Published in final edited form as:
Rev Endocr Metab Disord. 2010 March ; 11(1): 31–39. doi:10.1007/s11154-010-9131-7.

Diabetic cardiomyopathy, causes and effects

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Abstract

Diabetes is associated with increased incidence of heart failure even after controlling for coronary artery disease and hypertension. Thus, as diabetic cardiomyopathy has become an increasingly recognized entity among clinicians, a better understanding of its pathophysiology is necessary for early diagnosis and the development of treatment strategies for diabetes-associated cardiovascular dysfunction. We will review recent basic and clinical research into the manifestations and the pathophysiological mechanisms of diabetic cardiomyopathy. The discussion will be focused on the structural, functional and metabolic changes that occur in the myocardium in diabetes and how these changes may contribute to the development of diabetic cardiomyopathy in affected humans and relevant animal models.

Keywords

Diabetic cardiomyopathy; Diastolic dysfunction; Substrate utilization; Mitochondrial dysfunction; Uncoupling

1 Introduction

The concept of diabetic cardiomyopathy was first introduced by Rubler et al [1], and has subsequently been widely used by epidemiologists and clinicians. Diabetic cardiomyopathy describes diabetes-associated changes in the structure and function of the myocardium that is not directly attributable to other confounding factors such as coronary artery disease (CAD) or hypertension. It is important to note that in many patients, particularly those with type 2 diabetes, diabetes associated changes are amplified by the existence of these co-morbidities, which likely will augment the development of left ventricular hypertrophy, increase the susceptibility of the heart to ischemic injury and increase the overall likelihood of developing heart failure [2]. Several mechanisms have been implicated in the pathogenesis of diabetic cardiomyopathy. Changes in myocardial structure, calcium signaling and metabolism are early defects that have been described mainly in animal models and may precede clinically manifest cardiac dysfunction. However, subtle functional changes can be detected if specifically looked for.

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2 Changes in structure and cell survival signaling pathways

2.1 Left ventricular hypertrophy (LVH)

Increased left ventricular (LV) mass is an independent risk factor for heart failure and may occur independently of arterial blood pressure in Type 2 diabetes, and may contribute to reduced myocardial compliance [3]. The Framingham study reported a significant increase in LV wall thickness only in women with diabetes [4]. In contrast, the Strong Heart Study conducted in Native Americans, found that both men and women with diabetes had higher LV mass and wall thickness [5]. Furthermore, in a multi-ethnic population, the likelihood of having LV mass that exceeds the 75th percentile is greater in patients with Type 2 diabetes, after adjusting for various covariates including hypertension [6]. Indeed, in this same population, increased LV mass was observed only in patients with diabetes but not in patients with impaired fasting glucose or impaired glucose tolerance [7], suggesting that changes in myocardial geometry in diabetes might not be an early defect but rather a consequence of long term diabetes-associated changes such as hyperglycemia and/or obesity. Eguchi et al. [6] described a significant interaction between diabetes and central obesity on the risk for LVH. Furthermore, obesity promotes concentric LVH independently of hypertension [8]. Emerging evidence has implicated cytokines, produced by the expanded adipose tissue of obesity, in the development of LVH. For example, leptin is linked to cardiac hypertrophy in obese humans and directly induces cardiomycyte hypertrophy *in vitro* [9]. The mechanisms by which leptin induces LVH is not fully characterized but might involve endothelin 1- mediated reactive oxygen species (ROS) generation [10]. Similarly, resistin, which is also an adipokine that is released from macrophages, was shown to induce cardiomyocyte hypertrophy *in vitro* via IRS-1 and MAPK signaling pathways [11]. Epidemiological studies have suggested a correlation between circulating levels of the inflammatory cytokine interleukin 6, and the risk of obesity-associated heart failure [12]. Insulin resistance and hyperinsulinemia have been correlated with increased LV mass and may partially account for the association of cardiac hypertrophy and obesity [13], and is also correlated with increased risk of heart failure [14]. An increase in IRS1-associated PI3K activity was recently reported in cardiac biopsies obtained from patients with Type 2 diabetes [15]. Insulin signaling might act as a growth factor in the heart, as genetic deletion of insulin receptors leads to reduced cardiac size [16]. Taken together, these observations raise the intriguing possibility that hyperinsulinemia might contribute to diabetes and obesity-related LV hypertrophy.

2.2 Myocardial lipotoxicity

Type 2 diabetes which is often associated with obesity, leads to myocardial lipotoxicity that may contribute to cell death and thus to cardiac dysfunction and this topic has recently been reviewed in detail by us [17]. Thirty years ago, Regan et al [18] identified lipofuscin deposits, which are brown lipid-containing pigment granules, in transmural LV biopsies obtained from patients with Type 2 diabetes. Furthermore, myocardial triglyceride (TG) and cholesterol content were significantly increased in these samples. Similarly, Oil Red O staining of heart sections of non-ischemic failing hearts, revealed increased lipid deposition that was exacerbated by diabetes [19]. Recent advances in magnetic resonance spectroscopy, has enabled non-invasive assessment of myocardial triglyceride content. Diabetes, obesity, insulin resistance and impaired glucose tolerance are associated with increased intra-myocardial lipid that is independent of circulating concentrations of triglycerides [20]. This increase in cardiac triglyceride accumulation is associated with diastolic but not systolic dysfunction [20,21]. It is not clear if triglyceride accumulation is pathogenic per se or is a marker of the underlying metabolic milieu. Increased myocardial triglycerides were not observed in overweight but fairly well-controlled individuals with Type 2 diabetes [22]. This contrasts with the findings in obese diabetics with poorer control [20]. Improvement in

cardiac function in these relatively well-controlled patients, in response to treatment with metformin or TZDs occurred independently of changes in myocardial triglyceride content [22].

An increase in myocardial fatty acid uptake and oxidation has been described in humans with both Type 1 and Type 2 diabetes, as well as in many animal models [17,23,24]. Transgenic mouse models have suggested that an isolated increase in myocardial lipid uptake is sufficient to precipitate cardiomyopathy in the absence of hyperglycemia. For example, over-expression of proteins involved in cardiac FA transport such as long-chain acyl-CoA synthetase, glycosylphosphatidylinositol (GPI) membrane-anchored form of lipoprotein lipase or FA transport protein 1 resulted in lipotoxic cardiomyopathy in mice [25,26]. The exact mechanisms by which increased myocardial lipid uptake induces lipotoxicity and cardiac dysfunction are incompletely understood, but potential mechanisms have been recently reviewed [17]. Lipid-induced cell death might be an important contributor. For example, long-chain FA supplementation to chinese hamster ovary cells (CHO) at pathophysiologic concentrations induced cell death that was associated with increased de novo ceramide biosynthesis [27]. In parallel, inhibition of ceramide biosynthesis prevented lipotoxic cardiomyopathy in mice over-expressing a glycosylphosphatidylinositol (GPI) membrane-anchored form of lipoprotein lipase [28]. Since palmitate-induced cell death in CHO was not completely prevented by inhibition of ceramide biosynthesis [27], additional mechanisms by which FA induced-cell death were proposed. For example, long-chain fatty acids can change the dynamics of plasma and mitochondrial membranes by altering phospholipid composition. Detachment of cytochrome c from the mitochondrial inner membrane is a necessary step for cytochrome c release and initiation of apoptosis. The saturated long chain FA, palmitate, induces apoptosis in rat neonatal cardiomyocytes by diminishing the content of the mitochondrial anionic phospholipid, cardiolipin [29]. In addition, changes in the composition of endoplasmic reticulum (ER) membrane phospholipids have also been observed in lipotoxic conditions, which precipitate ER swelling and ER stress [30,31].

2.3 Increased oxidative stress

Although many studies have suggested that oxidative stress may play a critical role in the development of diabetic cardiomyopathy, the mechanisms involved in reactive oxygen species (ROS) production in diabetic hearts are not well understood. Human and animal studies have suggested that increased oxidative stress correlates with lipid overload, suggesting a role for FA in the generation of ROS (Fig. 1). Indeed, oxidative stress is increased in hearts isolated from the db/db model of Type 2 diabetes, which are also characterized by cardiac lipid accumulation and increased mitochondrial FA oxidation [32]. In db/db hearts, oxidative stress is exacerbated in the presence of fatty acids, which we believe leads to mitochondrial uncoupling. The mechanisms for increased mitochondrial ROS in this model cannot be fully explained by increased FA flux, because independent models, such as the Akita mouse model of Type 1 diabetes do not exhibit increased mitochondrial ROS generation or evidence of mitochondrial uncoupling despite increased rates of FA oxidation [33]. An important distinction between the hearts of Akita mice versus db/db or ob/ob mice is the presence of myocardial insulin resistance in obese models with insulin resistance, whereas in Type 1 diabetes models, insulin sensitivity is preserved. Interestingly, in mice with cardiac-specific deletion of insulin receptors, hydrogen peroxide production was increased and mitochondria were uncoupled even at stage when myocardial FA oxidation was reduced [34]. These data raise the intriguing possibility that myocardial insulin resistance may specifically predispose cardiac mitochondria to ROS overproduction via mechanisms that remain to be elucidated.

Although a large fraction of total cellular ROS is generated in the mitochondria, enzymatic systems capable of generating ROS in the cytosol such as NADPH oxidase can be modulated by diabetes [35,36]. ROS can also interact with other molecules such as nitric oxide (NO) to form nitrotyrosine species, which were found to be elevated in myocardial biopsies of humans with Type 2 diabetes [37]. Finally, in addition to ROS-induced cardiomyocyte cell death, these reactive molecules can also alter gene expression. In the diabetic fatty ZDF rats, increased ROS contributes to the switch in cardiac myosin heavy-chain gene expression from alpha to beta through the activation of NFkB, and antioxidant treatment was able to prevent this switch [38].

2.4 Cell death

When necrotic and apoptotic cell death have been evaluated in myocardial biopsies of diabetic subjects with heart failure that could not be attributed to myocardial ischemia, apoptosis and necrosis were increased in all cell populations within the heart. The co-existence of diabetes and hypertension, increased necrotic cell death further, whereas there was no additional increase in apoptosis [37]. Analysis of right atrial appendages obtained from Type 1 and Type 2 diabetic subjects, at the time of elective coronary artery bypass surgery, revealed an increase in apoptosis and necrosis at the time of tissue harvest, and an exaggerated increase when tissues from diabetics were subjected to ischemia and reperfusion [39]. Increased cardiomyocyte apoptosis has also been described in hearts of ob/ob and db/db mice [40]. The mechanisms for increased cell death are incompletely understood. A role for leptin deficiency has been postulated because treatment of ob/ob mice with leptin reduced apoptosis [40]. In addition to leptin deficiency, hyperglycemia has also been implicated in triggering cell death via a Rac1 mediated increase in NADPH and mitochondrial derived ROS in the hearts of db/db and STZ diabetic mice [41].

Activation of the renin-angiotensin system (RAS) correlated with increased oxidative stress, apoptosis and necrosis in cardiomyocytes and endothelial cells in the hearts of patients with diabetes and end stage heart failure, thereby representing another potential mechanism for cell death [37,42]. In this regard, it is important to note that inhibition of the RAS, reduced the rate of first hospitalization from heart failure and improved echocardiographic indices of LV diastolic function in patients with Type 2 diabetes [43–45].

2.5 Interstitial fibrosis

Diabetic cardiomyopathy is characterized by interstitial and perivascular fibrosis. Regan et al. [18] found a significant increase in collagen deposition around intramural vessels and between myofibers in heart biopsies form diabetic patients. In addition, a significant increase in collagen type III but not type I or VI was found in endomyocardial biopsies obtained from patients with Type 2 diabetes, who did not have significant CAD and hypertension [46]. Furthermore, diastolic dysfunction detected in a population of uncomplicated Type 2 diabetes correlated with pro-collagen type I carboxy-terminal peptide [47,48], suggesting a mechanistic role for myocardial fibrosis in myocardial dysfunction in diabetes. Similar to humans, some animal models with Type 2 diabetes also exhibited an increase in cardiac fibrosis even prior to the onset of hyperglycemia. Thus, increased extracellular fibrosis and collagen deposition was reported in the pre-diabetic stage in OLETF rats, a genetic model of diabetes that resembles human Type 2 diabetes [49]. The mechanisms for increased cardiac fibrosis in the diabetic heart are incompletely understood. A recent study reported an increase in TGFβ1 receptor II density in the diabetic myocardium. TGFβ is one of several cytokines the gene expression of which is enhanced by diabetes [50]. Increased CTGF expression and collagen deposition has also been observed in mouse models of STZ diabetes [51] that was associated with increased expression of PKCβ2. Similar changes were observed in the hearts of mice that lack insulin receptors in

cardiomyocytes (CIRKO mice), and was further augmented by isoproterenol treatment suggesting a role for impaired insulin action in diabetes-associated cardiac fibrosis [52]. Cardiac fibrosis has not been a uniform characteristic of all mouse models however. For example myocardial fibrosis was absent in db/db mice [53].

2.6 Changes in cardiac function

A number of studies have characterized functional changes that develop early in the course of diabetic cardiomyopathy. Early detection of these changes may play an important role in the design of clinical trials of novel or targeted therapeutic strategies and provide important parameters for monitoring the natural history of diabetic cardiomyopathy and its response to treatment.

2.7 Diastolic dysfunction (DD)

Diabetic cardiomyopathy in humans is characterized by DD, which may precede the development of systolic dysfunction. The use of flow and tissue Doppler techniques suggests a prevalence of DD as high as 40–75% in individuals with Type 1 and Type 2 diabetes without overt CAD [54,55]. Indeed, indices for DD such as E/E′ and E/A ratios (where E and A are the mitral peak velocity of early and late ventricular filling respectively and E′ is the early diastolic mitral annular velocity) were impaired in Type 2 diabetic patients [54,56]. Similarly, DD was found in animal models of Type 2 diabetes such as ob/ob and db/db mice and the ZDF rat. These animal models exhibit obesity, insulin resistance and mild or severe hyperglycemia and are suitable to investigate the effect of diabetes on cardiac function independently of micro and macro vascular complications given the absence of atherosclerosis in these models [57,58]. Thus, DD has been shown in db/db hearts both *in vivo* (by echocardiography) [59] and *ex vivo* (in working heart preparations) [60,61].

Several mechanisms have been proposed to explain Type 2 diabetes-associated DD such as increased cardiac lipid accumulation and altered calcium homeostasis. Diastolic but not systolic dysfunction was associated with increased cardiac triglyceride content in ob/ob mice [62]. Furthermore, these mice also exhibit impaired calcium reuptake that was associated with contractile dysfunction [53,63]. Similarly, reduced contractility in cardiomyocytes isolated from sedentary db/db mice was associated with increased diastolic sarcoplasmic reticulum (SR)-Ca^{2+} leak, reduced synchrony of Ca^{2+} release, lower peak systolic and diastolic Ca^{2+} and caffeine-induced Ca^{2+} release, consistent with a role for calcium in the DD seen in Type 2 diabetes. Interestingly, exercise training in these animals was able to normalize these parameters and to reverse contractile dysfunction [64].

2.8 Systolic dysfunction (SD)

Systolic dysfunction is a later manifestation, usually occurring after DD develops. Subtle SD is often not detected using standard 2-dimensional echocardiography techniques. However, using tissue Doppler strain analysis and measurements of peak systolic velocity, subtle abnormalities in systolic function have been described in up to 24% of randomly selected patients with diabetes mellitus after excluding subjects with CAD or LVH [65,66]. *In vivo* animal studies using MR imaging [67] or invasive catheterization with PV loop analysis, have revealed load dependent and independent indices of systolic dysfunction in various murine models [68]. Recent studies using PV loops have begun to compare contractile performance in Type 1 (STZ) versus Type 2 rodent models (Zucker Diabetic Fatty Rat). Both models revealed systolic dysfunction, but Type 1 diabetic models revealed delayed LV relaxation, whereas the Type 2 model revealed increased LV stiffness [69].

2.9 Impaired contractile reserve

Diabetic cardiomyopathy might be present even in asymptomatic subjects with normal resting LV dimensions and function. However in some of these individuals with early stage disease, LV dysfunction can be induced by exercise. In many of these subjects, impaired exercise-induced augmentation correlates with impaired myocardial sympathetic innervation [70]. Subsequent studies, revealed impaired exercise-induced augmentation in systolic performance in individuals with Type 1 and Type 2 Diabetes with no evidence of autonomic neuropathy or myocardial ischemia, and normal resting echocardiographic parameters (including tissue Doppler measurements) at baseline [71,72]. Thus, impaired cardiac performance after exercise could be a potential tool to detect early contractile dysfunction in diabetes. However, before this approach can be widely adopted, there will need to be consensus regarding normal age and gender-specific exercise responses and cutoffs below which impaired contractile reserve can be confidently diagnosed. Moreover, it will be critical to exclude CAD, other structural abnormalities or neurohumoral abnormalities (such as thyroid dysfunction) that could independently impair contractile reserves. Similar studies in animal models are relatively sparse. Contractile reserve as assessed by inotropic stimulation was reported to be unchanged as in the OLETF rats [73] or reduced in ob/ob mice [62,74]. It is important to note though that impaired inotropic reserves measured *in vivo* or *ex vivo* in animal models do not necessarily recapitulate the complex hemodynamic adaptations to exercise training.

As summarized in Fig. 2 and recently reviewed by us [75], multiple mechanisms may lead to impaired diastolic and systolic function and reduced contractile reserves in diabetic cardiomyopathy. This includes accumulation of advanced glycation end products, [76], adipokines [77], impaired myocardial insulin signaling [34], altered calcium homeostasis [53,63] and lipotoxicity [62].

2.10 Changes in myocardial metabolism

Many studies have implicated changes in myocardial substrate and energy metabolism in the pathogenesis of diabetic cardiomyopathy. In this section, we will discuss recent findings confirming the existence of metabolic changes in the heart of humans and animals with diabetes.

2.11 Altered substrate utilization

Diabetes is characterized by increased circulating concentrations of glucose and free fatty acid (FFA). Despite the presence of hyperglycemia, the diabetic heart relies almost completely on FFA utilization, with a coordinate decrease in glucose utilization. This pattern of substrate utilization has been described both in human and animal studies and have been reviewed in detail elsewhere [23,24,78]. There are a number of mechanisms that are responsible for this shift in substrate utilization. The earliest change that occurs in short term studies of high-fat fed mice is reduced myocardial GLUT4 content and a defect in GLUT4 translocation. This in turns leads to reduced rates of glycolysis and glucose oxidation. FA oxidation rates are subsequently increased most likely via the Randle cycle [79]. As high-fat feeding becomes more prolonged and diabetes ensues, increased delivery of FA substrates activate PPAR-alpha signaling pathways, which leads to transcriptional induction of enzymes involved in beta oxidation and increased expression of pyruvate dehydrogenase (PDH) kinase (PDK4), which further suppresses glucose oxidation by decreasing PDH activity [79,80]. In humans with Type 2 diabetes and heart failure, myocardial lipotoxicity was associated with evidence of activation of the PPAR alpha target gene carnitine palmitoyl-transferase 1 (muscle isoform, mCPT1), which regulates mitochondrial FA uptake [19].

Similar changes in substrate utilization occur in Type 1 diabetes, where transcriptional repression of GLUT4 via down regulation of the expression of its regulator myocyte enhancer factor 2C (MEF2C) is well described in mice [81]. In a recent human study, GLUT4 and MEF2C mRNA were significantly down regulated in failing hearts from diabetic subjects as opposed to failing hearts from non-diabetics [82]. Because fatty acids are considered an inefficient substrate, increased FA oxidation in diabetic hearts is often accompanied by an increase in myocardial oxygen consumption (MVO_2) and reduced cardiac efficiency in rodent models [83,84], and in obese and insulin resistant humans, as well as humans with Type 1 diabetes [85,86].

The challenge of future studies will be to determine if therapies that normalize myocardial substrate metabolism in diabetes mellitus will translate to lower prevalence of heart failure or improved long-term survival.

2.12 Mitochondrial dysfunction

In contrast to skeletal muscle, studies examining mitochondrial function in cardiac muscle of humans with diabetes have been challenging. Our contribution to the understanding of mitochondrial bioenergetics comes mainly from animal models of obesity and diabetes, and have been extensively reviewed [75,78,87]. In brief we and others have observed striking changes in mitochondrial morphology, remodeling of the mitochondrial proteome and decreased respiratory capacity in models of Type 1 and type 2 diabetes [32,33,74,88]. Thirty years ago, Reagan et al. [18] observed an increase in mitochondrial number with pleomorphism without swelling or distortion of cristae in the myocardium of patients with diabetes. Furthermore, using ^{31}P nuclear magnetic resonance spectroscopy, a number of groups provided evidence for decreased cardiac energetics (decreased pCR/ATP ratios) in Type 1 and Type 2 diabetic patients who were free of overt CAD [89–91]. However reduced PCr/ATP ratios have not been seen in all studies [92]. A recent study, in which mitochondrial function was directly measured in right atrial appendages obtained from diabetics at the time of coronary artery bypass surgery revealed direct evidence of reduced mitochondrial oxygen consumption and increased H_2O_2 emission [93]. Studies related to the response of the diabetic heart to ischemic preconditioning (IPC) have also identified a defect in the mitochondrial ATP-sensitive potassium channel that may impair the ability of the diabetic heart to be preconditioned and may contribute to their increased risk for myocardial infarction [94].

Our studies of the ob/ob and db/db mouse models of Type 2 diabetes identified mitochondrial uncoupling as an additional defect that contributes to mitochondrial dysfunction in obesity and insulin resistance [32,74]. We demonstrated increased state 4 respiration and reduced ATP synthesis in mitochondrial preparations obtained from ob/ob and db/db hearts that were pre-perfused with palmitate. This mitochondrial uncoupling further contributes to increasing oxygen consumption without a concomitant increase in ATP production, which contributes to decreased cardiac efficiency in these hearts. The mitochondrial uncoupling is largely mediated by uncoupling proteins and to a lesser extent by the adenine nucleotide translocase. Mitochondrial ROS generation or lipid peroxides such as hydroxynonenal have been shown to activate uncoupling proteins in heart muscle mitochondria [95] and were found to be increased in the hearts of db/db mice [32]. Interestingly, mitochondrial uncoupling was not observed in the hearts of mice with Type 1 diabetes [33,96]. One difference between the hearts of models of Type 1 and Type 2 diabetes is the existence of myocardial insulin resistance in *ob/ob* mice versus normal insulin sensitivity in the hearts of the Akita model of Type 1 diabetes, raising the possibility that myocardial insulin resistance might be causally linked to mitochondrial uncoupling. Indeed, our recent study of mitochondrial function in the hearts of mice with genetic

deletion of insulin receptors revealed the presence of mitochondrial uncoupling and oxidative stress in the absence of hyperglycemia [34].

3 Conclusion

Although the increase in cardiovascular mortality and heart failure is due in part to accelerated atherosclerosis, compelling epidemiological and clinical data indicate that diabetes mellitus increases the risk for cardiac dysfunction and heart failure independently of other risk factors such as CAD and hypertension. The existence of diabetic cardiomyopathy is becoming increasingly recognized and this review has summarized the associated structural, functional and metabolic changes. As the mechanisms responsible for diabetic cardiomyopathy continue to be elucidated, it is hoped that these insights will provide the impetus for novel therapies that are tailored to reduce the risk of heart failure in individuals with diabetes mellitus.

Acknowledgments

Dr. Boudina has been supported by the JDRF, and is currently supported by NIH P30 HL101310 and a Scientist Development Award from the American Heart Association. Dr. Abel is an Established Investigator of the American Heart Association and is supported by the American Diabetes Association and UO1 HL087947 (Animal Models of Diabetes Complications Consortium).

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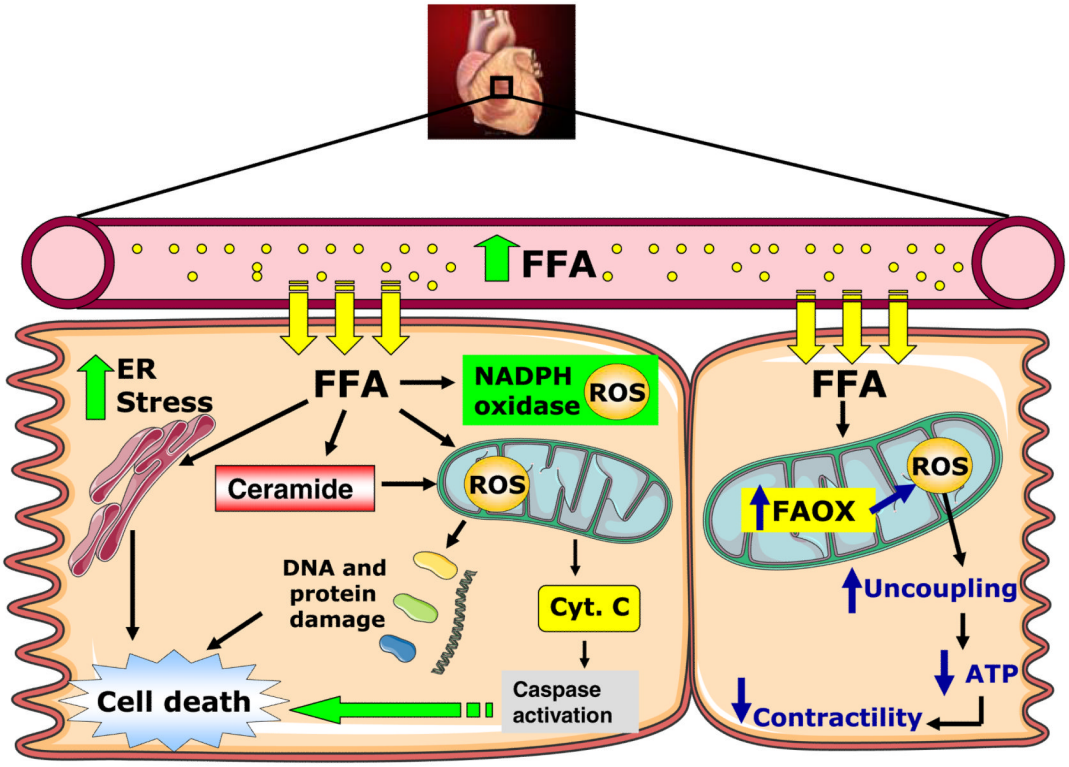

Fig. 1.

Mechanisms for FA-induced cardiac dysfunction in diabetes. Increased FA uptake in cardiomyocytes in vivo precipitates cardiomyocyte dysfunction by multiple mechanisms including increased mitochondrial and cytosolic ROS generation and ER stress. FA-mediated ROS generation leads to uncoupling of mitochondria, which reduces mitochondrial ATP production. FFA: free fatty acids; ROS: reactive oxygen species; ER: endoplasmic reticulum; Cyt. C: cytochrome c; FAOX: Fatty acid oxidation

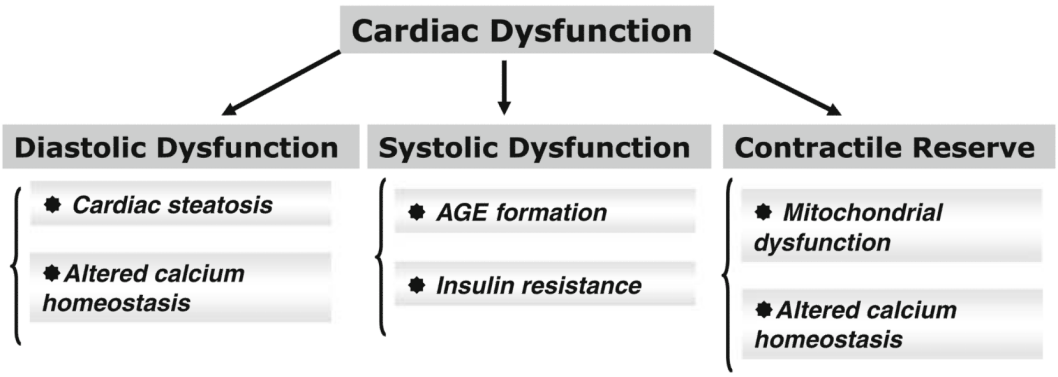

Fig. 2.
Cellular mechanisms that contribute to cardiac contractile dysfunction in diabetes