or physical stress. The name is derived from the appearance of the left ventricular angiographic image shown during an attack, like an octopus trap, "takotsubo" in Japanese. Outside Japan, it is also typically called as "transient apical ballooning", "stress cardiomyopathy", or "broken heart syndrome". Although Iga et al. [49] reported a case of similar pathological conditions with pheochromocytoma in 1989, the term "takotsubo cardiomyopathy" was first described in 1990 by Sato et al. in their report. Takotsubo cardiomyopathy is closely similar to acute coronary syndrome with ST elevation and therefore differential diagnosis is crucially important in the site of emergency care. In addition, special consideration is required when takotsubo cardiomyopathy is complicated by heart failure. This review briefly describes on diagnosis and therapy of takotsubo cardiomyopathy. Since its underlying pathophysiology appears fascinating, author will summarize recent progress in the conceptual advancement.

1. Diagnostic criteria

The diagnostic criteria are advocated by both Mayo Clinic [1] and the Japanese Circulation Society [2] (Table 1). Characteristics associated with pheochromocytoma are excluded in both criteria but cerebrovascular disease is differently considered. It is excluded from the diagnostic criteria of the Japanese Circulation Society but is not listed as an exclusion criterion of Mayo Clinic. Both diagnostic criteria require the absence of significant lesion on coronary angiograms. As mentioned above, the concept of this disease was originally advocated from Japan, but the Mayo Clinic criteria for diagnosis of takotsubo cardiomyopathy have been commonly and internationally used.

Wall motion abnormalities of takotsubo cardiomyopathy are typically characterized by apical systolic dysfunction and hyperdynamic basal contraction. The occurrence of such abnormalities varies with reports but apical pattern accounts for about 80–90% of the whole. Recently, however, the cases of apical-sparing pattern of motion abnormalities commonly in mid-ventricular and basal portions have been often reported. Some reports have described the right ventricular pattern that tends to follow a serious clinical course [3].

2. Epidemiology

Most of takotsubo cardiomyopathy cases have been conventionally reported from Japan. Therefore, this disease was once estimated to be peculiar to Japan. Reports from outside of Japan have been rapidly increased since 2000 and clinical studies of many cases have appeared on wide variety of medical journals (Table 2). This disease presents pathology mimicking acute coronary syndrome and therefore the differential diagnosis of such pathology is confusable. It was reported that

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Table 1
Diagnostic criteria.

I. Mayo Clinic criteria [1]
(1) Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
(2) The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
(3) New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
(4) The absence of pheochromocytoma and myocarditis.

II. Japanese Circulation Society criteria [2]
(1) Acute left ventricular ballooning of unknown cause.
(2) The left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap).
(3) Nearly complete resolution of the apical akinesis in the majority of the patients within a month.
(4) The contraction abnormality occurs mainly in the left ventricle, but the involvement of the right ventricle is observed in some cases.
(5) A dynamic obstruction of the left ventricular outflow tract is also observed.
(6) The absence of significant organic stenosis or spasm of a coronary artery, cerebrovascular disease, pheochromocytoma, viral or idiopathic myocarditis.

the occurrence of acute myocardial infarction provoked by earthquake was rapidly increased but it could be at least probably sure that some of them were considered to this disease. Actually, it was noted that half of such disease reported from Japan was found to be takotsubo cardiomyopathy [4]. One of the features of takotsubo cardiomyopathy is a predominant occurrence in elderly women. The reason is uncertain but reduction of estrogen level with menopause is noted as one of the major factors. A chronobiological pattern of this disease has been discussed in some reports. It has been described in some reports with a peak incidence of this disease in summer [5] and in the evening, which is different from myocardial infarction [6].

The most common subjective symptom is chest pain. Other less common symptoms are dyspnea, palpitations, and physical fatigue. These symptoms are commonly characterized by a preceding physical or emotional stress. Reported stressors are perioperative stresses, death of a family person, surprise party, septicemia, drug addiction, dobutamine or ergonovine stress test, lightning strike, and thyrotoxicosis. At first, abnormal stimulation of the sympathetic nervous system has been estimated to be a major mechanism, in terms of these characteristic pathological patterns.

Table 2
Major clinical studies on takotsubo cardiomyopathy.

Authors	Year	Number of patients	Main results
Elesber et al. [16]	2007	100	10% recurrence rate during 4.4 years
Sharkey et al. [46]	2010	130	In-hospital mortality rate 2%, recurrence rate 5%. All-cause mortality during follow-up higher than matched general population with most deaths occurring in the first year.
Eitel et al. [10]	2011	256	Myocardial edema (81%), inflammation (67%), and patchy late gadolinium enhancement (9%) on magnetic resonance imaging
Brinjikji et al. [17]	2012	24,701	Higher mortality in male than female (8.4% vs. 4.2%)
Sharkey et al. [6]	2012	186	Circadian pattern with a peak in the afternoon
Murakami et al. [47]	2014	107	High white blood cell count and brain natriuretic peptide level are associated with adverse in-hospital outcome
Citro et al. [48]	2014	227	LV ejection fraction, E/e′ ratio, reversible moderate to severe mitral regurgitation, age >75 years were predictors of major adverse events

3. Laboratory tests

The concentration level of plasma brain natriuretic peptide (BNP) increases in acute phase. This change is considered to reflect the ventricular wall stretch. Whereas, changes in cardiac biomarkers, such as creatinine phosphokinase and troponin T, are relatively slight than the expectation compared to the level of wall motion abnormalities. Elevation in the concentration level of the plasma catecholamine has been also reported. The elevation is more remarkable as demonstrated in patients with acute myocardial infarction and the elevation in the concentration level of epinephrine is especially remarkable [7]. Acute coronary syndrome with ST elevation is noted as one of the most typical diseases that require differential diagnosis with takotsubo cardiomyopathy. The differential diagnosis point has been suggested to be the presence of relatively remarkable elevation of the concentration level of brain natriuretic peptide (BNP) compared to troponin T (TnT). It has been considered that BNP/TnT ratio would be useful for the differential diagnosis [8].

4. Electrocardiogram

ST-segment elevation and subsequent T-wave inversion are almost always observed in precordial lead in acute phase. In some cases, these are associated with QT interval prolongation. A transient appearance of Q waves can be sometimes noted. Afterwards, inverted T wave flattens once and becomes prominent again. These phenomena are closely similar to those of acute anteroseptal myocardial infarction. As the differential diagnosis points, the absence of ST-segment elevation in V_1 and the presence of ST-segment depression in aVR (ST-segment elevation in aVR) are noted. Combination of both factors showed 91% sensitivity, 96% specificity, and 95% positive predictive accuracy in identifying this disease [9]. These electrocardiographic changes commonly normalize in several months. Characteristic T-wave inversion of takotsubo cardiomyopathy may be associated with sympathetic denervation. Large area of denervation compared to myocardial necrosis in this disease, in terms of a relatively prominent range of T-wave inversion compared to acute myocardial infarction can be estimated.

5. Ultrasonic echocardiography

In an early stage of the onset, echocardiography is needed to assess systolic dynamics and check for the presence of mitral valve insufficiency. Complication of left ventricular outflow tract stenosis is presented in 18 to 25% of patients with this disease. Anterior motion of mitral valve resulting from tethering by apical akinesis, as well as hyperdynamic basal contraction, is involved in this phenomenon. In some cases, sigmoid septum is considered to be involved in such pathology. Especially, when systolic murmur, refractory heart failure, and hypotension are presented, a possibility of this pathology should be considered.

6. Magnetic resonance and radionuclide imaging

Magnetic resonance imaging technique is helpful to assess not only a cardiac function with takotsubo cardiomyopathy but also myocardial tissue characteristics. Myocardial edema in the regions corresponding to the regions presenting systolic dysfunction is frequently detected on a T2-weighted image of this disease in acute phase. Positive delayed enhancement is detected in a few cases. However, it is still not revealed how these findings are associated with the subsequent clinical outcomes [10].

By radionuclide imaging, a thallium uptake in myocardial thallium scintigraphy was also slightly reduced [11]. Reduction of fatty acid metabolism during acute phase was also reported using ^{123}I-β-

methyliodophenylpentadecanoic acid (BMIPP) imaging [12]. Many studies on sympathetic imaging have been reported, because the presence of abnormal sympathetic activity is estimated to be one of the underlying factors of takotsubo cardiomyopathy. In the ^{123}I-metaiodobenzylguanidine (MIBG) imaging, reduction in the intramyocardial uptake of ^{123}I-MIBG is observed. In the positron emission tomography (PET), increase in the myocardial uptake of ^{11}C-hydroxyephedrine is observed. Conversely, reduction in uptake and abnormalities in fatty acid metabolism are also observed. Whereas defects on thallium myocardial scintigraphy are recovered early, defects on BMIPP and MIBG scintigraphy are recovered slowly. Especially, MIBG defects are more slowly normalized than BMIPP, suggesting that sympathetic denervation affects large area of ventricular myocardium.

7. Cardiac catheterization

One of the criteria of the diagnosis of this disease is the absence of identifiable lesion explaining wall motion abnormalities on the coronary angiographic image. The findings of plaque rupture or others suggesting acute coronary syndrome should be excluded. In some cases, coronary arterial spasm is observed in provocation tests. In such cases, the regions of the induced coronary vasospasms do not match the regions of wall motion abnormalities. Because of delayed filling of the contrast media which is detected often in coronary angiography, coronary microcirculatory disorder is noted as a pathogenesis of the disease. As this disease is associated with prominent contractile abnormality and stretch of apical and other regions in acute phase, delayed filling may be a phenomenon secondary to these factors. The left ventricular angiographic image in acute phase demonstrates typical takotsubo-like shape in the end-systolic phase.

8. Myocardial histopathological findings

Histopathological findings similar to catecholamine-induced cardiomyopathy are predicted, in terms of excessive catecholamine secretion supposed as one of the key factors in the onset of takotsubo cardiomyopathy. Myocardial biopsy findings have not been studied in detail so far. Nef et al. have reported detailed studies using pathological specimens obtained from myocardial biopsy of patients with takotsubo cardiomyopathy. In the immunohistochemical staining, decrease in α-actinin in the central area of cardiomyocytes, increase in collagen-1 in the extracellular matrix, and increases in CD^{68+} macrophages were demonstrated. Characteristic contraction band necrosis was observed by electron microscopic image [13].

9. Complications

Pump failure is a relatively common complication. In other cases, this disease is complicated by diverse arrhythmias such as atrial fibrillation and flutter, atrioventricular block, and the ventricular tachycardia and fibrillation. This disease is complicated by mural thrombus through hyperactivation of platelet function and coagulability probably caused by sympathetic activation, as well as through blood stagnation caused by apical contractile abnormality. This often results in complication of cerebral embolus. Anticoagulation therapy should be considered in acute phase. Cases of complication with cardiac rupture have been uncommonly reported as a fatal complication. A case of 82-year-old woman with takotsubo cardiomyopathy, with apical rupture identified by autopsy findings, who presented cardiac tamponade on the second day from the onset, has been reported [14].

10. Medical management

It may be possible to diagnose this disease in acute phase to some extent by subjective symptoms, electrocardiogram, and echocardiography. This disease can be successfully diagnosed with the presence of normal coronary arteries detected by urgent cardiac catheterization as well as the presence of characteristic left ventricular angiographic findings. Most of cases having a good prognosis without complications can be managed with follow-up alone. However, for patients complicated with shock or heart failure, specific treatment is needed (Fig. 1). In the case of takotsubo cardiomyopathy, it is crucial to determine whether contractile dysfunction or outflow tract obstruction is responsible for shock or heart failure. In the case of patients with this disease caused by contractile dysfunction, inotropic agents such as catecholamines are used but the inappropriate use of catecholamine triggers left ventricular outflow tract obstruction. In the case of patients with refractory heart failure, intra-aortic balloon pumping is used. Blood transfusion is given for patients with insufficient intravascular volume. No therapy has been established for left ventricular outflow tract obstruction. In the case of hemodynamics to which β-blockers can be administrated, short-acting intravenous infusion such as landiolol can be used. The use of β-blockers should be carefully considered, which may exacerbate QT-prolongation associated with this disease. Some report has described that the use of β-blocker with α_1-receptor blocking activity would be preferable because norepinephrine-mediated α_1-receptor stimulation could be involved in the onset of this disease; however, inappropriate peripheral vasodilation may exacerbate outflow tract obstruction. α_1-Receptor stimulants such as phenylephrine can be considered in case of shock. It has been also reported that levosimendan, a calcium sensitizer, is effective, though it is not approved for use in Japan. Phosphodiesterase inhibitors such as milrinone are one of the options, which are approved for use in Japan for intravenous infusion. In case of the presence of left ventricular outflow tract obstruction, intra-aortic balloon pumping should not be used. In case of refractory shock, percutaneous cardiopulmonary support is useful.

In takotsubo cardiomyopathy, systemic embolism is triggered by intra-cardiac thrombus. The underlying factor is the involvement of hypercoagulability due to sympathetic activation. Intravenous infusion of heparin and subsequent administration of anticoagulants such as warfarin are preferable from early phase.

There is little systematic information on cardiac rupture, which is limited to the extent of case reports. Among the accumulation data on 12 cases with cardiac rupture, onset of cardiac rupture was commonly noted in elderly patients, cases with high blood pressure, and those without administration of β-blocker. Early administration of β-blocker might be important for the prevention of cardiac rupture, similar to cardiac infarct.

In most of takotsubo cardiomyopathy, abnormal myocardial contraction is normalized in several days to several months. The recurrence rate is approximately 10%. There is no long-term therapy

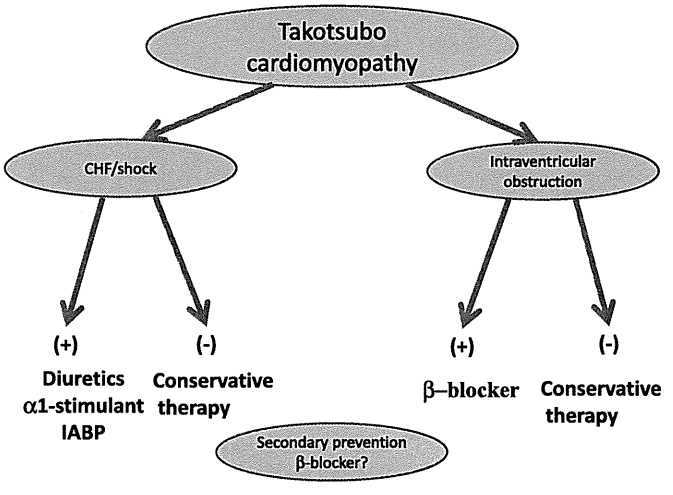

Fig. 1. Algorithm showing therapeutic strategies. CHF, congestive heart failure; IABP, intra-aortic balloon pumping.

established. The most likely mechanism underlying this disease is sympathetic hyperactivity and therefore β-blocker is expected to be helpful in the prevention. According to the study by Palla et al. on the orally administrated medications in 64 patients with takotsubo cardiomyopathy before arriving hospital, β-blocker was administered in 25% of patients. No significant difference was found in the levels of cardiac enzymes, left ventricular end-diastolic pressure, and ejection fraction between administrated group and non-administrated group [15]. No significant difference was either found in the administration frequencies of β-blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, aspirins, statins between recurrent cases and non-recurrent cases [16]. Although ACE inhibitors and β-blockers had been administered before hospital discharge, the effectiveness of such administrations in preventing recurrence would be suspicious.

11. Prognosis

Most of the reports on takotsubo cardiomyopathy have been focused on case examples; results of follow-up of many cases were conventionally hardly reported. Among them, analyses on the epidemiological data of many cases from the inpatient database of the United States were presented. In the analytical results on 6837 cases extracted from the database of 2008, in which age, gender, and patient's underlying factors were analyzed, the incidence of this disease was 8.8 times higher in women than in men and was 4.8 times higher in women older than 55-year-old than those younger than 55-year-old. Factors including smoking, heavy alcohol consumption, anxiety, and dyslipidemia were associated with the onset of this disease [5]. Analysis was carried out on the in-hospital death using the data of 24,701 cases of patients with takotsubo cardiomyopathy extracted from the database of 2008–2009. The overall in-hospital mortality rate was 4.2%. The common cause of death was non-cardiac disorders due to underlying diseases that triggered this disease. It was noted that acute renal failure, respiratory failure, stroke, non-cardiac surgery, etc. could be involved in 81.4% of deaths. The mortality rate of a group with severe underlying disease was 12.2% and that of a group with no underlying disease was 1.1%. The common causes of cardiovascular death are cardiogenic shock and systemic embolism. Other rare causes of death include cardiac rupture. The mortality rate of patients with this disease complicated with right ventricular dysfunction is also high as mentioned above. Difference in the mortality rate between men and women was prominent, where the mortality rate was 2.5 times higher in men than in women. The reason includes the fact that men have commonly suffered serious underlying diseases. It was highlighted that such underlying diseases determined a short-term prognosis of takotsubo cardiomyopathy, rather than cardiac death [17].

As described above, short-term prognosis of takotsubo cardiomyopathy is relatively good but some of patients have adverse outcomes with various complications such as pump failure and life-threatening arrhythmias. Prediction of such cases is attempted on admission to hospital. Electrocardiogram would be the easiest and simplest tool. Sum of ST-segment elevation in 12-lead electrocardiogram served as a predictor of adverse complications such as heart failure, cardiogenic shock, left ventricular outflow obstruction, life-threatening ventricular arrhythmias, and embolisms [18].

12. Molecular mechanisms of takotsubo cardiomyopathy

Factors of pathogenic mechanism underlying this disease are still uncertain but sympathetic hyperexcitation, coronary vasospasm, microcirculatory disorder, and lack of estrogen have been regarded as the most likely factors since earlier studies (Fig. 2).

12.1. Sympathoexcitation hypothesis

The hypothesis explaining that onset of this disease is principally caused by sympathetic excitation, is the most dominant one and this can be supported by the following evidences. It is supported by data and reports such as (i) commonly induced by physical and emotional stresses; (ii) similar cardiac dysfunction reported from the case of patients with pheochromocytoma; (iii) closely similar pathological images of cardiac dysfunction traditionally triggered by high dose of catecholamine to the pathological findings of takotsubo cardiomyopathy; (iv) cases of the development of this disease reported from the case of administration of catecholamines such as epinephrine and dobutamine [19]; and (v) administration of α/β-blockers, in a rat model, successfully controlling takotsubo cardiomyopathy-like pathologies triggered by immobilization stress [20].

Sympathetic excitation through hypothalamus triggers release of norepinephrine mainly from sympathetic nerve endings and epinephrine mainly from adrenal medulla. Actually, it has been reported that the concentrations of plasma norepinephrine and plasma epinephrine are more highly increased in patients with takotsubo cardiomyopathy than those in patients with acute coronary syndrome [7]. It is predicted that norepinephrine may trigger coronary vasospasm by stimulating α_1-receptor in coronary vessels. Meanwhile, norepinephrine-mediated β_1-receptor stimulation may trigger hyperdynamic basal contraction, because of a higher density of sympathetic nerve endings in the basal myocardium [21] and a higher content of norepinephrine in the basal myocardium [22]. Conversely, the apical myocardium has a higher density of β-receptors. The precise cause of presentation of apical systolic dysfunction is still unknown, however it has been suggested that neurogenic stunning may have a key role. As one of the molecular mechanisms of this event, signal switching mediated by stimulation of β_2-receptor by epinephrine has been advocated [23]. It is pointed out that the occurrence frequency of leucine-type genetic polymorphism of guanine nucleotide binding (G)-protein-coupled receptor kinase $(GRK)_5$ is higher in the patients with takotsubo cardiomyopathy [24]. In the leucine type with a higher GRK_5 activity than glutamine type, receptors are more likely to be uncoupled with sympathetic nerve stimulation. This could be involved in the apical stunning observed in this disease.

While the sympathetic activity hypothesis is firmly believed to be the most likely one, some studies argue that concentration level of plasma catecholamine could not always be elevated. The group of Harding et al. of the United Kingdom advocated that β_2-adrenoreceptor subtype densely distributed in cardiac apex could play a key role. They reported that high level of epinephrine could trigger signaling through β_2-receptor from stimulatory G-protein to inhibitory G-protein and thereby trigger typical apical systolic dysfunction in takotsubo cardiomyopathy. Different from β_1-receptor, β_2-receptor is coupled not only with stimulatory G-protein but also with inhibitory G-protein. Signal switching, advocated by Daaka et al. in 1997, is a concept where chronic stimulation of β-receptors switches from stimulatory to inhibitory signaling mediated through protein kinases A (PKA) [25]. Actually, Harding et al. revealed that the similar pathologies to takotsubo cardiomyopathy characterized by basal hypercontractility and apical systolic dysfunction were presented by a bolus of high dose of epinephrine in rats. The signaling via β_2-receptor is considered to promote cardioprotection, having effects of anti-apoptotic NFkB/BCL2 via PI3K/Akt signaling pathway. Instead, the mortality rate was increased by inhibitory G-protein pathway blockade with pertussis toxin. Conversely, β-blockers increased negative inotropic effect via inhibitory G-protein without change in the mortality rate. Levosimendan, calcium-sensitizer, with less effect of PKA activation, was effective for improvement in the pathologies of this disease in this model animal [26].

Results of imaging tests suggested the involvement of sympathetic nerve. On the sympathetic nerve imaging with ^{123}I-MIBG, the elevation

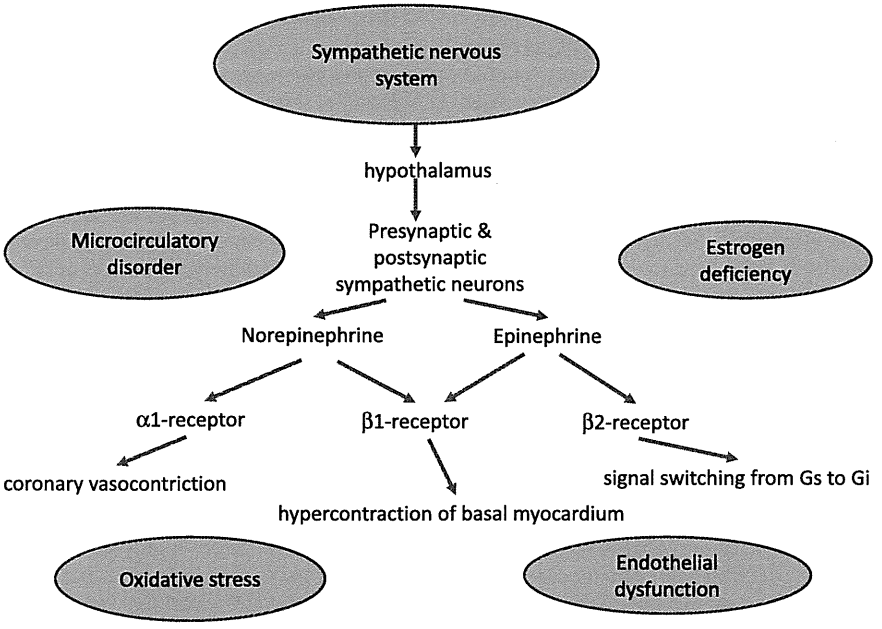

Fig. 2. Pathophysiological basis underlying takotsubo cardiomyopathy. Gs/Gi, stimulatory or inhibitory G-protein.

of the heart to mediastinum uptake ratio and washout ratio of the early image was demonstrated [27]. On PET imaging with ^{11}C-hydroxyephedrine, similar findings were obtained [28]. The concentration of norepinephrine sampled from the coronary sinus of patients with takotsubo cardiomyopathy was more highly increased than that from the aortic root. This revealed that sympathetic nerve activation is derived not only from adrenal medulla but also from the involvement of cardiac sympathetic nerves [29].

Intracellular calcium overload might be involved in contraction band necrosis, observed in histopathological findings of patients with takotsubo cardiomyopathy. Nef et al. carried out myocardial biopsy, and examined the tissues using real time PCR, western blot, and immunohistochemical staining in patients with takotsubo cardiomyopathy. Increase in the expression of sarcolipin in ventricles and decrease in the expression of sarcoplasmic reticulum calcium ATPase (SERCA2a) were revealed [30]. Sarcolipin is known to regulate the activity of SERCA2a via phospholamban and is involved in intracellular calcium overload in this disease. Other report has described that lipid accumulation mediated by sympathetic activation is involved. Shao et al. successfully induced takotsubo cardiomyopathy-like systolic dysfunction by a bolus of isoproterenol in mice. Oil red staining revealed a myocardial lipid accumulation. They highlighted on the decrease in ApoB lipoprotein which caused the accumulation. They revealed that isoproterenol-induced takotsubo cardiomyopathy-like systolic dysfunction could be protected by overexpression of ApoB. Therefore, it was also presumed that abnormal lipid accumulation mediated by sympathetic stimulation would be involved in apical stunning and electrophysiological disturbance [31]. As mentioned above, a lot of findings on the involvement of sympathetic nervous systems have been accumulated. It could be firmly believed to be the most likely mechanism underlying this disease. However, this disease cannot be explained solely by the sympathetic activation. Thus, the following hypotheses are also provided.

12.2. Coronary vasospasm hypothesis

Coronary vasospasm is induced in about 28% of provocation test during coronary angiography in patients with takotsubo cardiomyopathy [32,33]. The possibility of the involvement of coronary vasospasm in some of patients is at least undeniable. A hypothesis explained that this disease could be caused by plaque rupture not resulting in obstructive coronary disease, based on the presence of plaque rupture detected in the intravascular ultrasound findings of some patients with this disease [34]. However, it has been pointed out that wall motion abnormality does not always match with the coronary artery vascular distribution and histopathological findings are different from those observed in ischemic stunning [35]. Thus, coronary vasospasm involvement is so far considered to be negative. From the very first, coronary vasospasm is listed as an exclusion criterion in the diagnostic criteria.

12.3. Microcirculatory disorder hypothesis

Microcirculatory disorder is an attractive hypothesis for takotsubo cardiomyopathy, with delayed filling of the contrast media presented on coronary angiographic findings. The presence of sympathetic activation, microvascular spasm, and oxidative stress might support it as underlying factors. Whereas, there is a criticism that this is the only secondary phenomenon with wall motion abnormalities. The group of Mayo Clinic analyzed the coronary angiographic findings of patients with takotsubo cardiomyopathy and delayed filling determined by Thrombolysis in Myocardial Infarction myocardial perfusion grade was found in 69% of them [36]. Though this change might be considered to be a secondary phenomenon with apical wall motion abnormality, a report described that such change remained after the improvement of wall motion [15]. Kume et al. assessed the coronary flow reserve during acute phase and recovery phase using Doppler flow guide wire. The coronary flow reserve and decay of the diastolic blood flow velocity decreased during acute phase but improved with the improvement of wall motion abnormality during recovery phase [37].

12.4. Estrogen deficiency hypothesis

Takotsubo cardiomyopathy occurs predominantly in postmenopausal women. Increased sensitivity of β-receptor and low baseline concentration of catecholamine have been proposed as the cause. An alternative possibility of the involvement of deficiency in cardioprotective effect caused by reduction of estrogen may be highly supported by the predominant occurrence of this disease in postmenopausal women. This may lead to cardiomyopathy through elevated oxidative stress and endothelial dysfunction, with sympathetic nerve activation. Whereas microcirculatory disorder has been proposed as one of the pathogenic

mechanisms of takotsubo cardiomyopathy as mentioned above, estrogen has an effect to improve the endothelial function [38]. Syndrome X presenting repetitive anginal attack, with underlying microcirculatory disorder, also typically occurs in postmenopausal women; this may suggest an involvement of common mechanism in the process of takotsubo cardiomyopathy. It has been known that estrogen receptors are expressed on cardiomyocytes [39]. In addition, decrease in the level of SERCA2a, which controls intracellular calcium, in ovariectomized rats [40] and myofilament calcium hypersensitivity [41] and increase of β-adrenoreceptors [42] have been reported. Immobilization stress induces overexpression of c-Fos protein gene in response to stress in the heart/adrenal medulla [43]. Similar phenomenon has been observed in the central nervous systems (hypothalamus, locus coeruleus, amygdaloid nucleus, etc.) controlling the autonomic nerve function and the presence of estrogen receptors at these regions has been also observed [44]. Takotsubo cardiomyopathy is induced by immobilization stress but the pathologies can be prevented by pre-administration of estrogen [45]. Administration of estrogen increased the levels of atrial natriuretic peptide and heat shock protein 70 [43].

13. Conclusion

Pathological concept of takotsubo cardiomyopathy has been almost established, but a number of questions still remain, such as establishment of acute phase treatment, risk assessment, prophylactic measures against recurrence, and long-term prognosis. Many questions still also remain regarding the pathogenic mechanisms underlying takotsubo cardiomyopathy. Further research in all aspects and approaches are expected by accumulating large amount of database.

Conflict of interest

None.

Author contribution

Tsutomu Yoshikawa collects all the information and final disposition of the manuscript.

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３．　委託業務成果報告（合田あゆみ）

厚生労働科学研究委託費（循環器疾患・糖尿病等生活習慣病対策実用化研究事業）
委託業務成果報告

急性心不全におけるガイドラインベースの治療実施状況と予後因子規定に関する国際共同多施設レジストリ研究

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研究要旨

左房径は心臓超音波で簡単に測定できる簡便な指標であり、慢性心不全患者において予後予測指標となることが報告されている。本データベースを用い、左房径の拡大が、急性左心不全患者における予後予測に利用できるかを検討した。

A. 研究目的

左房径は心臓超音波で簡単に測定できる簡便な指標であり、その拡大は左室拡張末期圧の上昇、慢性的な左心室への負担を反映すると考えられている。左房径が急性心不全患者の予後予測因子となるかを検討した。

B. 研究方法

杏林大学付属病院、慶應義塾大学病院、榊原記念病院の3施設(WET-HF Registry)で、2006年から2012年まで急性心不全で入院した患者を検討した。930人のWET-HF Registry登録患者より、入院時に心臓超音波を施行していない患者、心房細動患者を除く511人が、研究対象となった。その中で、左室収縮能が保持されている(LVEF>40%)群(HFpEF群)と左室収縮能が保持されていない(LVEF<=40%)群(HFrEF群)の2群に分け比較を行った。エンドポイントは入院中の院内死亡(In-hospital death)、退院後の心血管死と心不全による再入院(Long-term composite endpoint)とした。

(倫理面への配慮)

各施設の倫理委員会で本研究に関する審査を受け、承認を得た。臨床疫学倫理指針に基づき、各施設で本研究に関する情報を広く公開し、包括同意を得た。

C. 研究結果

HFrEF群は274人、HFpEF群は237人であった。HFrEF群の平均左房径(LAD size)は42.8mmとHFpEF群(40.1mm)より有意に拡大していた。

また、In-hospital deathは34人に発生し、平均630日のfollow up期間中Long-term composite endpointは155人に発生した。

Cox生存解析において、HFrEF群で

は LAD size は強力な予後予測因子(Hazard Ratio 1.034 (1.005-1.063), p=0.020)であったが、HFpEF 群では有意ではなかった(Hazard Ratio 1.019 (0.995-1.040), p=0.071、下図参照)。

D. 考察

HFrEF 群では、LAD が拡大しているほど、長期予後不良であった。一方、HFpEF 群は LAD の拡大は予後予測因子とはならず、LAD の拡大で代償する前に急性心不全になっている可能性があると考えられた。もしくは、HFpEF 群の長期予後は、他の因子により規定されている可能性が考えられた。

E. 結論

HFrEF 群において、LAD size は有意な予後予測因子となるが、HFpEF 群においては予後予測因子とはならなかった。

F. 研究発表

1. 論文発表

なし

2. 学会発表

Yoichiro Uesugi, Ayumi Goda, Taku Inohara, Yasuyuki Shiraishi, Mitsuaki Sawano, Mayuko Yagawa, Keitaro Mahara, Toru Satoh, Hideaki Yoshino, Shun Kohsaka, Tsutomu Yoshikawa. Difference in the impact of left atrium size by presence/absence of LV systolic dysfunction among acute heart failure patients.

- 78th Annual Scientific Meeting of the Japanese Circulation Society Mar 23, 2014, Tokyo
- European Society of Cardiology Congress 2014, Balcerona, Aug 31, 2014

G. 知的財産権の出願・登録状況(予定を含む)

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

	Total		HFrEF		HFpEF	
Variables	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age	1.029 (1.016-1.041)	<0.001	1.030 (1.014-1.046)	<0.001	1.031 (1.008-1.055)	0.009
Female	1.114 (0.802-1.548)	0.519	0.867 (0.535-1.404)	0.561	1.524 (0.940-2.472)	0.088
Height	0.991 (0.973-1.009)	0.326	0.990 (0.965-1.016)	0.460	0.990 (0.963-1.018)	0.489
Body weight	0.988 (0.976-1.000)	0.054	0.988 (0.973-1.003)	0.119	0.987 (0.967-1.007)	0.191
ICM	1.179 (0.859-1.619)	0.308	1.714 (1.130-2.600)	0.011	0.770 (0.467-1.267)	0.304
DCM	0.930 (0.640-1.350)	0.702	0.779 (0.503-1.206)	0.263	1.313 (0.527-3.269)	0.559
Valve	1.292 (0.746-2.238)	0.361	1.320 (0.579-3.057)	0.516	1.360 (0.628-2.943)	0.436
sBP	0.993 (0.988-0.998)	0.009	0.994 (0.987-1.001)	0.072	0.992 (0.985-1.000)	0.055
Heart rate	1.000 (0.994-1.006)	0.975	0.993 (0.984-1.003)	0.161	1.004 (0.995-1.012)	0.395
Hypertension	0.665 (0.478-0.898)	0.009	0.592 (0.386-0.907)	0.016	0.754 (0.455-1.252)	0.275
Diabetes	1.366 (0.990-1.884)	0.057	1.647 (1.066-2.546)	0.025	1.191 (0.731-1.941)	0.483
Hyperlipidemia	0.801 (0.576-1.112)	0.185	1.112 (0.719-1.721)	0.633	0.551 (0.330-0.921)	0.023
Hemodialysis	1.425 (0.667-3.044)	0.360	1.213 (0.444-3.316)	0.707	1.671 (0.522-5.345)	0.387
COPD	1.075 (0.475-2.433)	0.863	1.552 (0.628-3.836)	0.341	0.460 (0.064-3.319)	0.441
Cerebrovascular disease	0.733 (0.386-1.392)	0.343	0.969 (0.468-2.008)	0.933	3.213 (1.047-9.857)	0.041
Anemia	1.499 (1.090-2.062)	0.013	1.433 (0.945-2.175)	0.090	1.569 (0.947-2.599)	0.080
Smoking	0.696 (0.485-0.998)	0.049	0.638 (0.392-1.040)	0.071	0.784 (0.458-1.342)	0.375
LAD	1.024 (1.009-1.040)	0.002	1.034 (1.005-1.063)	0.020	1.019 (0.998-1.040)	0.071
LVDd	1.008 (0.993-1.023)	0.326	1.006 (0.984-1.027)	0.611	1.005 (0.972-1.040)	0.756
LVDs	1.007 (0.996-1.020)	0.222	1.005 (0.987-1.025)	0.574	1.010 (0.979-1.042)	0.518
LVEF	0.989 (0.979-1.000)	0.046	1.006 (0.984-1.027)	0.611	1.005 (0.972-1.040)	0.758

図. 長期予後予測因子（多変量解析）

4.　委託業務成果報告（水野　篤）

別刷

Seasonal Changes in Systemic Volume Overload Are to Be Considered

急性心不全におけるガイドラインベースの治療実施状況と予後因子規定に関する国際共同多施設レジストリ研究

研究協力者：　聖路加国際病院循環器内科　水野　篤

研究要旨

これまでも疾患発症の季節性変動は発症率を中心に数多く報告されている。但し、報告はほとんど一般的な診断名からの「入院率」の報告であり、疾患ベースのレジストリデータでの予後そのものに対する研究報告はほとんど存在しない。本研究により心不全における季節性変動により、どのようなタイプの心不全入院があるかということ、さらに短期的な予後との相関を検討した。

A. 研究目的

季節性変動による心不全の臨床的パラメーターと院内のアウトカムへの寄与の定量化の詳細に対する検討を目的とした。

2014 年に発表された Hirai らの報告では582人の連続した心不全において、クリニカルシナリオ１という状況下における冬季の心不全入院が多いという事が明らかとなっている（図 1）。

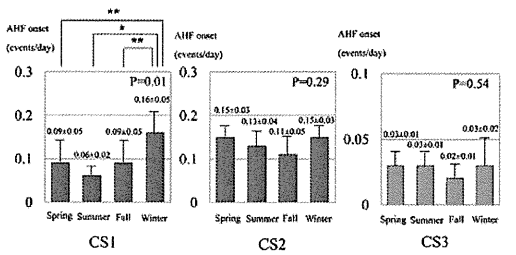


図１　クリニカルシナリオのタイプ別の季節別入院割合

さらに利尿薬の使用のない症例が冬の心不全の入院の独立因子という内容の報告も認められた（図 2）

Table 3. Clinical Characteristics of HF Patients With Winter Admission and Those With Other Seasons' Admissions (CS1, Multivariate Analysis)

Variable	Multivariate analysis OR (95% CI)	P value
Age	1.006 (0.980–1.033)	0.660
Male	1.084 (0.613–1.918)	0.782
EF ≥40%	1.560 (0.840–2.895)	0.159
T-bil	0.644 (0.350–1.183)	0.156
CRP	1.080 (0.987–1.181)	0.095
Loop diuretics	0.562 (0.256–0.798)	0.006

図２　クリニカルシナリオ１の状況下での冬季の入院に関連した因子

しかし、クリニカルシナリオ１というのは、Mebazaa らによれば、volume overload のない心不全ということである。このためこの結果はやや矛盾していると考えられた。

さらに、血圧よりも浮腫などの volume overload の具体的なパラメーター評価が重要であるが、これらは Hirai らの研究では評価されていなかった。

B. 研究方法

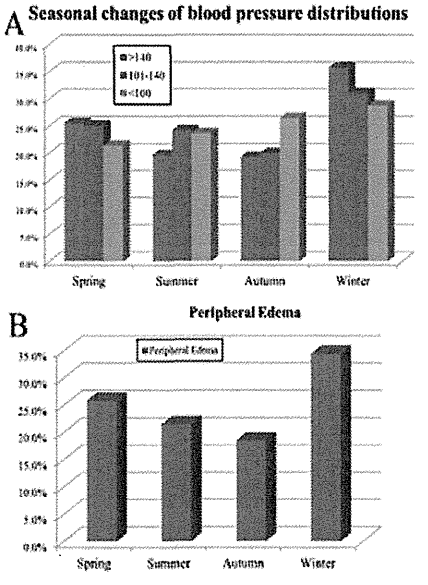
気象庁のデータベースからの気温・気圧のデータと当心不全レジストリデータベースとの連結を行い、一般的な手法で Hirai らの研究に対する補完的な統計解析を行った。

（倫理面への配慮）

多施設研究であり、連結可能匿名化でのデータ処理を行った。他、特に倫理的な問題は発生しないと考えた。

C. 研究結果

今回 我々は WET-HF レジストリ データを用いて、浮腫の季節性変動の評価を行った。具体的には 2006 年 4 月から 2013 年 12 月までの連続する心不全患者を対象に、Hirai らと同様の定義を用いた 4 季による心不全の収縮期血圧と浮腫の変化を検討した。



その結果、確かに 収縮期血圧 >140mmHg の心不全患者は冬に増加するが、同時に浮腫の割合も増加していることが判明した。これらは Hirai らによる血圧上昇のみでのクリニカルシナリオの評価は不十分であり、さらに利尿薬を使用しないことで冬の心不全入院が増加することをサポートする結果であると考えられた。

D. 考察

冬の心不全入院増加には血圧が高く、浮腫が強い患者の入院が関与している。これはこれまでの報告を加味して考慮すると日本人の食事形態から鍋などを中心とした、塩分増加などの影響もあると考えられる。心不全の治療においては利尿薬が大きな役割を果たすと考えられ、Hirai らの報告を加味すれば利尿薬をリスクの高い患者に先行投与することが可能となれば心不全入院を減少させることができるかもしれないと考えられた。

E. 結論

心不全患者において、入院患者の臨床的パラメーターは季節変動に影響を受ける。これらを加味した加療を今後検討していくことがより良い治療や予防、予後改善につながる可能性もあると考えられる。

F. 研究発表

1. 論文発表

Seasonal Changes in Systemic Volume Overload Are to Be Considered
Circulation Journal 2015 *in press*
Doi:http://dx.doi.org/10.1253/circj.CJ-14-1333

2. 学会発表

なし

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Seasonal Changes in Systemic Volume Overload Are to Be Considered

To the Editor:

We read with a great interest the recent paper by Hirai et al entitled "Clinical Scenario 1 Is Associated With Winter Onset of Acute Heart Failure".[1] A seasonal variation in acute heart failure (AHF) and its risk, particularly during the winter period, remains a valid clinical question, and the authors have stated that the lack of loop diuretics could predispose patients to decompensation. We would like to add several comments on their discussion of this topic.

First of all, the original clinical scenario by Mebazaa et al does not recommend classification based solely on systolic blood pressure.[2] A patient's clinical status, such as the degree of systemic volume overload (eg, peripheral edema), is to be considered. Clearly, this is of importance when agents for volume reduction (eg, loop diuretics) are considered.[3,4] In our own data on 1,882 consecutive AHF patients registered in the West Tokyo Heart Failure Registry (WET-HF; from April 2006 to December 2013), we observed both higher frequency of high blood pressure on presentation (systolic blood pressure ≥140 mmHg; **Figure A**), as well as the clinical sign of peripheral edema during winter (**Figure B**). Interestingly, the reduction in body weight during hospitalization was similar between different seasons. We believe that information on detailed clinical parameters, rather than sole classification based on systolic blood pressure, would be beneficial to understand the results and conclusion by Hirai et al that "only a lack of loop diuretic use was a contributing factor for winter onset of AHF in CS1 patients, whose treatment was usually vasodilators".

We would also like to emphasize that the current ACCF/AHA and ESC guidelines do not recommend the use of "clinical scenario" at this time,[3,4] because the prognostic and clinical significance of clinical scenarios has not been validated. This further underscores the need for a validated hemodynamic model, such as blood pressure, to validate these authors' hypothesis.

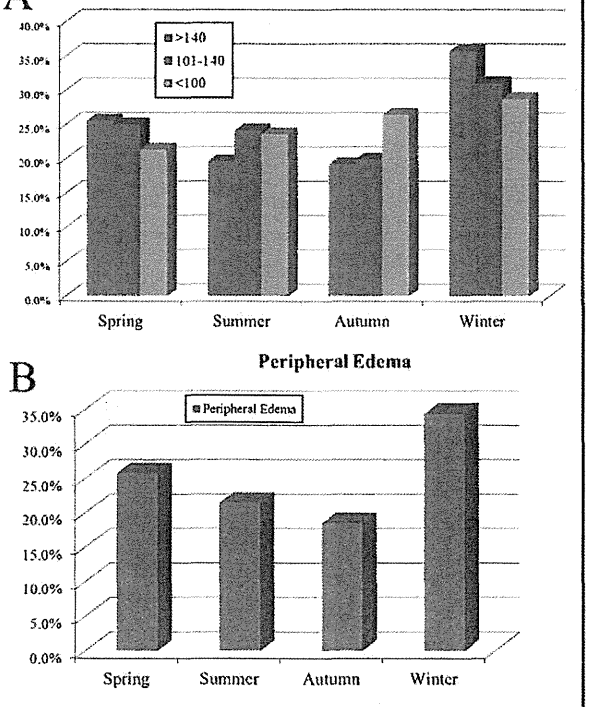


Figure. Seasonal changes in (**A**) systolic blood pressure distribution and (**B**) peripheral edema.

Disclosures

No conflicts of interest exist in this study.

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