Mechanisms of myocardial stunning in stress-induced cardiomyopathy

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Abstract

Stress-induced cardiomyopathy, in contrast to acute myocardial infarction, is a type of acute heart failure characterized by reversible left ventricular dysfunction. Cardiac imaging primarily reveals left ventricle myocardial stunning, 81.7% of which is apical type. Emotional or psychological stress usually precedes the onset of stress-induced cardiomyopathy, which is increasingly being recognized as a unique neurogenic myocardial stunning disease. To distinguish between acute myocardial infarction and acute viral or auto-immune myocarditis, this review summarizes specific mechanisms of myocardial stunning in stress-induced cardiomyopathy, such as calcium disorders, metabolic alterations, anatomical and histological variations in different parts of the left ventricle, and microvascular dysfunction.

Key words: Stress-induced cardiomyopathy; Myocardial stunning; Calcium disorders; Metabolic alterations; Coronary microvascular dysfunction

Introduction

Stress-induced cardiomyopathy, also known as Takotsubo syndrome (TTS), broken heart syndrome and apical ballooning syndrome, accounts for approximately 5–6% of all suspected cases of acute coronary syndrome in women [1]. This acute heart failure syndrome is characterized by myocardial hypocontractility from the mid left ventricle to the apex without clear coronary artery stenosis. The classical definition of myocardial stunning is cardiac mechanical dysfunction following complete recovery of coronary blood flow or transient myocardial ischemia. Cardiac systolic function can be restored within hours or days. In stress-induced cardiomyopathy, the LVEF usually recovers in the short term, whereas ECG changes and BNP levels may require 6–12 months to recover. Therefore, stress-induced cardiomyopathy is recognized as a unique neurogenic myocardial stunning disease. The precise pathophysiological mechanism of typical left ventricular stunning in the acute stage of stress-induced cardiomyopathy remains unclear. This review discusses the mechanisms of left ventricular myocardial stunning in stress-induced cardiomyopathy.

1. Calcium disorders

After calcium disorders in ventricular myocytes, myocardial stunning can be caused by several mechanisms, such altered release and uptake of calcium ions in the sarcoplasmic reticulum, and decreased sensitivity of calcium ions to muscle filaments. Fatal arrhythmias occur in 13.5% of patients with stress-induced cardiomyopathy. These patients typically have a low ejection fraction [2], which may be closely associated with a Ca^{2+} imbalance affecting cardiomyocyte contraction and relaxation. The influx of calcium ions via an L-type calcium current (ICa-L) is critical for the heart's excitation-contraction coupling, and causes the

release of Ca^{2+} from the sarcoplasmic reticulum. The intracellular Ca^{2+} then binds troponin C and causes cardiomyocytes to contract. The balance of sarcoplasmic reticulum and cytoplasmic calcium is primarily regulated by SERCA/PLB and RyR2 on the endoplasmic reticulum membrane, which is important in regulating cardiomyocyte contraction and relaxation [3].

The contraction and relaxation of cardiomyocytes in the acute and convalescent stages of stress-induced cardiomyopathy have been found to be slow, according to confocal microscopy, and to be associated with a slow peak value of the calcium transient and slow recovery of calcium in the sarcoplasmic reticulum, thus resulting in calcium transient stunning [4]. The ratio of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) to phospholamban (PLB) is the most important factor in sarcoplasmic reticulum Ca^{2+} recovery [5]. SERCA is a Ca^{2+}-ATPase in the myocardial sarcoplasmic reticulum that actively pumps cytoplasmic calcium into the sarcoplasmic reticulum. PLB is a phosphoprotein with 52 amino acid residues that binds the cardiomyocyte sarcoplasmic reticulum. It is found primarily in ventricular myocytes, and it interacts with SERCA via phosphorylation and dephosphorylation, thus regulating Ca^{2+} uptake. The SERCA/PLB ratio accurately represents myocardial diastolic and systolic activity, and changes in this ratio directly reflect changes in cardiac function [6]. In a study of ten patients with stress-induced cardiomyopathy, sarcolipin (SLN), which is expressed primarily in atrial myocytes, has been found to be highly expressed in left ventricular cardiomyocytes, and to decrease SERCA's activity and affinity for calcium ions in collaboration with phosphorylated PLB; however the expression of the sodium calcium exchanger NCX and ryanodine receptor 2 (RyR2) has not been found to increase [7]. Under

isoproterenol stimulation, pluripotent differentiated stem cells from patients with TTS show

increased cyclic adenosine monophosphate (cAMP) and subsequently pSer2808-RyR2, thus

increasing calcium leakage from the diastolic sarcoplasmic reticulum [8]. In vivo, an increase

in Ang II increases the expression of oxidized calmodulin-dependent protein kinase II (CaMKII)

and consequently the level of pSer2808-RyR2 [9]. Wang et al. have discovered that adult

cardiomyocytes, after 24-hour noradrenaline stimulation, show an increase in contraction

amplitude to the same extent as that after short-term (10-minute) stimulation. However, this

long-term stimulation is dependent not on an increase in PKA but on an increase in P-[17]

ThrCaMKII. The spatial conformation of RyR2 is altered by phosphorylated CaMKII [10], thus

suggesting that calcium ion disorders in stress-induced cardiomyopathy occur through a

multifaceted process. Other pathways in cardiomyocytes that cause phosphorylation and

oxidation of RyR2 may exist, involving the participation of various mechanisms, such as direct

sympathetic toxicity and excessive catecholamine. MicroRNA (miR)-16 and miR-26a have

been identified as blood specific markers in patients with stress-induced cardiomyopathy in

recent studies. Liam et al. have discovered that overexpression of miR-16 and miR-26a in

apical cardiomyocytes significantly decreases apical cardiomyocyte contractility while

increasing the contractility of cardiac basal cardiomyocytes stimulated by isoproterenol.

Further research has shown that overexpression of microRNAs associated with

stress-induced cardiomyopathy inhibits the voltage dependence of the ICa-L β1 protein

(voltage dependent L-type calcium channel subunit beta-1, CACNB1), thus decreasing the

calcium transient amplitude and calcium concentration in the sarcoplasmic reticulum [11].

Therefore, stress-induced cardiomyopathy ultimately decreases excitation-contraction

coupling and leads to myocardial stunning.

2. Metabolic alterations

Metabolic alterations are closely associated with myocardial stunning, according to recent research. Patients with stress-induced cardiomyopathy have metabolic alterations, particularly lipid metabolism, and myofibrillar structure destruction, that may decrease ATP utilization, in a crucial aspect in the myocardial stunning process. Fatty acids, which provide 65% of the ATP in cardiomyocytes, are the preferred substrate for myocardial utilization. FDG-PET has revealed abnormal apical metabolism in patients with acute stress-induced cardiomyopathy [12]. The utilization of free fatty acids decreases, and lipid droplets infiltrate into the apical segment of myocardial tissue [13]. The expression of the apolipoprotein B (ApoB) lipoprotein gene, which is involved in intracellular lipid transport, has been found to be diminished in left ventricular endocardial biopsies of patients with stress-induced cardiomyopathy. The cardiac function of the stress-induced cardiomyopathy model caused by isoproterenol has been found to significantly improve in mice overexpressing ApoB [14]. HL-1 cardiomyocytes placed in the plasma of patients with high concentrations of epinephrine or stress-induced cardiomyopathy inhibit electrical activity in a reversible manner. Excess lipids in cells accelerate cellular lipid oxidation, result in accumulation of cellular reactive oxygen species (ROS), and disrupt intracellular protein homeostasis and biofilm integrity [15]. In stress-induced cardiomyopathy, the left ventricle increases glucose uptake by increasing the expression of the glucose transport receptor, but glucose-6-phosphate, the end product of glycolysis, increases, thus indicating that glucose metabolism is abnormal in stress-induced cardiomyopathy [16]. Carnitine palmitoyltransferase-1b (CPT-1b) is a key enzyme that is

located on the mitochondrial membrane, where it regulates fatty acid oxidation. Its activity is regulated by malonyl coenzyme A (malonyl CoA), a product of Krebs cycle regulation. During stress-induced cardiomyopathy, the mRNA level of CPT-1b significantly increases in the apex of the heart, although the protein level does not change. Malonyl CoA overexpression may eventually result in the down-regulation or modification of fatty acid oxidation pathways. The mitochondrion is known as the powerhouse of the cell, and mitochondrial dysfunction is considered the primary mechanism linking myocardial stunning to stress-induced cardiomyopathy. Radionuclide Tc-99m sestamibi myocardial perfusion imaging has revealed that the mitochondrial membranes of cardiomyocytes are damaged in patients with newly diagnosed and recurrent stress-induced cardiomyopathy [17]. Mitochondria isolated from patients with stress-induced cardiomyopathy show diminished mitochondrial area and activity of the NADH-associated respiratory chain in vitro [4]. Tempol is a superoxide dismutase analogue that reduces ROS generated by stress-induced cardiomyopathy, thus decreasing mitochondrial swelling and increasing mitochondrial membrane potential [18]. The key factors in mitochondrial ROS production are oxidative phosphorylation associated with metabolism and mitochondrial respiratory chain dysfunction. Excessive ROS accumulation causes a continual loss of potassium ions and high-energy phosphate, and alters the concentrations of calcium ions in cells, thus decreasing cardiomyocyte contractility [19].

3. Anatomical and histological variations in various parts of the left ventricle

Apical myocardial stunning, which may be the basis of stress-induced cardiomyopathy, is caused by anatomical and histological differences between the apical and basal regions of the heart. In recent research, isolated single apical and basal cardiomyocytes cultured in vitro

showed no statistically significant differences in cAMP levels after β2 receptor activation, but the reactivity of β2 adrenergic receptor-dependent cAMP decreased because of the presence of more T-tubes and caveolar depressions in cardiac basal cardiomyocytes. Comparisons of apical and basal cardiomyocytes isolated from the same heart have indicated that apical cardiomyocytes are more responsive to cAMP, because their microdomains are composed of fewer T-tubes and caveolar depressions, and a lower cAMP buffer [20]. Cardiac sympathetic excitation produces cardiotoxicity in the heart, mainly through noradrenaline. MIBG is an analogue of guanidine, an adrenal nerve blocker, which is stored in the vesicles of sympathetic nerve endings. ^{123}I-MIBG myocardial imaging can be used to assess the changes in adrenergic nerve function in the myocardium. The H/M value in patients with stress-induced cardiomyopathy is significantly lower than that in patients with acute myocardial infarction, and it recovers after the onset of myocardial stunning [21].

In this process, the activation of the left stellate ganglion and cardiac sympathetic nerves can cause typical apex myocardial stunning, whereas midventricular myocardial stunning may occur after activation of the right stellate ganglion and cardiac sympathetic nerves. [22]. The density of basal sympathetic ganglia at the bottom of normal human hearts is approximately 40% higher than that at the cardiac apex; this finding appears to be inconsistent with the typical TTS-like changes in the left ventricle in stress-induced cardiomyopathy. However, β2 adrenergic receptors are more densely distributed in the heart's apex than the bottom, thus explaining the uneven distribution of β2 adrenergic receptor density, which is an important factor in maintaining sympathetic balance under physiological conditions. When stress-induced cardiomyopathy occurs, this physiological difference may result in a more

sensitive response of apical cardiomyocytes to catecholamine in the blood. In injection of large amounts of norepinephrine and isoproterenol into the jugular veins of rats, co-injection of isoproterenol induces greater apical myocardial stunning. Thus, increased β-adrenergic receptor density at the apex significantly contributes to left ventricular systolic dysfunction in stress-induced cardiomyopathy.

G protein coupled receptor kinase (GRK) is a key regulator of β-AR signal transduction and desensitization, which promotes and activates β-AR phosphorylation. β-arrestin, which acts as membrane translocation, effectively binds β-adrenergic receptors, thus restricting the distribution of β-AR on the cell membrane. In patients with acute TTS, endocardial biopsy has revealed overexpression of GRK2 and β-arrestin2. It is more prevalent in the cell membrane in stress-induced cardiomyopathy than in dilated cardiomyopathy. Decreased GRK2 and β-arrestin2 have been observed in the second biopsy during cardiac function recovery, thus indicating that GRK2 and β-arrestin2 play important roles in left ventricular dysfunction in stress-induced cardiomyopathy [23]. However, findings regarding whether GRK5 is involved in the progression of stress-induced cardiomyopathy are inconsistent across studies, and more research is needed to confirm this possibility [24], [25]. Circulating norepinephrine and epinephrine interact with β1 and β2 under physiological conditions. Adrenaline binds the β1 adrenergic receptor, which in turn activates the Gs protein-adenylyl cyclase (AC)-protein kinase A (PKA) pathway, thus resulting in a positive inotropic effect. Patients with stress-induced cardiomyopathy are stimulated by supraphysiological catecholamine concentrations in the blood and subsequently produce large amounts of PKA via stimulation of the β1 and β2 adrenergic receptor, thereby resulting in β2 adrenergic receptor

phosphorylation, further phosphorylation of GRK and recruitment of Gβγ. As a result of the change in β2 receptor binding from Gs to Gi, the coupling of the β2 adrenergic receptor and Gi protein decreases AC production and muscle strength [26]. This change is reversed when the concentration of circulating catecholamine decreases [27], [28]. The histological differences between the apex and the bottom of the heart make the apex more responsive to catecholamine in the acute stage of stress-induced cardiomyopathy. In this stage, changes in the β -adrenergic receptor signaling pathway have important roles in the occurrence of myocardial stunning. When the circulating catecholamine concentration falls below that in early stages of the disease, left ventricular myocardial stunning can be ameliorated. This aspect is the critical distinction between this disease and irreversible ventricular wall motion abnormalities caused by myocardial infarction.

4. Microvascular dysfunction

Patients with stress-induced cardiomyopathy experience emotional stress and physical injury, which primarily result in a sharp increase in blood catecholamine levels, owing to abnormal activation of the brain cardiac axis and sympathetic adrenal system [29]. Wittstein et al. have discovered that the plasma catecholamine concentration is several times higher in patients with acute TTS than in patients with ST-segment elevation myocardial infarction. One week after the onset of TTS, patients' plasma catecholamine levels have been found to remain higher than those in patients with ST-segment elevation myocardial infarction [30]. The rapid release of catecholamine causes transient ischemia of the myocardium via multiple coronary artery spasms and coronary microvascular dysfunction, thus resulting in local myocardial systolic dysfunction. In the autopsies of five patients with stress-induced cardiomyopathy,

endocardial or transmural myocardial necrosis has been observed. The International Center

for stress-induced cardiomyopathy has registered the coronary angiography results of 1,016

patients with stress-induced cardiomyopathy, 64.2% of whom had coronary atherosclerosis.

Notably, 41.2% of the patients had non-obstructive coronary atherosclerosis, and 23% had

obstructive arteriosclerosis and clearer slow blood rheology of the anterior descending branch

[31], [32], [33]. In patients with stress-induced cardiomyopathy, the fractional flow reserve and

thrombolysis in myocardial infarction frame counts have been measured. The findings

indicated no significant abnormalities in coronary artery function, thus demonstrating that

stress-induced cardiomyopathy fundamentally differs from the irreversible phased dyskinesia

caused by severe vascular occlusion. Noninvasive microvascular assessment, such as

myocardial perfusion magnetic resonance imaging, has indicated that microvascular

dysfunction may play a major role in the pathogenesis of stress-induced cardiomyopathy.

Microvascular dysfunction is unevenly distributed in the dominated area of three coronary

arteries, among which anterior descending artery microvascular dysfunction is more common

and clear. The area of abnormal myocardial stunning is approximately the same as that of

microvascular dysfunction in the acute stage of stress-induced cardiomyopathy [34].

Increasing evidence indicates that stress-induced cardiomyopathy cannot be clearly

distinguished from coronary artery obstructive disease. The original coronary atherosclerosis

of stress-induced cardiomyopathy, particularly in the anterior descending branch, may cause

transient and severe myocardial ischemia due to vasospasm resulting from high plasma

catecholamine, thus leading to myocardial stunning at the apex of the left ventricle.

Conclusion

Although most left ventricular systolic function can be restored in most patients with

stress-induced cardiomyopathy, the risk of serious in-hospital complications is comparable to

that of patients with acute coronary syndrome. Because of the complex mechanisms of

brain-heart interaction, the differences between myocardial stunning caused by the acute

stage of stress-induced cardiomyopathy versus myocardial infarction include not only the

short-term recovery of systolic function in the former, but also the association between the

long-term presence of diastolic dysfunction and the prognosis of stress-induced

cardiomyopathy [35].

Consequently, better understanding of stress as a distinct myocardial stunning disease is

critical to differentiate it from the typical myocardial stunning caused by severe coronary artery

stenosis. This review discussed the causes of transient systolic dysfunction of the left

ventricular apex, including calcium ion disorders, metabolic alterations, coronary artery

spasms, and microvascular dysfunction. However, because clinical samples of stress-induced

cardiomyopathy are difficult to obtain, and animal models have limitations, the pathological

mechanism of left ventricular systolic dysfunction cannot be fully explained. More research is

needed to establish the pathogenesis of stress-induced cardiomyopathy.

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Conflicts of interest

The authors declare they have no conflicts of interest.

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