Transient left ventricular dysfunction (tako-tsubo phenomenon): Findings and potential pathophysiological mechanisms

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Tako-tsubo-like left ventricular dysfunction phenomenon (TTP) is characterized by transient left ventricular apical ballooning associated with symptoms, electrocardiographic changes and minimal cardiac enzyme release in the absence of coronary artery disease. Initially described in Japan, TTP occurs worldwide, predominantly in women and frequently after emotional or physical stress. Symptoms include anginal chest pain, dyspnea and syncope. Electrocardiographic ST elevations may be present only for several hours, and are followed by negative T waves that persist for months. Arterial hypertension is found in up to 76% of TTP patients, hyperlipidemia in up to 57% and diabetes mellitus in up to 12%. Potential pathophysiological mechanisms for TTP include catecholamine-induced myocardial stunning or hyperkinesis of the basal left ventricular segments, coronary vasospasm, plaque rupture, myocarditis and genetic factors. TTP patients should be monitored similarly to myocardial infarction patients because organ failure, cardiogenic shock, ventricular fibrillation or rupture may occur. Beta-blockers are indicated, whereas catecholamines and nitrates should be avoided. The long-term prognosis is unknown.

Key Words: *Ampulla cardiomyopathy; Left ventricular ballooning; Tako-tsubo phenomenon; Transient left ventricular dysfunction*

Tako-tsubo-like left ventricular dysfunction phenomenon (TTP) has primarily been described in Japan. It is characterized by transient left ventricular apical ballooning in the absence of coronary artery disease associated with symptoms, electrocardiogram (ECG) changes and minimal cardiac enzyme release (1). In patients suffering from TTP, ventriculography and echocardiography reveal the shape of a 'tako-tsubo', which is a pot used for trapping octopuses in Japan. In several cases, an atypical TTP variant, with hypokinesis of the anterior and posterior walls, and normokinesis of the apex has been described, and named 'chestnut-shaped' transient regional left ventricular hypokinesis (2-4).

TTP often mimics acute myocardial infarction (1,5,6). It has been described predominantly in women and frequently occurs after emotional or physical stress (7). The etiology of TTP is unknown. The present review, based on a MEDLINE search, summarizes the current knowledge regarding the prevalence, clinical presentation, laboratory findings, cardiac and noncardiac abnormalities, suggested pathophysiological mechanisms, therapy and prognosis of TTP.

Un dysfonctionnement ventriculaire gauche transitoire (phénomène takotsubo) : Observations et mécanismes physiopathologiques potentiels

Le phénomène de dysfonctionnement ventriculaire gauche de type takotsubo (PTT) est caractérisé par un ballonnement apical transitoire du ventricule gauche associé à des symptômes, des changements électrocardiographiques et une libération minimale de l'enzyme cardiaque, en l'absence de coronaropathie. Décrit pour la première fois au Japon, le PTT s'observe partout dans le monde, surtout chez les femmes et souvent après un stress affectif ou physique. Les symptômes sont les douleurs angineuses, une dyspnée et une syncope. À l'électrocardiographie, il se peut que les surélévations du segment ST ne soient visibles que quelques heures, suivies d'ondes T négatives qui persistent pendant des mois. On remarque une hypertension artérielle chez jusqu'à 76 % des patients atteints du PTT, une hyperlipidémie chez jusqu'à 57 % d'entre eux et un diabète sucré chez jusqu'à 12 %. Les mécanismes physiopathologiques potentiels du PTT sont une sidération myocardique induite par la catécholamine ou une hyperkinésie des segments ventriculaires gauches basaux, un vasospasme coronaire, une rupture de plaque, une myocardite et des facteurs génétiques. Les patients atteints du PTT devraient être suivis comme s'ils avaient subi un infarctus du myocarde, en raison du risque d'insuffisance organique, de choc cardiogène et de fibrillation ou de rupture ventriculaire. Les bêtabloquants sont indiqués, tandis que les catécholamines et les nitrates sont à éviter. On ne connaît pas le pronostic à long terme de cette maladie.

PREVALENCE

TTP, also named 'ampulla' cardiomyopathy or 'transient left ventricular apical ballooning', was first described in 1991 in an English abstract of a Japanese article (8). Similar clinical presentations were also reported as "human stress cardiomyopathy" (9,10), "stress-induced myocarditis" (11), "anteroapical stunning" (12) and "reversible myocardial contraction abnormalities with an acute noncardiac illness" (13-15). To establish the diagnosis of TTP, other conditions such as coronary disease, pheochromocytoma, subarachnoid hemorrhage, subdural hematoma and acute myocarditis must be excluded (1,16-18). TTP has been reported in Japan in more than 300 patients, including six large case studies (Table 1) (19-24). In North America, TTP has been reported in 81 patients, including four larger studies (25-28). In Europe, TTP has been reported in 47 patients, including two larger studies (2,29). Recently, TTP cases have been reported in Latin America (30) and Russia (31). The prevalence of TTP among cases of acute coronary syndrome or myocardial infarction is listed in Table 2.

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TABLE 1
Characteristics of patients with tako-tsubo-like left ventricular dysfunction

Characteristics	Country (reference)								
	Japan (19)	Japan (20)	Japan (21)	United States (25)	Belgium (29)	Japan (22)	Japan (23)	Japan (24)	Germany (2)
Patients, n	88	30	17	16	13	9	7	16	25
Demographics									
Mean age, years	67	70	74	71	62	66	75	66	69
Women, %	86	93	82	100	92	89	86	88	92
Cardiovascular risk factors, %									
Arterial hypertension	48	40	18	NI	NI	44	71	NI	76
Diabetes mellitus	12	7	0	NI	NI	11	NI	NI	10
Smoking	NI	NI	6	NI	NI	NI	NI	NI	18
Hyperlipidemia	24	NI	18	NI	NI	11	57	NI	36
Precipitating events, %									
Preceding emotional stress	20	17	24	38	23	22	14	44	60
Preceding physical stress	43	17	77	44	46	33	71	NI	64
Symptoms, %									
Chest pain	67	67	53	69	62	33	71	63	72
Dyspnea	7	20	NI	25	39	56	29	NI	24
Syncope	NI	7	NI	6	0	11	29	6	4
Electrocardiogram findings, %									
ST elevation	90	100	82	81	46	100	86	63	76
T wave inversion	83	43	100	100	100	100	100	100	92
Cardiac enzymes, %									
Elevated cardiac enzymes	56	NI	NI	100	100	89	86	NI	92
Complications in the acute phase, %									
Arrhythmias	27	3	NI	NI	NI	NI	71	NI	12
Heart failure	22	3	NI	44	46	NI	29	NI	8
Ventricular thrombus	NI	NI	NI	NI	NI	NI	0	NI	4
Transient left ventricular pressure gradient	18	NI	NI	13	15	NI	NI	19	8
In-hospital mortality	1	0	0	0	8	0	0	6	4

NI No information

CLINICAL PRESENTATION

Symptoms of TTP include anginal chest pain, dyspnea and syncope (Table 1). TTP occurs frequently after acute emotional or physical stress (Table 3).

In the acute phase of TTP, pulmonary edema (eventually leading to respiratory failure), cardiogenic shock, ventricular tachycardia, ventricular fibrillation, atrial fibrillation with a high ventricular response, bradycardia, left ventricular rupture, ventricular septal perforation, and left ventricular thrombus formation with subsequent stroke or renal infarction have been reported (Table 1) (2,19,20,23,25,26,32-39).

The reported prevalence of the cardiovascular risk factors of arterial hypertension, hyperlipidemia, diabetes mellitus and smoking in TTP is provided in Table 1. Additional cardiovascular disorders include previous cerebral infarction (23), syncope of unknown origin (23), sick sinus syndrome (23,40), chronic or paroxysmal atrial fibrillation (22,23,40-42), aortic regurgitation due to a bicuspid aortic valve (32) and angina pectoris (22).

Other underlying disorders reported in patients with TTP include depression (23,43,44), dementia (23), chronic emphysema (23), chronic obstructive pulmonary disease (20,43), hyperthyroidism (20,42), retroperitoneal fibrosis (45), Shy-Drager syndrome (40), hypokalemia-related myopathy (46), Guillain-Barré syndrome (47,48), myasthenia gravis (49), syndrome malin (44), amyotrophic lateral sclerosis (50), metabolic myopathy (51), Parkinson's disease (44), neurosis (22), pulmonary fibrosis (22), alcoholism (22,46), acute renal failure

(22), hepatic cirrhosis (52), chronic pancreatitis (52), rheumatoid arthritis (20) and dysphagia (53).

LABORATORY FINDINGS

ECG changes in the acute phase include ST elevation in leads V_4 to V_6 more often than in leads V_1 to V_3 (Table 1), which may be present for only several hours. The ST segment then normalizes, and is followed by the development of negative T waves in V_1 to V_6 , I and aVL that persist for weeks to months. The QT interval is initially often prolonged and may shorten only after weeks (5,6,20,21,26,29,35,54). ST depression and Q wave development rarely occur (2,19,23).

Serum levels of creatine kinase, creatine kinase (muscle and brain) and troponin may be normal or only slightly elevated, and are unexpectedly low in view of the extent of myocardial akinesia seen in an acute phase (Table 1). The increase in plasma brain natriuretic peptide levels can be observed in the acute phase (55). In a study of 10 TTP patients, a correlation between the degree of basal hyperkinesia and plasma brain natriuretic peptide levels was found (56).

Echocardiography shows apical ballooning of the left ventricle and hypercontraction of the basal segments. The akinesia is more extensive than the area supplied by any one coronary vessel (21). Occasionally, a left ventricular intraventricular gradient with high velocity in the basal segments may be detected (12,41). The apical ballooning regresses during follow-up, and normalization of the echocardiogram is usually seen within four to eight weeks. Coronary angiography shows

TABLE 2
Prevalence of tako-tsubo-like left ventricular dysfunction phenomenon (TTP) in patients undergoing coronary angiography

Country (reference)	Cohort	Patients with TTP	Patients investigated	Prevalence, %
Japan (8)	AMI	5	415	1.2
Japan (55)	AMI	13	637	2.0
Japan (70)	ACS	10	573	1.7
Japan (54)	ACS	10	450	2.2
Germany (2)	ACS	25	1085	2.3
				6.0 (women)
				0.3 (men)
United States (25)	ACS	16	NA	2.2

ACS Acute coronary syndrome; AMI Acute myocardial infarction; NA Not available

no significant coronary stenoses, but ventriculography shows apical ballooning of the left ventricle and hypercontraction of the basal segments (2,19,23). As seen on echocardiography, the akinesia is more extensive than the area supplied by one coronary vessel. Occasionally, a left ventricular intraventricular gradient may be detected (19,24,25,37,40). Coronary spasm may be visible on angiography, or may be provoked by acetylcholine or ergonovine administration in up to 80% of patients (8,19-22,24,40). Intravascular ultrasound (IVUS), performed on five consecutive TTP patients, showed a single, ruptured, atherosclerotic plaque in each patient in the middle portion of the left anterior descending coronary artery (57).

Myocardial biopsy has been performed in several cases with TTP and revealed unspecific findings such as adipose tissue, mild interstitial lymphoid infiltration, slight interstitial fibrosis, mildly atrophic myocardial fibres and small numbers of mononuclear cells (4,16,20-23,53).

SUGGESTED PATHOPHYSIOLOGICAL MECHANISMS

Increased catecholamine levels may be induced by physical or emotional stress, thereby leading to myocardial stunning via myocardial adrenoreceptors, as has been suggested by an animal model of TTP (58,59). A similar mechanism is hypothesized to occur in transient left ventricular dysfunction and ECG abnormalities which are found in patients with subarachnoid hemorrhage (18). It is possible that estrogen deficiency may enhance this reaction (60,61). The idea that TTP is related to a disturbance of cardiac sympathetic innervation is supported by scintigraphic findings. Perfusion defects in the anteroapical wall are detected by thallium-201 (^{201}Tl) myocardial scintigraphy without technetium-99m pyrophosphate uptake in the matching area; extensive perfusion defects are also detected around the apex by ^{123}I -iodine metaiodobenzylguanidine scintigraphy (42,44,46,47,55,62-64). When assessed semiquantitatively, the metaiodobenzylguanidine images had higher defect scores than those with ^{201}Tl scintigraphy during the acute phase, as well as throughout the following year.

It is not clear why the ventricular apex is selectively vulnerable and subsequently balloons, but anatomical and physiological factors may, in part, explain this phenomenon, in that the left ventricular apex does not have a three-layered myocardial structure (65). Moreover, in feline and canine hearts, the adrenoreceptor density and activity varies between the basal and apical segments (66-68).

TABLE 3
Emotionally and physically stressing conditions associated with tako-tsubo-like left ventricular dysfunction

Stressing condition	Reference
Emotional	
Acute psychosis	19
Death/funeral of family member	19-21,24-26,29,41,52,62
Diagnosis of cancer	12
Excessive alcohol consumption	19
Insomnia	32
Legal proceeding	25
Losing money in casino	25
Medical examination	21
Meeting involving a sexual harassment case	79
Near-drowning	19
Panic attack	19,26
Patient's dog caught in a raccoon trap	25
Public presentation	19-21
Quarrelling	12,19,21,43,52,62,79
Spouse leaving for war	25
Upsetting telephone call	54
Travelling	21
Physical	
Cerebral disorder	
Cerebrovascular accident	15,16,19,29
Epilepsy	15,19
Respiratory disorder	
Aspiration	54
Bronchial asthma	15,19,25,26,29,33
Nasal bleeding	54
Pneumonia	15,19,26,29,40,41
Pneumothorax	19,80
Pulmonary embolism	19,78
Thoracocentesis, lung biopsy	19,26
Tracheostomy, intubation, mechanical ventilation	19,26,50
Unusual physical stress	
Cold	23
Dancing	54
Delivery	19
Noncardiac surgery	15,19,25,33,45,77
Plasmapheresis	49
Traffic accident/external injury	19,21,29,34,70,79
Unusual effort	19,21,23,29,43,54
Metabolic disorder	
Acute renal failure, dialysis	19,25
Alcohol withdrawal	15,46
Diabetic coma	19
Hypoglycemia	19
Rhabdomyolysis	15,26,44
Sepsis	15
Cardiovascular disorder	
Aortic angiogram	26
Electrophysiological study	21
Peripheral embolism	19
Ventricular fibrillation/tachycardia	19,81
Gastrointestinal disorder	
Acute cholecystitis	19,25
Balloon-occluded retrograde transvenous obliteration of esophageal varices	52
<i>Clostridium difficile</i> colitis	25
Endoscopic retrograde cholangiopancreatography	52
Gastric endoscopy	33
Gastrointestinal bleeding	41
Intestinal perforation	25,55
Pancreatitis	19
Pain	
Bilateral leg numbness	55
Lumbago	70
Severe knee joint pain	55

Coronary vasospasm, induced by sympathetic discharge, is another hypothesis for the pathophysiology of TTP (8,19,69). One argument against this includes the observation that left ventricular dysfunction in TTP is not confined to the supply area of one coronary artery. Microvascular spasm is another possible mechanism for inducing myocardial ischemia in TTP (52,64,70-73). Investigations of TTP patients with technetium-99m tetrofosmin myocardial single photon emission computed tomography have documented a decreased uptake during the acute phase of TTP, suggesting that impaired coronary microcirculation may play a role in TTP (21,52,64,70). However, impaired coronary microcirculation could not be demonstrated by using a Doppler guidewire or contrast echocardiography in a further study (21).

Metabolic abnormalities in TTP have been detected by resting ^{201}Tl and ^{123}I -beta-methyl-*p*-iodophenyl pentadecanoic acid dual-isotope myocardial single photon emission computed tomography. The total defect score with ^{123}I -beta-methyl-*p*-iodophenyl pentadecanoic acid was greater than the reduced uptake with ^{201}Tl . This discrepancy improved gradually during follow-up. These findings suggest that in TTP, myocardial fatty acid metabolism is more severely impaired than myocardial perfusion (3,71).

An abnormally long course of the left anterior descending coronary artery, perfusing a relatively wide area including the anterior and apical segments, and part of the inferior area of the left ventricle, has been shown in single TTP cases, but this is not a consistent finding in all reported cases (57,69).

An acute coronary syndrome with early reperfusion and extensive left ventricular stunning is another theory of pathogenesis that is substantiated by IVUS findings (57). Because atherosclerotic plaques in elderly women are a rather unspecific finding when using IVUS, this hypothesis should be tested in a larger number of patients (74).

Myocarditis is an unlikely pathogenetic mechanism for TTP in the view of unspecific findings on myocardial biopsies (21,23), the lack of a preceding infection and the absence of markers of inflammation in most cases.

A further theory assumes that catecholamine-induced hyperkinesis of the basal segments may induce dynamic left ventricular outflow-tract obstruction, eventually leading to apical ballooning (41). A predisposition to left ventricular outflow-tract obstruction occurs in patients with a sigmoid interventricular septum and small left ventricular volumes. This left ventricular geometric configuration is predominantly found in elderly, hypertensive women. In the setting of adrenergic stimulation and/or hypovolemia, dynamic left ventricular outflow-tract obstruction may become manifest (75,76). As a consequence of obstruction, apical and anterior wall stress and left ventricular filling pressure increase, while systemic blood pressure decreases. Increased oxygen demand and reduced coronary perfusion pressure may combine to produce myocardial ischemia and stunning. This theory is supported by the high prevalence of arterial hypertension in TTP (Table 1). One argument against this is that an intraventricular gradient is not documented in all TTP patients. On the other hand, the time interval between the onset of TTP and the investigation for an intraventricular gradient varies considerably in reported cases (12,19,24,25,37,40,41). The role of hyperkinesis and development of an intraventricular gradient as a mechanism for TTP will only be clarified by studies that investigate those patients in the acute phase of TTP.

Studies that address a familial occurrence of TTP have not been performed. The occurrence of TTP in two sisters, however, may point to a potential genetic predisposition (43).

THERAPY

Patients with TTP should be monitored and managed in the same way as those who have suffered from a myocardial infarction. Mechanical ventilation may be necessary, given that up to 77% of these patients suffer from respiratory stress (26). Hemodynamic complications, such as cardiogenic shock and pulmonary edema, or arrhythmias, such as atrial fibrillation and torsade de pointes, should be treated as usual, such as with the use of intra-aortic balloon counterpulsation (12,19,23,25,29,53,77). Care should be taken in the administration of catecholamines and nitrates, especially if an intra-ventricular gradient is present, because both substances may further increase the gradient, aggravate the ballooning and lead to further hemodynamic deterioration (12,37,41,77). Whether anticoagulation should be administered in cases with large apical akinesia is controversial (32,38). Although no randomized studies are available, it seems reasonable to give beta-blockers to patients in the acute and chronic phases, and possibly indefinitely, to prevent recurrences (12,40). Implantation of a cardioverter defibrillator was reported in one patient in whom ventricular fibrillation may have induced TTP (23).

COURSE AND PROGNOSIS

Regression of the akinesia occurs after five to 40 days. Normalization of the ECG occurs after seven to 191 days, which is always later than the normalization of ventricular contraction. The prognosis of TTP is assumed to be good, but deaths due to multisystem organ failure, cardiogenic shock, ventricular fibrillation and ventricular rupture have been reported in the acute phase (37,38,78). Recurrences of TTP have been observed after eight months to six years (19,40).

There are only small series reporting on the long-term prognosis of TTP. One study of seven patients (23) reported that during a follow-up period of one to four years, one patient died from noncardiac causes two years after TTP. Another study of three patients (45) reported no cardiac events during a 12- to 18-month follow-up period, and the largest study of 72 TTP patients (19) observed one sudden death during a 13-month follow-up period. Another patient died suddenly three months after TTP (51).

CLINICAL IMPLICATIONS

Preliminary data confirm that TTP is not confined to Japan; the same prevalence has been observed in Western populations with acute coronary syndromes as that in Japan (Table 2). Reasons for missing the diagnosis of TTP include: a time delay between the acute event and cardiac catheterization; possible omission of ventriculography in cases with normal coronary angiograms; omission of echocardiography in the acute phase during which the akinesia occurred or of follow-up echocardiography to confirm the normalization of left ventricular dysfunction; and elderly women with acute coronary syndromes possibly undergoing coronary angiography less often than men.

TTP should be considered as a differential diagnosis in patients with acute coronary syndromes, especially women, and if the onset of symptoms was associated with emotional or physical stress. To detect TTP, ventriculography or echocardiography

should be performed in patients with acute chest pain, ECG changes and left ventricular akinesia, but with normal coronary arteries or only slight irregularities insufficient to explain the extent of akinesia. In patients with these indications, TTP should be considered, and follow-up studies by ECG and

echocardiography should be performed to confirm the diagnosis. During the acute phase of TTP, these patients need the same intensity of monitoring and therapy as patients with myocardial infarction. Because the long-term prognosis of TTP is largely unknown, follow-up studies are necessary.

REFERENCES

1. Abe Y, Kondo M. Apical ballooning of the left ventricle: A distinct entity? *Heart* 2003;89:974-6.
2. Schneider B, Stein J. Tako-tsubo-like transient left ventricular dysfunction: Prevalence and clinical findings in a western population. *Circulation* 2004;110(Suppl III):III-697. (Abst)
3. Oguri A, Uozumi H, Sawaki D, et al. ["Chestnut-shaped" transient regional left ventricular hypokinesis with abnormal myocardial fatty acid metabolism, not corresponding to the coronary artery territories: A case report.] *J Cardiol* 2004;43:273-80.
4. Shimizu M, Takahashi H, Fukatsu Y, et al. [Reversible left ventricular dysfunction manifesting as hyperkinesis of the basal and the apical areas with akinesis of the mid portion: A case report.] *J Cardiol* 2003;41:285-90.
5. Ogura R, Hiasa Y, Takahashi T, et al. Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: Comparison with the findings of acute anterior myocardial infarction. *Circ J* 2003;67:687-90.
6. Kurisu S, Inoue I, Kawagoe T, et al. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: Comparison with acute myocardial infarction with minimal enzymatic release. *Circ J* 2004;68:77-81.
7. Bybee KA, Kara T, Prasad A, et al. Systematic review: Transient left ventricular apical ballooning: A syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004;141:858-65.
8. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: A review of 5 cases.] *J Cardiol* 1991;21:203-14.
9. Cebelin MS, Hirsch CS. Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. *Hum Pathol* 1980;11:123-32.
10. Pavin D, Le Breton H, Daubert C. Human stress cardiomyopathy mimicking acute myocardial syndrome. *Heart* 1997;78:509-11.
11. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 18-1986. A 44-year-old woman with substernal pain and pulmonary edema after severe emotional stress. *N Engl J Med* 1986;314:1240-7.
12. Villareal RP, Achari A, Wilansky S, Wilson JM. Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc* 2001;76:79-83.
13. Pajouh M, Bahler RC. Hyperacute respiratory failure causing transient left ventricular dysfunction. *Am J Med* 2004;116:784-5. (Lett)
14. Levine GN, Powell C, Bernard SA, Sherman D, Faling LJ, Davidoff R. Acute, reversible left ventricular dysfunction in status asthmaticus. *Chest* 1995;107:1469-73.
15. Sharkey SW, Shear W, Hodges M, Herzog CA. Reversible myocardial contraction abnormalities in patients with an acute noncardiac illness. *Chest* 1998;114:98-105.
16. Ohtsuka T, Hamada M, Kodama K, et al. Images in cardiovascular medicine. Neurogenic stunned myocardium. *Circulation* 2000;101:2122-4.
17. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: Neurogenic stunned myocardium. *J Am Coll Cardiol* 1994;24:636-40.
18. Birns J, Sabharwal N, Senior R. Diagnosis of subarachnoid hemorrhage indicated by transthoracic echocardiography. *J Am Soc Echocardiogr* 2003;16:995-8.
19. Tsuchihashi K, Ueshima K, Uchida T, et al; Angina Pectoris-Myocardial Infarction Investigations in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol* 2001;38:11-8.
20. Kurisu S, Sato H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: A novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002;143:448-55.
21. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol* 2003;41:737-42.
22. Kawai S, Suzuki H, Yamaguchi H, et al. Ampulla cardiomyopathy ('Takotsubo' cardiomyopathy) – reversible left ventricular dysfunction: With ST segment elevation. *Jpn Circ J* 2000;64:156-9. (Erratum in 2000;64:237).
23. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. *QJM* 2003;96:563-73.
24. Yamasa T, Ikeda S, Ninomiya A, et al. Characteristic clinical findings of reversible left ventricular dysfunction. *Intern Med* 2002;41:789-92.
25. Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol* 2004;94:343-6.
26. Seth PS, Aurigemma GP, Krasnow JM, Tighe DA, Untereker WJ, Meyer TE. A syndrome of transient left ventricular apical wall motion abnormality in the absence of coronary disease: A perspective from the United States. *Cardiology* 2003;100:61-6.
27. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539-48.
28. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472-9.
29. Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: First series in white patients. *Heart* 2003;89:1027-31.
30. Gaspar J, Gomez Cruz RA. [Tako-tsubo syndrome (transient antero-apical dyskinesia): First case reported in Latin America and review of the literature.] *Arch Cardiol Mex* 2004;74:205-14.
31. Dupliakov DV. [Ball-shaped spherical dilation of the left ventricular apex or "Takotsubo" cardiomyopathy.] *Kardiologia* 2004;44:97-9.
32. Sasaki N, Kinugawa T, Yamawaki M, et al. Transient left ventricular apical ballooning in a patient with bicuspid aortic valve created a left ventricular thrombus leading to acute renal infarction. *Circ J* 2004;68:1081-3.
33. Kurisu S, Inoue I, Kawagoe T, et al. Left ventricular apical thrombus formation in a patient with suspected tako-tsubo-like left ventricular dysfunction. *Circ J* 2003;67:556-8.
34. Pereira Moral JR, Segovia Cubero J, Oteo Dominguez JE, Ortiz Oficialdegui P, Fuentes Manso R, Martin Judez V. [A case of transient left ventricular apical ballooning with an unusual complication.] *Rev Esp Cardiol* 2002;55:1328-32.
35. Matsuoka K, Nakayama S, Okubo S, Fujii E, Uchida F, Nakano T. Transient cerebral ischemic attack induced by transient left ventricular apical ballooning. *Eur J Intern Med* 2004;15:393-5.
36. Barrera-Ramirez CF, Jimenez-Mazuecos JM, Alfonso F. Apical thrombus associated with left ventricular apical ballooning. *Heart* 2003;89:927.
37. Matsuoka H, Kawakami H, Koyama Y, et al. "Takotsubo" cardiomyopathy with a significant pressure gradient in the left ventricle. *Heart Vessels* 2000;15:203.
38. Akashi YJ, Tejima T, Sakurada H, et al. Left ventricular rupture associated with takotsubo cardiomyopathy. *Mayo Clin Proc* 2004;79:821-4.
39. Sakai K, Ochiai H, Katayama N, et al. Ventricular septal perforation in a patient with takotsubo cardiomyopathy. *Circ J* 2005;69:365-7.
40. Kyuma M, Tsuchihashi K, Shinshi Y, et al. Effect of intravenous propranolol on left ventricular apical ballooning without coronary artery stenosis (ampulla cardiomyopathy): Three cases. *Circ J* 2002;66:1181-4.
41. Barriales Villa R, Bilbao Quesada R, Iglesias Rio E, Bayon Meleiro N, Mantilla Gonzalez R, Penas Lado M. [Transient left ventricular apical ballooning without coronary stenoses syndrome: Importance of the intraventricular pressure gradient.] *Rev Esp Cardiol* 2004;57:85-8.
42. Miyazaki S, Kamiishi T, Hosokawa N, et al. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy associated with hyperthyroidism. *Jpn Heart J* 2004;45:889-94.

43. Pison L, De Vusser P, Mullens W. Apical ballooning in relatives. *Heart* 2004;90:e67.
44. Kawabata M, Kubo I, Suzuki K, Terai T, Iwama T, Isobe M. 'Tako-tsubo cardiomyopathy' associated with syndrome malin: Reversible left ventricular dysfunction. *Circ J* 2003;67:721-4.
45. Glöckner D, Dissmann M, Behrens S. [Atypical acute myocardial ischemia syndrome with reversible left ventricular (LV) wall motion abnormalities ("apical ballooning") without significant coronary artery disease.] *Z Kardiol* 2004;93:156-61.
46. Suzuki K, Osada N, Akashi YJ, et al. An atypical case of "takotsubo cardiomyopathy" during alcohol withdrawal: Abnormality in the transient left ventricular wall motion and a remarkable elevation in the ST segment. *Intern Med* 2004;43:300-5.
47. Iga K, Himura Y, Izumi C, et al. Reversible left ventricular dysfunction associated with Guillain-Barré syndrome – an expression of catecholamine cardiotoxicity? *Jpn Circ J* 1995;59:236-40.
48. Hiraga A, Nagumo K, Suzuki K, Sakakibara Y, Kojima S. [A patient with Guillain-Barré syndrome and recurrent episodes of ST elevation and left ventricular hypokinesis in the anterior wall.] *No To Shinkei* 2003;55:517-20.
49. Arai M, Ukigai H, Miyata H. [A case of transient left ventricular ballooning ("takotsubo"-shaped cardiomyopathy) developed during plasmapheresis for treatment of myasthenic crisis.] *Rinsho Shinkeigaku* 2004;44:207-10.
50. Takayama N, Iwase Y, Ohtsu S, Sakio H. ["Takotsubo" cardiomyopathy developed in the postoperative period in a patient with amyotrophic lateral sclerosis.] *Masui* 2004;53:403-6.
51. Stöllberger C, Huber JO, Valentin A, Finsterer J, Slany J. Kardiogener Schock durch Takotsubo-Syndrom bei einer beatmeten Patientin mit neuromuskulärer Erkrankung. *Wien Klin Wochenschr* 2005;117:A10. (Abst)
52. Ito K, Sugihara H, Kawasaki T, et al. Assessment of ampulla (takotsubo) cardiomyopathy with coronary angiography, two-dimensional echocardiography and ^{99m}Tc-tetrofosmin myocardial single photon emission computed tomography. *Ann Nucl Med* 2001;15:351-5.
53. Nyui N, Yamanaka O, Nakayama R, Sawano M, Kawai S. 'Tako-tsubo' transient ventricular dysfunction: A case report. *Jpn Circ J* 2000;64:715-9.
54. Matsuoka K, Okubo S, Fujii E, et al. Evaluation of the arrhythmogeneity of stress-induced "takotsubo cardiomyopathy" from the time course of the 12-lead surface electrocardiogram. *Am J Cardiol* 2003;92:230-3.
55. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K. 123I-MIBG myocardial scintigraphy in patients with "takotsubo" cardiomyopathy. *J Nucl Med* 2004;45:1121-7.
56. Akashi YJ, Musha H, Nakazawa K, Miyake F. Plasma brain natriuretic peptide in takotsubo cardiomyopathy. *QJM* 2004;97:599-607.
57. Ibanez B, Navarro F, Cordoba M, M-Alberca P, Farre J. Tako-tsubo transient left ventricular apical ballooning: Is intravascular ultrasound the key to resolve the enigma? *Heart* 2005;91:102-4. (Lett)
58. Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: A possible animal model of 'tako-tsubo' cardiomyopathy. *Circ J* 2002;66:712-3.
59. Ueyama T, Senba E, Kasamatsu K, et al. Molecular mechanism of emotional stress-induced and catecholamine-induced heart attack. *J Cardiovasc Pharmacol* 2003;41(Suppl 1):S115-8.
60. Ueyama T, Hano T, Kasamatsu K, Yamamoto K, Tsuruo Y, Nishio I. Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of tako-tsubo (ampulla) cardiomyopathy. *J Cardiovasc Pharmacol* 2003;42(Suppl 1):S117-9.
61. Ueyama T. Emotional stress-induced tako-tsubo cardiomyopathy: Animal model and molecular mechanism. *Ann NY Acad Sci* 2004;1018:437-44.
62. Owa M, Aizawa K, Urasawa N, et al. Emotional stress-induced 'ampulla cardiomyopathy': Discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. *Jpn Circ J* 2001;65:349-52.
63. Moriya M, Mori H, Suzuki N, Hazama M, Yano K. Six-month follow-up of takotsubo cardiomyopathy with I-123-beta-methyl-iodophenyl pentadecanoic acid and I-123-meta-iodobenzyl-guanidine myocardial scintigraphy. *Intern Med* 2002;41:829-33.
64. Doue T, Ito K, Yuba T, et al. [A case of "takotsubo" cardiomyopathy observed with myocardial scintigraphy from the acute phase.] *Kaku Igaku* 2002;39:511-8.
65. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45:248-63.
66. Mori H, Ishikawa S, Kojima S, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovasc Res* 1993;27:192-8.
67. Upsher ME, Weiss HR. Relationship between beta-adrenoceptors and coronary blood flow heterogeneity. *Life Sci* 1989;44:1173-84.
68. Lathers CM, Levin RM, Spivey WH. Regional distribution of myocardial beta-adrenoceptors in the cat. *Eur J Pharmacol* 1986;130:111-7.
69. Inoue F, Takaoka M, Kumura H, et al. [So-called "ampulla" cardiomyopathy associated with coronary vasospasm compared with acute myocardial infarction showing similar abnormal left ventricular wall motion: Two case reports.] *J Cardiol* 2002;39:29-38.
70. Ito K, Sugihara H, Katoh S, Azuma A, Nakagawa M. Assessment of takotsubo (ampulla) cardiomyopathy using ^{99m}Tc-tetrofosmin myocardial SPECT – comparison with acute coronary syndrome. *Ann Nucl Med* 2003;17:115-22.
71. Kurisu S, Inoue I, Kawagoe T, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* 2003;41:743-8.
72. Ako J, Kozaki K, Yoshizumi M, Ouchi Y, Tsuchihashi K. Transient left ventricular apical ballooning without coronary artery stenosis: A form of stunning-like phenomenon? *J Am Coll Cardiol* 2002;39:741-2.
73. Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998;351:1165-9.
74. Briguori C, Tobis J, Nishida T, et al. Discrepancy between angiography and intravascular ultrasound when analysing small coronary arteries. *Eur Heart J* 2002;23:247-54.
75. Come PC, Bulkley BH, Goodman ZD, Hutchins GM, Pitt B, Fortuin NJ. Hypercontractile cardiac states simulating hypertrophic cardiomyopathy. *Circulation* 1977;55:901-8.
76. Sandstede J, Lipke C, Beer M, et al. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol* 2000;10:438-42.
77. Nagao T, Ohwada T, Hashimoto M, Aoki K, Shimizu H, Katayama M. [Intra-aortic balloon pumping is effective for hemodynamic management of catecholamine resistant ampulla (takotsubo) cardiomyopathy.] *Masui* 2004;53:799-802.
78. Kai R, Yasu T, Fujii M, et al. [Apical ballooning by transient left ventricular dysfunction (so-called "ampulla" cardiomyopathy) associated with therapy for acute pulmonary thromboembolism: A case report.] *J Cardiol* 2001;38:41-6.
79. Connelly KA, MacIsaac AI, Jelinek VM. Stress, myocardial infarction, and the "tako-tsubo" phenomenon. *Heart* 2004;90:e52.
80. Akashi YJ, Sakakibara M, Miyake F. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy associated with pneumothorax. *Heart* 2002;87:e1.
81. Akashi YJ, Nakazawa K, Kida K, et al. Reversible ventricular dysfunction (takotsubo cardiomyopathy) following polymorphic ventricular tachycardia. *Can J Cardiol* 2003;19:449-51.