Catecholamine Cardiac Toxicity: A Unifying Diagnosis for the "Ballooning" Syndromes, Takotsubo, Brain Injury and Hyperadrenergic States Associated with Left Ventricular Dysfunction.

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Introduction

Takotsubo, ampulla, apical ballooning or stress cardiomyopathy is an entity that was first described in 1990 but is only now reaching the surface of clinical consciousness.[1-5] However, literature describing case reports of unexplained acute cardiac events, pheochromocytoma associated left ventricular dysfunction, the mechanism underlying brain injury associated left ventricular dysfunction, stress-related sudden death and even "voodoo death" suggests the possibility that a unifying mechanism may underlie all of these illnesses and that Takotsubo is but one face of a single entity.

Animal models of catecholamine exposure and in Vitro experimentation have established that cathecholamines in high concentration may produce a toxic effect upon myocytes. Available evidence points to a neurogenic catecholamine surge as the etiology of most ventricular wall motion abnormalities and elevation of cardiac markers associated with brain injury. Meanwhile, commonality of the observed triggers of the "ballooning" syndromes, in their potential to be a source of catecholamine surge, and similarities in histological observations to cocaine and catecholamine induced injury provide suggestive evidence that catecholamine toxicity is the root cause of the ballooning syndromes as well as pheochromocytoma cardiomyopathy. Moreover, the syndrome is best termed catecholamine *cardiac* toxicity (CCT) as abnormalities in myocardial function are observed in conjunction with abnormal coronary artery behavior. In this review, we center discussion upon Takotsubo and its variants, drawing analogy to potentially related pathophysiology in an attempt to suggest a unifying pathophysiology

for a variety of seemingly disparate clinical entities and offer rationale for potential treatment.

For example, an interesting 1980 study from Cleveland examined autopsies of individuals who died after physical assault but had no internal injuries.[6] Eleven of 15 subjects had myofibrillar degeneration and other findings comparable to lesions described after cocaine abuse, ischemia, in animal models of stress cardiomyopathy or catecholamine exposure. Age matched and cardiac disease matched control subjects showed little or no evidence of such changes.

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In patients developing apical or other ballooning syndromes, the sentinel clinical event is characterized by rapid onset of a focal, ventricular wall motion abnormality (apical, mid-ventricular or basal), chest discomfort and dyspnea (in patients capable of expressing symptoms) typically following a trigger for intense adrenergic discharge. The source of adrenergic discharge may be intrinsic (pheochromocytoma, neurogenic) or extrinsic (commonly used and illicit drugs) with the precipitating event highly variable.(Table 1) The reasons for an individual's susceptibility to cardiac toxicity is unclear but there is a recognized predilection for post-menopausal women. In the acute phase, the electrocardiogram may mimic findings of acute myocardial infarction though in patients with relatively few risk factors for atherosclerosis or those presenting long after onset, a long-QTc with a repolarization abnormality is the most consistent finding. Although most patients have brief, slight elevation in cardiac markers in conjunction with a relatively large area of akinesis, most do not have evidence of epicardial coronary artery disease but they do have evidence of coronary endothelial dysfunction. Symptoms, hemodynamic derangements and objective findings on imaging and electrocardiography

are transient but histological evidence suggests that clinically apparent events may simply be the tip of the iceberg and almost 1 in 10 will have another, clinically apparent event. With or without supportive care, ventricular function will return to normal, with ECG abnormalities closely following recovery of wall motion. However, during the acute event, complications such as shock, arrhythmia and death may occur. Unfortunately, the true natural history remains incompletely defined due to a general lack of clinical recognition.

Incidence

In 2005, almost all case reports and case series that contained information about individual patients with "Takotsubo" cardiomyopathy were included in a uniform analysis. Unfortunately, at least some potentially related patients affected by what we propose to be CCT were likely missed in that the search parameters for the study were limited to Tako-Tsubo, takotsubo, and apical cardiomyopathy. Furthermore, clinical recognition and reporting creates somewhat of an ascertainment bias such that a clearer picture of event epidemiology may become apparent in the future, perhaps after creation of a multicenter registry. Although, the majority of reported cases are women above the age of 65 (93.5%), males and children may be affected.[7-9] Takotsubo cardiomyopathy was originally reported in Japan. As a result awareness and reporting bias the literature such that asians represent the largest group described (57.2%). However, there is no compelling evidence to suggest a predilection for the syndrome in people of asian descent.[8,10] In fact, in multiple ethnic groups, among patients referred for urgent angiography for suspected myocardial infarction, the incidence of probable

catecholamine cardiotoxicity ranges from 0.7-1.7%.[11-14]At the same time, the predilection for women creates the incorrect impression that affected patients do not have concomitant coronary artery disease.[15]

Physical or emotional stress is the precipitant in the vast majority of reported cases.[16,17] The best example of the close association with emotional duress are the observations made in Niigata, Japan in 2004. On the day of a major earthquake, "Takotsubo" syndrome was recognized in 11 people out of a population of over two million.[9] Over the subsequent month, aftershocks brought the toll up to 25. The incidence or recognition of the syndrome was 24-fold greater near the stress inducing epicenter of the earthquake as compared to surrounding areas.[9,18]

Most reports of what has been grouped as "stress" cardiomyopathy, describe a severe, apical wall motion abnormality accompanying electrocardiographic evidence of an injury current and later apical repolarization abnormality but there are several variants. The most common variant is a severe circumferential, basal akinesis sparing the apex.[19-22] In addition, isolated mid-ventricular akinesis, sparing both the base and apex, and varying degrees of right ventricular involvement have been reported.[14,23-29] Right ventricular involvement is detected by MRI in 26% of patients with a classic Takotsubo-type presentation, typically in patients with more severe LV dysfunction. Similar to the left ventricle, all segments of the right ventricle may be affected. Patients with evidence of RV involvement have a more severe reduction of LVEF.[30] Patients with a non-apical presentation suffer less severe hemodynamic embarrassment and have less T-wave inversion on their ECG.[31] This fact may create a second ascertainment bias in that, in the absence of severe hemodynamic compromise, the presence of "stress" related ventricular

dysfunction may often go unrecognized. For example, patients hospitalized with sepsis syndrome subjected to radionuclide assessment of left ventricular performance, or echocardiography 30-63% of patients have segmental wall motion abnormalities, while 11% (4 of 35 patients) have generalized wall motion abnormalities.[32-34] Though, clearly not all patients are afflicted with "stress" cardiomyopathy or CCT, some of these patients may have been affected but went unrecognized were it not for a screening study of left ventricular wall motion.

Table 1. Reported Triggers of Takotsubo-type, Basal and Mid-Ventricular Ballooning Syndromes.

Pulmonary Disease
- Asphyxia[35,36]
- Pneumothorax[36]
- Lobectomy[37]

Emotional States
- Social stressor[38-41]
- Sex[42]
- Earthquake[9,18]

Severe or Poorly Tolerated Concurrent Illness
- Trauma[43]
- Pancreatitis[44]
- New onset atrial fibrillation[45]
- Pneumopericardium[46]
- Adrenal insufficiency[47,48]
- ICU care[49]
- Sepsis[50]
- Hemophagocytic lymphohistiocytosis[51]

Neurological Disease
- Seizure[52-55]
- Transverse myelitis[56]
- Epidural KCL[57]
- Guillian-Barre[58]
- Brain tumor[59,60]
- Colloid Cyst and increased ICP[61]
- NMS[62]
- Meningitis[63]
- Subarachnoid hemorrhage[64-68]
- Posterior leukoencephalopathy syndrome in p-ANCA-associated vasculitis[69]

Known or Suspected Triggers for Catecholamine Surge
- Anaphylaxis[70]
- Thyrotoxicosis[71]
- Fall in elderly[72]
- Automobile accident[73]
- Polymorphic VT with 90 second downtime[74]
- Alcohol withdrawal[75,76]
- Opiate withdrawal[7,77]
- Pheochromocytoma[22,78]
- Paraganglioma[28]
- Lightning strike[68]
- Hypoglycemia[79,80]
- Postural Orthostasis Tachycardia Syndrome[81]
- Cocaine[82]
- Methamphetamine[83]
- Epinephrine injection[84,85]
- Dobutamine[86]

General Anesthesia/Surgery
- Abdominal surgery[62,87]
- Hip Surgery[88]
- Liver transplantation[89]
- Cardiopulmonary bypass[90]
- GETA for surgery[91-94]

Unknown Mechanisms
- Treadmill test[95]
- Pacemaker placement[96]
- Cardioversion[97]
- Cardiac RF ablation[98-100]
- VEGF antagonist[101]

Etiology

When patients with the common constellation of clinical settings, objective findings and clinical course of the ballooning syndromes were first recognized, the similarity between the transient wall motion abnormality seen in affected patients and episodes of ischemic stunning due to coronary artery disease led to proposals for an etiology of epicardial or microvascular vasospasm or unobserved thrombosis.[40,102-105] Although most reports that include coronary angiography with provocative testing for spasm do not report a high frequency of epicardial vasospasm the timing of evaluation with respect to the onset of illness and methods used to promote spasm are highly variable and transient abnormality of epicardial coronary artery function cannot be reliably excluded as either a source of ventricular dysfunction or promulgation of functional abnormalities.[16,17] Thus, the possibility that multi-vessel spasm is at least partly responsible has not been adequately examined.

Transient, abnormal coronary microvascular dysfunction, implying coronary endothelial dysfunction, is a consistent observation in Takotsubo cardiomyopathy and is reported in animal models of brain death.[106-109] Coarse measurement using the TIMI frame count in 16 women with Takotsubo cardiomyopathy revealed abnormal flow velocity in *all three* coronary arteries imaged during the acute phase of illness.[110] Meanwhile, measurement of coronary flow velocity reserve (CFVR) in 8 affected women during the acute and recovery phases of Takotsubo cardiomyopathy, revealed an abnormal CFVR of 1.7 that rose to a normal 2.5 at follow-up.[111] In an animal model of experimental brain death, brain death is associated with a concurrent decline in cardiac

output and CFVR to values similar to those reported for Takotsubo.[109] The observation of transient, abnormal microvascular function in association with the typical wall motion abnormality does not establish causation. While it is possible that distal multi-vessel epicardial vasospasm produced ischemic stunning and an apical wall motion abnormality, this would not offer a satisfying explanation for the remaining "ballooning" syndromes. The fact that abnormal flow reserve is generalized allows the possibility that the coronary arteries and arterioles may be affected in conjunction with the myocardium. The concurrent increase in myocardial oxygen consumption and abnormal coronary flow reserve offer the possibility that a combination of norepinephrine toxicity and ischemia are the source of myocyte dysfunction.

Nuclear scintigraphy in the acute and recovery phase offers interesting insights into proposed etiology for the ballooning syndromes as well as proposed associated phenomenon. In the acute phase of apical ballooning or Takotsubo, uptake of ^{99}mTc-tetrofosmin, ^{201}Thallium, ^{123}I-beta-methyl-iodophenylpentadecanoic acid (BMIPP), and ^{123}I-meta-iodobenzylguanidine (MIBG) uptake is impaired in a pattern consistent with the observed wall motion abnormality but normalizes over time.[103,112-118] MIBG imaging of the heart is used to image adrenergic neurons while BMIPP examines utilization of fatty acids. Therefore, some derangement of sympathetic innervation of the heart and energy metabolism corresponds to regions of abnormal flow tracer uptake. Positron emission tomography performed using ^{18}F-fluorodeoxyglucose and ^{13}N-ammonia or ^{201}Thallium-SPECT demonstrates impaired glucose uptake that is also disproportionate to any abnormality in perfusion.[119-121] Abnormalities in tracer uptake, particularly of ^{99}mTc-tetrofosmin and ^{201}Thallium need not necessarily imply a perfusion defect: indeed, tracers

such as tetrofosmin, Sesta-MIBI and Thallium accumulate in myocardium as a function of perfusion, capillary permeability, active myocardial uptake and/or transmembrane electrical potential and may thus appear to be abnormal when actual myocardial perfusion is not.[122-125] In the case of thallium, the potassium analog's uptake may be impaired in myocytes with impaired energy metabolism of any source. Therefore, affected myocardium displays abnormal energy metabolism and sympathetic innervation that is transient and may not be *solely* related to abnormal myocardial perfusion.

Similar to the ballooning syndromes, patients with brain injury have abnormalities in nuclear tracer uptake. Unfortunately, results are not quite as uniform. In 41 patients with subarachnoid hemorrhage screened with both ^{99}mTc-methyl-isobutyl-isonitrile (MIBI) and MIBG, all patients had normal MIBI scans. The mean age was 54 years and 32 patients were female. Of the 12 patients with abnormal MIBG uptake, 10 were female. Nine patients had global and three regional abnormalities in MIBG uptake. Abnormal MIBG uptake was associated with an increased dose of α-adrenoceptor agonist therapy. Abnormal MIBG uptake was also associated with an increased likelihood of left ventricular wall motion abnormality and Troponin I release.[126] On the other hand, two of four patients with imaging performed within the first week of SAH, who also had ECG findings typical of Takotsubo cardiomyopathy, had abnormal Thallium scans.[127]

In patients with pheochromocytoma, cardiac MIBG uptake is inversely proportional to circulation catecholamine concentration.[128,129] While not routinely offering a pattern of MIBG uptake similar to Takotsubo, the reduction in MIBG uptake suggests that high concentrations of local catecholamine concentration may alter the

MIBG scan and by inference, the abnormalities seen in Takotsubo are the result of focal norepinephrine excess.

Serial cardiac biopsies, performed in eight patients with a typical Takotsubo presentation, in the acute phase revealed vacuoles of different size, intracellular accumulation of glycogen and disorganization of contractile and cytoskeletal proteins. Extracellular matrix proteins were increased. Signs of apoptotic cell death were absent. After functional recovery, all described alterations showed a nearly complete reversibility.

An examination of gene expression during the acute and chronic phases of catecholamine cardiac toxicity suggests that energy metabolism and inflammatory response are major targets of activity. In table 2, the timing and activity of various genes and gene sets are shown.The acute phase is dominated by oxidative stress communication systems with a later emphasis upon energy metabolism in recovery suggesting an acute response to stress or injury to which the myocyte can respond and recover favorably.

Table 2.[130,131]

Acute-upregulation	Late-upregulation
Nrf-2	targets of the Akt/PKB
c-fos	*oxidative phosphorylation*,
fos B	*mitochondrial genes*
c-jun	
jun B	
NGFI-A	
NGFI-B	
GPX1	
CAT	
RPS6	
eIF4E	
targets of the Akt/PKB	

targets NF-κB and BcL-X_L	

An abundance of data from patient observations and animal models provide strong evidence that myocytes may be adversely affected by catecholamines and that a catecholamine surge is the source of these events. Although inconsistently reported, patients affected by the subgroup categorized as "Takotsubo" cardiomyopathy have elevated circulating catecholamine concentrations. Unfortunately, this is not particularly helpful in terms of cause and effect when such a large proportion of the studied patients are hemodynamically unstable at presentation.[117,132,133]

In 1978, Mosinger, et. al. examined the impact of catecholamine on isolated, perfused rabbit hearts.[134] Exposure to epinephrine or norepinephrine for 4 h produced small, pale, opaque lesions that were irreversible. Microscopic examination revealed necrosis similar to that of myocardial infarction. In fact, exposure to catecholamines or mimics such as tyramine and isoproterenol produces three populations of myocytes, normal, degenerated with disarray of myofibrils and necrotic.[135,136] Interestingly degenerated or necrotic cells are more prevalent at the apex of the heart.[137,138] Uniformly throughout the heart, mitochondrial changes (accumulation, variation of size, swelling, loss of cristae), dilation of sarcoplasmic reticulum or T-tubules and nuclear changes are seen.[136] Relative sparing by pretreatment with β-adrenoceptor antagonists establishes with certainty that catecholamines, acting through their respective receptors initiate an intracellular response that destroys contractile machinery and that may result in cell death.[139-141]

Norepinephrine can drastically increase intracellular cAMP leading to intracellular calcium overload leading to cell death.[141] Exposure of adult cardiac muscle cells to norepinephrine results in a concentration-dependent decrease in viability and mRNA and protein synthetic function accompanied by release of creatine kinase. Norepinephrine-mediated cell toxicity is attenuated by beta-adrenoceptor blockade and mimicked by selective stimulation of the beta-adrenoceptor. The alpha-adrenoceptor appears to be relatively less important.[141] In rats given a single injection of isoproterenol (5 mg/kg) or vehicle, LV function is impaired 1 day afterward improving at 3 days. Similarly, in adult myocytes in-vitro exposed to isoproterenol, myocyte death is observed. The fraction of dead myocytes peaks 1 day after exposure decreasing thereafter. In fact, all inotropic agents except dopamine produce myocyte death, with necrotic myocytes (2-8%, $p < 0.01$) more prevalent than apoptosis (0.06-0.5%, $p < 0.05$). The incidence of necrosis induced by 20 mmol/kg (about 4mg/kg) of an inotropic agent is substantial. It is far greater with subcutaneous norepinephrine (8%) than epinephrine, isoproterenol (4 %), dobutamine or milrinone (2%).[142]

In the 1970's, animal models of "stress" were developed, using a "pharmacologic" restraint or exposure to high gravitational force or electrical shock. Similar models have been used more recently to recreate a "stress" cardiomopathy. Animals exposed to stressors display sudden death, ECG changes and cardiac lesions identical to the effects of catecholamine toxicity.[143-145] The ability to incite the syndrome is modified by estrogen, adrenergic receptor blockade, atropine and vagotomy.[140,145,146] Both myocardium and associated coronary arteries are influenced to varying degrees by the stressor.[139] In the acute phase, after application of a stressor, focal myocardial

necrosis with infiltration of mononuclear inflammatory cells is seen. Surviving myocytes have reduced glycogen stores, accumulation of lipid and swollen mitochondria with focal loss of mitochondrial cristae. Similar to cells exposed to catecholamine, degenerating cells are seen with myofilaments lacking normal cross-striations. In cells with mitochondrial and myofibrillar damage, the sarcoplasmic reticulum and the T system contain numerous dilated vesicles.[140,147] Necrotic lesions are eventually replaced by interstitial fibrosis.[148]

Thus, catecholamines may have a direct and lethal, toxic effect upon cardiac myocytes that is histologically identical to that observed in animal models of acute physiologic "stress" and very similar to humans with a Takotsubo presentation. The histology and models used to recreate stress are consistent with many of the triggers observed to produce many of the stunning syndromes arguing strongly that the stress-stunning syndromes are a manifestation of catecholamine cardiac toxicity.

Source of Catecholamine

In many of the reported patients with apparent catecholamine cardiac toxicity, a source of catecholamine is readily apparent such as, pheochromocytoma, paraganglioma, and exogenous epinephrine administration.(Table 1) In other settings, emotional stress, general anesthesia and brain injury, multiple scenarios for the release of catecholamine are possible. However, one must make congruent the relatively consistent presence of focal abnormalities in wall motion with a toxic effect of catecholamine. A relative difference in receptor density may conceivably produce focal abnormalities after systemic catecholamine release from the adrenal glands. However, although differences

in beta-adrenoceptor concentration in the whole heart have been reported with various myopathies, regional variation has not.[149-151] Further, there are no data regarding the inhomogeneity of norepinephrine uptake at the neural cleft, which may also lead to regional increases in norepinephrine concentration.

A more likely explanation for regional wall motion abnormality is that the source of high concentrations of norepinephrine resulting in toxicity is cardiac sympathetic nerves. The complicated network of plexi that eventually produce the cardiac nerves are such that one may postulate that neurogenic discharge from specific central sites influencing symptathetic tone may be carried along one nerve pathway inserting to a specific region of the heart but not others. Regional, intense neurogenic discharge increases local norepinephrine concentrations to toxic concentrations briefly augmenting contractility but eventually producing contractile dysfunction and death. In an animal model of ischemia, ischemia induced local norepinephrine concentrations in the myocardium, likely neurogenic in origin, approach those established in the in Vitro model to produce norepinephrine myotoxicity.[152] By simultaneously affecting both myocardium and the epicardial vessels and arterioles, acute dysfunction of contractile apparatus and energy metabolism is accompanied by impaired coronary flow or autoregulation of coronary flow, exacerbating or prolonging the effect of the acute event.

In this review, brain injury as a source of acute myocardial dysfunction is grouped with other known sources of catecholamine cardiac toxicity due to the rather remarkable similarities in clinical appearance, course and proposed mechanisms. Left ventricular wall motion abnormality after brain injury is a well recognized phenomenon with rather sophisticated observations dating back many years that offer even further insight into the

syndrome of catecholamine cardiac toxicity. Observed ECG and left ventricular wall motion abnormalities have been most completely described and studied in the setting of subarachnoid hemorrhage (SAH) but a variety of brain lesions have been reported to alter autonomic tone and produce ECG abnormalities.

The majority of patients with subarachnoid hemorrhage manifest some form of ECG abnormality, generally within the first three days after presentation. These abnormalities include, prolonged QTc interval >460 ms in 16%, ST segment elevation in 9-10%, ST depression in 3% and T wave inversion in 7%. Elevation of troponin I may be seen as well and is most closely associated with a QTc interval >460 ms.[66,153] The severity of ECG abnormality is a function of the severity of brain injury and appears to carry prognostic information.[154-157] The complete pattern of the well described "Takotsubo" presentation has been well described in populations with SAH.[158-160] As with the non-neurologic presentations, almost all patients are women. In addition, not all wall motion abnormalities fit neatly into the Takotsubo classification. In a retrospective examination of the Mayo Clinic's neurological ICU database, 24 patients with SAH associated cardiac dysfunction were identified; eight of whom fit into the classical description of Takotsubo. All were women and the severity of their neurologic defect was great.[161]

Brain injury, particular right insular stroke, is associated with a hyperadrenergic state and ST-segment elevation.[162,163] The right insular cortex and quadrigeminal cistern, influence autonomic tone. Interestingly, the right insular cortex is activated by "air hunger" a known trigger of catecholamine cardiotoxicity. [164-168] After brain injury, 7-28% of patients have elevated troponin concentrations and almost 30% exhibit left ventricular

wall motion abnormalities. [66,165,169-171] Changes in the ECG and wall motion occur in the absence of epicardial vasospasm and changes do not correlate with abnormalities in myocardial perfusion.[127,172,173] Although myocardial perfusion is apparently normal, sympathetic innervation is not suggesting an abnormality in sympathetic discharge to the heart.[126]

In 182 patients with subarachnoid hemorrhage, six adrenoceptor polymorphisms were studied to determine their influence upon troponin I release and left ventricular ejection fraction after brain injury.[174] Several polymorphisms (1165C>G *ß1AR* Arg389Gly [rs1801253], 79C>G *ß2AR* Gln27Glu [rs1042714], *α2AR* deletion 964del12bp del322-325) that impair norepinephrine reuptake from nerve terminals or receptor function were associated with an increased likelihood of troponin I release or decline in LVEF. A combination of two such polymorphisms was associated with a more than 15-fold increase in the likelihood of troponin release and a second combination with a 10-fold increase in the likelihood of observing a decline in LVEF. This, as well as reports of family members developing Takotsubo cardiomyopathy after unrelated stressors, provides very strong evidence that the source of cardiac dysfunction after brain injury is norepinephrine and that a genetic predisposition for its appearance exists.[174,175]

In an animal model of SAH, when cardiac abnormalities are seen, there is no evidence of coronary artery spasm by coronary angiography or of significant myocardial hypoperfusion.[176] Hearts from animals following acute, experimental SAH exhibit enhanced sensitivity to norepinephrine infusion and sympathetic nerve stimulation, and are more prone to develop arrhythmias. However, hypersensitivity of the heart may not be explained solely by changes in norepinephrine release or by beta-receptor density.[64]

SAH produces an abrupt rise in norepinephrine and epinephrine concentration minutes after the event that correlates to subsequent release of CK and troponin T.[65]

If the origin of norepinephrine in stress related patients and brain injury is neurogenic, it may explain the varied regional wall motion abnormalities that have been reported. All major sympathetic cardiopulmonary nerves arise from the stellate ganglia and the cervical sympathetic trunks below the level of the cricoid cartilage. These sympathetic cardiopulmonary nerves usually consist of 3 nerves on the right side and 4 on the left. Parasympathetic cardiopulmonary nerves connect with sympathetic cardiopulmonary nerves anterior and posterior to the main pulmonary artery to form the ventral and dorsal cardiopulmonary plexuses. Emerging from these plexuses to innervate the ventricles are 3 distinct relatively large cardiac nerves, the right and left coronary cardiac nerves and the left lateral cardiac nerve.[177] Individual cardiac nerves in the dorsal mediastinum of man may be capable of modifying heart rate, total peripheral vascular resistance, or coronary artery resistance. The left-sided cardiac sympathetic efferent innervation of the left ventricle diverges to innervate the left ventricle by a number of nerves including the dorsal mediastinal, ventral mediastinal, and left lateral cardiac nerves.[178-180] Varied regional innervation may combine with known dysynchronous and uncoordinated nerve discharge to produce regional abnormalities.[181]

Additional evidence in favor of catecholamine as the source of brain injury associated wall motion abnormalities comes from an interesting study of patients with acute stroke. Patients with acute stroke were categorized according to the presence or absence of coronary artery disease. Cardiac wall motion abnormalities in association with stroke were seen far more frequently in patients without symptomatic coronary artery

disease and left insular stroke. The absence of wall motion abnormality in the patients with coronary disease offers the possibility that their medical regimen, often including a beta-blocker, protects them from cardiac effects of brain injury though this particular relationship was not established by this study.[182]

Estrogen

While we have offered evidence that for the ballooning syndromes associated with a physiologic or emotional stressor the relationship with female gender is strong; with the brain injury syndromes the relationship with female gender is possible and with pheochromocytoma and exogenous catecholamine we have no idea, the suggestion that gender influences catecholamine cardiac toxicity is compelling. After immobilization stress, animals previously subjected to ovariectomy experience a reduction in left ventricular function that is not seen in those animals given estrogen supplementation.[183] Ovariectomy significantly increases depolarization-induced NE release from cardiac symptathetic nerve terminals, an effect that is abolished by estrogen supplementation.[184] Within the brain, estrogen influences neuronal behavior modulating autonomic tone.[185-188] Therefore, the predilection of catecholamine cardiac toxicity for post-menopausal women may be a function of the influence of estrogen upon the threshold and capacity for abrupt, severe adrenergic discharge from a neurogenic source.

The predilection of the ballooning syndromes and brain injury associated LV dysfunction for post-menopausal women implies estrogen or its absence as a source of risk. Through multiple mechanisms, estrogen influences autonomic tone, signal transduction in the brain and even cardiac receptor populations. Removal of estrogen by

surgical menopause induces a decline in cardiac vagal modulation with a shift toward sympathetic hyperactivity that returns to the baseline condition after 3 months of estrogen replacement therapy.[189] Estrogen supplementation in perimenopausal women selectively attenuates vasoconstrictor responses to norepinephrine and reduces total body norepinephrine spillover after a stress stimulus, an index of sympathetic neural activity.[190] In perimenopausal women given a 10-min mental arithmetic test, estradiol blunted stress related increases in blood pressure, cortisol, ACTH, plasma epinephrine and norepinephrine, and total body norepinephrine spillover.[191]

Table. Brain Regions Influenced by Estrogen[185,186]

		Efferent pathways
lateral septum	amygdala	lateral hypothalamic area
paraventricular hypothalamic nucleus	hypothalamus	central nucleus of the amygdale
dorsomedial hypothalamic nucleus		parabrachial nucleus
medial amygdaloid nucleus		autonomic preganglionic nuclei
lateral periaqueductal gray		
laterodorsal tegmental nucleus		
locus coeruleus		
paraventricular thalamic nucleus		
nucleus of the solitary tract		

Natural history

The syndrome of catecholamine cardiac toxicity typically begins soon after an initiating stressor, be it an emotional or physiological stressor, a neurogenic event or spontaneous release from a non-neurogenic source. It begins with sinus tachycardia, often in association with chest discomfort and dyspnea. The ECG will then reveal transient ST-

segment elevation (88%) that is indistinguishable from acute myocardial infarction.[8,17,192-195] Concurrent with ECG changes, left ventricular function is impaired with a focal wall motion abnormality in the basal, mid-ventricular or apical left ventricle. The right ventricle may also be variably affected in patients with severe hemodynamic embarrassment. The syndrome may be considered as manifesting an onset, acute decompensation, established dysfunction and recovery phase. During the acute phase, with an abnormal ECG and wall motion abnormalities, complications such as shock, LV thrombus formation, stroke, pericarditis, wall rupture, ventricular tachycardia, heart block and death may be seen with a frequency, using current reports of up to 20%.[74,196-207] When the wall motion abnormality is apical, acute distortion of ventricular geometry may produce dynamic left ventricular outflow tract obstruction and mitral regurgitation. [40,208-211] Due to the fact that the vast majority of reports describe individual cases or small series, there is a sense that the illness is benign. Currently reported complications are seen in almost 20% of cases with death in 3.2%.[8] The most common complication is shock followed by left ventricular thrombus formation and congestive heart failure.[8] As these events become more clinically apparent, the relative frequency of complication and death will likely decline, approaching the true risk.

Cardiac markers are minimally elevated and BNP concentration variably raised.[212-214] Nuclear perfusion scans may suggest a perfusion defect of variable severity. Generally, examination by MRI reveals viable myocardium and may enhance with T2-weighted imaging suggesting myocardial edema.[112,114,215-218] Ventricular wall motion abnormalities closely follow ECG repolarization abnormalities. The evolution by ECG associates with clinical behavior, sinus tachycardia lasting minutes to hours appears

during onset, ST-elevation lasting 1-3 days followed by deep T-wave inversion and QT prolongation lasting 2 weeks to 2 months is send during acute decompensation and established dysfunction and finally recovery to a normal ECG is seen in the recovery phase.[214] As T-inversion resolves, wall motion returns to normal. The time course for full evolution is generally 2-4 weeks with substantial variability. [219] One patient has been reported with abnormal wall motion one year after the event suggesting permanent injury or infarction.[220]

Following resolution, lasting effects upon the left ventricle are difficult to discern. Histologically, there is evidence of fibrosis and rarely, pathological Q-waves may persist. The extent of injury varies substantially. In one case report, apparent "Takotsubo" cardiomyopathy resulted in death due to cardiac rupture. Transmural myocardial necrosis with hemorrhage was found at the rupture site. There were also foci of coagulation and contraction band necrosis with mononuclear lymphocyte infiltrations in other heart regions, and the intensity and distribution of these pathological changes corresponded to the distribution of the LV contraction abnormalities seen on premortem ventriculography.[211]

Episodes may reoccur with significant stressors, in one instance paroxysmal atrial fibrillation, but interestingly, the pattern of wall motion abnormality may not be identical. [45,221-224] Over a four year period, fully one-third of patients will experience recurrent episodes of chest discomfort and 10% will redevelop the full blown syndrome.[225]

Treatment

The majority of clinical evidence addressing catecholamine cardiotoxictiy exists in case reports and clinical series. Therefore, virtually nothing is known of potential

treatments that may either speed recovery or prevent subclinical or clinically evident recurrence. Based upon the proposed mechanism, a calcium entry antagonist should be of value. There is some evidence that limiting calcium entry into the myocyte may protect from catecholamine cardiotoxicity. When, in an animal model, diltiazem pretreatment (20 mcg/kg/min for 5 min. followed by 10 mcg/kg/min x 90 min) is followed by norepinephrine (4 mcg/kg/min for 90 min) or saline infusion, left ventricular ejection fraction and size are unchanged in pretreated animals. Control animals develop mild contraction band necrosis with diltiazem partially alleviating the severity of histological damage.[226]

As previously noted, animal models suggest that pretreatment with adrenergic receptor antagonist should be of value. Meanwhile, if epicardial vasospasm in any way contributes to myocardial injury and dysfunction, beta-adrenoceptor antagonism could prove detrimental. In a retrospective database examination of "Takotsubo cardiomyopathy" with an endpoint of follow-up LVEF, chronic treatment with beta-blockers, ACE-inhibitors, calcium channels blockers and aspirin did not alter outcome. However, since most patients recover without specific therapy and so few experience recurrence, this data is far from definitive, in fact, not even really informative.

The information currently available suggests that the mechanism of developing left ventricular wall motion abnormality and left ventricular dysfunction after brain injury, pheochromocytoma or any trigger for neurogenic norepinephrine release such as emotional stress is catecholamine cardiac toxicity; cardiac because myocardium, epicardial vessels and coronary arterioles may be affected.[227] The central pathophysiology is cellular calcium overload suggesting that treatment with a calcium

channel antagonist will be of value. Additionally, should the epicardial vessels and arterioles be affected as well, treatment with a calcium channel antagonist would incur no additional risk, unlike β-adrenoceptor antagonists. With an estimated population incidence that is very low and a reported recurrence rate of 10%, identified patients represent an important target for therapy; one, which as yet requires additional evidence but whose investigation should center upon the value of calcium channel antagonists. Until trials can be completed, the data is sufficiently compelling to suggest that patients with identified CCT, who may be exposed to additional stressors such as the need for surgical intervention, prophylactic calcium channel antagonist therapy with a non-dihydropyridine calcium channel antagonist should be strongly considered. Additional treatment options include estrogen replacement in mature women, though this option carries additional thrombotic and carcinogenic risk, and aggressive antagonism of adrenergic receptors. A registry of affected patients with their long-term therapy and frequency of syndrome recurrence is badly needed to guide initial diagnostic treatment and long term medical therapy choices.

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