STRESS INDUCED MYOCARDIAL STUNNING: TAKOTSUBO SYNDROME

YUSUF HASSAN, M.D.

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Yusuf Hassan, M.D.,
Faculty Veterans Affairs Medical Center Dallas,
Assistant Professor of Medicine, Division of General Internal Medicine
University of Texas Southwestern Medical Center at Dallas, Texas

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Takotsubo Cardiomyopathy

Introduction

In 1990 Satoh and colleagues described a syndrome consisting of an acute onset of transient extensive akinesia of the apical and mid portions of the left ventricle without significant epicardial coronary artery stenosis, accompanied by chest pain, ECG changes and minimal enzymatic release, associated with stress. *Satoh H, et al, Takotsubo type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Han M, et al. [Clinical aspect of myocardial injury: from ischemia to heart failure] (Japanese). Tokyo: Kagakuhyouronsya, 1990:56-64.*
Cases of stress-induced cardiomyopathy have been described for a long time. Some of the earliest reports are from Japan. In 1991 Satoshi Kurisu MD and colleagues proposed the term "tako-tsubo-like left ventricular dysfunction". Because the echocardiographic appearance of a round bottom and narrow neck: resembling a pot used to trap octopuses in Japan- Tako means octopus and Tsubo means pot. [2]
The striking predilection for Japanese patients in literature and the largely anecdotal case reports from other parts of the world initially suggested a unique geographic and/or racial distribution, with origin in Asian culture. Indeed, this cardiomyopathy has yet to achieve recognition within the greater physician community in most parts of the world. [3]

The common theme in all these cases is a reversible left ventricular dysfunction, EKG changes, and coronary catheterization showing normal coronaries or very minimal coronary atherosclerotic disease, minimal elevation of cardiac enzymes and at least in reported cases, a good prognosis with a low risk of recurrence.
The purpose of this discussion is to firstly define typical cases. Go over some of the epidemiologic features of this syndrome. Try to assess the frequency and prevalence of this disorder. Highlight and present examples of typical clinical features, laboratory abnormalities and echocardiographic and catheterization findings of this disease. Talk about the pathophysiology and mechanism of this disease. Assess the available data and to figure out ways of studying this disorder in the future.

Case 1

A 44 years old woman was admitted to hospital with chest pain. Her symptoms started after she was informed that her 17 years old son has committed suicide. The pain was severe "crushing" and substernal with radiation to the left shoulder. The pain persisted for six hours and she was taken to the hospital.
In the emergency room pain was not relieved after three sublingual nitroglycerin tablets. EKG was unchanged from a routine tracing several months earlier. Her blood pressure was recorded to be 70/60. Normal saline was given intravenously improving the blood pressure to 120/80. Blood pressure decreased to 80/60 again after administration of lidocaine for ventricular ectopy. Aggressive fluid resuscitation with two and a half liters of normal saline resulted in-patient developing pulmonary edema. She required inotropic support and the blood pressure improved to 130/80.
Her lab work showed AST of 89 U (normal, 7 to 39), LDH of 318 U (normal, 88 to 230), and a CK of 269 (normal, 20 to 191). Echocardiogram showed no evidence of chamber enlargement but global decrease in the left ventricular contractility that bordered on akinesia.

She was transferred to Mass General. Her coronary risk factors were hypercholesterolemia 15 years earlier and smoking. She had a positive family history of coronary artery disease, her mother died of a myocardial infarction at age 69. Her father was alive but had a myocardial infarction at a young

age. There was no history of toxic or chemical exposure, pregnancy or foreign travel. She drank seven bottles of beer a week
Her exam was significant now for a normal blood pressure of 110/70, pulse of 110, and S3 heard on auscultation of the heart. Routine laboratory findings including creatinine and urea were within normal limits. EKG now showed non-specific ST-T wave changes. Q waves were present in leads V1 and V2 and a delayed progression of R waves. CK was now 132U. Chest radiograph showed a complete resolution of pulmonary edema.
A coronary angiogram showed a complete normal left main, less than 40% narrowing in the mid right coronary. Left ventriculographic study showed apical and anterolateral akinetic area and a good basal contraction. The estimated ejection fraction was 34%.
A right ventricular endomyocardial biopsy at lower power showed foci of interstitial mononuclear-cell infiltration. On high power there was myocyte necrosis with focal interstitial mononuclear-cell infiltration.
Case Record of the Massachusetts General Hospital, NEJM May 8th, 1986 [1]

Case 2

62-year-old women presented with 24hours history of anterior chest pain and throat discomfort after an argument with her daughter. Physical exam showed tachycardia. An EKG showed diffuse symmetric T-wave inversion with prolonged QT (QTc of 570). During the next 12 hours she developed progressive cardiovascular compromise with hypotension and pulmonary edema. She needed initiation of intra-aortic balloon counter pulsation, and a dopamine infusion.
Echocardiogram showed anteroapical akinesis, systolic anterior motion of mitral valve, dynamic left ventricular outflow tract gradient of 40mmhg, with no other evidence of HOCM. The gradient improved after administration of 5mg of Metoprolol. She required intravenous fluids, and further support with intravenous Phenylephrine. She continued to receive beta-blockers. Cardiac enzymes were flat. Thallium scintigraphy showed no evidence of irreversible injury to the myocardium. There was no clinical evidence of sarcoidosis and myocarditis. Serial EKGs showed improvement of the above-mentioned changes. Coronary angiography showed minimal plaque in the left anterior descending artery. Left ventriculography confirmed severe anteroapical wall motion abnormality and pull back pressures registered an LVOT gradient of 44mmhg.
Patient gradually improved and a repeat echo after a month showed normalization of wall motion abnormality and the systolic function.

Jan 2001, Mayo Clinic [4]

Although initially described in Japan, and while it was thought earlier that this might be a geographically restricted syndrome. There is several case series now reported from the United States. A recent series described 22 patients with reversible cardiomyopathy triggered by psychologically stressful events occurring in older women and mimicking evolving acute myocardial infarction or coronary syndrome. These cases were seen over a period of two and a half years at the Minneapolis Heart Institute Foundation Minneapolis MN [3]
Another series reports 12 patients from University of Massachusetts Medical School, Worcester, Mass and University of Pennsylvania-Presbyterian Medical Center Pa, with "Takotsubo syndrome". The author concluded that it is possible that with a wide spread use of echocardiography, coupled with increased recognition of this syndrome will result in this diagnosis being made more commonly. [5]
Finally 19 patients from Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center in Baltimore were reported in *The New England Journal of Medicine, Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress, Wittstein et al, NEJM, Feb 10, 2005.* [6]

Prevalence:
The incidence of myocardial infarction with normal coronaries has been reported to be approximately 3%. [22] Studies from Japan indicate a prevalence of 1.5% among patients presenting with chest pain and ST elevation on electrocardiogram [7].
The syndrome accounted for 2.2% of all the ST elevation Myocardial Infarctions presenting to a referral hospital in the United States from 2002 to 2003, [30]
However since these numbers are based on case reports and case series, it is impossible to know the real prevalence of this disorder.

Clinical Presentation:
A Meta analysis by Kevin A. Bybee and colleagues of seven case series found that most of these patients are women (range, 82% to 100%). The mean age of patients presenting with the syndrome was 62 to 75 years (overall range 10 to 88 years) [9].
Most common presenting symptom is Chest pain at rest 33% to 71%. Shortness of breath is the second most common symptom and occasionally patients presented with syncope, [7] [9]

Preceding Stressors:

Most are associated with **emotional stress** ranging from death of a close relative to a surprise party to fear of public speaking. And there are many interesting stories of stress induced cardiomyopathy related to many diverse emotional stressors. [3] [6]
One such description is a quote from eighteenth century surgeon John Hunter "My life is at the mercy of any scoundrel who chooses to put me in a passion". [10]

But emotional stressors are not the only ones described in association with this syndrome, there are numerous case reports and series describing this syndrome in patients with more a **physiological** than an emotional stressor. In one series from Minneapolis Heart Institute 22 patients referred to cardiology service for consultation for electrocardiographic abnormalities or for hypotension, pulmonary edema, tachycardia, hypoxemia or a presence of a third heart sound on auscultation. These patients included patients with CNS injury n=6, sepsis n=3, acute pulmonary disease n=3, drug over dose or metabolic abnormalities n=7 and post surgical patients n=3. Not unlike patients with emotional stress these patients were also older average age 56.3 years, and although mostly women 82%, there were more men reported in this study. [11]

There are reports of occurrence of this form of cardiomyopathy associated with many other diseases including **subarachnoid hemorrhage;** seven patients with ST segment elevation without previous history of heart disease and normal coronaries on cardiac catheterization n=7, [42]
Status Asthmaticus, three cases of rapidly reversible severe myocardial depression are described. Ejection fraction was reduced to 11-34%. Follow up echo three to eight days later showed marked improvement of the left ventricular function. Two of these patients had no evidence of hypoxia; the third one was hypoxic and had a positive screen for cocaine. One patient had normal cath and a negative right ventricular biopsy. The other two had no history of coronary atherosclerotic disease. [13]
Anaphylaxis, profound reversible myocardial depression after anaphylaxis. *Lancet 1988; 1:386-388.* [14]

Pheochromocytoma, *reversibility of catecholamine cardiomyopathy in a child with pheochromocytoma. NEJM 1987; 316:793-97* [15]

Treatment of premature labor with β2-Sympathomimetics, pulmonary edema associated with β2-Sympathomimetic treatment of premature labor. *Anaesthesia Intensive Care 1984; 12:143-151* [16]

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. A 64 years old alcoholic was admitted for hypokalemia and muscle weakness. On the fifth hospital day he suffered a cardiopulmonary arrest for five minutes after he had demonstrated signs of alcohol withdrawal. EKG had demonstrated ST elevation in leads 1, aVL and V (2-6). An emergent cardiac catheterization showed normal coronaries. [17]

Reversible Cardiomyopathy as the Autonomic involvement of **neuroleptic malignant syndrome**, [18]

This syndrome has also been described in head trauma and post operatively in patients undergoing non cardiac surgery, and in patients with **laryngeal obstruction**.

Acute onset and aggravation of various systemic disorders (**cerebrovascular accident, epileptic attacks, exacerbation of bronchial asthma, acute abdomen**), **noncardiac surgery and emotional and physical problems** (sudden accidents, death/funeral of a family member, inexperienced exercise, quarreling or excessive alcohol consumption, vigorous exercise), have all been reported as triggering factors. [19]
The clinical features of the nineteen patients from Johns Hopkins are given in the following table [6]

Table 1. Clinical Characteristics of 19 Patients with Stress Cardiomyopathy on Admission.*

Patient No.	Age	Sex	Race or Ethnic Origin	Coronary Risk Factors	Emotional Stressor	Clinical Presentation			
						Time after Symptom Onset†	Heart Rate	MAP	Symptoms
	yr					*hr*	*beats/min*	*mm Hg*	
1	62	F	B	HTN, smoking	Mother's death	12	71	96	Chest pain
2	63	F	AA	HTN, Chol	Car accident	1	86	52	Heart failure; hypotension
3	48	F	W	HTN, Chol, smoking	Surprise reunion	4	85	88	Chest pain
4	60	F	W	HTN	Surprise party	2	109	53	Chest pain; hypotension (IABP)
5	66	F	W	HTN, FH	Father's death	5	63	91	Chest pain
6	77	F	W	HTN, FH	Husband's death	6	106	98	Chest pain
7	52	F	W	Smoking	Friend's death	2	92	50	Chest pain; hypotension (IABP)
8	52	F	W	HTN	Father's death	5	88	93	Chest pain
9	32	F	W	Chol, FH	Mother's death	1	74	90	Chest pain
10	61	F	W	Chol	Fear of procedure	1	108	45	Chest pain; shock (IABP)
11	66	F	W	Smoking	Fierce argument	2	66	109	Chest pain
12	87	F	W	HTN, Chol, DM	Friend's death	1	99	75	Chest pain
13	69	M	W	HTN, Chol	Court appearance	2	81	73	Chest pain
14	50	F	W	None	Fear of choking	2	84	100	Chest pain; heart failure
15	71	F	W	None	Public speaking	1	67	108	Chest pain
16	76	F	W	HTN, DM, smoking	Husband's death	2	109	101	Chest pain
17	65	F	W	HTN, Chol, smoking	Armed robbery	2	95	91	Chest pain
18	71	F	W	HTN	Son's death	6	70	66	Chest pain; VF
19	27	F	A	None	Tragic news	3	64	52	Chest pain; hypotension

* MAP denotes mean arterial pressure, B Bermudan, HTN hypertension, AA African American, Chol hypercholesterolemia, W white, IABP intraaortic balloon pump, FH family history, DM diabetes mellitus, VF ventricular fibrillation, and A African.
† Values are times from the onset of symptoms to presentation at the emergency department.

Typical Echocardiographic Abnormalities:

Left Ventricular Ejection Fraction

The median Left Ventricular Ejection Fraction was reported to 0.20, in the series from Hopkins, on the first day of admission. [6]

And it was 24±10 in the series reported from Minneapolis Heart Institute. [3]

Global left ventricular systolic function was abnormal in all but one patient in this series and the initial left ventricular function score was 3.0 (2.5, 4.0). [11]

Wall Motion Abnormality

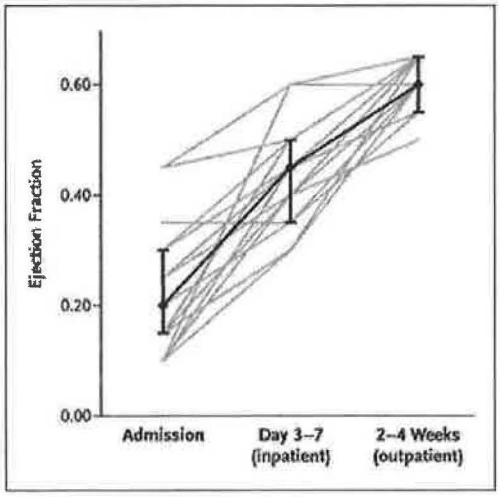
Echo done within an average of 1.6 days showed regional wall motion abnormalities involving the anterior wall and apex. The median initial anterior wall motion score was 2.6 (2.0, 3.0), while the median initial basal wall motion score was 1.0 (1.0, 2.0); this difference was significant (p less than 0.001). The initial basal wall motion was hyperkinetic in four of twenty two patients. [11]

Preserved basal function, moderate to severe dysfunction in the midventricle, and apical akinesis or dyskinesis was seen in the Hopkins series, (mean echocardiographic scores, 1.2+/-2, 3.2_+ 0.5, 3.7_+0.5, respectively. [6]

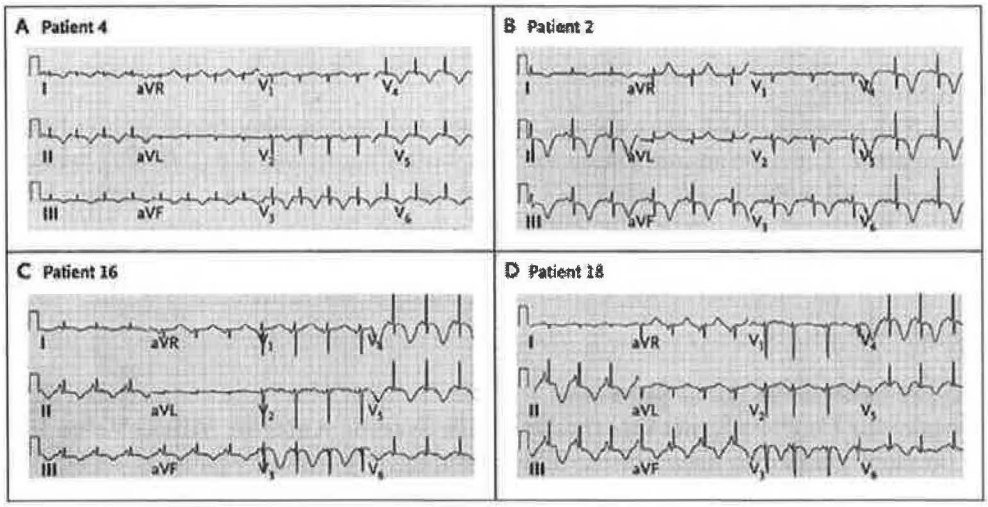
Normal or Hyper contractile Basal Segment

Dynamic Ventricular Outflow Tract Obstruction with Systolic Anterior Mitral Valve Motion, outflow tract pressure gradient is usually from 30 to 40mmhg, [4]. In some patients the outflow tract obstruction became apparent after initiation of Dobutamine and resolved with discontinuation of the drug. These patients are more likely to present with hypotension [3]. One series also reported appearance of a dynamic systolic murmur, which resolved after improvement in the echo appearance [4].

These echocardiographic findings improved almost universally in all patients within days. [6]



Electrocardiography Findings



The ECG changes observed in these patients (n=22) are of particular interest. Anterior ST-segment elevation consistent with epicardial injury was present in half of these patients. The majority of the patients had either anterior Q waves or poor R-wave progression followed by R-wave regrowth with improvement in wall motion on echo.

The most striking ECG finding was the gradual evolution of deep T-wave inversion and QT-interval lengthening in the precordial leads V2 to V5. Of note, T-wave inversion was also present in the limb leads (especially lead II) in the majority of patients.

Peak T wave inversion occurred, an average of 5 days (1 to 20 days) after admission. The peak T-wave inversion averaged -7.8 mm (range, -2 to -15 mm). Greatest T wave inversion was seen in V3 and V4.

Each patient also developed progressive lengthening of the QTc interval in those leads with T wave inversion. QTc lengthening occurred in parallel with T wave inversion. Maximum QTc prolongation occurred an average of 3.9 days (range 1 to 16 days) after admission. The maximum QTc interval averaged 600 ms (range, 500 to 730 ms). None of these patients developed torsades de pointes ventricular tachycardia.

This was a retrospective study where the patients were admitted for a non cardiac illness and were referred to cardiology consult service due to ECG abnormalities or clinical deterioration (hypotension, pulmonary edema, tachycardia, hypoxemia, or S3 gallop).

[11]

Common EKG findings included out of 22 consecutive patients

1) Convex ST- segment elevation (2 to 3 mm), usually in V1 to V3 (n=13), associated with T-Wave inversion in the same leads in 10 patients on admission and with evolution in three others

2) T-wave inversion (without ST elevation), usually in 1, avl, and precordial leads, and becoming more prominent and diffuse with time (n=5)
3) Absence of ST-segment and T-wave abnormalities (n=4), but presence of subsequent T-wave inversion in the precordial leads in 3 patients

Circulation Feb 1, 2005 [3]

Time course: ST elevation in inferior leads 11, 111, and aVL, and V3 to V6 continued and exacerbated within the first 24hour after admission, and continued for 48hour after the time of presentation and then evolved into deep inverted T waves which persisted for a month and then normalized [29].

Other observers have reported a more classical anterior wall myocardial infarction pattern with ST elevation almost diffusely with subsequent appearance of Q waves. [7]

The other common findings on EKG include prolonged PR interval in the 26% of patients, diffuse T wave inversion 16%, Pathological Q waves V1, V2 and V3 in 37% and in AVL in 26%. Within 48 hours 100% of patients had marked prolongation of QTc, median value 542 milliseconds, range 490 to 592. QTc prolongation was the first finding to resolve followed by the T wave inversion and, which only resolved partially and the pathological Q waves resolved before discharge with restoration of R wave progression. [6]

The ECG during the acute phase exhibited ST-segment elevation in leads II, III, and aVF in five of the ten patients; the precordial leads in 10 patients and leads I and aVL in seven. The follow-up ECGs exhibited obvious T-wave inversion. These changes persisted for more than several weeks range 43 to 400 days, although all patients had a normal left ventricular function within a few weeks (range 7 to 27 days).
The ECG in the subacute phase demonstrated a significantly long QT interval, QT dispersion, and TpTe dispersion, and the ECGs in the acute and chronic phases had significantly lower QT intervals. Despite these changes none of the patients experienced sudden death or malignant arrhythmias.
Reporalization dispersion, such as QT interval, which is a measure of the interlead QT variability reflects a regional variation in ventricular repolarization and may represent an electrophysiologic substrate for arrhythmias. And QT dispersion is influenced by the extent of myocardial damage. Takotsubo Cardiomyopathy is rarely associated with malignant arrhythmias. This may be because of a rapid recovery of the myocardium. Also the selective sparing of the base of the heart is thought to be partly the reason. [20]

Cardiac Catheterization

Cardiac catheterization confirms the echocardiographic findings of reduced left ventricular ejection fraction.

Left Ventricular Ejection Fraction,
Ranging from 15 to 40% *Sharkey et al, Circulation 2/1/2005* [3]
Ranging from 0.39 to 0.49 *Bybee et al, Annals 12/7/2004* [9]
Interquartile range of 0.15 to 0.30 *Wittstein et al, Nejm 2/10/2005* [6]
82% of patients had moderate to severe left ventricular impairment *Raymond JACC 03/1988: 471-477* [21]

Left Ventricular Wall Motion Abnormalities
Left ventriculography showed akinesis in the apical, diaphragmatic and anterolateral segments, and hyperkinesis in the basal segments. [7]

An analysis of left ventricular wall motion from the right anterior oblique left ventriculogram revealed a wall motion abnormality of the anterior wall and apex in all the 13 patients. This wall motion abnormality extended to involve the apical segment of the inferior wall in 12 of the 13 patients. [11]

Contrast enhanced left ventriculography revealed apical and midventricular akinesis or dyskinesia with normal contractility of the base. *Wittstein et al, Nejm 2/10/2005* [6]

All (22 patients) exhibited a large wall motion abnormality that involved akinesia or hypokinesia of the distal one half to two thirds of the LV chamber, which created a distinctive "apical ballooning" appearance associated with basal hyper contractility at end systole [3].

Coronary angiography
Coronary angiography invariably shows either normal or arteries with minimal disease. There have been some reports of coronary vasospasm at the time of angiography but these reports are an exception. 1/22 patients in *Sharkey et al, Circulation 2/1/2005* [3]

Provocative tests
Ergonovine has been used for diagnosing Prinzmetal Angina, and is very sensitive for diagnosing this disorder, Braunwald Text Book of Cardiology. Provocative tests have been done using ergonovine in 16 of 74 patients and showed abnormal results in 5 of 16 patients. [21]
In subacute period (24±11days; range 13 to 53 days) vasospasm was assessed in 48 of 88 patients by using intracoronary acetylcholine administration, and demonstrated vasospasm in 10/48 patients [19].
Induction of coronary vasospasm by acetylcholine was negative in all four patients. One of the four received the provocation on the first hospital day, and the other three cases underwent this test during the second catheterization and none of them entered a vasospastic state [7]

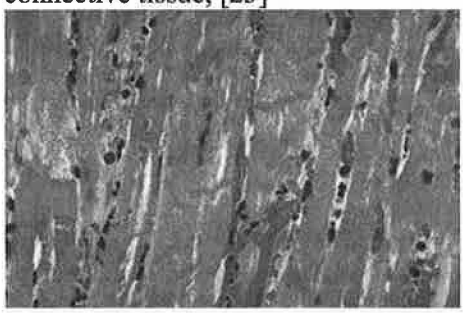
The coronary spasm provocation test was positive in 10 of thirty patients, with four having a single coronary artery spasm and six had multivessel spasm. [23]

Transient Intraventricular Pressure Gradient

3/3 patients in the case series from *Rollo P. Vallareal mayo clinic proceeding 2001; 76:79-83* showed a pressure gradient varying form 40 to 64 mmHg.
A transient, dynamic intraventricular pressure gradient due to obstruction in the left ventricular cavity can develop as a result of dyskinetic apical and mid-ventricular segments with hyperdynamic function of the basal segments. This complication is documented in 13 to 18% of the patients and can be accompanied by mitral regurgitation due to systolic anterior motion of the mitral valve leaflets and chordal apparatus. [9]
In acute phase 12 of the 72 patients had a significant intraventricular pressure gradient of greater than 30 mm Hg. However no patient exhibited residual pressure gradient in subacute period. [19]

Endomyocardial Biopsy

Of the five patients who underwent biopsy four had interstitial infiltrates consisting primarily of mononuclear lymphocytes and macrophages and contraction bands without myocyte necrosis. The other patient had an extensive inflammatory lymphocytic infiltrate and multiple foci of contraction band myocyte necrosis. [6]
Four studies reported endomyocardial biopsy results in the acute phase of the syndrome n=18, with no evidence of myocarditis [9].
Two endocardial biopsies from the right ventricle showed slight microscopic interstitial fibrosis. [29]
Endomyocardial biopsy was performed in 3 patients. Microscopic examination of the specimen revealed focal myocytolysis, mild mononuclear cell infiltration, or slight increase of loose connective tissue, [23]



Contraction Band Fibrosis, Zugibe et al 1998 p.142 [77]

Autopsy Findings

A 33 years old patient died suddenly while running a marathon ten years after his initial presentation with stress cardiomyopathy. His autopsy revealed anterior wall myocardial fibrosis, septal aneurysm and normal coronaries without any evidence of a myocardial infarction. [21]

Cardiac Magnetic Resonance Imaging

CMR was performed within 5 days in 21 of 22 patients in the series from Minneapolis Heart Institute, and in 13 days in the one remaining patient. Delayed gadolinium hyper enhancement was not present in 21 of the 22 patients, consistent with viable myocardium and the absence of myocardial scar and infarction. One patient who presented in cardiac arrest, showed hyper enhancement confined to the LV apex, which represented a small infarct. LV wall-motion abnormalities were virtually confined to the midventricular and distal segments of the LV. In 20 of the 21 patients with early post event CMR, abnormal regional wall motion affected areas of the LV involving multiple vascular territories, more than one territory in 95% and all the three vessels in 90%. [3]
In five (n=19) patients from the Hopkins series, who underwent cardiac MRI cine studies confirmed the pattern and degree of left ventricular dysfunction seen on echocardiography. None of the patients had evidence of myocardial necrosis on contrast-enhanced imaging. [6]

Table 3. **Proposed Mayo Criteria for the Clinical Diagnosis of the Transient Left Ventricular Apical Ballooning Syndrome***

1. Transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3. New electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion)
4. Absence of
   - Recent significant head trauma
   - Intracranial bleeding
   - Pheochromocytoma
   - Obstructive epicardial coronary artery disease
   - Myocarditis
   - Hypertrophic cardiomyopathy

* All 4 criteria must be met.

Bybee et al Annals of Internal Medicine 12/7/2004, Volume 141. Number 11 [9]

Management

Acutely patients were treated according to established guidelines for ST-elevation myocardial infarction or acute coronary syndrome with combinations of negative inotropic agents (beta-blockers, orally or intravenously), aspirin, nitrates (sublingual or intravenous), and heparin. Vasopressor agents (e.g., dobutamine and dopamine) were administered to 8 patients with marked hypotension to sustain cardiac output and systemic blood pressure; 4 of these patients also required mechanical and hemodynamic support with intra-aortic balloon counter pulsation (for 1 to 2 days). One received thrombolytics and two received IIb/IIIa antagonists because of clinical interpretation of an ST-elevation myocardial infarction. Patients were discharged and maintained on medications, including ace inhibitors or Angiotensin Receptor Blockers n=14, beta blockers n=11 and calcium antagonists n=3. Of the 22 patients 19 were taking ACE inhibitors/ Angiotensin Receptor Blockers, beta blockers or both after hospital discharge.
Eight patients with hemodynamic compromise showed higher peak troponin values and lower initial ejection fraction. (24% vs. 31%). [3]

The authors of the Hopkins series concluded, "the treatment of stress cardiomyopathy beyond standard supportive care for congestive heart failure with diuretics and vasodilators remains largely empirical. Because our data implicate massive catecholamine release in stress-induced myocardial stunning, we avoid using pressors and beta-agonists whenever possible and rely on mechanical circulatory support in patients with severe hemodynamic compromise". [6]

Left ventricular asynergy completely improved without any specific treatment, such as administration of digitalis, angiotensin converting enzyme inhibitors or Beta-Blockers, but assisted circulation during the acute phase was useful. [29]

PROGNOSIS:

Short-Term Follow-up

Each of the 22 patients survived their acute event. In 21 patients hospital discharge was prompt (6±3 days), at which time functional status had recovered and was restored to asymptomatic pre-event levels. One patient had cardiac arrest and had reversible anoxic encephalopathy. Other in hospital complications were transient conduction abnormalities, including complete heart block n=1, left anterior hemiblock, or posterior hemiblock n=2, paroxysmal atrial fibrillation n=2, and a small left ventricle apical thrombus. Left ventricular ejection fraction improved rapidly returning to a normal range, assessed by CMR or 2D echocardiography, during the recovery 24±29 days after admission and as early as five days or less in 7 patients.

Long-Term Follow-Up

Complications and risk of relapse

"Six years before the present admission, one patient had been hospitalized abroad for a similar clinical syndrome of cardiogenic shock with extensive anteroapical akinesia for which intra-aortic balloon counter pulsation was needed. Coronary angiography and left ventriculography four weeks after the acute episode were completely normal". Another patient presented five months after her ventricular fibrillation with apical ballooning, with vague chest complaints and deep negative T waves in the anterior leads. Coronary angiogram was again normal, and the complaints did not recur in the following three months. *We considered this episode to be "aborted" apical ballooning* [26].

Two patients in this series required hemodynamic support for 3 days. Several patients experienced episodes of non-sustained ventricular tachycardia, n=3, paroxysmal atrial fibrillation n=2.
One patient had repeated episodes of syncope. The cause of syncope was diagnosed on ECG monitoring to be ventricular tachycardia with a short coupled ventricular premature beat. She received an implantable cardioverter defibrillator.
During a follow up period varying from one to four years, one patient died from non-cardiac cause, two years after the episode of cardiomyopathy, and the other six did not have any cardiac events. (Total number of patients in the study 7). [9]

Each of the 22 patients was living 12±10 months (range 1 to 32 months) after their initial cardiac event; 20 experienced virtually complete recovery with normal activity, whereas two patients continued to have chest pain. And another two patients survived a second similar clinical event triggered by psychological stress three and ten months after the first occurrence, respectively; at the time of the second event, one was on aspirin and a Statin drug, and the other patient was taking a beta blocker and calcium channel blocker, and aspirin, statin, ace inhibitor and sublingual nitroglycerin [3].
The overall prognosis of patients presenting with the syndrome seems to be favorable; reported in-hospital mortality rates range from 0% to 8%. The largest series, which included 88 patients, reported an in-hospital mortality rate of 1%. [19]
Pulmonary edema or significant left-sided heart failure during the acute phase was reported in 3% to 46% of patients, and some patients required insertion of an intra-aortic balloon pump. [9]

"When medical support is provided initially, patients with stress cardiomyopathy have rapid clinical and echocardiographic improvement and have an excellent prognosis. In the four years that we have followed these patients, none have died, had a recurrence, or had a decline in left ventricular function". [6]

Pathogenesis:

Catecholamine and Stunned Myocardium

Patients in the Hopkins series had day 1 or 2, plasma levels of catecholamine (i.e., epinephrine, nor epinephrine, and dopamine) among patients with stress cardiomyopathy compared with seven patients with Killip class III myocardial infarction, and "similar clinical presentations and were expected to have high sympathetic tone". These values in the stress cardiomyopathy group were two to three times the values in the patients with myocardial infarction and 7 to 34 times published normal values. Initial levels of plasma dihydroxyphenylalanine, dihydroxyphenylglycol, and dihydroxyphenylacetic acid among patients with stress cardiomyopathy were approximately twice the values among patients with myocardial infarction and two to three times the normal values, consistent with the presence of enhanced catecholamine synthesis, neuronal reuptake, and neuronal metabolism, respectively.

Plasma levels of metanephrine and normetanephrine, which are extraneuronal catecholamine metabolites, were also proportionately increased. Plasma levels of neuropeptide Y, which is stored with catecholamine in postganglionic sympathetic nerves and adrenal chromaffin cells and released during stress, was markedly, increased among patients with stress cardiomyopathy, as were plasma levels of brain natriuretic peptide and serotonin.

By hospital 7, 8, or 9, plasma levels of most catecholamine, neuronal metabolites, and neuropeptides in patients with stress cardiomyopathy were one third to one half of the peak values but remained substantially higher than those in patients with myocardial infarction.

"Our data suggest the activation of the adrenomedullary hormonal system, with marked elevation in plasma epinephrine and metanephrine levels. Enhanced sympathoneural activity is also suggested by increased plasma levels of dihydroxyphenylalanine, dihydroxyphenylglycol, nor epinephrine, and normetanephrine, reflecting increased synthesis of nor epinephrine, neuronal reuptake and metabolism, spillover, and extraneronal metabolism, respectively". [6]

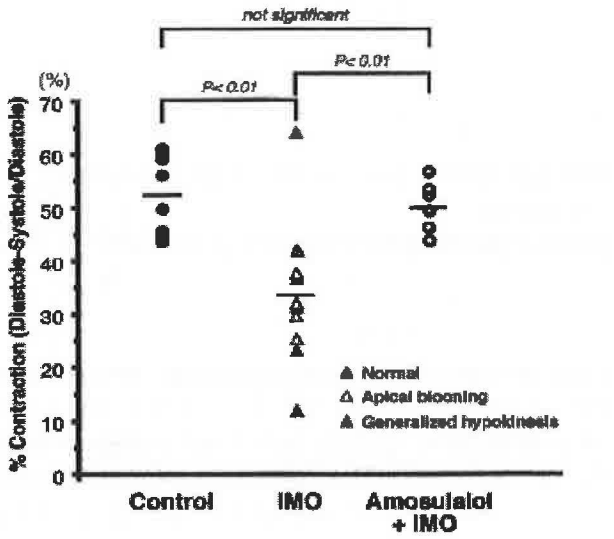
Table 2. Plasma Catecholamine and Neuropeptide Levels.*

Variable	Patients with Stress Cardiomyopathy (N=13)			Patients with Killip Class III Myocardial Infarction (N=7)			Normal Value
	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	
	median (interquartile range)						
Catecholamine precursor (pg/ml)							
Dihydroxyphenylalanine	2859 (2721–2997)†	2495 (2386–2761)†	1656 (1065–2011)	1282 (1124–1656)	1203 (1193–1873)	907 (749–937)	1755‡
Catecholamines (pg/ml)							
Epinephrine	1264 (916–1374)†	1044 (733–1118)†	348 (180–550)	376 (275–476)	330 (220–385)	275 (220–311)	37‡
Norepinephrine	2284 (1709–2910)†	1573 (1235–2589)†	1142 (525–1252)	1100 (914–1320)	829 (727–914)	541 (516–660)	169‡
Dopamine	111 (106–146)†	77 (63–110)	56 (47–77)	61 (46–77)	61 (61–77)	38 (30–61)	15‡
Neuronal metabolites (pg/ml)							
Dihydroxyphenylglycol	2706 (2382–3131)†	2689 (2246–2842)†	2161 (2093–2416)§	1625 (1412–1702)	1583 (1497–1668)	1259 (1191–1446)	800‡
Dihydroxyphenylacetic acid	2758 (2573–3077)	2598 (2354–2892)†	1345 (1194–1682)	1513 (1211–1648)	1228 (1026–1362)	1009 (908–1059)	1497‡
Extraneuronal metabolites (pg/ml)							
Metanephrine	178 (140–187)	509 (385–789)	659 (590–738)§	106 (89–124)	203 (177–213)	205 (189–243)	59‡
Normetanephrine	216 (130–319)	456 (229–569)	661 (551–696)§	160 (145–170)	196 (181–209)	271 (225–288)	55‡
Peptides (pg/ml)							
Neuropeptide Y	186 (162–236)§	185 (158–214)†	136 (90–182)§	77 (60–90)	69 (61–71)	60 (40–65)	51¶
Brain natriuretic peptide	1033 (805–1783)§	450 (205–684)	142 (72–236)	264 (192–483)	268 (249–574)	297 (142–419)	10–93‖
Serotonin and metabolite (pg/ml)							
5-Hydroxytryptamine	2585 (2165–2816)†	2379 (2290–2900)†	1602 (864–1989)	1308 (1074–1721)	1214 (1114–1643)	1065 (1003–1251)	1004**
5-Hydroxyindoleacetic acid	5596 (4531–7380)	7839 (5698–9644)	6471 (3308–7074)	3977 (3604–6074)	4607 (4128–6003)	4282 (3887–4416)	6730**

* All P values are for comparison of levels in patients with Killip class III myocardial infarction measured at similar times.
† P<0.005.
‡ Data are from Goldstein et al.[22]
§ P<0.01
¶ Data are from Onuoha et al.[20]
‖ Data are from Redfield et al.[12]
** Data are from Spreux-Varoquaux et al.[23]

There is evidence from animal experiments that catecholamine excess cause stress induced cardiomyopathy.

A similar stress induced cardiomyopathy can be reproduced in rats by immobilizing them for thirty minutes on their backs on a board, and can be prevented by giving them αβ-blocker before the stressful event.



Emotional Stress Induces Transient Left Ventricular Hypocontraction in the Rat via Activation of Cardiac Adrenoreceptors: a Possible Animal Model of 'tako-tsubo' cardiomyopathy, Ueyama et al; Circulation Journal. 2002; 66:712-713 [24]

There are case reports of this ST elevation improving in these patients with administering metoprolol and clonidine [11].

123-I-metaiodobenzylguanidine (MIBG) scintigraphy is used to localize pheochromoctoma. It is compound resembling norepinephrine, and is taken up by adrenergic tissue and norepinephrine containing nerve endings.
MIBG uptake scan done on the 16th hospital day showed a markedly high wash out ratio (46.2 $\pm$ 11.4%). Three months later the wash out ratio was 28.2$\pm$8.3%.
In this case the plasma norepinephrine concentration was noted to be high before the left ventricular dysfunction could be documented. From these findings one suspects that the course of dysfunction is related to catecholamine increase, but the heart failure did not cause the release of the catecholamine. Coronary vasospasm could not be induced in this patient [29].

Not all observers have found same results in one study the circulating norepinephrine ranged from 291 to 977 pg/ml, normal range 100 to 450 pg/ml, and epinephrine levels were only minimally elevated.

In one of the 30 patients right coronary angiography revealed a severe delay in perfusion of contrast medium with ST elevation but no narrowing of the epicardial coronary arteries. Indicating that microvascular coronary vasospasm might be one of the mechanisms.
The authors concluded that catecholamine excess was not the cause for this syndrome because catecholamine levels in many of their patients were not clearly elevated. Circulating catecholamine levels were normal in three and slightly elevated in another three of the thirty patients reported. [23]

A possible explanation of pathogenesis of this disorder is catecholamine mediated myocardial stunning and myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic-AMP mediated calcium overload. Catecholamine is also a potential source of oxygen derived free radicals and, in animal models, causes myocyte injury, which can be attenuated by antioxidants. Free radicals can interfere with sodium and calcium transporters resulting in increased transsarcolemmal calcium influx and cellular calcium overload [6].

Epicardial Coronary Vasospasm

Most patients have no angiographic evidence of epicardial spasm. Patients often demonstrate contractile abnormalities in multiple vascular territories.
An alternative mechanism is microvascular spasm, suggesting sympathetically mediated microcirculatory dysfunction.

Epicardial coronary vasospasm, particularly vasospasm of left anterior descending artery is an unlikely explanation for this syndrome due to several reasons, coronary angiogram showed normal or minimally diseased anterior descending artery. A single artery i.e. left anterior descending artery territory cannot explain the regional wall motion abnormality. Inferior wall T wave changes are not observed in anterior descending artery ischemia, and a sestamibi perfusion test performed in one patient during ST elevation showed heterogenous area, inconsistent with the vascular distribution of an epicardial coronary artery. [11]

The precise etiologic basis of transient LV apical wall motion abnormalities could not be determined. In this series provocative vasospasm was confirmed in only 10 of the 48 patients. Therefore multiple vasospasm is not thought to be the main cause. Another possibility is myocardial ischemia due to microvascular spasm.
As has been shown in the neurogenic stunned myocardium during acute cerebrovascular accidents and catecholamine cardiomyopathy during the endocrine crisis of pheochromocytoma, enhanced sympathetic activity might be a cause of a similar type myocardial damage.
This novel heart syndrome might be one of the clinical models of stress related sudden death. [19]

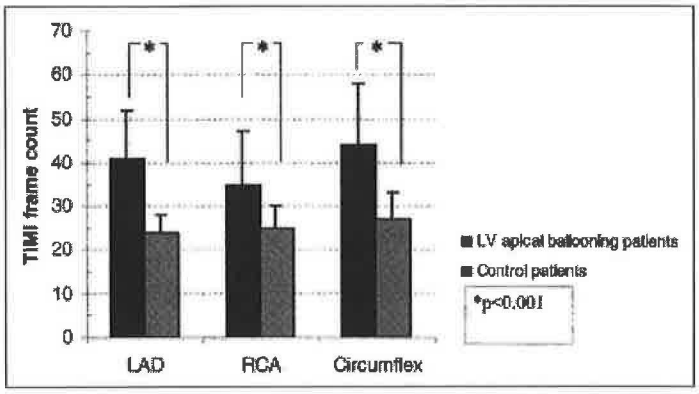
Only on of the 22 patients in the Minneapolis Heart Institute series presented with diffuse multifocal and multivessel coronary vasospasm, a causal mechanism suggested by some authors, either spontaneous or provoked in the catheterization laboratory. Other mechanisms proposed for this cardiomyopathy include microvascular spasm, impaired fatty acid metabolism and transient obstruction to LV outflow. Cardiac MR Studies identify diffusely distributed wall-motion abnormalities that encompassed LV myocardium in more than 1 coronary arterial vascular territory in 95% of patients and in the vascular distribution of all three epicardial coronary arteries in 90%. Also CMR studies performed during hospital admission were uniformly consistent with preserved myocardial viability i.e. absence of delayed hyper enhancement with gadolinium, without evidence of acute myocardial infarction, infiltrative or inflammatory processes, necrosis and loss of cellular membrane integrity, or scar formation [3].

Acute coronary angiography revealed spontaneous multivessel coronary vasospasm in three of the thirty patients in this study. The coronary spasm provocation test was positive in 10 of thirty patients, with four having a single coronary artery spasm and six had multivessel spasm. These patients also had T-wave inversion and QT interval prolongation. [23]

There is one case report of a patient with transient left ventricular dysfunction who had spontaneous simultaneous 3- vessel spasm during coronary angiography. [78]

Impairment of Coronary Microcirculatory Function

In 16 women with transient left ventricular apical ballooning syndrome in a United States Thrombolysis In Myocardial Infarction (TIMI) frame counts were evaluated during the acute period. Patients generally presented with anterior ST-elevation acute coronary syndrome in the absence of obstructive coronary disease. All patients had LV apical wall motion abnormalities. An acute emotional or physiologic stressor preceded most cases. TIMI frame counts were abnormal in patients and often abnormal in all 3 major coronary vessels, suggesting that the diffuse impairment of coronary microcirculatory function may play a role in the pathogenesis of the syndrome.
The mean TIMI frame count in the patients with apical ballooning were significantly larger in all 3 major coronary arteries compared with matched controls (left anterior descending [corrected]: 41±11 vs. 24± 4; left circumflex 44±14 vs. 27 ± 6; right coronary artery: 35±12 vs. 25± 5; p values less 0.001 for all comparisons). Two patient had repeat angiography and demonstrated normalization of their TIMI frame counts in all 3 epicardial vessels.



Bybee et al, American Journal of Cardiology 2004; 94:343-346 [30]

TIMI Frame Count A Quantitative Method of Assessing Coronary Artery Flow

C. Michael et al, Circulation. 1996; 93:879-888 [57]

In normal patients and patients with myocardial infarction, the number cineframes needed for dye to reach standardized distal landmarks was counted to objectively assess index of coronary blood flow. After standardizing the method in 78 patients without myocardial infarction this method was used to assess coronary flow in patients with myocardial infarction. After analyzing 393 patients with myocardial infarction the authors concluded that cine frame count was increased in the culprit artery 90 minutes after thrombolysis and improved but remained increased after 18 to 36 hours. More

strikingly the CTFC was also increased in the non culprit arteries. But improved to that of normal arteries in one day.
Is Takotsubo simply a subset of patients with either acute vasospasm or a thrombus that is lysed fairly rapidly, leaving delayed filling of the microcirculation, or do patient with myocardial infarction have a Takotsubo like abnormality in their microcirculation?

Injection of nicordanil into the coronary arteries during the acute phase of the syndrome acutely reduces the extent of ST-segment elevation.
It is unclear whether coronary microvascular dysfunction is the primary mechanism involved in the pathogenesis of the syndrome or is simply an associated secondary phenomenon [9].

When Takotsubo cardiomyopathy was compared with acute coronary syndrome patients with 99m Tc-tetrofosmin myocardial SPECT, acutely on admission and at three to nine days after attack and at one month after attack (ten patients with Takotsubo syndrome and sixteen with ACS) the uptake was severely reduced in both groups of patients but more so in ACS patients. The authors concluded that impaired microcirculation might be a causative mechanism of Takotsubo cardiomyopathy. [67]

Myocardial Stunning
Braunwald and Kloner in 1982 reviewed myocardial ischemia and concluded that it is not always an all or none phenomenon. That is, at least in dog model, any ischemia lasting for less than twenty minutes results in a reversible change in the heart. This change is in the metabolism and physiology but is also apparent in ultrastructural abnormalities seen in these hearts. They found a close correlation with ATP depletion, resulting from anaerobic metabolism, and these changes. Fifteen minutes of ischemia results in 50% reduction in ATP content. Morphologic changes present in the myocardium were wide I bands, suggesting either myocardial relaxation or stretching of the adjacent contracting cells, depletion of glycogen granules, clumping and margination of nuclear chromatin, and mild intrafibrillar and mitochondrial edema. They coined the term "myocardial stunning". The duration of myocardial stunning depended on duration of ischemia and baseline myocardial health, but could last up to seven days.
The Stunned Myocardium: Prolonged, Postischemic Ventricular Dysfunction. Eugene Braunwald, MD, And Robert A. Kloner, MD. Circulation Vol. 66, No 6, December 1982 [31]

Several observations argue against a "classic" acute myocardial infraction as the underlying cause in stress induced cardiomyopathy. Firstly no significant obstruction of an epicaridal coronary artery is visualized. Secondly, the akinetic zone does not correspond to the perfusion territory of a single epicardial coronary artery. More specifically the akinesia of the apical portion of the inferior wall extends well beyond what would be expected in the case of ischemia in the territory of the left anterior descending coronary artery. Thirdly there is very limited rise in the cardiac markers. In addition a striking normalization of systolic left ventricular function over a few weeks time is observed in all survivors.
Different mechanisms may be at play in different patients with a similar clinical picture.
All patients do not present with ST elevation, in fact some of the patients present with normal EKG, arguing against a stenotic or a vasospastic event, in which we would expect immediate ECG changes.
The severe myocardial hypocontractility with very limited release of cardiac enzyme and complete recovery over a relatively short period of time is reminiscent of myocardial stunning. Also the observed ECG abnormalities included symmetrical diffuse T wave inversion and QT prolongation, a pattern that has been associated with left ventricular stunning in unstable ischemic syndromes. However this stunning is not because of epicardial artery occlusion or coronary vasospasm (very limited evidence of vasospasm on provocative tests).

Sympathetic over-activity plays an important role in pathogenesis as evidenced by invariable presence of triggering events including internal and external stress [26].

Clinical features as well as myocardial metabolic abnormalities noticed in this syndrome are consistent with myocardial stunning: catecholamine induced neurogenic stunning. To some extent the sympathetic nervous system is likely involved in the pathogenesis of the syndrome, considering that apical ballooning can be induced in a rat model of emotional stress that is prevented by pretreatment with combined α adrenoreceptor and β adrenoreceptor blockade. The predominant apical involvement may be explained by anatomic differences in the sympathetic innervation of the heart. [30]

Mitochondrial Dysfunction

Cardiomyopathy has been reported in patients taking amphetamines. [45]
Use of ecstasy at doses not high enough to cause microscopic myocardial changes in mouse heart, produced ultrastructural changes visible by electron microscopy and there were a slight increase in the number of altered mitochondria, this was constantly present in both the atrium and the ventricle of MDMA-exposed mice. Remarkably, when ecstasy was administered during noise exposure, a dramatic and significant increase in the number of altered mitochondria was measured. These cardiac effects are likely to be sustained by increased noradrenalin release and subsequent mitochondrial calcium entry as indicated by previous studies carried out on both MDMA and noise exposure. [32]
Maco Gesi et al, pharmacology and toxicology 2002 Jull; 91(1): 29- 33

Myocardial Perfusion and Fatty Acid Metabolism in Patients With Tako-Tsubo-Like Left Ventricular Dysfunction
Satoshi Kurisu et al, Journal of American College of Cardiology, Volume 41, No. 5, 2003:743- 748
[33]
In this study of Japanese patients rest Thallium-201 and Iodine-123-beta-methyl-p-iodophenyl pentadecanoic acid (123 I –BMIPP) dual-isotope myocardial single-photon emission computed tomography (SPECT) in 14 patients with Tako-tsubo-like LV dysfunction, were compared. TIMI Frame Count was also measured in 28 patients and 20 controls subjects. The early SPECT images showed a more marked reduction in BMIPP uptake indicating an abnormality in fatty acid metabolism. This discrepancy improved in 29 ± 6 days.
Discrepancy between myocardial perfusion and fatty acid metabolism shown in this study is explained by the fact that in aerobic conditions 70% to 80% of energy source is beta oxidation of fatty acids. In ischemic conditions the beta oxidation in mitochondria is immediately reduced. TIMI frame counts were increased in the patients indicating microvascular ischemia (coronary angiography had not shown any epicardial artery lesions or vasospasm).
This indicates a dysfunction in coronary microcirculation and mitochondrial dysfunction ala stunned myocardium.

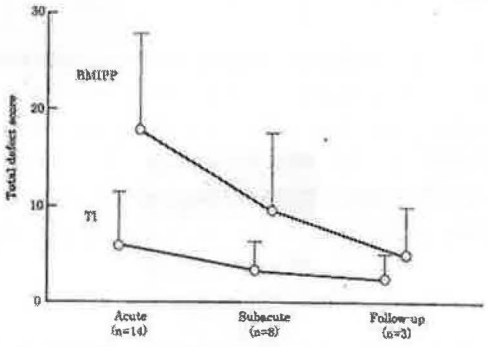


Figure 1. Time course of myocardial perfusion and fatty acid metabolism assessed by serial rest ^{201}Tl and ^{123}I-BMIPP dual-isotope myocardial single-photon emission computed tomography performed at 5 ± 3 days (acute phase), 15 ± 3 days (subacute phase), and 29 ± 6 days (follow-up) after onset. Myocardial fatty acid metabolism was more severely impaired than myocardial perfusion during the early phase and improved gradually during follow-up.

Rest Technetium-99m tetrofosmin myocardial imaging was performed in thirteen patients during the acute phase. There was a significantly decreased uptake at the apex of the left ventricle in 11 patients (85%). The apical abnormality returned to uniform between 25 and 90 days after the onset. The mechanism of uptake of TF by myocytes was reported as via a metabolism-dependent process, and subcellular localization was in the mitochondria. Thus, it was suggested that the scintigraphic abnormality was caused by the abnormalities in the mitochondria. Although the exact mechanism is not known participation by catecholamine is suggested [34].

What can Pheochromocytoma tell us about this condition?

Focal Myocarditis Associated With Pheochromocytoma
Van Vliet et al, Nejm May 19th, 1966: 1102-1108 [35]

In this trial cardiac pathology in 26 patients with diagnosis of pheochromocytoma on autopsy was studied. This was compared to findings in 60 rats, given very high doses of intravenous norepinepherine.
The microscopic findings were very similar to those seen in patients with stress- induced cardiomyopathy (*Wittstein et al, Nejm 2/10/2005).* These included disseminated focal myocardial lesions characterized by focal degeneration and necrosis of myocardial fibers, with predominant histiocytes. Diffuse edema of the myocardium. These findings were predominantly on the inner two thirds of the myocardium and most often appeared around small blood vessels. There was also disseminated fibrosis, again more prominent around the small blood vessels.
The pathology in the rats differed depending on the time of sacrifice and the number of norepinepherine doses given. In myocardium of those that had died within twenty four hours after a single injection of L-norepinepherine diffuse edema and minor alternations of myocardial nuclei were present. In those dying after two injections there were foci of muscle necrosis with infiltration of inflammatory cells, primarily histiocytes; these foci were situated about the small blood vessels. Examination of the myocardium of the 27 rats killed after three, four and eight weeks had increased amounts of fibrous tissue. [35]

Clinically there are many case reports of pheochromocytoma presenting with cardiomyopathy, which is reversible after treatment of underlying cause. [36] Interestingly some of these patients

demonstrate a similar dynamic left ventricular out flow tract obstruction of mild to moderate degree, and was reversible after treatment. [37]
Another case report was on a 39 years old man who died because of an undiagnosed pheochromocytoma, and had presented with end stage heart failure and on autopsy had patchy interstitial fibrosis and broad band of fibrosis beneath the endocardium with normal coronary arteries. [38]

Szakacs and Cannon described 17 cases of pheochromocytoma, which demonstrated acute myocarditis with no evidence of significant coronary atherosclerotic disease.
A case report of a 34 years old woman who had presented with a two weeks history cardiac failure is described. Echocardiography showed a non dilated lv with severely impaired systolic function. Endomyocardial biopsy indicated myocarditis and she was diagnosed as post viral myocarditis. Interestingly her EKG showed QT prolongation and diffuse T Wave inversion. She continued to be symptomatic for the next two weeks and was admitted with worsening signs of heart failure. Endomyocardial biopsy showed mild focal interstitial infiltrate of lymphocytes with scanty myocytolysis. After episodes of labile hypertension a diagnosis of pheochromocytoma was made. After removal of the tumor her symptoms and ventricular ejection fraction improved to normal. [39]
In catecholamine-induced cardiomyopathies linked to pheochromocytoma, myocardial lesion consists of a degeneration and focal necrosis of cardiac myocytes, secondarily associated with inflammatory reaction and fibrosis. The characteristic lesion is a particular myofibrillar degeneration called contraction band necrosis. Focal myocardial necrosis or myofibrillar degeneration lesions identical to these have been seen in experimental animal models subjected to major stress, as well as in humans, especially during necropsies of patients dying suddenly by homicide following physical assault without directly lethal lesions.
The mechanisms of these lesions are thought to be either ischemia induced by vasospasm, and modifications in the permeability of the sarcolemma resulting in increase in sarcoplasm calcium concentration which leads to myocyte necrosis [40].

Neurogenic Stunned Myocardium

ECG changes occur in 50% to 100% of patients with Subarachnoid Hemorrhage, with most common abnormalities being ST segment and T wave changes with QT prolongation. Some patients have evidence of structural cardiac damage. Plasma level of creatine kinase myocardial isoenzyme is mildly elevated in 20 to 50% of patients. Contraction band necrosis is found at autopsy and has been produced in experimental SAH models. Echocardiographic studies have demonstrated reversible abnormalities of left ventricular contractility. Coronary angiography or autopsy examination shows normal coronary arteries. Hypovolemia has been implicated as a risk factor for symptomatic vasospasm in these patients.
In a retrospective non controlled trial wall motion abnormalities associated with SAH occurred exclusively in patients with elevated CK MB values greater than 2%, female sex with 9/47 female patients having wall motion abnormalities and none of the 25 men demonstrated any changes. There was no correlation between laterality and site of aneurysm with the wall motion abnormality. Of the nine of 72 patients with wall motion abnormality, one developed pulmonary edema, one developed hypotension and four had both. All nine patients had diffuse T wave inversion and QTc prolongation. The striking female preponderance in this study has been observed before in other studies.
Contraction band necrosis is the most likely cause of wall motion abnormalities seen in these patients. This is thought to result from excessive exposure to catecholamine and cellular calcium entry, leading to a hyper contracted state [41].

Similarly Kono and colleagues reported (n=12) that SAH patients presenting with ST elevation in V4 through V6 demonstrated apical wall motion abnormality with normal coronaries on coronary angiogram. This wall motion abnormality improved over time (seven patients). Five patients of SAH with only T wave flattening had normal wall motion [42].
The mechanism of is thought to be an increase in norepinephrine release due to hypothalamic stimulation.

Is there a catecholamine excess state in Subarachnoid Hemorrhage?
Neil-Dwyer et al, BMJ October 7, 1978, p 990 to 992 [43]
In their study they found urinary catecholamine levels to be markedly elevated. They also gave 45 patients with subarachnoid hemorrhage propranolol and phentolamine and placebo to another 45 patients in a double blind placebo control manner. This study was not powered to find a difference in mortality and had equal number deaths in the two groups, (n=6). But the patients dying in the active treatment group had fewer EKG abnormalities, and on autopsy they had none of the necrotic myocardial lesions seen in the placebo group: 2 had focal necrotic lesions of the muscle fibers, and four had focal necrotic lesions with inflammatory cells. Interestingly both groups had marked changes in their hypothalamus with perivascular hemorrhage and endothelial edema.
They concluded that the myocardial abnormality in SAH was secondary to catecholamine excess and could be prevented with the use of alpha and beta blockers.

Is there evidence from other diseases that catecholamine excess can cause myocardial dysfunction?

Indeed in animal studies isoproterenol infusion in large doses causes myocardial necrosis
Kahn et al Ann N. Y. Acad Science 1969
A case report of a 45years old woman given high dose dextroamphatamine at 25mg four times a day for depression is described. She presented a year later with signs of heart failure. She continued to take dextroamphatamine and died of refractory heart failure six years later. Her postmortem showed widely patent coronary arteries and strikingly free of atheroma. Light microscopy showed widespread interstitial edema with a scattered predominantly lymphocytic and histiocytic cellular infiltrates. Muscle fiber degeneration with small areas of muscle necrosis was seen. Patchy fibrosis was apparent.
Electron microscopy revealed widespread abnormalities of the myocardial fibers with extensive margination of nuclear chromatin, marked interfibrillar edema, and severe mitochondrial abnormalities, including loss of matrix with presence of large itramitochondrial granules. [45]

Data from a study by Cebelin and Hirch found myocardial contraction band necrosis in eleven of the fifteen victims of assault, who died after twenty four to forty eight hour without internal injuries sufficient enough to explain their death. Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. [46]

Myocardial contraction band necrosis has been found in children dying of asthma. But in one such study by Drislane and colleagues these changes were found in only four of the thirteen patients who had died of acute severe asthma. Similar changes were also found in three of the nine patients dying of cystic fibrosis, and one of the eight victims of trauma. This study did not explain why without a similar degree of stress and lack of exposure to sympathomimetic drugs (the postulated mechanism in patients with asthma) the "control" patients had similar histological changes. [47]

Viral Myocarditis?

Although the histological findings of mononuclear infiltrate and myocyte necrosis can also be seen in viral myocarditis, elevated viral titers including coxsackievirus, cytomegalovirus, influenza, mumps, rubella, adenovirus, or echovirus are not detected in paired serum examinations in these patients. [34] [55]

Why the apex is more prone to Catecholamine induced myocardial dysfunction?

Discrepancy of sympathetic innervation between apical and basal portion of the heart
In this report of six months follow up of takotsubo cardiomyopathy with I-123 Beta Methyl Iodophenylpentadecanoic acid (BMIPP), I-123-meta-iodobenzyl-guanidine (MIBG) myocardial scintigraphy is presented.
Apex was defined one third of the inside of a bull's eye image. In acute phase decreased uptake in the apical region was seen in BMIPP imaging and early MIBG imaging, the former evaluating myocardial dysfunction in terms of fatty acid metabolism. Three months later, decreased uptake in the apical region recovered in BMIPP imaging, but not in early MIBG imaging. And this discrepancy persisted at six months.
The total (for the whole heart) wash out rates increased in the acute phase (40%), decreased after 3 months (16%) and normalized after six months (30%).
Wash out rate reflects cardiac sympathetic activation and it increases with increasing severity of heart failure. Increased WR in acute phase indicate sympathetic activation to compensate for decreased cardiac output. (WR 40%) (Normal 27±7%). This sympathetic activation is thought to result in basal hyperkinesias and may account for the dynamic obstruction seen in some patients. Apical wash out at this time was 26%, low compared to the rest of the heart. In three months period however the wash out rate at the apex was 37%, while total wash out was 16%. Indicating increased sympathetic stimulation at the apex at three months. At six months the total WR was 29% and apical WR was 30%.
The authors speculated that the discrepancy of sympathetic innervation between the left ventricular apical and basal region plays an important role at the onset of takotsubo cardiomyopathy, though it becomes stabilized during the course of the recovery. Although it is unclear whether this the cause or effect of the takotsubo cardiomyopathy [48]

Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli, in this article published in Cardiovascular Research in 1993, Hidezo Mori and colleagues studied three hypotheses in dogs

1) Compared regional contractile changes in response to graded cardiac sympathetic nerve stimulation between, anterior, middle, and posterior regions of the basal segments, and between basal, middle and apical regions with a difference in nerve density.
2) Compared regional contractile and metabolic responses to stimulation of adrenergic receptors and adenylate cyclase between the apical and basal segments.
3) And evaluated regional heterogeneity in Beta Adrenergic receptor density and tissue Noradrenalin content.

Regional sympathetic cardiac innervation was determined semi-quantitatively using graded stimulation with increasing frequency and measuring end systolic pressure with a monometer placed in the appropriate area of the cardiac cavity and end systolic length and rate of shortening was determined by enodcardial ultrasound probes.
The right and left sided sympathetic nerves were stimulated alternatively.
Regional contractile and metabolic responses to various adrenergic stimuli were compared in the basal and apical regions, including graded cardiac sympathetic nerve stimulation, constant infusion

of isoprenaline, and adenylate cyclase stimulation with forskolin derivative, 6-(3dimethylamino-propionly). Descending aorta was clamped immediately after recording the changes induced by these agents for fifteen seconds to until the end systolic pressure was at the baseline control level. Myocardial biopsies were obtained to check cyclic AMP levels. Similar procedure was repeated with noradrenaline infusion.

Regional variation in sympathetic innervations was determined by checking noradrenalin levels in different regions of the heart. Adding H-dihydro-alpernolol and checking the retained radioactivity after washing determined density of receptors.

With noradrenaline administration the degree of change of normalized end systolic length was significantly more marked in the apical region. The time taken for local shortening was also shorter. And these results were consistent whether the heart was denervated or not.

Isoprenaline administration resulted in decreased end systolic pressure and increase in the heart rate; similar results were seen with Forskolin derivative. There was no significant difference between the basal, middle and apical portions of the heart without aortic clamping. But with clamping, by matching the aortic pressure to the control, greater decrease in end systolic length was seen in the apical region. Thus the lack of statistical difference in normalized end systolic length before pressure matching could be explained by the additional decremental action of these drugs on after-load, which makes it difficult to distinguish the degree of increase in local inotropism using local contractile parameters.

Tissue baseline Cyclic AMP was slightly lower in apical region, although it was significantly higher after administration of forskolin derivative and noradrenaline infusion.

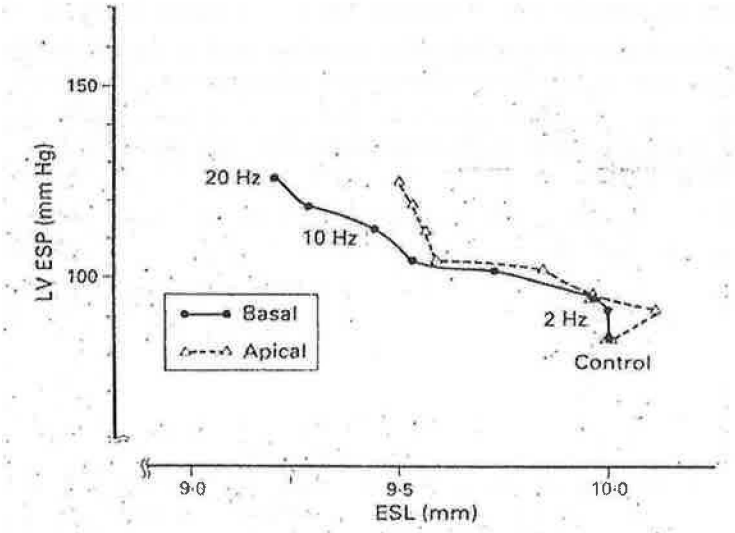


Figure 4 ESP-ESL from basal and apical regions: left cardiac sympathetic nerve stimulation. LV ESP=left vetricular end systolic pressure; ESL=end systolic length. SEM of normalised ESL ranged from 0.07-0.22 and 0.05-0.13 mm in the basal middle and apical regions. SEM of LV ESP ranged from 5-12 mm Hg.

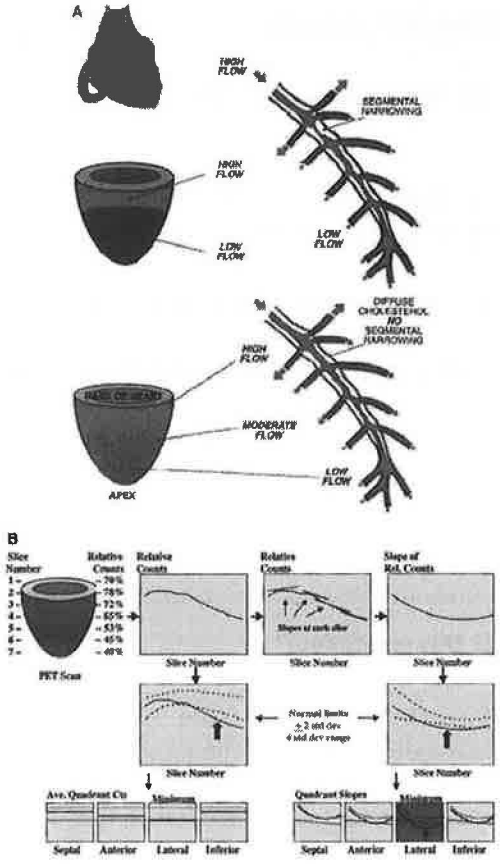
This study concludes that apical myocardium has an increased responsiveness to adrenergic stimuli and compensates, at least in part, for its sparse sympathetic innervation. The increased beta receptor density in apical myocardium indicates the underlying mechanism. Also the lack of difference in the ESP-ESL changes during graded cardiac stimulation, and lower tissue noradrenaline concentration in the apical myocardium, indicates that apical myocardium can compensate for its sparse sympathetic nerve innervation.

The significantly greater decrease in normalized end systolic length and higher cyclic AMP content during noradrenaline infusion in the apical region than in the basal middle region suggested

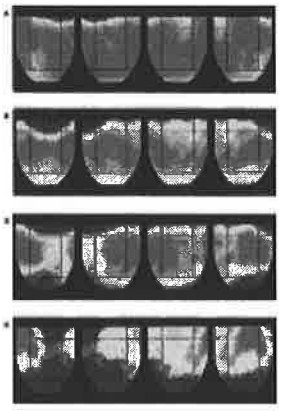
increased responsiveness of beta adrenergic receptor and/or second messenger in the apical region. As indicated by an increased production of Cyclic AMP by an adenylate cyclase stimulator-forskolin derivative.

The consequence of early and rapid apical shortening is a gradient from the apex to the base of the heart and ventricular out flow tract during early systole. There is also a phenomenon of active relaxation of the ventricular apex resulting in suction of blood during early rapid filling phase. These considerations lead to the concept that the increased responsiveness of the apical myocardium to adrenergic activity could be an important mechanism in increasing the efficiency of the left ventricular filling and ejection, especially during exercise or under other conditions involving a short cardiac cycle. [49]

In order to study their hypothesis that patients without a significant segmental occlusion and having diffuse coronary atherosclerotic disease have a longitudinal gradient from the base to the apex of the heart, Gould et al, divided patients (n=1001) in five groups. Group one was healthy volunteers, and group two through four had varying degree of segmental coronary narrowing with abnormal uptake on resting PET scanning, with group two being the severe disease. Group five had no segmental coronary narrowing and had a normal resting PET scan. [54]



A, Longitudinal, base-to-apex myocardial perfusion abnormality caused by diffuse coronary artery narrowing compared with segmental perfusion defects caused by localized stenoses. B, Longitudinal analysis protocol. Purple arrows and purple box indicate abnormal longitudinal, base-to-apex distribution of relative activity outside 2 SD of normal control subjects in absence of segmental localized perfusion defect.



As shown in the figure above they were able to demonstrate in patients with normal resting PET progressively worsening gradient of decreased uptake from base to the apex with stress. The first panel represents a normal PET with dipyridamole. Although none of these patients had significant segmental coronary artery stenosis, the PET scan showed a progressive base to apex gradient in these patients with diffuse coronary atherosclerotic disease.

In patients with segmental coronary artery narrowing this gradient could be demonstrated in mild to moderate disease.

Thus, in mild to moderate coronary artery disease without quantitatively significant segmental perfusion defects caused by flow-limiting stenoses, there are quantitatively significant, graded, longitudinal, base-to-apex perfusion abnormalities with minimum quadrant slopes that are significantly worse than normal control subjects because of diffuse coronary artery disease.

This study verifies for the first time in a large study population the hypothesis of widely prevalent, significant fluid dynamic effects of diffuse coronary artery disease manifest as a graded, longitudinal, base-to-apex myocardial perfusion gradient by cardiac PET perfusion imaging after dipyridamole stress as a noninvasive marker of diffuse coronary artery disease not observed in normal volunteers. It is commonly present and quantitatively severe enough to be outside ±2 SD of normal control subjects before regional segmental perfusion abnormalities become severe enough to fall outside the normal limits. [54]

Are certain patients more prone to get this syndrome?

Clearly the answer is yes, in spite of being exposed to stress often, not many people get this disorder. There is data to show that certain individuals might be more sensitive to catecholamine. In one such experiment Mitchell and Shapiro gave intravenous adrenaline to a 21 years old who had presented with symptoms suggestive of acute myocardial infarction earlier. They were able to show that intravenous adrenaline but not saline would cause marked ST segment depression and T-wave

inversion. These symptoms could not be reproduced if saline was given to the patients, but reappeared when saline was administered with the patient being told that she was getting adrenaline. [80]

But comparing catecholamine levels in healthy volunteers being stressed either by repeated venipuncture or by mental stress, showed that the female volunteers had significantly lower increase in their catecholamine levels, compared to males. [71]

Thus it might be attractive to think that certain populations would be more "at risk" for this syndrome, it is difficult to conclude with existing data. Further studies with such susceptible cohorts, e.g., patients with panic disorder, followed prospectively would be the only way of finding an answer.

Key Summary Points [9]

- The transient left ventricular apical ballooning syndrome is a novel cardiac syndrome. It is characterized by peculiar transient apical "ballooning" of the left ventricle, which is the result of characteristic wall-motion abnormalities in the left ventricular apex and mid-ventricle
- Despite the absence of obstructive epicardial coronary artery disease, clinical presentation in patients with the syndrome can be similar to that of patients with ST-segment elevation myocardial infarction.
- Postmenopausal women seem to be most at risk for developing the syndrome.
- An episode of acute emotional or physiologic stress seems to often precede presentation with this syndrome.
- Patients with this syndrome should be monitored and treated for left heart failure, dynamic intraventricular obstruction, arrhythmias, and mechanical complications should they develop.
- Patients with this syndrome have a favorable prognosis.
- **The cause of this syndrome is not yet known.**

Case 1 in this presentation is from Case Records Of The Massachusetts General Hospital, Thomas J. Ryan M.D., had the following conclusion
"I am reluctant to end this discussion without suggesting the possibility of a Catecholamine-induced myocarditis because of the dramatic relationship between the onset of symptoms and the substrate for adrenergic discharge of circulating epinephrine and nor epinephrine occasioned by tragic news. However attractive this construct may be, it should be recognized as conjecture that is probably well beyond proof." [1]

How good then is the Data for this disorder?

As is obvious from the above discussion what we know of this syndrome is based on case reports and case series, and conclusion drawn from other diseases. So how good are these methods of investigation?

Case reports are preliminary observations and highly subject to subsequent refutation, e.g. extracranial-intracranial anastomosis for preventing stroke recurrence was thought to be effective

based on many case reports, until two large randomized trials found it not only ineffective but also harmful.
This method does not permit the discrimination of the valid from the interesting but erroneous.
A case series is a nonexperimental study in which an investigator simply reports his observations e.g. exposure to stress leads to cardiomyopathy. All the reader can conclude is that cardiomyopathy can (not necessarily must) follow stress. These observations although thought provoking are prone to over-interpretation by the authors. [50]

As can be very well imagined these reports are prone to many biases

1) The observer has a preconceived idea what this disorder should look like, as in this case, it presents in women mostly post menopausal, who following either an emotional or physical stress have chest pain and certain EKG and Echocardiographic findings. So assuming our understanding of this disease is far from complete, are we ignoring and therefore not finding this disorder in other groups with different clinical presentation? Therefore introducing a **Selection bias**.
2) **Recall bias** is introduced when we seek a certain exposure for a certain disease. As in this case we may ask leading questions like "Mrs. S are you really sure nothing stressful happened before your symptoms started"? This also makes it less likely for the investigator to look for other equally important contributing or causative factors.
3) **Observation Bias** is introduced when measurements are conducted or interpreted by the investigator, human factors introduce inaccuracies. An example would be an investigator reading an echocardiogram expecting certain wall motion abnormalities.
4) These studies are notoriously poor in establishing a cause-and-effect relationship [51].
5) It is impossible to rule out a **chance occurrence** of this rare abnormality with a rather frequent happening of stress [51]

There are however many unanswered questions

- Why does this syndrome affect women more than men?
- Due to the selection bias in all these studies, can we conclude that this is a unique disorder, or is it really just a rare presentation of a known disorder?
- Does it exist in other forms, where presentation is not so striking and therefore not easily recognized?
- Can some of the cases of sudden death and death occurring in stressful circumstance be explained with this disorder?
- Does this disorder coexist with other more common diseases, particularly myocardial ischemia which in itself is a stressful state?
- Why despite a relatively common occurrence of stressful events is this disorder so rare?

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