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Diabetic Cardiomyopathy: Cardiac Changes, Pathophysiological Mechanisms, Biologic Markers, and the Available Therapeutic Armamentarium

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1. Introduction

Patients with diabetes mellitus (DM) exhibit greatly increased cardiovascular morbidity and mortality. The increased mortality of patients with DM stems from the more frequent development of heart failure (HF) (Bell, 2003a; Jaffe et al., 1984; Kamalesh, 2007; Marwick, 2006; Solomon et al., 2002). In the past, the high incidence and poor prognosis of HF in diabetic patients was attributed to the concurrent presence of hypertension and/or myocardial ischemia. However, follow-up studies have shown that the increased risk for developing HF persists in DM patients even after adjusting for concomitant risks such as coronary artery disease and blood pressure (Ho et al., 1993; Kannel & McGee, 1979). It is now well established that DM increases the risk of cardiovascular morbidity and mortality by promoting cardiomyopathy, a distinct entity independent of coronary artery disease, hypertension or other known cardiac risk factors with origins in diabetic cardiac muscle (Bell, 1995; Cohen, 1995; Hamby et al., 1974; Regan et al., 1977; Spector, 1998).

According to a new study commissioned by the Centers for Disease Control and Prevention, 25.8 million children and adults in the United States, or 8.3% of the population, have DM, with about 1.9 million new cases of DM being diagnosed annually (Centers for Disease Control and Prevention, 2011). Worldwide, the number of people with DM has more than doubled since 1980 to 347 million (Danaei et al., 2011). With the global burden of DM rising, it is likely that the incidence of diabetes-induced cardiomyopathy and subsequent HF will continue to increase in this high-risk population. The goal of this chapter is to review the structural and functional changes in the diabetic heart and the pathophysiological mechanisms involved in the development of diabetic cardiomyopathy, taking into account the most recent developments in basic and clinical research. An overview of the latest advances in therapeutic approaches to treat diabetic cardiomyopathy will also be presented. Particular attention is given to the role of oxidative stress in the pathogenesis of diabetic cardiomyopathy and the potential of anti-oxidative therapy. The value of newly identified candidate biomarker proteins in assessing disease presence and progression, prognosis, and efficacy of therapies in the setting of diabetic cardiomyopathy will also be discussed.

2. Cardiomyopathy in diabetes

Sustained DM leads to a deterioration of heart function that is independent of any of the known concomitant risk factors and pathologies that are frequently seen in DM patients such as dyslipidemia, coronary artery disease, thrombosis, myocardial infarction (MI), and hypertension. The clinical presentation of cardiac dysfunction in DM patients without evidence of any of these other risk factors was first reported by Rubler et al. in 1972 (Rubler et al., 1972) based on postmortem findings of HF in diabetic patients free of coronary disease. These and similar findings have been reported in numerous other clinical studies (Bell, 2003a; Boyer et al., 2004; Devereux et al., 2000; Fang et al., 2003, 2005; Galderisi et al., 1991; Hamby et al., 1974; Kannel et al., 1974; Regan et al., 1977; Zabalgoitia et al., 2001) and animal models (Borges et al., 2006; Hamblin et al., 2007a; Kaul et al., 1995, 1996; Kralik et al., 2005; Loganathan et al., 2006; Mihm et al., 2001; Shen et al., 2005, 2006). This has led to the increased recognition that DM produces damage to cardiac muscle without depending on the co-existence of other cardiovascular risk factors. This unique form of heart disease in the absence of clinically detectable atherosclerosis and/or coronary artery disease has been termed "diabetic cardiomyopathy". This diabetes-related cardiomyopathy affects the myocardium secondary to DM and is accompanied by a prolonged decline in cardiac function. This unique cardiac phenomenon has been documented to progress to HF in both type 1 and type 2 DM patients.

2.1 Contemporary clinical epidemiology of diabetic cardiomyopathy

Older cardiovascular epidemiological studies showed that 30% of diabetic subjects without overt cardiac disease had LV dysfunction (Beljic & Miric, 1994; Di Bonito et al., 1996; Nicolino et al., 1995). However, this prevalence was based on standard echocardiography testing which frequently was not able to detect mild and early diastolic dysfunction (Bell, 2003b). Contemporary assessments of the epidemiology of diabetic cardiomyopathy using more rigorous Doppler methods demonstrate that the prevalence of diabetic cardiomyopathy is much higher than was previously believed, and in addition, emphasize the ominous impact of DM on myocardial function by highlighting the high prevalence of pre-clinical diabetic cardiomyopathy in the diabetic population and its strong association with an adverse prognosis (Kiencke et al., 2010; Van Den Hurk et al., 2010). In an ambulatory clinic-based sample of middle-aged, overweight-to-obese individuals with prevalent DM for an average duration of over 10 years, diabetic cardiomyopathy was present in 48% of patients as assessed by Doppler echocardiography (Kiencke et al., 2010). Of note, diastolic function was abnormal in 38% of the DM patients studied (Kiencke et al., 2010). The use of flow and tissue Doppler techniques suggests an even higher prevalence of diastolic dysfunction (as high as 40% to 60%) in individuals with type 1 and type 2 DM without discernable coronary heart disease (Boudina & Abel, 2007; Di Bonito et al., 2005; Poirier et al., 2001; Shivalkar et al., 2006). The high incidence of such diastolic dysfunction and its association with HF and with mortality (From et al., 2010) underscore the existence of diabetic cardiomyopathy as a very serious clinical condition.

2.2 Diagnostic indices

Cardiomyopathy in type 1 or type 2 DM is associated with a cluster of common cardiac abnormalities (Table 1). The most frequent and earliest detectable functional abnormality in

diabetic cardiomyopathy is impaired diastolic function (Fang et al., 2003, 2005; Karamitsos et al., 2007), owing to reduced elasticity of the diabetic myocardium as a result of interstitial collagen deposition. The reduced diastolic function early in the time course of DM is followed by late decreases in systolic performance (Devereux et al., 2000; Fang et al, 2003; Mildenberger et al., 1984; Raev, 1994; Von Bibra et al., 2005). Diabetic cardiomyopathy in humans is also manifested by left ventricular hypertrophy (LVH) (Devereux et al., 2000; Kannel et al., 1974; Ozasa et al., 2008). Although no single diagnostic test for diabetic cardiomyopathy exists, the use of different imaging modalities (echocardiography, cardiac MRI) makes it possible to detect the phenotypic features of this condition (Asghar et al., 2009). Echocardiography is the diagnostic method that can achieve early detection of diabetic cardiomyopathy since it can detect structural myocardial changes (LVH and increased cardiac mass) in addition to evaluation of diastolic and systolic heart dysfunction (Mytas et al., 2009). As a result, echocardiography based methods currently stand as the preferred diagnostic approach for diabetic cardiomyopathy in clinical practice (Maya & Villarreal, 2010).

Abnormality	Manifestation (Stage of Disease)
Diastolic Dysfunction	Early
Systolic Dysfunction	Late
Left Ventricular Hypertrophy	Late
Myocardial Fibrosis	Late

Table 1. Diagnosis of Diabetic Cardiomyopathy

Although brain natriuretic peptide (BNP), a hormone secreted by the ventricles of the heart in response to ventricular volume and pressure overload, is both sensitive and specific for HF, research has shown that BNP is of limited diagnostic utility for diagnosing diabetic cardiomyopathy (Fang et al., 2005; Valle et al., 2006). This is due in part to the fact that BNP cannot reliably distinguish between systolic and diastolic HF, which limits its use in diabetic cardiomyopathy (Asghar et al., 2009; Fang et al., 2005; Maisel et al., 2003). Furthermore, the triggers for BNP secretion (increased intraventricular volume and pressure) does not occur in patients with subclinical, asymptomatic diabetic cardiomyopathy (Mytas et al., 2009; Stevanovic et al., 2006). In light of these findings, it is recommended that BNP not be used in isolation to diagnose or exclude diabetic cardiomyopathy (Fang et al., 2005; Kamalesh, 2007).

3. Cardiac changes

3.1 Structural remodeling

3.1.1 LVH

Data from the Framingham Heart Study (Kannel et al., 1974) as well as the Strong Heart Study (Devereux et al., 2000) indicated a disproportionate increase in LV mass and wall thickness among DM patients as compared to non-DM patients, even after adjusting for other cardiac risk factors (Devereux et al., 2000). In a recent multi-ethnic population study, the presence of type 2 DM, independent of body size, was associated with a 1.5-fold increase in risk of having LV mass >75th percentile of the general population (Eguchi et al., 2008). While LVH has consistently been linked to the increased incidence of cardiovascular events in a variety of high-risk patient groups, several studies have demonstrated that this cardiovascular risk is further enhanced by the presence of DM and thereby portends an

especially poor prognosis (Boner et al., 2005; Struthers & Morris, 2002; Valensi et al., 1997). Emerging evidence has implicated the diabetic milieu of hyperinsulinemia, insulin resistance, hyperglycemia, and increased non-esterified fatty acids in the pathophysiology of LVH in DM patients. In addition, higher circulating levels of the hormone leptin have been linked to the development of LVH in obese diabetic humans. Disruption of downstream leptin signaling leading to leptin excess and resistance has been implicated as a novel pathophysiological mechanism by which leptin contributes to adverse remodeling. The consistency of results demonstrate a clear impact of DM *per se* on increased LV mass that encompasses the development of diabetes-related LVH.

3.1.2 Increased connective tissue collagen deposition and fibrosis

Diabetic cardiomyopathy has been documented to be characterized by myocardial fibrosis. A significant increase in collagen deposition has frequently been observed in heart biopsy samples from DM patients without significant coronary artery disease (Regan et al., 1977; Shimizu et al., 1993; Van Heerebeek et al., 2008). Similar to humans, increased cardiac collagen deposition has also been observed in animal models of DM (Bhimji et al., 1986; Spiro & Crowley, 1993). In addition, an increase in the formation of advanced glycation end products (AGEs) has also been reported to occur in the myocardium of DM patients (Van Heerebeek et al., 2008) which cross-link with collagen and increase its tensile strength. The excess deposition of collagen as well as AGE cross-linking of collagen induced by DM has been shown to augment LV stiffness of the failing diabetic heart in the absence of coronary artery disease (Van Heerebeek et al., 2008). Because excessive LV stiffness of the diabetic heart is an important contributor to worsening HF in patients with DM, increased myocardial collagen and AGEs are thought to be important therapeutic targets for modulating the development of diabetic cardiomyopathy and subsequent HF.

3.2 Functional alterations

3.2.1 Diastolic dysfunction

LV diastolic dysfunction has been reported to be the earliest detectable functional defect in diabetic cardiomyopathy (Fang et al., 2003, 2005; Karamitsos et al., 2007; Valle et al., 2006) and is characterized by increased LV end-diastolic pressure and a decreased LV end-diastolic volume (Hamblin et al, 2007a; Regan et al., 1977). The higher filling pressures are a result of reduced diastolic ventricular compliance which thereby alters diastolic filling and HF ensues. Diastolic dysfunction is a common functional abnormality in diabetic cardiomyopathy that has been related to myocardial fibrosis occurring in response to hyperglycemia. The early reductions in diastolic performance have been found to be followed by progressive reductions in systolic function during the later stages of diabetic cardiomyopathy. Therefore, diastolic dysfunction may not necessarily exist in isolation in the setting of diabetic cardiomyopathy.

3.2.2 Systolic dysfunction

In both human and animal models of type 1 and type 2 DM, systolic functional disorders have been shown to be associated with a reduction in ejection fraction (EF), fractional shortening (FS), and cardiac output (CO) (Mihm et al., 2001; Mildenberger et al., 1984; Mytas et al., 2009). *In vivo* animal studies using invasive catheterization have revealed load-dependent and -independent indices of systolic dysfunction in diabetic hearts (Hamblin et

al., 2007a; Van Den Bergh et al., 2006). Comparative investigation of cardiac dysfunction in rodent models of type 1 and type 2 DM suggest that systolic dysfunction may be more pronounced in type 1 diabetic cardiomyopathy (Radovits et al., 2009).

4. Mechanisms of diabetes-induced cardiomyopathy

4.1 Derangements in cardiac energy metabolism

The primary metabolic defect observed in diabetic hearts is an exaggerated reliance on fatty acid metabolism due to reduced insulin production or insulin resistance. As a result, cardiac glucose uptake and utilization declines while free fatty acid use and oxidation by the diabetic heart increases. The augmented fatty acid metabolism of the diabetic heart leads to intracellular lipid accumulation, energy deprivation and ultimately cardiomyopathy (An & Rodrigues, 2006). Accumulation of lipids can result in increased non-oxidative production of toxic lipid products that precipitate cell death and decrease myocardial contractile dysfunction, thereby inducing myocardial lipotoxicity. In addition, the metabolic switch to increased usage of free fatty acids impairs cardiac energy efficiency in the diabetic heart due partly to the fact that glucose utilization is about 10% more efficient at generating ATP per O_2 consumed (2.58 vs. 2.33 ATP/ oxygen atom) (Wang et al., 2006a).

We and others have shown that type 1 DM alters the protein composition of cardiac mitochondria to accommodate the increased oxidation of fatty acids (Hamblin et al., 2007a; Shen et al., 2004). In-depth mining of the type 1 diabetic myocardial proteome by proteomic analysis revealed that half of the altered proteins were localized to the mitochondria (Hamblin et al., 2007a; Shen et al., 2004). Most of the cardiac protein changes were due to increased content of enzymes required for fatty acid metabolism and oxidation (e.g. acyl coenzyme A thioester hydrolase, acyl CoA dehydrogenase) (Hamblin et al., 2007a; Shen et al., 2004). These findings identify a specific 'type 1 diabetic' pattern of cardiac proteome changes indicative of diabetic cardiomyopathy and its attendant altered metabolic phenotype of enhanced fatty acid utilization.

4.2 Advanced Glycation End products (AGEs)

AGEs are a heterogeneous group of molecules formed from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids (Peppa et al., 2003). The formation of these sugar-derived substances is markedly accelerated in DM because of the increased availability of glucose (Peppa et al., 2003). A common consequence of their formation is covalent cross-link formation with proteins such as collagen which decrease the compliance of the extracellular matrix (ECM) (Brownlee, 2000; Singh et al., 2001). In the myocardium, this may lead to ventricular stiffness (Bell, 1995; Spiro & Crowley, 1993) with resultant impaired diastolic function. Increased activation of the diacylglycerol (DAG)-protein kinase C (PKC) signal transduction pathway has been shown in hearts of streptozotocin (STZ)-diabetic animals (Inoguchi et al., 1992) and activation of this pathway has been documented as a mechanism linking AGEs to diabetic complications (Mamputu & Renier, 2002; Way et al., 2001).

AGEs are not only directly damaging through covalent modification of proteins but they also contribute to the increased production of reactive oxygen species (ROS) by binding to the receptor for advanced glycation end products, RAGE (Wang et al., 2006a). The resulting RAGE activation by AGEs has been shown to lead to an increased generation of intracellular ROS (Brownlee, 2001).

4.3 Renin-Angiotensin-Aldosterone System (RAAS)

It is well recognized that DM is characterized by enhanced up-regulation of the local and systemic RAAS. Although the basis for dysfunction of the RAAS system in the setting of DM remains incompletely understood, its activation during DM has been demonstrated to be associated with increased oxidative damage which in turn activates the death pathways implicated in myocardial cell apoptosis and necrosis (Frustaci et al., 2000; Privratsky et al., 2003). These myocyte and non-myocyte alterations in diabetic hearts resulting from increased activation of RAAS induces impairment of ventricular function. The benefits of RAAS blockade in preventing and reversing diabetic cardiomyopathy in DM patients (Asghar et al., 2009) underscore the importance of dysregulated RAAS in the pathogenesis of diabetic cardiomyopathy.

4.4 Mitochondrial dysfunction

Abnormalities in myocardial mitochondrial function have been reported in human as well as animal models of DM. Morphological study of diabetic cardiomyopathy in OVE26 mice, a chronic model of type 1 DM, revealed a significant increase in mitochondrial area and number as well as focal regions with severe damage to mitochondria (Shen et al., 2004). Mitochondria isolated from these OVE26 diabetic hearts exhibited a reduced respiratory control ratio due to lower state 3 respiration (Shen et al., 2004), indicating impaired mitochondrial function. Similar observations have also been reported in STZ and other animal models of DM (Kuo et al., 1983; Pierce & Dhalla, 1985; Tomita et al., 1996). Impairment in mitochondrial respiratory capacity has also been shown to occur in diabetic human hearts. The most comprehensive and direct evidence to date for the presence of myocardial mitochondrial dysfunction in human diabetes comes from a recent study examining mitochondrial respiration in the atrium of type 2 diabetic human myocardium (Anderson et al., 2009). This study demonstrated decreased mitochondrial respiratory capacity with palmitoyl-carnitine and glutamate in atrial tissue of type 2 DM individuals. Collectively, these findings provide solid evidence of impairment of mitochondrial function in both type 1 and type 2 diabetic hearts which may contribute to or amplify derangements in cardiac energetics that have been linked to contractile dysfunction in diabetic cardiomyopathy over time.

4.5 Myocardial fibrosis

Interstitial and perivascular fibrosis has been described in the myocardia of patients and animals with DM. Most of this has been documented to be composed of collagen fibers (Shimizu et al., 1993). In that regard, the percentage of type III collagen in the perimysium and perivascular region has been reported to be significantly higher in the hearts of patients with DM, indicating the occurrence of collagen remodeling (Shimizu et al., 1993). It has been suggested that although collagen is a major determinant of ventricular stiffness, alterations in collagen phenotype may play an important role in the impaired LV diastolic filling that is typical of diabetic cardiomyopathy (Shimizu et al., 1993).

As indicated earlier in this chapter, it has been demonstrated that collagen is particularly susceptible to AGE cross-linking (Susic et al., 2004). The cross-linking of collagen molecules to each other not only leads to loss of elasticity but also impairment of collagen degradation, leading to further collagen accumulation or fibrosis (Wang et al., 2006a). As a result, the cross-linking of collagen molecules due to accelerated AGEs formation in the diabetic heart

is thought to be an important mechanism that contributes to the myocardial fibrosis and resulting decreased myocardial compliance characteristic of diabetic cardiomyopathy.

4.6 Myocardial oxidative stress: A key contributor to diabetic cardiomyopathy

Oxidative stress is defined as an imbalance between the generation of free oxygen radicals (FORs) and the antioxidant defense system. In the simplest of terms, a free radical is any atom or molecule that has an unpaired electron in their outer orbit making that atom or molecule a highly reactive species. Free radical production occurs via the addition of an electron or by its removal in a reduction/oxidation reaction. Due to its unique diradical configuration, oxygen is a major intracellular source of radical species. A sequential univalent reduction of oxygen gives rise to reactive intermediate products (Kaul et al., 1993; Singal et al., 1988). A single electron reduction of oxygen gives rise to superoxide anion (O_2^-), which can act as both a reducing and an oxidizing agent. The relatively short half life of superoxide anion limits its diffusion away from the site of its generation. The divalent reduction of oxygen yields the nonradical species, hydrogen peroxide (H_2O_2). H_2O_2 has a relatively long half life and therefore can travel significant distances, causing damage at sites distant from its origin. A three electron reduction of oxygen yields the hydroxyl radical (OH^-), which is the most reactive and potent of all the FORs. Addition of a fourth electron results in the formation of water.

FORs are neutralized by various cellular defense mechanisms consisting of enzymatic [(superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx)] and non-enzymatic (vitamin E, β-carotene, vitamin C) antioxidants (Palace et al., 1999). However, during pathological conditions, the delicate balance between FOR production and the protective antioxidant defense system may shift in favor of a relative increase in free-radical production and resultant FOR-induced tissue injury via lipid peroxidation of polyunsaturated fatty acids located in the cell membrane. Hyperglycemia can elevate levels of FORs by increasing mitochondrial superoxide anion production or by the process of glucose auto-oxidation (Eriksson & Borg, 1993; Nishikawa et al., 2000).

Early experimental evidence implicating myocardial oxidative stress in diabetic cardiomyopathy was mainly derived from reports evaluating the rate of lipid peroxidation. Increased cardiac levels of thiobarbituric acid reactive substances (TBARS) and lipid peroxides were observed in rats with STZ-induced diabetic cardiomyopathy (Jain & Levine, 1995; Kaul et al., 1996; Nishio et al., 1998). More recently, F_2-isoprostanes (F_2-IsoPs), a novel class of prostaglandin F_2-like compounds formed *in vivo* by non-enzymatic free radical-catalyzed peroxidation of arachidonic acid (Montuschi et al., 2004; Morrow et al., 1990), have emerged as one of the most reliable approaches to assess oxidative stress status *in vivo* (Montuschi et al., 2004). Of these, 8-*iso*-prostaglandin $F_{2\alpha}$ (8-*iso* $PGF_{2\alpha}$) has recently been shown to be a specific and sensitive quantitative index of oxidative stress *in vivo* (Delanty et al., 1997). We and others have found that in STZ rats with type 1 diabetic cardiomyopathy, LV levels of 8-*iso* $PGF_{2\alpha}$ were significantly increased *in vivo* (Hamblin et al. 2007a, 2007b; Xia et al., 2007). Collectively, these experimental animal studies demonstrate that diabetic cardiomyopathy is associated with greater myocardial oxidative stress burden.

Intermediates in the pathway of formation of IsoPs are endoperoxides, which are reduced to form F_2-IsoPs but also undergo rearrangement to form isomeric ketoaldehydes termed isoketals (IsoKs) (Roberts et al., 1999). IsoKs are remarkably reactive compounds that adduct almost instantaneously and irreversibly with lysine (Lys) residues on proteins and cross-link

proteins (Iyer et al., 1989; Jirousek et al., 1990; Salomon et al., 1987) and as such, would be expected to profoundly alter protein function. Because myocardial ischemia can induce oxidative stress and the high incidence and poor prognosis of post-MI HF in DM patients has been linked in part to the presence of an underlying diabetic cardiomyopathy, we have recently performed a preliminary study in which we measured the levels of IsoK-lysyl-lactam adducts in STZ-diabetic post-MI rat hearts at 4 weeks after induction of MI using liquid chromatography electrospray tandem mass spectrometry (LC/MS) methods (Fukuda et al., 2005). Levels of IsoK-lysyl-lactam adduct were increased strikingly in the viable LV myocardium of diabetic infarcted rats compared with the same LV region in non-diabetic infarcted hearts (Fig. 1). These results clearly demonstrate that IsoK adducts are selectively increased in diabetic post-MI hearts. Protection of diabetic hearts from the downstream effects of these novel products formed via the IsoP pathway of free radical-mediated lipid peroxidation deserves evaluation as a new therapeutic approach for the prevention and treatment of oxidative-dependent cardiac complications of DM, including cardiomyopathy.

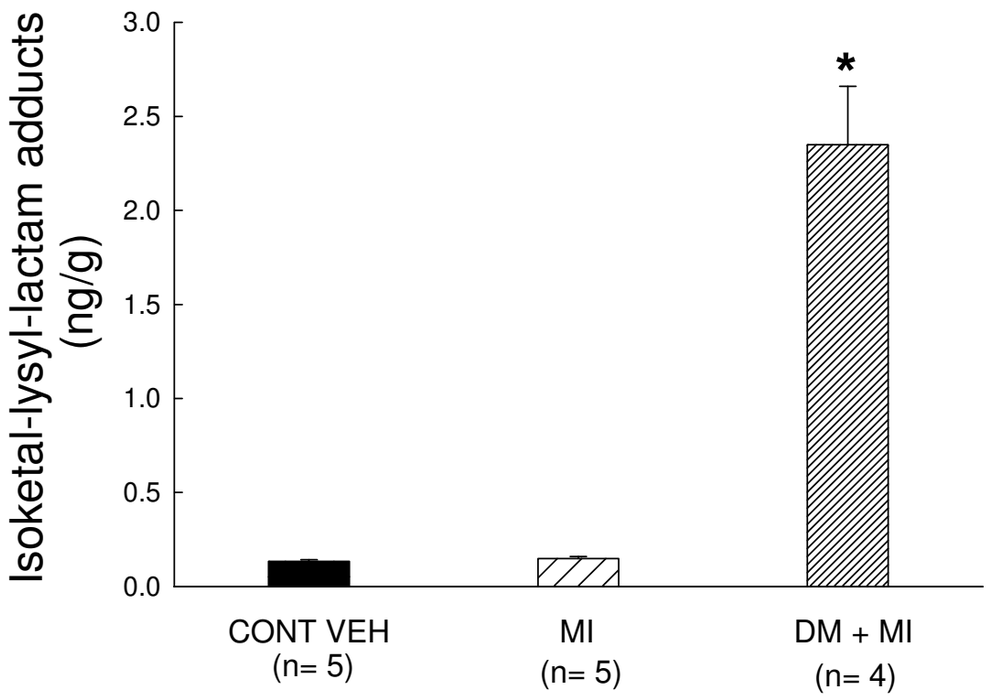

Fig. 1. Myocardial isoketal–lysyl-lactam adducts increase in DM + MI.

Myocardial isoketal–lysyl-lactam adducts in control vehicle (CONT VEH), MI, and DM + MI rats at 4 weeks post-MI. The levels of isoketal–lysyl-lactam adducts were measured in the surviving myocardium remote from the site of infarction. *Significantly different ($P<0.05$) from CONT VEH and MI groups.

Increased FOR production has also been shown to be involved in triggering cardiomyocyte apoptosis associated with diabetic cardiomyopathy (Cai et al., 2002). In addition, recent investigations have suggested that DM induces an inflammatory response by oxidative mechanisms, which may contribute to the development of diabetic cardiomyopathy (Garcia-Bailo et al., 2011). These synergistic impacts of myocardial oxidative stress in the presence of DM suggest that it is a major player in the pathogenesis of diabetic cardiomyopathy.

5. Candidate cardiac-specific biologic markers of diabetic cardiomyopathy

Proteomics (the concept of characterizing global alterations in protein expression of cells, tissues, and organs in health and disease) has become a powerful tool in the search for clinically useful biomarkers of disease and treatment response. Since the sum of the temporal alterations in proteins ultimately promotes or reflects the particular disease state, proteins represent an array of potential disease-specific markers and drug targets (Chaurand et al., 2004). Until recently, information concerning alterations that occur in the diabetic myocardial proteome and in the cardiac proteome of hearts with diabetic cardiomyopathy was lacking because proteomics had not been used to examine global cardiac protein changes that occur in diabetic cardiac complications. In an effort to bridge this gap, we recently performed proteomic analysis of diabetic cardiomyopathy utilizing two-dimensional difference gel electrophoresis and mass spectrometry (DIGE/MS) techniques (Hamblin et al., 2007a). Employing this technology, we established a specific 'type 1 diabetic' pattern of cardiac proteome changes indicative of diabetic cardiomyopathy (Hamblin et al., 2007a). We found that a high proportion (50%) of the altered proteins that could be identified by MS were localized to the mitochondria, many of which were up-regulated and involved in fatty acid metabolism. Specifically, protein expression levels for acyl coenzyme A thioester hydrolase and acyl CoA dehydrogenase, both of which are involved in fatty acid oxidation (J.J. Kim & Battaile, 2002), were found to be elevated 2-to 2.5-fold in the LV myocardium of rats with STZ-induced diabetic cardiomyopathy (Hamblin et al., 2007a). Our finding by proteomic analysis that these fatty acid utilization proteins are significantly more abundant in type 1 diabetic cardiomyopathy has been confirmed in proteomics-based studies of diabetic cardiomyopathy in OVE26 mice (Shen et al., 2004). Taken together, these consistent proteomic results show that elevated cardiac fatty acid utilization proteins are associated with diabetic cardiomyopathy and, hence, could serve as candidate markers and indicators of diabetic cardiomyopathy. As such, these results represent a starting point for the identification and development of a panel of cardiac biomarkers able to delineate diabetic cardiomyopathy. Continued proteomics-based studies of diabetic cardiomyopathy are essential to rapidly expand the range of biomarkers that is required for the emergence of new and successful protein diagnostics of diabetic cardiomyopathy.

6. Therapeutic strategies for the treatment of diabetic cardiomyopathy

6.1 Glycemic control

Until recently, clinical trials examining the effectiveness of good glycemic control in reducing cardiovascular events in diabetics has produced mixed results. The publication of 2 randomized intervention trials, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial and the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial, showed that lowering of blood glucose in type 2 diabetics to near-normal levels did not significantly reduce cardiovascular events and actually increased mortality (Gerstein et al., 2008; Patel et al., 2008). However, these results were obtained from middle-aged and older patients with a long duration of DM and a high risk of cardiovascular disease. A recent epidemiologic analysis of the cardiovascular effect of glucose lowering in patients with type 2 DM revealed that patients with high levels of co-morbidity may receive diminished

cardiovascular benefit from intensive blood glucose control (Greenfield et al., 2009). Furthermore, the ACCORD trial was not designed to test whether patients with HbA_{1c} levels below 7.5% receive greater benefit from intensive glucose lowering (Gerstein et al., 2008). Examination of the hazard ratios for the primary outcome and death from any cause in relation to glycated hemoglobin levels at baseline in the ACCORD trial showed a fewer number of events in type 2 DM patients with HbA_{1c} levels at baseline < 8%, suggesting a better response to therapy than patients with higher HbA_{1c} levels. This hypothesis is supported by a recent epidemiologic analysis of the cardiovascular effect of glucose lowering in type 2 DM patients whereby HbA_{1c} levels of 7.0% or less at baseline was associated with a lower 5-year incidence of cardiovascular events (Greenfield et al., 2009).

A series of recent reports have also established that improved glycemic control reduces the subsequent risk of any cardiovascular disease event in type 1 DM. The most convincing clinical evidence in support of this paradigm stems from the Diabetes Control and Complications Trial (DCCT) in which the DCCT randomly assigned 1441 patients with type 1 DM to receive either intensive diabetes therapy (three or more daily injections of insulin or insulin treatment with an external pump) or conventional diabetes therapy (one or two daily injections of insulin) for a mean of 6.5 years (DCCT, 1993). After treating them for a mean of 6.5 years, mean HbA_{1c} was 7.2% in the intensive therapy arm and 9.0% in the conventional treatment arm. Although a reduction in the risk for macrovascular events was observed in the intensive diabetes therapy arm, it did not achieve statistical significance (DCCT, 1993). After completion of this component of the DCCT, ninety-three percent of the 1441 patients were continued to be followed up as part of an ongoing observational study (Epidemiology of Diabetes Interventions and Complications [EDIC] study). After a mean follow-up of 17 years, intensive diabetes therapy, as compared to conventional therapy, reduced the risk of a cardiovascular event by 42% (Nathan et al., 2005). These beneficial effects were observed despite non-significant differences in mean HbA_{1c} concentrations between the previous intensive and conventional therapy groups at year 11 of the EDIC study, indicating intensive diabetes therapy has long-term, sustained beneficial effects on the risk of cardiovascular disease in patients with type 1 DM (Nathan et al., 2005).

The recent publication of an observational study involving type 1 DM patients has demonstrated the benefits of optimum glycemic control in reducing specifically the risk of HF in type 1 DM (Lind et al., 2011). The positive association between glycated hemoglobin and risk of HF in fairly young patients with type 1 DM together with the finding that tight control of glycemia in type 1 diabetes can prevent HF besides other aspects of cardiovascular disease (Lind et al., 2011) indicates a potential for prevention of HF with improved glycemic control. Given that patients with poorly controlled type 1 DM, as in those included in this recent observational study, have a high probability of diabetic cardiomyopathy, these results suggest that intensive glucose control be initiated as early as possible in people with type 1 DM to reduce the risk of cardiovascular complications, including cardiomyopathy and HF. In that regard, evidence that diabetic cardiomyopathy does not develop in patients with tightly controlled type 1 DM (Konduracka et al., 2007) supports the use of anti-hyperglycemic agents as part of the treatment regime for diabetic cardiomyopathy.

6.1.1 Sulfonylureas

Sulfonylureas are agents that act to increase insulin release from the beta cells in the pancreas and thus are almost exclusively used in the management of type 2 DM. Clinical studies examining the use of sulfonylureas in diabetic HF are rather limited but have produced conflicting results due in large part to the fact that the subjects included in these studies either had pre-existing cardiovascular disease or were at high risk of cardiovascular events (Simpson et al., 2006). In animal models of STZ-induced diabetic cardiomyopathy that are devoid of cardiovascular co-morbidities, chronic treatment with glyburide, the most widely used sulfonylurea, ameliorated the decline in myocardial function associated with diabetic cardiomyopathy (Mozaffari et al., 1989). Clearly, further studies are needed to determine the benefits of these drugs in patients with DM and HF.

6.1.2 Metformin

Metformin is a member of the insulin-sensitizing drugs that was previously contraindicated in patients with HF due to concerns over lactic acidosis. Although its use is still strongly cautioned, recent evidence from three cohort studies in which metformin therapy was compared with other anti-hyperglycemic agents demonstrated that metformin treatment was associated with a lower risk of all-cause mortality and all-cause hospital admissions (Eurich et al., 2007). In addition, metformin therapy has been reported to improve outcomes in older patients with DM and HF (Masoudi et al., 2005). Metformin has also been demonstrated to have favorable actions on the development of diabetic cardiomyopathy in Zucker diabetic rats (ZDF) (Forcheron et al., 2009).

6.1.3 Thiazolidinediones (TZDs)

The TZDs [PPARγ (peroxisome–proliferator–activated receptor γ) receptor agonists] are primarily insulin-sensitizing agents that have been shown to exert beneficial effects on the myocardium. However, due to their propensity for fluid retention, their use is limited to patients in New York Heart Association (NYHA) functional class I-II HF. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) is currently the only completed cardiovascular (CV) outcomes study with a thiazolidinedione and remains the only large-scale, prospective, secondary prevention trial carried out entirely in patients with type 2 DM (Betteridge et al., 2008). The results from this study demonstrated that the TZD pioglitazone does not increase the risk of macrovascular events or worsen outcomes in those who develop signs of heart failure in a high-risk population with type 2 DM with macrovascular disease (Betteridge et al., 2008). Even when the increased incidence of signs of HF (with a normal ejection fraction) was taken into account, the overall CV benefit of pioglitazone remained (Betteridge et al., 2008). These results suggest that from a safety perspective, the favorable cardiovascular effects of pioglitazone treatment outweigh any inherent risks (Betteridge et al., 2008).

6.1.4 Incretins: A new line of therapy

Incretins are hormones produced by the gastrointestinal tract in response to nutrient entry that act to regulate postprandial glucose homeostasis. Among several incretin hormones, glucagon-like peptide-1 (GLP-1) stimulates insulin secretion in a glucose dependent fashion. As a result, an important safety advantage of incretin-based therapy is the abolishment of risk for hypoglycemia. Currently, there are two types of incretin-based

drugs that have been developed to improve the effects of glucagon-like peptide-1 (GLP-1): incretin mimetics such as GLP-1 receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, which potentiate the incretin hormones by inhibiting the enzyme responsible for their degradation.

The GLP-1 receptor agonists mimic the actions of endogenous GLP-1 and are currently marketed as exenatide and liraglutide. Clinical trials of GLP-1 analogues have demonstrated improved LV function in patients with LV dysfunction after acute MI (Nikolaidis et al., 2004) and in patients with chronic advanced HF (Sokos et al., 2006). In an observational study involving patients with DM and HF, administration of GLP-1 over a period of three days improved the glycemic state and caused a trend towards improvement of parameters expressing LV function in DM patients with stable HF (Thrainsdottir et al., 2004). The beneficial actions on cardiac function reported so far with GLP-1 analogues provide a rationale for their use in DM patients with cardiomyopathy (Jax, 2009).

The DPP-4 inhibitors are newer drugs and currently marketed products include sitagliptin, saxagliptin, and vildagliptin. Cardiovascular outcomes as well as safety trials using this class of incretin-based drugs in patients with DM is underway to determine their efficacy and safety.

6.2 RAAS blockade

6.2.1 Renin inhibitors

The discovery that the binding of prorenin or renin to the prorenin/renin or (pro)renin receptor results in the augmented formation of angiotensin I has led to the development of direct renin inhibitors. Cardiac (pro)renin receptor expression has recently been documented to be increased in experimental diabetic cardiomyopathy (Connelly et al., 2011). Blockade of RAAS via administration of the direct renin inhibitor, aliskiren (10 mg/kg per day for 6 weeks duration), reduced cardiac over-expression of both (pro)renin mRNA and protein in diabetic TGR (mRen2)-27 rats, a transgenic rodent model that following the induction of STZ-diabetes develops diabetic cardiomyopathy (Connelly et al., 2011). Just as importantly, the reduced cardiac pro(renin) receptor expression with aliskiren treatment was associated with improved cardiac structure/function (Connelly et al., 2011). Given these exciting findings, direct renin inhibitors, particularly aliskiren, are ripe for further evaluation as novel therapeutics to modulate/prevent diabetic cardiomyopathy.

6.2.2 Angiotensin Converting Enzyme (ACE) inhibitors

Treatment with ACE inhibitors has been shown to exert an ameliorative effect on diabetic cardiomyopathy in both diabetic animals and diabetic patients. Administration of ramipril (2.5 mg/day) for 3 months to asymptomatic type 2 DM patients with echocardiographic indices of early diabetic cardiomyopathy improved echocardiographic indices of LV diastolic function in these patients (Symeonides et al., 2007). The reversal of indices of diabetic cardiomyopathy in these type 2 DM patients with ramipril was accompanied by a reduction of plasma BNP levels (Symeonides et al., 2007). In an experimental rat model of diabetic cardiomyopathy, administration of captropril (13 mg/kg) for 8 weeks in rats with clear cardiomyopathy improved the myocardial structure and cardiac function (C.H. Zhang et al., 2008). Taken together, these results suggest that treatment with ACE inhibitors can exert a beneficial effect on the development of diabetic cardiomyopathy.

6.2.3 Angiotensin Receptor Blockers (ARBs)

ARBs have emerged as a promising treatment modality for diabetic cardiomyopathy. Damage to the myocardial ultrastructure of rats with diabetic cardiomyopathy has been shown to be reduced by the type 1 angiotensin II receptor blocker (AT_1RB) valsartan (C.H. Zhang et al., 2008). In DM patients with cardiomyopathy as assessed by Doppler echocardiography, the administration of the ARB telmisartan resulted in improved echocardiographic and biochemical indices of diabetic cardiomyopathy (Symeonides et al., 2007). Since a majority of patients develop dry cough with ACE inhibitors, the cardioprotection afforded by ARBs offer the distinct advantage of having better compliance.

6.3 β-blockers

Until recently, patients with DM were less likely to be prescribed β-blockers due in part over fears of worsening insulin resistance and lipid metabolism. However, the realization of the importance of the sympathetic nervous system in the release of vasoactive substances (Murarka & Movahed, 2010) and the demonstrated benefit of β-blockers in other forms of HF has led to β-blockers being accepted as a mainstay in the treatment of DM patients with HF. The utility of β-blockade has also been demonstrated in experimental models of diabetic cardiomyopathy. Chronic treatment with the β-blocker metoprolol (β1-selective inverse agonist) has been shown to improve cardiac function in STZ-induced diabetic cardiomyopathy in rats as evidenced by significant increases in cardiac output (Sharma et al., 2008). Treatment with bisoprolol (β1-selective antagonist) for 3 months reversed myocardial hypertrophy and changes in diabetic cardiomyopathy rats (J.N. Zhang et al., 2003). Clinical trials to evaluate β-blocker intervention in patients specifically with diabetic cardiomyopathy are lacking and should be conducted to exploit this recent experimental data.

6.4 Antioxidants

As the pathogenesis of diabetic cardiomyopathy involves oxidative stress, antioxidants have received considerable interest as a therapeutic strategy. Several different approaches, such as dietary supplementation, administration of pharmacological agents with antioxidant properties, and over-expression of antioxidant enzymes to augment antioxidant defense mechanisms, have proven to be effective in reversing diabetic cardiomyopathy in animal models of both type 1 and type 2 DM.

Vitamin E, a lipid-soluble and potent antioxidant, has been shown in diabetic rats to evoke cardioprotective effects against diabetic cardiomyopathy. We have previously reported that dietary supplementation with vitamin E (2000 IU of tocopherol acetate/kg of feed) beginning early after the onset of type 1 DM in rats and continuing for a period of 8 weeks improved LV function as evidenced by a significant improvement in LVSP, LVEDP, and +dP/dt compared with un-supplemented DM rats (Hamblin et al., 2007b). The improved LV hemodynamic function of type 1 diabetic cardiomyopathy rats supplemented with vitamin E was accompanied by significantly reduced levels of myocardial oxidative stress (Hamblin et al., 2007b). Specifically, vitamin E blunted the diabetes-induced amplification of myocardial 8-*iso* $PGF_{2\alpha}$ and oxidized glutathione (GSSG) formation (Hamblin et al., 2007b). Vitamin E administration has also been documented to be associated with a significant decline in apoptosis, lipid peroxidation, protein oxidation, and enhancement of the antioxidant defense system, suggesting that this antioxidant may promote a convalescing

effect on diabetic cardiomyopathy through the attenuation of oxidative stress and abrogation of apoptotic signals (Shirpoor et al., 2009). These findings demonstrate the usefulness of vitamin E as a protective anti-oxidative agent against cardiac sequel of DM involving cardiomyopathy.

Resveratrol, the principal effector constituent of red wine, has been shown to improve cardiac function in diabetic cardiomyopathy (Huang et al., 2010; Sulaiman et al., 2010). Oral administration of resveratrol (2.5 mg/kg body wt/day) to STZ-diabetic rats for 15 days has been shown to result in a direct cardioprotective effect on the diabetic myocardium (Thirunavukkarasu et al. 2007). Resveratrol treatment of chronic diabetic mice resulted in a tremendous improvement of all functional parameters to the extent that cardiac function was comparable to age-matched controls (Sulaiman et al., 2010). These data demonstrate that resveratrol can prevent diabetes-induced decline in cardiac function and resultant cardiomyopathy. Studies have revealed that resveratrol treatment improves cardiac dysfunction of diabetic myocardium in part via modulation of oxidative stress proteins (Dekkers et al., 2008). The recognition that resveratrol treatment up-regulates the protein expression of the antioxidant enzyme catalase in diabetic hearts (Dekkers et al., 2008) is further evidence of its ability to increase protection against oxidative stress.

Tempol is a membrane-permeable SOD mimetic that has been shown to attenuate the effects of FORs (Thiemermann et al., 2001). *In vivo* treatment with the antioxidant tempol (1 mmol/l in drinking water) for a period of 4-weeks to mice rendered insulin-resistant by deficiency of the insulin-sensitive GLUT4 transporter significantly and potently attenuated cardiac hypertrophy in concert with tempol up-regulated ventricular expression of thioredoxin-2 (confirming an antioxidant action) (Ritchie et al., 2007). Since the pre-diabetic insulin-resistant heart exhibits many features of diabetic cardiomyopathy, including both left ventricular dysfunction and structural abnormalities such as cardiac hypertrophy and fibrosis (Ritchie et al., 2007), these results indicate that tempol should be considered for preventing oxidative stress and cardiomyopathy in the diabetic heart.

Metallothionein (MT), a cysteine-rich protein, is a potent antioxidant owing to its high thiol content. Using a cardiac-specific, MT-overexpressing transgenic (MT-TG) mouse model, MT has been shown to be effective in preventing diabetic cardiomyopathy through the suppression of oxidative damage (Cai et al., 2005, 2006; Liang et al., 2002). Supplementation with Zinc (Zn), a potent inducer of MT, prevented the increases in cardiac morphological impairment, fibrosis, and dysfunction observed in diabetic mice without Zn supplementation (Wang et al., 2006b). Silencing of MT expression with small-interfering RNA abolished the prevention of diabetic cardiomyopathy by Zn supplementation (Wang et al., 2006b). These results demonstrate that Zn supplementation protects against diabetic cardiomyopathy via cardiac MT induction and suggest Zn supplementation, with cardiac MT induction, as a potential therapeutic approach to prevent diabetic cardiomyopathy.

Targeted over-expression of the antioxidant proteins SOD and catalase to the heart has been shown to be effective in reducing diabetic cardiomyopathy (Shen et al., 2006; Ye et al., 2004). Chronic over-expression of catalase has been documented to eliminate excess FOR production in diabetic cardiomyocytes concomitant with preservation of normal cardiac morphology and contractile function (Ye et al., 2004). Over-expression of the mitochondrial antioxidant protein manganese SOD (Mn SOD) has been reported to protect against the formation of exogenous oxidants and also completely normalize contractile function in both type 1 and type 2 models of diabetic cardiomyopathy (Shen et al., 2006).

Although a number of previous large randomized placebo-controlled clinical trials have failed to show any beneficial effects of antioxidants (in particular vitamin E) on cardiovascular events, recently published literature suggests that these clinical trials of antioxidants and cardiovascular diseases may be fatally flawed (Blumberg & Frei, 2007; Roberts et al., 2007; Traber et al., 2008). Implicit in the majority of randomized placebo-controlled clinical trials that have previously explored the benefits of antioxidants is that the antioxidants tested effectively suppressed oxidative stress status but this was never determined (Roberts et al., 2007). Furthermore, not including elevated oxidative stress in patient eligibility criteria substantially reduces statistical power to detect antioxidant or cardiovascular effects (Block et al., 2008; Roberts et al., 2009). To that end, it has recently been reported that *"the negative evidence regarding vitamin E supplements from previous randomized clinical trials is more a reflection of inadequate study design and methods of analysis than proof of failure of vitamin E in primary prevention"*(Blumberg & Frei, 2007). Data obtained in experimental animals must obviously be extrapolated to the clinical arena with caution. Nevertheless, the present findings suggest that vitamin E and other antioxidants may confer cardiovascular benefit in select patients who are diabetic and in greater oxidative stress. Indeed, support for this paradigm has recently been demonstrated in a retrospective analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial where vitamin E administration to diabetic individuals homozygous for the haptoglobin (Hp) 2 allele, which confers markedly less antioxidant protection against hemoglobin-induced oxidation, was shown to result in a 50% reduction in non-fatal MI and cardiovascular death (Levy et al., 2004). The validity of these findings have subsequently been confirmed in Hp 2-2 DM individuals in a prospective, double-blind, placebo-controlled trial of vitamin E (Milman et al., 2008). These positive results impel future clinical trials to study the efficacy of antioxidants specifically in patients with diabetic cardiomyopathy.

6.5 Cell transplantation

Transplantation of stem cells has emerged as an alternative therapeutic approach to improve cardiac function in the post-MI setting as well as in ischemic cardiomyopathic hearts. However, until recently, stem cell therapy studies had not been evaluated in the diabetic heart. In the past few years, cell transplantation has begun to be examined in the setting of diabetic cardiomyopathy. Transplantation of bone marrow mesenchymal stem cells (MSCs) into the hearts of STZ-diabetic rats via injection into the femoral vein has been shown to improve the cardiac function of diabetic cardiomyopathy through increased angiogenesis and attenuation of cardiac remodeling (N. Zhang et al., 2008). Bone marrow MSC transplantation has also been reported to improve cardiac function in the rat diabetic cardiomyopathy model through an anti-apoptotic effect (Li et al., 2008). Treatment combining smooth muscle cell (SMC) transplantation via intramyocardial injection and insulin therapy has been shown to result in the preservation of heart function in STZ-diabetic rats with cardiomyopathy as assessed by echocardiographic and hemodynamic techniques (B.O. Kim et al., 2008). Although the clinical significance of these studies will require further testing and confirmation in other animal models of DM, cell transplantation holds great promise for the treatment of diabetic cardiomyopathy.

7. Conclusions and future directions

The full spectrum of diabetic cardiomyopathy encompasses a progression from subclinical LV diastolic and systolic dysfunction to clinically overt symptomatic HF. Recognition and

treatment of diabetes-induced myocardial dysfunction in its infancy is paramount for the prophylaxis of ensuing cardiomyopathy and HF. Thus, there is an eminent need for early detection of this clinical entity. In that regard, the knowledge that structural and functional alterations of a particular disease state are preceded by changes in proteins has led to the recent application of proteomics to the field of DM. The use of proteomic technologies, such as mass spectrometry, provides an ideal vehicle into this arena. Analysis of protein expression profiles in serum and tissues from diabetic animals and humans is now underway and will increase our power to identify early and subtle abnormalities of cardiac dysfunction in DM. One can also foresee the use of this technology to help establish biomarkers that are predictive for risk of developing diabetic cardiomyopathy. The potential capability of proteomics to elucidate protein changes occurring in response to pharmacological therapeutics is a particularly exciting application of this technology. Studies of drug-induced proteomic changes will be required to determine the ability of this molecular technology to correlate changes in protein expression with efficacy of established and novel therapies for cardiomyopathy in DM. The recent development of more sensitive and sophisticated echocardiographic techniques such as tissue Doppler, strain, strain rate, and ultrasonic tissue characterization appears helpful in identifying early myocardial dysfunction in asymptomatic patients with DM. Integration of proteomics with sensitive diagnostic imaging modalities holds tremendous potential for the comprehensive detection of preclinical cardiac dysfunction in patients with DM and thus should facilitate earlier therapeutic intervention to prevent cardiomyopathy and subsequent HF in this high-risk patient population.

8. Acknowledgments

Supported by National Heart, Lung, and Blood Institute grant 5 R01 HL089385-02 (to M.F. Hill). I gratefully acknowledge Salisha Hill, B.Sc., for expert consultation on proteomic technologies and proteomics approaches.

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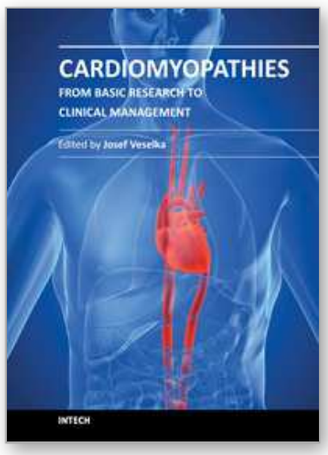

Cardiomyopathies - From Basic Research to Clinical Management
Edited by Prof. Josef Veselka

ISBN 978-953-307-834-2
Hard cover, 800 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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