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REVIEW

A new insight of mechanisms, diagnosis and treatment of diabetic cardiomyopathy

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Abstract Diabetes mellitus is one of the most common chronic diseases across the world. Cardiovascular complication is the major morbidity and mortality among the diabetic patients. Diabetic cardiomyopathy, a new entity independent of coronary artery disease or hypertension, has been increasingly recognized by clinicians and epidemiologists. Cardiac dysfunction is the major characteristic of diabetic cardiomyopathy. For a better understanding of diabetic cardiomyopathy and necessary treatment strategy, several pathological mechanisms such as impaired calcium handling and increased oxidative stress, have been proposed through clinical and experimental observations. In this review, we will discuss the development of cardiac dysfunction, the mechanisms underlying diabetic cardiomyopathy, diagnostic methods, and treatment options.

Keywords Diabetic cardiomyopathy · Cardiac dysfunction · Impaired calcium handling · Oxidative stress · Fatty acid · Ion channel · Diagnosis · Treatment

Introduction

Diabetes mellitus (DM) is a major chronic disease affecting a large population across the world. It has been estimated that there will be 300 million people with diabetes by 2050 [1]. Cardiovascular diseases, especially coronary artery disease (CAD), account for 70% deaths among diabetic patients. In addition to clear CAD influence, in 1972, Rubler reported several diabetic patients with heart failure under normal coronary artery condition and subsequently brought up a new clinical entity—diabetic cardiomyopathy [2]. With experimental and clinical study for 30 years, diabetic patients and animals have been recognized with increasing risk to develop cardiovascular disease including heart failure even without CAD or hypertension. Diabetic cardiomyopathy is considered as depressed ventricular function, which further results in pathologically myocardial, structural, and functional changes. To date, several pathological mechanisms underlying diabetic cardiomyopathy have been proposed and we are attempting here to review the current knowledge on this topic.

Cardiac dysfunction

The concept of diabetic cardiomyopathy is defined as ventricular dysfunction without evidence of CAD or hypertension. Diabetic patients are at increasing risk to develop CAD and hypertension. However, the existence of diabetic cardiomyopathy is considered to occur even without presence of CAD or hypertension. Diabetic cardiomyopathy is a specific cardiomyopathy, which may affect the myocardium secondary to diabetes. This cardiomyopathy may in fact occur in combination with CAD or hypertension, and therefore be a significant contributing factor to diabetic fatality. In either clinic or animal experiments, however, in order to isolate diabetic cardiomyopathy, CAD and hypertension have been excluded. Therefore, diabetic cardiomyopathy is a disease development affecting myocardial remodeling and eventually leads to cardiac diastolic and systolic dysfunction.

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Diastolic dysfunction

Diastolic dysfunction is a major characteristic in diabetic cardiomyopathy. Initially, scientists recorded cardiac dynamic parameters using cardiac catheterization and demonstrated a decrease in left ventricle end-diastolic volume and an increase end-diastolic pressure in diabetic patients without CAD [3]. However, the abnormal diastolic function in patients was mainly studied by using Doppler techniques. It has been reported that there is a significant impairment in diastolic function in individual with Type 1 and Type 2 diabetes but even without CAD and HF [4]. Study on Type 2 diabetic patients with normal blood pressure and glucose levels implicated over 50% diastolic abnormality compared to healthy controls [5, 6]. Furthermore, animal model of Type 2 diabetes, Zucker diabetic fatty (ZDF) rat and *db/db* mice, presented a diastolic dysfunction in left ventricle. Independent of atherosclerosis, these animal models were characterized with insulin resistance, obesity, and different level of hyperglycemia, which might lead to cardiac complications [7, 8]. Scientists using *db/db* mouse model assumed a possible mechanism underlying Type 2 diabetes related diastolic dysfunction. They proposed an increased fatty acid uptake by and altered calcium homeostasis in cardiomyocytes, which caused an elevated cardiac triglyceride concentration and contractile dysfunction. Decreased contractility is associated with impaired sarcoplasmic reticulum (SR) Ca^{2+} release, which probably exerts an impact on diastolic abnormality [9–11]. Detailed calcium homeostasis in diabetic cardiomyocytes may be directly related to diastolic dysfunction and needs further investigation.

Systolic dysfunction

Systolic dysfunction is the reduced myocardial ability of ejecting blood, which is a later development after diastolic dysfunction occurring in diabetic cardiomyopathy. Although several studies have confirmed that systolic dysfunction is associated with diabetes, there is a lack of specific and conclusive reports [12]. Clinically, standard two dimensional (2D) echocardiography may possibly miss the detection of subtle systolic dysfunction. Recently, a couple of sensitive methods, such as tissue Doppler strain analysis, can detect systolic abnormalities in diabetic patients with diastolic dysfunction [13–15]. Besides, experimental investigations in rodent models implicated systolic dysfunction by magnetic resonance imaging and pressure–volume loop measurement in both Type 1 and Type 2 diabetes [16–18]. Clinical evidence from diabetic patients reveals, with decreased systolic function, a shortened ejection time and prolonged pre-ejection along attenuated relaxation of left ventricle ejection fraction [19]. More careful investigation of cardiac systolic function in diabetic animal model may clarify this issue further.

Pathological mechanisms

Rodent is considered as an ideal animal model to study potential mechanisms underlying diabetic cardiomyopathy owing to relatively resistant to develop atherosclerosis, which provides researchers the diabetic cardiomyopathy without contribution of CAD [20]. Currently, several diabetic rodent models have been developed, such as streptozotocin (STZ) induced diabetic model, to reflect the Type 1 diabetes; and diet-induced obesity and diabetes model, to represent the Type 2 diabetes. Genetic modified models, such as *ob/ob* and *db/db*, are also used to study the pathology of Type 2 diabetes. Although rodents have different cardiac cycle, ion channel expression and contractile protein isoforms from human, they have very similar genomes with human, and have typical diabetic phenotypes such as hyperglycemia, insulin deficiency, and insulin resistance [21]. These characteristics further result in diabetic cardiomyopathy through cellular pathological changes, which may be composed of impaired calcium handling, increased oxidative stress, altered metabolism, mitochondrial dysfunction, cardiac autonomic neuropathy, activation of renin-angiotensin system, and abnormal ion channel activity [22, 23]. In following sections, we will discuss these underlying mechanisms in details.

Impaired calcium handling

Intracellular calcium (Ca^{2+}) performs a significant role in regulating cardiac contractile function. In cardiomyocytes, the mechanism of calcium-induced calcium release initiates the myocardial contraction by increasing intracellular calcium concentration via activation of Ca^{2+} channel, activation of ryanodine receptor, and reduced sodium/calcium exchanger process [24]. For relaxation to occur, intracellular calcium concentration $[Ca^{2+}]_i$ decreases to diastolic level through activated sarcoplasmic reticulum (SR) Ca^{2+} pump (SERCA2a), increased sodium/calcium exchanger process and activation of sarcolemmal Ca^{2+} ATPase to speed up Ca^{2+} uptake [25]. In diabetic cardiomyocytes, calcium homeostasis is altered by reduced activity of sodium/calcium exchanger and ATPase and decreased sarcoplasmic reticulum Ca^{2+} uptake [26, 27]. Isolated Type 1 diabetic rat cardiomyocytes exhibit the decreased activity of ryanodine receptor and SR Ca^{2+} ATPase associated with attenuated SR Ca^{2+} store and reduced Ca^{2+} efflux via sodium/calcium exchanger [28]. Studies on Type 2 diabetes animal model also display the depressed Ca^{2+} efflux and SR Ca^{2+} load and reduced

expression of ryanodine receptor [29]. Furthermore, in both Type 1 and Type 2 diabetes, decreased expression of SERCA2a and sodium/calcium exchanger is observed [30, 31]. Noda et al. [32] demonstrated, in isolated diabetic cardiomyocytes, a declined contraction amplitude and lower relaxation velocity compared to controls. Mitochondrial investigation on diabetic models has suggested that reduced calcium uptake is closely related to the development of hyperglycemia. STZ-induced diabetic rats showed a lower calcium uptake in cardiomyocytes versus that in controls [33]. It has also been revealed that accumulated calcium is not preserved by diabetic cardiomyocytes owing to an increased opening of mitochondrial permeability transition pore (MPTP) [34]. Therefore, these investigations implicated impaired calcium homeostasis in diabetic hearts, result in decreased cardiac contractility and dilation.

Increased oxidative stress

Increased production of reactive oxygen species (ROS) is another major progression of diabetic cardiomyopathy. It has been reported that approximately 90% ROS is produced by mitochondria in myocardial tissue [35]. Mitochondria produced ROS can cause protein damage by oxidation or lipids oxidation to form lipid peroxidation products, causing protein or phospholipid damage. ROS is also able to increase DNA damage which is caused by reduced activity of DNA repairing pathways, especially the pathway involved in mitochondrial DNA repairing [36]. Moreover, interaction between ROS and nitric oxide (NO) generates nitrotyrosine species may lead to impaired mitochondrial respiration. Experimental study on human myocardial samples reveals that cardiomyocyte apoptosis is associated with an increase in 3-nitrotyrosine [37]. Similar evidence is also obtained in STZ-induced Type 1 diabetes model [38]. In addition, tyrosine nitration is involved in cardiac mitochondrial protein in Type 1 diabetic mice. It is reported that increased 3-nitrotyrosine is associated with increased apoptosis in myocardial tissue [39]. Overexpression of antioxidant protein, metallothionein, is proven to reduce nitration damage [38]. Similar investigation on Type 1 diabetic OVE26 mice implicated that overexpressed metallothionein is able to normalize oxidized glutathione and recover contractile dysfunction [40]. Thus, these evidences have demonstrated oxynitrate damage pathway in diabetic cardiomyopathy.

ROS defense mechanism is involved in oxidative damage as well. Manganese superoxide dismutase (MnSOD) is a major antioxidant, which preserves cardiomyocytes from superoxide-induced damage by converting superoxide to H_2O_2 [41]. Data from *db/db* mice of Type 2 diabetes have revealed that the upregulation of MnSOD activity is associated with an increased mitochondrial H_2O_2 [42]. Type 1 diabetes mouse model study also shows an increased level of MnSOD, leading to normalized mitochondrial morphology and cardiac function [43]. In contrast, declined ROS scavenging proteins in cardiomyocyte cytosol compartment contribute to oxidative damage in the cells in diabetes [44].

Despite the mitochondrial ROS production, generated ROS from cytosol in myocardial tissue also plays an important role in diabetes. Advanced glycation end (AGE) products and increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity contribute to oxidative damage, even rising mitochondrial ROS [45, 46]. It has been hypothesized that AGE formation is associated with hyperglycemia, resulting in cytosolic ROS production induced by AGE receptor; and the whole process eventually causes MPTP opening and mitochondrial dysfunction [45]. It has been reported that cytosolic ROS induced MPTP opening in cardiac ischemia [47]. In fact, an antidiabetic medicine, metformin, has a working mechanism to cause inhibition of MPTP opening in diabetic rats [48].

Altered metabolism

Elevated fatty acid (FA) uptake contributes significantly to the development of diabetic cardiomyopathy. Generally, constant ATP production is strongly linked to appropriate FA and glucose oxidation by continuous demand of the heart. However, in diabetic myocytes, metabolism utilization shift to higher level free FA and decreased glucose substrate because of insulin resistance and hyperlipidemia. A significantly elevated utilization of free FA by cardiomyocytes has been demonstrated in human and animal studies [23, 49–51]. In responding to increased level of myocardial FA, the nuclear receptor transcription factor, peroxisome proliferator-activated receptor (PPAR), in cardiomyocytes is activated via mitochondrial beta-oxidation through over-expression of necessary enzymes [52]. PPAR-alpha is responsible for the FA utilization pathway and regulates FA uptake and oxidation by controlling expression of necessary enzymes [53]. Deficient PPAR-alpha animal model investigation revealed a decreased FA oxidation and reduced activity in FA utilization pathway [54]. In contrast, PPAR-alpha is increased with insulin-resistance in another animal model study [55]. In addition, free FA is able to cause lipid accumulation by inhibiting pyruvate dehydrogenase, which is detrimental to myocardial energy production [56]. Lipid accumulation leads to the production of non-oxidative molecules—ceramide, a lipid-toxic product. It has been reported that increased ceramide generation is associated with contractile dysfunction and cell apoptosis [57]. Increased myocardial oxygen consumption is closely related to FA utilization,

which caused relative cardiac ischemia due to significantly high level oxygen used by FA oxidation [58, 59]. Duncan et al. [55] demonstrated the reduced ATP production associated with increased FA oxidation in obese-induced diabetic mice, which suggested a reduced efficiency of cardiac mitochondria function. Similarly, study on Type 2 diabetic animal models implicated increased mitochondrial oxygen consumption and FA oxidation accompanied by a decreased cardiac efficiency and function [60]. Clinical evidence from women with insulin resistance also showed that the increased FA oxidation caused cardiac inefficiency, which might further result in decreased cardiac function [61].

Mitochondrial dysfunction

It has been widely reported that mitochondrial dysfunction is closely associated with diabetic cardiomyopathy [62, 63]. Thirty years ago, scientists demonstrated impaired function of mitochondrial respiration in *db/db* mice model, indicating diabetes probably induced mitochondrial structural and functional alteration [64]. Recent study reveals that a decreased mitochondrial respiration is closely linked to down-regulation of oxidative phosphorylated protein in diabetic mice, suggesting impaired cardiac contractility caused by reduced ATP production [65]. Furthermore, decreased oxidative capacity of mitochondria has been observed in Type 1 diabetic mice model [66]. It has also been demonstrated that lower level of ATP synthesis is associated with reduced activity of mitochondrial oxidation, which may contribute to the decrease in calcium uptake and cardiac dysfunction [67]. Mitochondrial functional un-coupling is a major contributor to mitochondrial dysfunction. ATP synthesis is tightly coupled with increased oxidative activity of mitochondria. Lower level of creatine phosphorylation occurs with reduced ATP synthesis protein in STZ-induce diabetic hearts, which is associated with attenuated mitochondrial function [68]. In addition, over-expression of beta-oxidation proteins has been found in diabetic hearts with down-regulation of electron transport proteins; and increased beta-oxidation decreases electron transportation resulting in reduced ATP production in mitochondria [62, 69]. Diabetic ob/ob mice investigation exhibits reduced ATP generation with higher consumption of oxygen in mitochondria, proving existence of mitochondrial uncoupling in diabetic cardiomyopathy [65].

Cardiac autonomic neuropathy (CAN)

Diabetic cardiovascular autonomic neuropathy is associated with sympathetic and parasympathetic dysfunction in the myocardium, contributing to the impaired diastolic function [70]. Study on Type 1 diabetic patients without ischemic heart disease showed that severe CAN was correlated with abnormal cardiac diastolic filling [71]. Higher level of ventricular fibrillation was reported in diabetic patients, suggesting high sympathetic activity in diabetes [72]. Besides, ventricular filling abnormalities are most prominent in patients with autonomic neuropathy [73]. In addition to abnormal diastolic filling, an abnormal systolic blood pressure in response to standing up was significantly associated with reduced mitral E/A ratio (ratio of early to late peak mitral filling wave velocities). The E/A ratio has been shown to be significantly reduced in patients with autonomic neuropathy, suggesting a significant correlation between E/A ratio and autonomic neuropathy [74]. Studies also revealed that parasympathetic dysfunction was associated with abnormal cardiac function. It was reported that lower level of heart rate variation during deep breathing was correlated with abnormal diastolic peak filling rate in diabetic patients [75].

Diabetic vasculopathy and microangiopathy

In diabetes, a reduction was found in coronary blood flow reserve without apparent CAD [76]. Vascular remodeling and vasomotor symptom are cumulatively enhanced by increased production of glycated proteins and in particular an increased vascular growth factors, which are caused by impaired NO production due to hyperglycemia [76]. Some observational studies reported that vascular endothelial growth factor (VEGF) might perform a significant role in response to cardiac injury. Studies on diabetic and insulin-resistant rats revealed that VEGF mRNA and protein level expression were decreased in myocardium [77]. However, clinical evidence from patients with myocardial infarction suggested that the expression of VEGF mRNA was dramatically increased in cardiomyocytes [78]. Animal study also reported that down-regulation of VEGF probably contributed to the development of diabetic cardiomyopathy. It is also revealed that cardiac dysfunction was normalized after gene transfer of a plasmid encoded human VEGF into cardiomyocytes [79]. Besides, study on STZ-induced diabetic rats demonstrated that impaired angiogenic response and reduced VEGF were correlated with increased expression of endothelin 1 in ventricles whereas antagonism of endothelin receptor normalized VEGF signaling and cardiac dysfunction [80].

Pathologically, microangiopathy may considerably impact on diabetic cardiomyopathy. Abnormal permeability of diabetic capillaries causes periarterial fibrosis and focal subendothelial proliferation and fibrosis, leading to microangiopathic alterations such as arteriolar thickening, capillary microaneurysm, and capillary density reduction [81]. Myocardial and ventricular hypertrophy may be the result of endothelial dysfunction and abnormal protein synthesis in endothelial cells, which facilitate the attachment of

leukocytes and monocytes [82]. Study on diabetic patients without overt CAD also showed that distal atherosclerosis is associated with coronary microangiopathy [83].

Activation of the renin–angiotensin system (RAS)

In the development of diabetic cardiomyopathy, activation of RAS has been well recognized. Experimental evidence has suggested the activation of RAS, which is associated with increased oxidative damage, endothelial cell and cardiomyocyte apoptosis, further causes increased cardiac fibrosis and contractile dysfunction [37]. It has been reported that angiotensin-receptor signaling pathway causes the elevated oxidative activity by NADPH, resulting in the oxidative damage of cardiomyocytes to apoptosis and the increased interstitial fibrosis [84]. Moreover, the increase in angiotensin-II induces a production of ROS, which leads to oxidative damage to cardiomyocyte and endothelial cell apoptosis [85, 86]. Angiotensin-II is also a recognized factor to induce ischemia by causing calcium overloading in cardiomyocytes through reduced activities of sodium/calcium exchanger, sodium/hydrogen exchanger and opening of T-type calcium channels. Up-regulation of RAS may induce myocardial ischemia in diabetic heart through these mechanisms [87–89].

In STZ-induced diabetic rats, inhibition of RAS and use of antioxidant are shown to decrease the production of ROS, which reduces the cardiac dysfunction via restoration of sarcoplasmic calcium handling and reverse of the SR Ca^{2+} loading [90, 91]. Similarly, insulin-like growth factor-1 (IGF-1) has been shown to reduce RAS, which leads to the decrease in cardiac apoptosis and the slow-down of development of diabetic cardiomyopathy [92, 93].

Ion channel abnormalities

Altered metabolism causes reduced Ca^{2+} uptake as discussed above, and changes ion channel activity in cardiomyocytes. Decreased $[Ca^{2+}]i$ transients triggered by electrical stimulations have been reported in diabetic cardiomyocytes, following reduced caffeine induced SR calcium release, which lead to the depressed cardiac contracture [94–96]. Combined with decreased activity of SR calcium pump, it is believed that altered cardiac action potential may be involved in diabetic cardiomyopathy. Experimental study on diabetic rat hearts implicated an increase in calcium currents, a decrease in calcium-independent transient outward currents (I_{to}) and prolonged action potential [97–101]. Diminished I_{to} may prolong the duration of calcium influx through voltage-gated calcium channels, resulting in the delayed repolarization of cardiac action potential [102, 103]. Increased action potential duration in diabetic cardiomyocytes induces depressed sodium/calcium exchanger activity, result in the inhibition of calcium efflux and constant elevation of intracellular calcium concentration, which may be responsible for cardiac diastolic dysfunction—typical phenotype of diabetic cardiomyopathy [99]. Voltage-clamp study exhibits depressed I_{to} activity in isolated diabetic cardiomyocytes, which is normalized to control level by insulin treatment [104]. It has been proposed that inhibition of I_{to} is attenuated by decreased glucose phosphorylation activation of thioredoxin system. Reducing activity of thioredoxin inhibits the increase in I_{to} by insulin. It is, therefore, suggested that I_{to} activity is regulated by redox pathway of thioredoxin system [105]. Diabetic cardiomyopathy is so far linked to an increase in Ca^{2+} currents and a decrease in the I_{to} current and prolonged action potential duration. Detailed biophysical analysis of ion channel kinetics and functional coupling of ion channel modification to cardiac function warrant further careful single cell studies.

Mechanisms so far proposed above for the diabetic cardiomyopathy are summarized in Table 1, although further confirmation and detailed analysis are needed to establish pathology of the disease (Table 1).

Human studies

Diabetes mellitus is a well-recognized risk factor to develop heart failure (HF) and the existence of diabetic cardiomyopathy has been suggested by many epidemiologists and clinicians [106]. Study on diabetic patients reveals that, compared to age-matched control subjects, the frequency of HF is twice in diabetic men and five times in diabetic women [107]. Despite CAD or hypertension, the incidence of HF in diabetic patients increases persistently. Study on diabetic population shows that cardiac structural alteration is consistent with systolic dysfunction and left ventricular (LV) hypertrophy, suggesting subsequent development of HF particularly in the presence of CAD or hypertension [108–111]. As discussed above, diastolic dysfunction is the major characteristic in diabetic cardiomyopathy patients, which may eventually develop to systolic dysfunction [112]. Echocardiography performed on Type 1 diabetic patients without overt CAD revealed that diastolic dysfunction was associated with increased atrial filling, decreased early diastolic filling, increased number of supraventricular premature beats and extended isovolumetric relaxation [113]. Study on patients with Type 1 diabetes without clear macrovascular or microvascular complications showed early structural and functional changes such as left ventricular (LV) wall thickness, ejection fraction reduction and increased diastolic diameter [114]. Similar study on Type 2 diabetic patients reported over 30% subjects diagnosed with diastolic dysfunction

Table 1 Summary of proposed mechanisms responsible for diabetic cardiomyopathy

Cause	Mechanism
Impaired calcium handling	Altered calcium homeostasis by reducing Na^+/Ca^{2+} exchanger activity, SERCA activity and SR Ca^{2+} uptake
Increased oxidative stress	Increased ROS production, AGE formation and association between ROS and NO lead to myocardial apoptosis and cardiac ischemia
Altered metabolism	Decreased glucose oxidation and increased FA-beta oxidation cause cardiac inefficiency, pyruate oxidation results in apoptosis
Mitochondrial dysfunction	Attenuated ATP production and mitochondrial uncoupling
Cardiac autonomic neuropathy	Decreased sympathetic/parasympathetic myocardial innervation with impaired ventricular diastolic filling
Vasculopathy and microangiopathy	Abnormal VEGF expression leads to cardiac dysfunction and diabetic capillaries cause periarterial fibrosis
Activation of RAS	Myocardial fibrosis and apoptosis
Ion channel abnormalities	Depressed I_{to} activity and prolonged action potential may be responsible for cardiac diastolic dysfunction

Na^+/Ca^{2+} sodium/calcium exchanger, *SERCA* sarcoplasmic reticulum Ca^{2+}-ATPase, *SR* sarcoplasmic reticulum, *ROS* reactive oxygen species, *AGE* advanced glycation end-product, *NO* nitric oxide, *FA* fatty acid, *VEGF* vascular endothelial growth factor, *RAS* renin-angiotensin system, I_{to} calcium-independent transient outward current

[115, 116]. Clinical study with flow and tissue Doppler techniques showed up to 60% subjects with diastolic dysfunction in both Type 1 and Type 2 diabetic patients without apparent CAD [117, 118].

Diagnostic methods

Compared to pathological mechanisms, epidemiologists and clinicians mainly focus on the diagnosis of diabetic cardiomyopathy. Clinically, diabetic patients may take several years to develop overt diabetic cardiomyopathy. Thus, it is very important to detect the disease before the apparent HF.

Echocardiography is able to detect significant cardiac abnormalities before the onset of symptomatic HF. Early cardiac abnormalities are mainly characterized by diastolic dysfunction, which is in the presence of depressed LV ejection fraction with a reduction in early diastolic filling, an increase in atrial filling and prolongation of isovolumetric relaxation [119]. A large amount of echocardiography studies demonstrated that increased LV mass was associated with micro-albuminuria, reduced LV systolic chamber size and abnormal LV function [106, 120, 121]. Study on diabetic patients with or without hypertension also showed that aortic stiffness was associated with abnormal diastolic function, suggesting that aortic stiffness may play a role in the development of LV hypertrophy and diastolic dysfunction in diabetic patients by increasing end-systolic wall stress [122].

Tissue Doppler echocardiographic imaging (TDI) provides a high-velocity, low-amplitude filter to myocardium, enabling the assessment of myocardial tissue velocity. TDI is capable of differentiate the independent alterations from preloaded results, contributing a particular tool for defining systolic and diastolic dysfunction [123]. TDI also quantifies circumferential and longitudinal cardiac contraction. Radial (short-axis) contraction of the LV is dependent on the integrity of the circumferential myocardial fibres, whereas longitudinal (long-axis) contraction depends on the integrity of the longitudinal fibres. Because of ventricular remodeling, ischemia and fibrosis cause relative increase in short-axis velocity compared to a decrease in long-axis function [124].

3D echocardiography has been validated the superiority compared to 2D echocardiography in examining LV function. This new technique has not been applied to clinical practices yet. 3D echocardiography is not dependent on geometric assumptions to calculate LV volumes, which enable it to assess odd shapes, abnormal wall motion in ventricles and cardiomyopathy in patients [125]. Currently, Real-time 3D echocardiography is applied to experimental rats to investigate regional LV systolic and diastolic dysfunction [126].

Although there are several other diagnostic methods, such as computed tomography (CT), magnetic resonance imaging (MRI) and single photon emission CT (SPECT), echocardiography is still the matured and wide-used technique in clinic cardiomyopathy diagnosis. Additionally, echocardiography is considered to be a useful tool to evaluate the presence of systolic and diastolic dysfunction and LV hypertrophy in diabetic patients.

Treatments

Several reagents have been shown to cause beneficial effect on diabetic cardiomyopathy. IGF-I has been proven as a treatment for diabetic cardiomyopathy. It is able to improve cardiomyocyte insulin sensitivity and facilitate glucose metabolism [127]. IGF-I also normalizes the

calcium homeostasis in diabetic cardiomyocytes, preventing the decrease in SERCA level and improving cardiac contractility in diabetics [128]. Study on diabetic rats cardiomyocytes showed normalized contractile capacity after IGF-I treatment. In addition, IGF-I may increase cardiac output and eject volume [129].

The angiotensin-converting enzyme inhibitors, such as captopril, also show the beneficial in the treatment of diabetic cardiomyopathy [130]. Captopril is capable of decreasing ventricular hypertrophy and capillary network remodeling, attenuating extracellular matrix proteins proliferation [131]. In addition to captopril, angiotensin-converting enzyme inhibitors can decelerate sodium-hydrogen exchange, the angiotensin II-modulated stimulation, lessening ischemia-induced calcium overload [132].

Treatment with β-blockers shows decreased extracellular matrix proteins and regressed cardiac hypertrophy in diabetic rat hearts [133]. Carvedilol, a third generation β-blocker, has shown additional beneficial effects such as antioxidant and antiproliferative in diabetic cardiomyopathy [134]. Treatment with carvedilol also showed a significant reduction in mortality in patients with HF [135].

Future research

As discussed above, proposed mechanisms underlying diabetic cardiomyopathy have widely broaden the pathology of disease through animal models and human patients. Although some treatment options have been suggested, specific therapeutic target of diabetic cardiomyopathy remain unknown. Clinical trials have been performed on limited number of patients and data is not conclusive. Therefore, epidemical and clinical study may be employed on the base of large number of patients with diabetic cardiomyopathy in the future. In addition, a large number of cellular and molecular investigations have been performed in the past decades. The mechanisms underlying diabetic cardiomyopathy are still controversy. Hence, specific mechanisms or clinical factors closely linked to diabetic cardiomyopathy need to be demonstrated in future study. Besides, single cardiomyocyte study of diabetic cardiomyopathy may provide valuable data to clarify the pathological mechanisms. Overall, clarification of pathogen of diabetic cardiomyopathy will provide therapeutic and diagnostic targets.

Summary

Diabetes mellitus has been recognized as the major morbidity and mortality for decades. In addition to CAD and hypertension, diabetic patients have a great chance to develop cardiovascular diseases, which are induced by hyperglycemia, insulin resistance and insulin deficiency. Clinical evidence and experimental data on diabetes have demonstrated diabetic cardiomyopathy, which is associated with cardiac structure remodeling and functional inefficiency. Recent studies on diabetic patients and animal models have elucidated possible mechanisms underlying

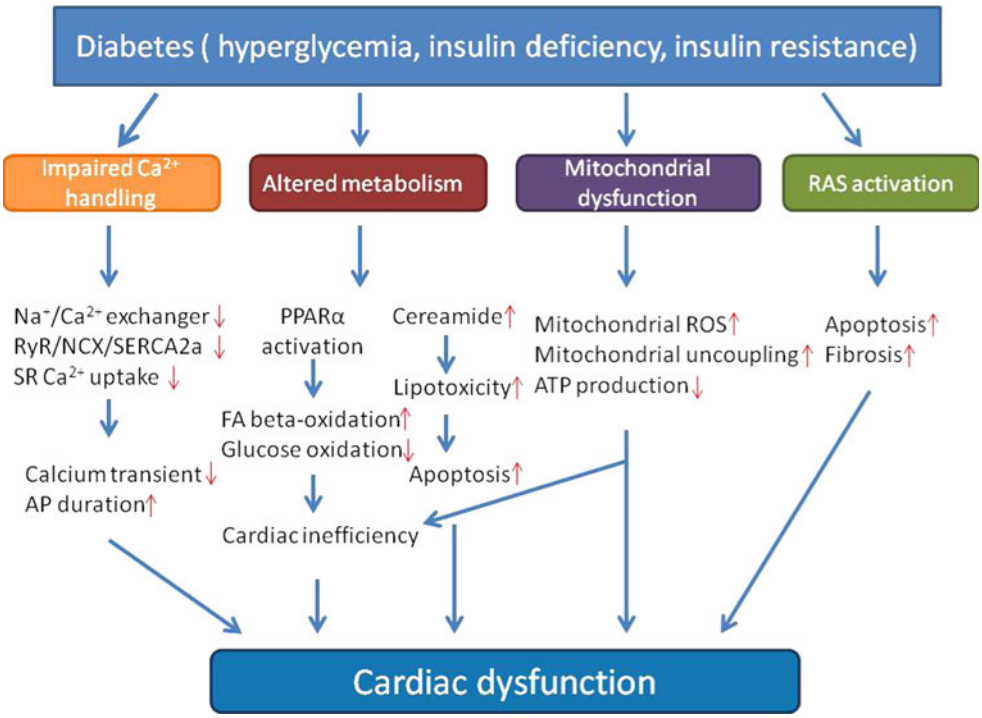

Fig. 1 Proposed mechanism of impaired cardiac function in diabetes. *RyR* ryanodine receptor, *NCX* sodium/calcium exchanger, *SERCA2a* sarcoplasmic reticulum Ca^{2+}-ATPase 2a, *SR* sarcoplasmic reticulum, *AP* action potential, *PPARα* peroxisome proliferator-activated receptpr alpha, *FA* fatty acid, *ROS* reactive oxygen species

diabetic cardiomyopathy and provided novel insights of cellular and pathophysiological pathways in cardiovascular complications in diabetes, including diabetic cardiomyopathy (show in Fig. 1). Although several treatments have been provided beneficial effects to diabetic cardiomyopathy, there is still no specific therapeutic strategy to manage diabetic cardiomyopathy, largely due to lack of mechanism details of cardiomyopathy. It is therefore necessary to further clarify the pathological mechanisms underlying diabetic cardiomyopathy in future research.

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