Takotsubo cardiomyopathy (TCM) is a transient myocardial stunning, typically showing apical ballooning. Although catecholamine toxicity, vasospasm, and disturbed microcirculation have been implicated, the precise pathophysiology of TCM is unknown. We present a two-step energy failure hypothesis which could explain the clinical course and pathogenesis. Sudden stress-induced increase in cardiac energy demand of normal subjects can be compensated for by additional supply of long chain fatty acids released from triglycerides stored in adipose tissues. Subjects at high risk for TCM cannot tolerate such stress-induced energy demand/supply imbalance, which triggers initial energy failure and induces myocytes' stunning in vulnerable mid- and apical myocardial segments. Receptor-mediated uptake for energy substrates then declines due to impairment of contraction-dependent recruitment of responsible transporters (e.g. CD36). This in turn induces the second energy failure, which prolongs the myocardial stunning. Eventually, spontaneous or therapeutic improvements in the energetics awaken the heart.

Keywords: BMIPP, Cardiac energetics, Hypothesis, Long chain fatty acid, Myocardial stunning, Takotsubo cardiomyopathy
maximum contractility. We reported on clinical phenotypes of human genetic deficiency of CD36 and ATGL (11, 12), both of which are important molecules for cardiac energetics. CD36 deficiency presenting impaired supply of LCFAs to the heart often leads to cardiomyopathy and coronary artery diseases (11). ATGL-deficient patients suffering from severe heart failure requiring cardiac transplantation, showed a novel phenotype called TG deposit cardiomyovascularopathy (TGCV) (12, 13), characterized by massive cardiomyocyte steatosis and unique atherosclerosis with TG-deposit smooth muscle cells. In TGCV, affected cells suffer from energy failure and lipotoxicity caused by ATGL deficiency at cellular levels (13). These clinical observations in two genetic models above strongly led us to consider that impaired energetics may be relevant for the pathogenesis of human cardiovascular diseases.

Even though having higher energy demand, the heart stores only small amounts of TGs, the deposit form of energy substrates. LCFAs derived from food are stored as TGs in adipose tissues, found in subcutaneous, visceral, pericardial, and perivascular lesions (14). When required, TGs are hydrolyzed and the released LCFAs are then delivered as energy substrates to the heart by paracrine as well as from circulation (15). Iodine-123 labeled 15-(4-iodophenyl)-3-(R, S)-methyl-iodophenyl pentadecanoic acid ($^{123}$I-BMIPP) (16) is a radioactive analogue for LCFA, widely used in clinics to image myocardial LCFA metabolism and diagnose patients with myocardial infarction, angina pectoris, and hypertrophic cardiomyopathy (17). In normal subjects, $^{123}$I-BMIPP is rapidly accumulated into the myocardium after intravenous injection of the agent and transiently trapped in the TG pool of myocardial cells, and then metabolites of the agent are gradually washed out from the cells due to a mitochondrial $\beta$ oxidation. The relatively slow kinetics of the agent compared to corresponding natural LCFAs allows visualization of the fatty acid metabolism of myocardium. The image also reflects the shift of energy utilization depending on the regional abnormalities occurred under various myocardial disorders (18, 19).

Here, our hypothesis states that energy failure triggered by severe demand/supply imbalance may lead to TCM. Furthermore, we will discuss whether our hypothesis can be integrated with previous findings, and finally how we can test our hypothesis.

Two energy failure steps involved in TCM (Fig. 1)

1. Initial energy failure due to imbalance between energy demand and supply.

Strong and unexpected stress stimulates the sympathetic nerve system and increases the heart rate and myocardial contraction, resulting in increased energy demand in the heart. It should be noted that these sympathetic stimuli simultaneously increase lipolysis in the adipose tissue, where hormone-sensitive lipase, phosphorylated by catecholamine, and other lipases hydrolyze TG to produce LCFAs (15), which are supplied to the heart. In normal subjects, the stress-induced increase in cardiac energy demand can therefore be compensated for by an increase in energy supply from adipose tissues.

A hypothetical balance between energy supply and demand in TCM patients, described in previous reports, is illustrated in Fig. 2. Patients with anorexia nervosa (20) or malnutrition (21) suffer from a deficient supply of energy substrates such as LCFAs and glucose due to the loss of adipose tissue and starvation. Postmenopausal women and elderly people appear to have sufficient adipose tissue, but their adipocytes generate less lipolysis and are resistant to sympathetic stimuli (22). Subjects with genetic CD36 deficiency have defective uptake of LCFA (9, 23). Subjects using drugs and compounds which...
increase sympathetic activities are at high risk of a surge in energy demand. Patients with pheochromocytoma, paraganglioma (24), hyperthyroidism, and athletes with little body fat and engaged in strenuous activities are at the highest risk due to increased demand for and reduced supply of energy. Because these subjects cannot tolerate sudden stress, initial energy failure can be triggered.

We also need to mention about circumstances and situations at the onset of TCM. Disasters and critical medical conditions such as earthquake and subarachnoid hemorrhage affect food intake and appetite. Subjects with stress may be obligated to fasting and away from foods mentally as well as physically. This nutritional disadvantage may increase the risk for initial energy failure.

2. Second energy failure due to akinesis/non-contraction-induced impaired uptake of energy substrates

Energy substrates for heart are taken up by cell surface transporters and receptors. CD36 is one of major transporters responsible for taking up LCFAs (9). Many previous papers described that, in TCM patients, the uptake of BMIPP was defective in the akinetic myocardium and that BMIPP is useful for the diagnosis for TCM (25-28). During the recovery phase of TCM, however, these uptakes can become normalized, as shown in Fig. 3. Furthermore, even in in vitro biological experiments using rodents’ cardiomyocytes, cell surface and membrane translocation of CD36 was found to be contraction-dependent (29). If this finding applies to human transporters in vivo, TCM-associated stunning in the myocardium can be expected to impair the translocation of the transporter for energy substrates to the cell surface. This would then trigger the second energy failure, which prolongs myocardial stunning.

3. The recovery phase

During the second energy failure, affected cardiomyocytes survive using alternate and low-energy substrates such as amino acids or ketone bodies, and subsequent spontaneous or therapeutic improvement in energetics awakens the myocytes. Once they start contracting, these myocytes recruit the transporters for LCFA and glucose to the cell surface to regain their major energy source for maximum contractility.

**Takotsubo shape and energy failure**

1. Possibility of segmental difference of myocardial workload and energy demand

The myocardial fibers in the left ventricle, which consist of three layers, contract/relax and rotate and twist the ventricle, providing the substantial mechanical power required for systole/diastole. Previous cinefluorographic studies demonstrated that mid- and apical segments were more hyperkinetic than the basal one. In addition, recent studies including 2-dimensional speckle tracking demonstrated that the mid- and apical myocardium may be subject to higher longitudinal strains than the basal one (30). It has also been reported that apical ventricular segments have higher concentrations of adreno-receptors (4). Therefore, it is tempting to speculate that cardiomyocytes in the mid- and apical region feature a higher physiological workload and more energy demand than those in the basal region, although the energetics at the single cardiomyocyte level needs clarification. We therefore consider the mid- and apical myocardium to be more susceptible to initial energy failure than the basal one.

2. Epicardial adipose tissue (EAT) as emergent energy source for the heart

The mid- and apical myocardia are usually overlapped anatomically with EAT, whereas the basal one are not. Previous in vitro study mentioned that EAT may be a local energy source for the heart (31). We think that EAT may function as an emergent and supplementary source for delivering LCFA to the adjacent myocardium with higher energy demand at the time of sudden and massive stress. While EAT has much lower volume than subcutaneous and visceral fat, it is much closer to the heart which may be advantageous for delivering energy source, especially during collapse due to disaster and stress. Under pathological conditions resulting in less EAT, such as starvation and emaciation, myocardium overlapped with EAT may be more susceptible to energy failure. In this connection, rodent models for TCM (32) have no EAT or certainly less than human.

The ampulla shape is common, but not observed in all TCM cases (7, 33), which may be explained by possible individual differences in segmental susceptibility to energy failure and the distribution and volume of EAT.
Relationship with previous findings and other hypotheses

1. Catecholamine cardiotoxicity

Many papers have reported enhanced catecholamine levels in TCM patients (3, 4). We believe that catecholamine surge is an important condition for initial energy failure and could explain some pathological findings such as contraction band necrosis and interstitial edema (4). As long as the balance between energy demand and supply is maintained, catecholamine alone cannot account for the development of TCM.

2. Epicardial coronary vasospasm and impaired microcirculation

In studies including the initial case series (1), some TCM patients exhibited epicardial coronary vasospasm (4-7). In addition, impaired coronary microcirculation and microvascular constriction (34-36) have been proposed as a possible underlying mechanism for TCM. In these hypotheses, irrespective of epicardial artery or microvasculature, vasoinconstriction or spasms associated with increased catecholamines are believed to be involved in the pathogenesis of TCM. It is particularly of importance to know possible relationship between impaired microcirculation or microvascular constriction and energy failure hypotheses. It is noted that some patients with TGCV, which is a model for energy failure as described above, suffer from vasospastic angina (37, 38). Experimental and clinical studies for vascular or microvascular energetics, of which information is currently scarce, are important issues for near future.

To test hypothesis

Myocardial energetics in TCM patients could be tested with magnetic resonance spectroscopy, but this technique has not been widely used. It may be worth testing in subsequent clinical trials whether administration (e.g. intracoronary) of an alternative energy source can relieve symptoms and shorten the recovery phase for TCM patients. We believe that cardiomyovascular energetics can be important for understanding as yet unexplained, unknown, or undefined cardiovascular diseases.

Contributors

KH raised the concept of hypothesis and wrote the manuscript. KS, YI, YS, and HN contributed to the construction of hypothesis based upon their specialties.

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Conflicts of interest

We declare that we have no conflicts of interest.

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