Ampulla Cardiomyopathy
(Takotsubo Cardiomyopathy)—A Review

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Abstract

The ampulla cardiomyopathy (Takotsubo Cardiomyopathy) also known as stress- induced cardiomyopathy (SICD), or broken heart syndrome, mimics acute coronary syndrome, typically characterized by transient regional systolic dysfunction involving the left ventricle apex and midventricle with hyperkinesis of the basal segments. Pathophysiology of this disease has been investigated by myocardial scintigraphy in recent years. The etiology may be related to catecholaminergic or adrenoreceptor- hyperactive cardiomyopathy, but also may be multifactorial. In this article, we provide a brief review of the literature regarding the prevalence, the possible etiology, risk factors, electrocardiographic and echocardiographic findings, clinical manifestation, diagnostic criteria, prognosis and treatment. (J Intern Med Taiwan 2009; 20: 473-483)

Key Words: Apical ballooning syndrome(ABS), Stress-induced cardiomyopathy (SICD), Broken heart syndrome

Introduction

Transient left ventricular apical ballooning also known as Takotsubo cardiomyopathy or "broken heart syndrome" has been described by investigators worldwide. There have been several cases reported in Japan's journals between 1990 and 2001. It was first described by Sato et al and Dote et al and was named "Takotsubo" -shaped cardiomyopathy due to its unique "short neck round-flask" -like LV apical ballooning resembling the tako-tsubo (Japanese for octopus pot or trap) of Japan¹.² In recent years, a lot of patients with clinical presentation resembling acute myocardial infarction, such as chest pain, electrocardiography(EKG) abnormalities and elevated cardiac markers, have been found to have normal coronary arteries during the procedure of coronary angiography. The syndrome is characterized by transient left ventricular apical wall motion abnormality with hyper-or-normal-contraction of the basal region resulting in characteristic "ballooning" of the apex of the left ventricle. Besides, the transient regional systolic dysfunction also involves the right ventricle³ and recently, a new variant of transient LV ballooning,
defined as "atypical" ampulla cardiomyopathy, was reported. The LVG of this atypical ampulla cardiomyopathy showed dilatation and akinesis of midventricle with a hypercontractile apex and base. By the review of Cocco G et al, the stress hormones appear to play a central role in the pathogenesis. So the term "stress-induced cardiomyopathy" (SICMP) may be the most accurate to show the entity of this disease. Because the prognosis of this disease is better than acute myocardial infarction, it is very important to differentiate this from acute coronary syndrome (ACS).

Prevalence

The prevalence of apical ballooning syndrome is not known. Recently, a prevalence of 2-2.2% of this syndrome was described in patients presenting with ST-elevation myocardial infarction or unstable coronary syndrome in the United States. But in fact, we think the syndrome is probably underdiagnosed due to the use of thrombolytic agents sparing the intervention of coronary angiography. The most common population presenting with this syndrome is older women especially after a physically or emotionally stressful event. The cause of female predominance is not known. Although females are the majority of patients, reported in over 90% of the cases, there appear to be no difference between the genders for presenting symptoms, age at onset, precipitating type of stress, or adverse outcome. There was no identified triggering event in up to 22% of patients. Caucasians were more likely to present with emotional stress in comparison to Asians.

Pathogenesis

This type of LV dysfunction has been reported to develop concomitantly with many different types of disorders, including coronary arterial spasm, phaeo-chromocytoma, "Guillain-Barre" syndrome, emotional stress, endocrine disease, pneumothorax, and subarachnoid haemorrhage. However, the relationship to these diseases is unclear. It is debatable about the pathophysiology. The recognition of "apical ballooning" as a distinct entity does not necessarily imply that all cases have the same underlying pathophysiology. Indeed, the major variation in clinical presentation suggests that different mechanisms may be at play in different patients with a similar clinical picture. There have been many reported theories on the etiology of ampullar cardiomyopathy in recent years, including acute myocarditis, diffuse coronary vasospasm, rupture of a nonobstructive plaque followed by spontaneous thrombolysis, transient LV outflow tract obstruction, catecholamine-mediated cardiotoxicity, microvascular dysfunction, hypoplastic coronary artery or cardiac autonomic imbalance.

1. Acute myocarditis: Acute myocarditis has also been considered a possible cause of this syndrome. However, endomyocardial biopsies performed from the area around the LV apex in 18 patients with transient LV apical ballooning failed to demonstrate histopathologic evidence of myocarditis. Sharkey et al, using cardiac magnetic resonance imaging in 22 patients, did not show the typical profile of myocarditis, such as delayed enhancement with gadolinium. Now it is considered a secondary cause of transient LV apical ballooning, because the apical ballooning pattern has been rarely described in cases of acute myocarditis.

2. Diffuse coronary vasospasm: Spontaneous multivessel coronary vasospasm was present in a few patients, and inducible multivessel coronary vasospasm was seen in only 13 of 73 patients tested across case series reported by Bybee et al. This mechanism may be related to only some of the cases of this syndrome or as a result of increased autonomic tone or exceptional spasmogenic stimuli.
(emotional upset or severe acute pain resulting in increased blood levels of catecholamines and/or stress-related neuroreceptors)\textsuperscript{20}

3. Nonobstructive plaque followed by spontaneous thrombolysis: Spontaneous intermittent coronary recanalisation and reocclusion resulting from a variable combination of thrombosis and vasoconstriction are frequent during the early phase of ACS\textsuperscript{21}. Transient coronary artery occlusion/reperfusion episodes may lead to myocardial stunning and akinesia of the myocardium supplied by the coronary artery. When occlusion episodes are short enough, release of blood markers of myocardial ischemia and necrosis is minimal with total recovery of cardiac function\textsuperscript{16}. Ibanez B et al have postulated that a large left anterior descending artery (LAD) that wraps around the apex could explain the syndrome if there was a ruptured plaque in the mid LAD followed by early reperfusion. However, the anatomic distribution of this syndrome involving all 3 coronary territories is not consistent with a ruptured plaque in a single coronary territory. Apical distribution of the right ventricular wall akinesia appears to be less common but it may suggest that apical ballooning syndrome does not follow a single coronary territory.

4. Transient LV outflow tract obstruction: By the report of Villareal et al\textsuperscript{12}, the patients with a sigmoid interventricular septum, small left ventricular outflow tract (LVOT), reduced left ventricular volumes (primarily women) and an abnormal orientation of a slack mitral apparatus have a geometrical predisposition to dynamic LVOT obstruction, which may manifest in the setting of intense adrenergic stimulation or hypovolaemia. With LVOT obstruction, apical and anterior wall stress and left ventricular filling pressures increase while systemic blood pressure decreases, which leads to a state of oxygen mismatch for the apex. Eventually myocardial ischemia, stunning, regional wall motion abnormalities and associated T-wave changes occurred. This may be why the women with the smaller left ventricular size, especially in the setting of catecholamine excess, predispose to the development of this disease\textsuperscript{23}.

5. Catecholamine mediated cardiotoxicity: Catecholamine mediated cardiotoxicity is the most widely proposed mechanism given that patients typically present with a preceding history of extreme psychological and/or physical distress implying increased sympathetic activity with a direct catecholamine toxic effect on the cardiac myocytes\textsuperscript{20}. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP - mediated intracellular calcium overload resulting in reversible ventricular dysfunction\textsuperscript{20,24}. Besides, there are case reports describing cocaine abuse\textsuperscript{25} or pheochromocytoma-related\textsuperscript{26} apical ballooning syndrome, consistent with the important role of catecholamines in the pathogenesis of these syndrome. Although measurement of catecholamine levels in patients presenting with takotsubo cardiomyopathy have been conflicting, this may be in part due to the extremely short half-life of epinephrine (3 minutes) and given the fact that most patients arrive to the emergency room at least 30 minutes (> 10 half lives) after the inciting event\textsuperscript{27}.

6. Microvascular dysfunction: Coronary angiography identifies epicardial lumen vessel anatomy, but is inadequate for assessing microcirculation and may underestimate peripheral myocardial perfusion. Different perfusion between subendocardial and subepicardial perfusion is followed by regional wall motion abnormalities (detected by echocardiography) and thereafter by chest pain and/or ECG changes. Microvascular dysfunction has been shown to be evidenced by decreased coronary flow (measured by flow velocity with Doppler wire or frame count analysis)\textsuperscript{28,30}, myocardial scintigraphy or contrast echocardiography\textsuperscript{12,31}. In the assessment of the TIMI
myocardial perfusion grade (TMPG), an index of myocardial perfusion, abnormal myocardial perfusion was present in 69% of patients with apical ballooning syndrome. The perfusion abnormality involves multiple coronary territories in most (86%) patients, and the severity of perfusion defect correlates with the extent of myocardial injury. Under stressful situations, excess norepinephrine might be secreted from the sympathetic nervous system, which might provoke microvascular spasm via alpha-2 receptors. Sympathetic nerves are also distributed to smaller vessels such as intramuscular arterioles, but parasympathetic nerves are only distributed to the epicardial and subepicardial arteries. Therefore the influence of the sympathetic nerve extends to the coronary microcirculation. Besides, acute psychological stress has been shown to induce endothelial injury via beta-1 adrenoreceptors in humans, which led to microvascular dysfunction.

7. Hypoplastic coronary artery: Severe stress, cold weather, and night time reduce physiologic coronary dilatation. Under these circumstances, the coincidental occurrence of catecholaminergic hyperactivity would further increase heart rate, contractility, oxygen consumption, and platelet aggregability and thus create a sudden hemodynamic burden. In patients with a normal coronary system, an increased catecholaminergic effect (e.g., with pheochromocytoma) affects the whole heart, where normally the basal and middle regions of the ventricle are hemodynamically more involved. If myocardial ischemia occurs, pathologic changes (stunning, dyskinesia) will first occur in these regions, while less demanding apical region will show a less important dysfunction. Accordingly, in these pathologies, dyskinesia is seen in the proximal and middle areas, with almost no involvement of the apex.

In a report, 40% of SICMP women has hypoplastic (smaller and shorter) branching vessels from the posterior descending coronary artery (which is the terminal aspect of either the right coronary artery in 90% of cases or of the left circumflex coronary artery in 10% of cases) supplying the posterior and inferior apical region. The small caliber of these coronary arteries decreases the amount of secondary vasodilatation and favors a regional circulatory mismatch, in the end reducing oxygen reserve. If all coronary arteries would be similarly affected, these effects would be generalized and affect the most metabolically active regions of the heart. This explains the classical preference of SICMP for apical and median dyskinesia of the left ventricle and of the right ventricle.

8. Cardiac autonomic imbalance: Activation of the sympathetic branch of the autonomic nervous system or an increase in the level of catecholamines may result in cardiac adrenergic stimulation. Despite of the fact that there are greater densities of sympathetic nerves at the base of the heart than in the apex, there is evidence that apical myocardium has enhanced responsiveness to sympathetic stimulation, potentially making the apex more vulnerable to sudden surges in circulating catecholamine levels. Greater adrenoreceptor density in the apex of LV may be an important contributory factor to this phenomenon. Scintigraphic imaging using 123I-iodine-labeled metaiodobenzylguanidine (123I-MIBG) allows adrenergic neuronal function to be assessed noninvasively. MIBG defects are noted at times of functional disorders in the sympathetic nervous system or when denervation of the sympathetic nerves in the myocardium occurs due to severe ischemia. Decreased myocardial 123I-MIBG uptake in the distal anterior, inferior, and apical walls was detected in ampullar balloon syndrome. Neurological stunned myocardium may play an important role in the mechanism for the onset of neurological ampulla cardio-myopathy, 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. The hypothesis focusing on direct myocardial
effects of high catecholamine levels was also proved by the exam of PET imaging with $^{11}$C
hydroxyephedrine$^{36}$.

A diffuse reduction in the uptake of MIBG indicates downregulation of beta- adrenergic
receptor density induced by high levels of circulatig plasma cate-cholamines in patients with
heart failure$^{27}$, so on that basis the MIBG defect on mid- to apical region in ampular balloon syndrome
may imply that the apical myocardium is vulnerable to ischemic damage in the setting of excessive
catecholamines.

Risk Factors

Eighty-five percent of SICMP patients are
postmenopausal women. It has been suggested that
an estrogen deficiency might be a predisposing
factor by inducing endothelial dysfunction. The
majority of SICMP patients also have other cardio-
vascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). More-
over, a stressful event, either psychic (53%) or
somatic (8%), is present in 65% of SICMP patients$^{3}$. All of these factors may lead to endothelial
dysfunction, increased platelet aggregation, or both,
a situation with high risk for a cardiovascular
complication.

Clinical Symptoms and Signs

The clinical profile of ampulla cardiomyopathy
typically includes those symptoms associated with
ACS and may resemble acute heart failure. Severe
chest pain (CCS class III) and moderate to severe
dyspnea (NYHA class III) are reported in 92% and
in 60% of cases, respectively. Tachycardia is always
present, and 70% of patients have an arrhythmic
pulse$^{3}$. Most patients are hypertensive, but during
the crisis blood pressure is variable, depending on
the hemodynamics. In severe cases, especially when
there is right ventricular involvement, apical
balloon syndrome may induce a pleural effusion$^{10}$.
In a study of 97 Japanese patients with tako-tsubo
cardiomyopathy, 10% had significant CAD, but
there was no significant difference in clinical
characteristics between patients with CAD and
those without CAD$^{42}$.

Electrocardiographic Findings

Kuris et al stated that the admission ECG
usually showed ST-segment elevation (Fig. 1-A) or
T-wave inversion in leads V3-6 and that the T-wave
became inverted within 2 days (Fig. 1-B) and the
T-wave inversion deepened progressively to its first
negative peak, which occurred at approximately 3
days$^{41}$. In a recent case series of 105 patients
identified with ABS, 34.2% had ST-segment
elevation or new LBBB on EKG at admission,
30.4% had T-wave inversions, 32% had nonspecific
ST-T abnormalities and the others showed
nonspecific ST-T abnormalities or normal EKG$^{41}$. Ogura et al found that the ratio of the ST-segment
elevation in leads V4-6 to V1-3, the absence of
reciprocal changes and the absence of abnormal
Q-waves were useful for differentiating ampulla
cardiomyopathy from anterior wall MI$^{46}$. In 24% of
cases, there is a prolonged PR interval, mostly with
a first-degree AV-block; in 45% supraventricular
beats; in less than 5% of cases, a left or right bundle
branch block can appear; 37% of cases have pathological Q waves in three or more leads (mostly
V1-3); 33% of cases have ventricular premature
beats and 23% of cases have a ventricular ta-
chycardia; giant negative T waves are seen in
86% of cases, especially on the 3rd day and, rather
characteristic for apical balloon syndrome, again
after 2-3 weeks. In 20% of cases, the T changes
may be seen years later$^{45}$. The QT interval is
pathologically prolonged in 50% of cases. The
Serum Enzymes

In 85% of cases, BNP is greatly increased (>1000 pg/ml)\(^5\), confirming the relevant cardiac failure. In 50%, C-reactive protein (CRP) is elevated (>9 mg/l), which may indicate a poorer prognosis. There may be moderate increase in CK, CK-MB, troponin and myoglobin\(^7\).

Echocardiogram

Transthoracic echocardiography will identify regional wall abnormalities, typically akinesia of the LV apex and/or the mid-portion of the LV (Fig. 2-A,B). Typically the area of LV dysfunction usually involves a larger territory than that supplied by one epicardial coronary artery. Right ventricular apical involvement can also occur in this syndrome, which can be detected using echocardiography\(^41,46\). A variant of this disease is now recognized involving the base or mid cavity of the left ventricle and sparing the apex\(^40\). It is interesting that if stress occurs again during the process of healing after this first episode, the reactivity or sensitivity differs to the second excessive catecholamine stimulation between the basal- to mid-portion and the apical area, resulting in a hypercontractile LV apex with an akinetic basal- to mid- LV\(^90\).

Other Diagnostic Tools

Besides traditional two-dimensional echocardiography, there have been published reports about the new tools in differentiating takotsubo cardiomyopathy form acute myocardial infarction, such as cardiac magnetic resonance imaging (MRI)\(^51\) and two-dimensional speckle tracking echocardiography\(^42\). In patients with acute phase of ampulla cardiomyopathy, the cardiac MRI will show diffusely distributed segmental wall motion abnormalities and absence of first-pass perfusion hypoenhancement and of delayed enhancement. However the two- dimensional speckle tracking
echocardiography will show that LV dysfunction is circular, with similar velocities recorded among all basal LV segments, among all middle segments, and among all apical segments.

Complication and Prognosis

Complications could occur early in the course of apical ballooning syndrome. Donohue et al. summarized the prevalence of complications by reviewing the reported cases in the literature, as follows: cardiogenic shock in 6.5%, congestive heart failure in 3.8%, ventricular tachycardia in 1.6%, and death in 3.2% respectively. Other rare but serious complications have been described, such as ventricular septal defect, ventricular fibrillation, pneumothorax, left ventricular rupture, torsades de pointes, complete atrioventricular (AV) blockstroke, and apical thrombus formation. T-wave inversion and physical stress appear to increase the risk of complications. Furthermore, age was independently associated with a higher mortality. Recurrent ampulla cardiomyopathy is seldom, with one study reporting a recurrence rate of 11.4% over 4 years after initial presentation. The time-to-recurrence ranges from 3 months to 13 years after initial episode.

Management and Treatment

There is no randomized trial to evaluate the effect of any treatment in these patients. In the acute phase, the treatment is supportive. In rare cases, intraaortic balloon pump may be necessary in hemodynamically unstable patients. Medical regimens include the use of β-blockers, angiotensin-converting enzyme inhibitors, aspirin and diuretics. Because catecholamines could have a causative role in stress-induced cardiomyopathy, therapy with epinephrine, inotropic agents such as dobutamine, or both might lead to worsening of the condition, although in the absence of clinical studies this is a theoretical concern. The potential role of catecholamines has prompted the empirical use of β-blockers, with the goal of preventing recurrence. In one case report, verapamil failed to prevent recurrent apical ballooning syndrome. On the other hand, Obon Azuara et al. describe a patient with previous history of left ventricular ballooning syndrome who presented with recurrent chest pain and dynamic left ventricular obstruction responding promptly to beta-blocker treatment. This observation suggests that beta-blockers may play a role in the treatment of these patients. In a study, long-term use of angiotensin-converting enzyme inhibitors before the onset of TC was protective against cardiogenic shock, sustained ventricular arrhythmia, and death in the acute phase. In the case of apical thrombus formation or thromboembolic complications, anticoagulation should be beneficial until left ventricular recovery is documented. However, no case report or studies are available to evaluate the necessity of these medications for the recovery of the left ventricular function. There is also no consensus about the length of the treatment.

Guideline for Diagnosis

Guidelines for the diagnosis of ampulla cardiomyopathy were recently established in Japan.

1. Definition: Takotsubo (ampulla) cardiomyopathy is a disease exhibiting an acute left ventricular apical ballooning of unknown cause. In this disease, the left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap). There is nearly complete resolution of the apical akinesis in the majority of the patients within a month. The contraction abnormality occurs mainly in the left ventricle, but involvement of the right ventricle is observed in some cases. A dynamic obstruction of the left ventricular outflow tract (pressure gradient difference, acceleration of blood flow, or systolic cardiac murmurs) is also observed.

2. Exclusion criteria: The following lesions and abnormalities from other diseases must be
excluded in the diagnosis of takotsubo (ampulla) cardiomyopathy.

(1). Significant organic stenosis or spasm of a coronary artery. In particular, acute myocardial infarction due to a lesion of the anterior descending branch of the left coronary artery, which perfuses an extensive territory including the left ventricular apex (An urgent coronary angiogram is desirable for imaging during the acute stage, but coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion or a lesion involved in the abnormal pattern of ventricular contraction).

(2). Cerebrovascular disease and pheochromocytoma: These patients have an apical systolic ballooning similar to that in takotsubo cardiomyopathy, but with a known cause. Such patients are diagnosed as "cerebrovascular disease with takotsubo-like myocardial dysfunction" and are differentiated from idiopathic cases. Other exclusion criterias comprise viral and idiopathic myocarditis.

3. References for diagnosis

(1). Symptoms: Chest pain and dyspnea similar to those in acute coronary syndrome. Takotsubo cardiomyopathy can occur without symptoms.

(2). Triggers: Emotional or physical stress may trigger takotsubo cardiomyopathy, but it can also occur without any apparent trigger.

(3). Age and gender difference: Known tendency to increase in the elderly, particularly females.

(4). Ventricular morphology: Apical ballooning and its rapid improvement in the ventriculogram and echocardiogram.

(5). Electrocardiogram: ST segment elevations might be observed immediately after the onset. Thereafter, in a typical case, the T-wave becomes progressively more negative in multiple leads, and the QT interval prolongs. These changes improve gradually, but a negative T-wave may continue for several months. During the acute stage, abnormal Q-waves and changes in the QRS voltage might be observed.

(6). Cardiac biomarkers: In a typical case, there is only modest elevations of serum levels of cardiac enzymes and troponin.

(7). Myocardial radionuclear study: Abnormal findings in myocardial scintigraphy are observed in some cases.

(8). Prognosis: The majority of the cases rapidly recover, but some cases suffer pulmonary edema and other sequelae or death.

Conclusion

Takotsubo cardiomyopathy is a distinct type of heart failure. Although its origin was not clearly demonstrated, coronary vasospasm, acute myocarditis, and other substantial diseases that have been previously described were ruled out as causes. Heart failure in this cardiomyopathy might completely reverse without treatment, and had a good prognosis once past the severe state. This cardiomyopathy should be noted as a cause of sudden cardiac death in individuals without obvious heart disease.

Although catecholaminergic or adrenoceptor-hyperactive cardiomyopathy is a possible instigating factor, it is more likely that the pathogenesis of the condition is multi-factorial. Further studies are needed to confirm this. Up to the present time, there have been at lest 17 cases reported in Taiwan, in which a female preponderance was also noted[60]. Emergency room physicians and cardiologists should take notice in daily practices for early suspicion and confirmation of diagnosis. Every patient must be treated as a case of STEMI until proven otherwise.

References


壺腹形心肌病變—文獻回顧

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摘  要

壺腹形心肌病變又稱為壓力性心肌病變或中斷性心臟微候群(broken heart syndrome)，臨床症狀與急性冠心症相仿。病人會有短暫性左心室尖端及心室中段等部位收縮功能減損，同時合併基部收縮過度。病理生理學在最近幾年已使用心臟核子醫學攝影廣泛所研究。致病機轉可能與兒茶酚胺或腎上腺受體過度活化所造成之心肌病變有關，但也有可能是多發性的。在本文中我們回顧文獻中有關此疾病之盛行率、可能致病因、危險因子、心電圖及心臟超音波特徵、臨床表現、診斷準則、預後及治療。