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Regenerative Medicine: Potential Mechanisms of Cardiac Recovery in Takotsubo Cardiomyopathy

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Abstract

Takotsubo cardiomyopathy is an increasingly reported cause of acute chest pain and acute heart failure, and is often associated with significant hemodynamic compromise. The illness is remarkable for the reversibility in systolic dysfunction seen in the disease course. While the pathophysiology of takotsubo syndrome is not completely elucidated, research suggests the presence of a cytoprotective process that allows the myocardium to recover following the inciting insult. Here, we summarize molecular and histologic studies exploring the response to injury in takotsubo disease and provide some discussion on how they may contribute to further investigations in cardiac recovery and regeneration.

Keywords

Takotsubo Cardiomyopathy; Heart Failure; Catecholamines; G-Protein Signaling

Introduction

Takotsubo cardiomyopathy (also known as transient apical ballooning, stress cardiomyopathy, and ampulla cardiomyopathy) is a recently described condition in which patients are found with signs of acute myocardial infarction without clear evidence of coronary artery pathology to explain the presentation [1]. It is estimated to comprise almost 2% of all suspected acute myocardial infarctions [2].

A striking feature of this disorder is the degree to which the observed ventricular dysfunction is reversible, despite significant acute cardiopulmonary decompensation patients can experience [1,3-8]. Patients may require intensive supportive measures including vasopressors, inotropic infusions, and cardiac assist devices, then make significant improvement in a relatively short amount of time. They often show recovery despite multiple

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attacks of Takotsubo syndrome (TKS). Elesber and colleagues followed 100 patients hospitalized for the disease and observed that ten suffered a recurrent episode within a five-year follow-up interval [6]. Interestingly, their four-year survival did not significantly differ from that of an age/gender-matched cohort. Though models estimating the long term mortality in TKS have varied, [6,9] there may be a cardio-regenerative aspect to the condition, since mortality and morbidity appears to not be as severe as the degree of ventricular functional impairment may suggest.

Some features of TKS mimic those of chronic forms of heart failure, however its remarkable reversibility, is unique. As such, it is an attractive disease to study, since insights into its pathogenesis and recovery from injury may provide new ideas on how to induce cardiac myocyte protection and rehabilitation in chronic or progressive cardiomyopathies. The precise molecular mechanisms of the disease are poorly understood, however, and much work is needed to elucidate the means of tissue restoration in takotsubo cardiomyopathy. In this casebased review, we present a unique patient history that poignantly illustrates the remarkable reversibility of cardiac dysfunction in this disease and highlight the latest research on the molecular mechanisms of the disorder and how they enable TKS myocardium to rapidly and nearly-completely recover.

Case Report

A 76-year old woman with history of previously-resected meningioma was admitted to Stanford Hospital in 2002 following a witnessed seizure. Her EKG showed anterolateral ST-segment elevations. Serial serum troponins were analyzed, with peak value 11.4 ng/mL during the hospitalization. She underwent cardiac catheterization, but no coronary artery stenoses were visualized. An echocardiogram demonstrated impaired systolic function (estimated left ventricular ejection fraction 35-45%) and akinesis of the distal half of the left ventricle with a dyskinetic apex. The patient was managed medically, and MRI revealed a lesion in the intracranial fossa consistent with recurrent meningioma. She was discharged on prophylactic phenytoin.

The patient was hospitalized again in 2007 following another seizure. Her EKG showed ST-segment elevations in leads V2-6, with troponin elevation to 5.5ng/mL. Cardiac catheterization again revealed normal coronary arteries, apical ballooning of her left ventricle with inferior and anterior wall akinesis, and ejection fraction less than 20% (Figure 1). Her right atrial pressure was 17mm Hg, cardiac output 3.1L/min, and cardiac index 1.9L/min/m². She exhibited signs of cardiogenic shock with hypotension, hypoxia, pulmonary edema, and high right heart pressures, and was placed on continuous dopamine infusion. Her mean arterial pressure decreased despite up titration of dopamine, and she underwent placement of an intra-aortic balloon pump. Her blood pressure recovered thereafter, and she was weaned off of the inotrope and balloon pump. An echocardiogram demonstrated akinesis of the apical two-thirds of the heart with preservation of the basal segments. The patient's clinical condition improved considerably, and she was discharged. In light of the breakthrough seizures, the patient's neurologists attempted to increase her phenytoin dose, but the patient was unable to tolerate it due to symptomatic hypotension.

The patient was subsequently admitted in 2009, 2011, 2013, and 2014. Each time, she complained of severe left-sided chest pain following observed or suspected seizure. Her workup during these presentations found ST segment EKG changes and elevated troponins, while echocardiograms showed variable degrees of left ventricular dysfunction and apical ballooning consistent with takotsubo cardiomyopathy. She was managed medically on each of her hospital admissions. Two weeks following her latest admission in January 2014, she underwent a follow-up echocardiogram, which revealed completely normal left ventricular size and function with estimated ejection fraction of 67%. She was asymptomatic at this time. To our knowledge, her clinical presentation represents the longest duration of follow up described for any individual with a diagnosed takotsubo cardiomyopathy.

Mechanisms of Injury

It is well established that takotsubo disease often follows an emotionally stressful event in humans [1]. Animal models such as immobilization of rats can be used to induce left ventricular dysfunction and apical ballooning akin to that seen in TKS [10]. This phenomenon is both spontaneously reversible and associated with high circulating catecholamine levels. Indeed, rats exposed to high doses of isoproterenol or epinephrine develop acute, transient heart failure with ischemic ST segment changes on electrocardiogram and depressed left ventricular function [11,12].

In humans, Wittstein and colleagues compared a small cohort of 13 patients with takotsubo cardiomyopathy with 7 patients with Killip class III myocardial infarction and found significantly higher plasma epinephrine and norepinephrine levels in the takotsubo group [13]. TKS-like reversible acute heart failure has also been reported to occur in patients with pheochromocytoma [14-16]. High dose catecholamine is known to be toxic to myocardial cells [14], and it has been suggested that the higher adrenergic receptor density in the apex versus the base of the heart accounts for differential injury leading to the characteristic “ballooning” of the left ventricular apex seen on cardiac imaging [1,17,18]. The complex pathophysiology of TKS also involves elements of coronary microvascular impairment, decreased endothelial nitric oxide production, and obstruction of left ventricular outflow, though theories suggest that an initial catecholamine flood is the trigger and greatest contributor to the disease process [19].

Role of Catecholamines

It is believed that catecholamines contribute to depressed cardiac function in several ways. First, they can generate deleterious degradation products and free radicals via mitochondrial injury, which are directly toxic to vascular and muscular cells of the heart [20,21]. Second, they may lead to alterations in intracellular calcium homeostasis by stimulating calcium-regulatory proteins such as sarcolipin, which cause sarcoplasmic reticulum ATPases to become less responsive to calcium, thus contributing to decreased cardiomyocyte contractility [22].

A particularly intriguing mechanistic finding, however, is that epinephrine, which drives inotropy by binding β_2 adrenoceptors at physiologic concentrations, may actually cause

negative inotropic effects at abnormally high levels such as seen in takotsubo disease [23]. This is theorized to occur via a process known as “stimulus trafficking”: Normally, β_2 adrenoceptors coupled to stimulatory G_s proteins are activated by epinephrine. Surges of epinephrine, however, lead to switching of this signal trafficking to β_2 adrenoceptors coupled to inhibitory G_i proteins instead [24]. This would account for the temporary contractile depression seen in TKS. Presumably, return of physiologic levels of epinephrine would allow switching back to G_s from G_i -coupled β_2 adrenoceptors and recovery of systolic function.

Though seemingly counterintuitive, this behavior is hypothesized to be a mechanism of cardioprotection in cases of stress/epinephrine overload. For example, Paur and colleagues developed a model in which high doses of epinephrine were injected into rats, which developed reversible ventricular apical depression [12]. Interestingly, when G_i proteins were inhibited in these animals using pertussis toxin pretreatment, the myocardial stunning was not seen. The authors then used β_2 -blockade to prevent adrenoceptor shifting from G_s to G_i and found that these rats had significantly higher mortality when administered epinephrine boluses. *In vitro*, G_i -overexpressed myocytes were protected from isoproterenol-induced cell death compared to control myocytes [12].

Insights from Histology

Tissue samples obtained from takotsubo patients and animal models also support the view of a cardioprotective process sparing myocytes in the illness. These biopsy specimens display unique histologic features including contraction band necrosis, interstitial inflammatory cell infiltration, and myocardial fibrosis which are inconsistent with those seen in ischemic cardiac necrosis [14,18,19,22,25]. Many of the changes, particularly the disruption of contractile proteins, increased collagen fibrosis, and vacuolization were found to be reversed on serial biopsies of four TKS patients corresponding with their clinical recovery [25]. In their study, Nef and colleagues also analyzed the four patients' samples for apoptotic markers such as Complement-9, TUNEL (Terminal deoxynucleotidyl transferase dUTP nick end labeling) positivity, and morphologic changes via electron microscopy, interestingly finding no association. As such, they postulated that the vacuolization patterns seen suggested the existence an underlying protective mechanism that prevented apoptosis of the affected cells despite the initial cardiac insult. Indeed, microarrays from TKS patient cardiac biopsies (compared to control specimens) showed upregulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) cell survival pathway, which is known to be anti-apoptotic [26]. Thus, acute impairment of ventricular function could be due to damage in the contractile elements (loss of actin and myosin), increased extracellular matrix proteins causing fibrosis, and depressed myocyte functional capacity, rather than direct cell death [19]. Survival past the initial catecholamine-induced injury would subsequently enable the stunned, but still-living cells to recuperate, clear fibrotic tissue, and restore healthy myocardium.

Conclusion

Takotsubo cardiomyopathy is a distinctive form of heart failure in which patients exhibit considerable acute loss of myocardial function, but usually experience complete recovery of cardiac function after the initial disease manifestation. The molecular pathophysiology is incompletely understood, but the above investigations shed some light on the response of heart tissue to supraphysiologic levels of catecholamine. Both *in vitro* and *in vivo* studies suggest that cardiomyocytes harbor a protective mechanism from epinephrine-induced apoptosis, namely a switch in G_s to G_i coupling of the β_2 adrenoceptor, following an episode of catecholamine overload. This explanation may account for some of the differences between chronic heart failure, where persistently-elevated catecholamines are seen, and takotsubo disease, where supraphysiological catecholamine levels are only transiently elevated. If this is indeed the case, the development of ways to enhance G_i coupling to the β_2 adrenoceptor could represent a new therapeutic approach for reducing cardiac myocyte loss in chronic heart failure. Additionally, elucidating downstream pathways from this relationship, such as the PI3K/AKT system and other pro-survival pathways may generate novel anti-apoptotic agents.

This is yet likely a simplified explanation for the response to injury in a complex environment involving the interplay between myocytes, endothelial/vascular elements, inflammatory cells, and connective-tissue generating cells. Whether there may be a role of a certain population of progenitor cells in the adult heart tissue in the TKS regenerative process remains to be seen. One intriguing study has reported that cardiac stem cells appear to respond differently to catecholamine overload states compared to mature myocytes [11]. Nevertheless, the insights and opportunities gained from this unique disorder, along with its many unanswered questions, warrant further investigation for researchers in regenerative medicine.

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Figure 1.

Cardiac catheterization showing apical ballooning of the patient's left ventricle with basal hyperkinesis and apical akinesis, characteristic of the "octopus trap" shape in takotsubo cardiomyopathy during diastole (left) and systole (right). Ejection fraction was estimated at less than 20%.