Diabetic cardiomyopathy: Where are we 40 years later?

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Diabetic cardiomyopathy is a cardiac disease that arises as a result of the diabetic state, independent of vascular or valvular pathology. It manifests initially as asymptomatic diastolic dysfunction, which progresses to symptomatic heart failure. The compliance of the heart wall is decreased and contractile function is impaired. The pathophysiology is incompletely understood, but appears to be initiated both by hyperglycemia and changes in cardiac metabolism. These changes induce oxidative stress and activate a number of secondary messenger pathways, leading to cardiac hypertrophy, fibrosis and cell death. Alterations in contractile proteins and intracellular ions impair excitation-contraction coupling, while decreased autonomic responsiveness and autonomic neuropathy impair its regulation. Extensive structural abnormalities also occur, which have deleterious mechanical and functional consequences.

Key Words: *Cardiomyopathy; Diabetes mellitus; Heart failure; Metabolism; Oxygen free radicals; Remodelling*

Diabetes is associated with increased cardiovascular morbidity and mortality. Before 1972, this was attributed solely to the effects of diabetes on the vasculature. However, in 1972, Rubler et al (1) first described diabetic cardiomyopathy, a specific type of cardiomyopathy that occurs in the absence of ischemia or valvular disease. Clinically, diabetic cardiomyopathy is manifested initially by asymptomatic diastolic dysfunction that progresses to systolic dysfunction. Diabetic cardiomyopathy can cause heart failure on its own, and contributes to accelerated heart failure when it presents with other cardiovascular complications, most notably hypertension and ischemic heart disease. The prevalence of diabetic cardiomyopathy is alarmingly high; recent studies using Doppler ultrasound have demonstrated a prevalence of 40% to 60% in diabetic patients (2).

The etiology of diabetic cardiomyopathy is still poorly understood, but a picture of the process is beginning to emerge. Two major precipitating factors have been identified, both of which precede the development of diabetic cardiomyopathy and are unique to the diabetic state (Figure 1). The first is hyperglycemia, a major mediator of many diabetic complications. The second relates to the effect of diabetes on cardiac metabolism. Whereas the normal heart derives its energy from carbohydrates (20% to 40%) and fatty acid metabolism (60% to 80%), the diabetic heart relies almost exclusively on fatty acids as an energy source (3). The impairment in cardiac

La myocardiopathie diabétique : Où en sommes-nous 40 ans plus tard ?

La myocardiopathie diabétique est une maladie cardiaque qui se déclare à cause de l'état diabétique, indépendamment d'une pathologie vasculaire ou valvulaire. Elle se manifeste d'abord sous forme de dysfonction diastolique asymptomatique, puis elle dégénère en insuffisance cardiaque symptomatique. La souplesse de la paroi cardiaque diminue et la fonction contractile se détériore. On ne comprend pas tout à fait sa physiopathologie, mais elle semble être déclenchée tant par l'hyperglycémie que par des modifications au métabolisme cardiaque. Ces modifications induisent un stress oxydatif et activent plusieurs voies messagères secondaires, lesquels provoquent une hypertrophie cardiaque, une fibrose et la mort cellulaire. Des altérations aux protéines contractiles et aux ions intracellulaires compromettent le couplage excitation-contraction, tandis que la diminution de la réactivité et de la neuropathie autonomes nuit à sa régulation. Des anomalies structurelles généralisées se produisent également et ont des conséquences mécaniques et fonctionnelles délétères.

function seen in diabetic cardiomyopathy occurs by two general mechanisms. The compliance of the heart wall is decreased, and contractility is also decreased.

MECHANISMS OF DECREASED COMPLIANCE

Myocellular hypertrophy and myocardial fibrosis decrease the compliance of the heart wall in diabetes. Interstitial deposition of glycogen in the subendocardium also decreases compliance. However, compliance is also reduced by increased cross-linking of collagen as a consequence of hyperglycemia.

Prolonged exposure of proteins to hyperglycemia over weeks or months causes them to undergo a series of nonenzymatic reactions with glucose, eventually forming advanced glycosylation end products (AGEs). AGEs are able to form protein-protein cross-links throughout the collagen molecule, which normally only contains cross-links at the N and C terminals. Increased cross-linking of collagen leads to loss of elasticity (3).

CARDIAC METABOLISM AND OXIDATIVE STRESS

The heart requires a constant supply of ATP, which is derived mainly from fatty acid and carbohydrate metabolism. Although fatty acid oxidation produces more ATP, glucose oxidation is more efficient in terms of oxygen consumption. For optimal

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Figure 1) Overview of the etiology of diabetic cardiomyopathy. AGE Advanced glycosylation end products; NO Nitric oxide; PKC Protein kinase C; PPAR- α Peroxisome proliferator-activated receptor- α ; SNS Sympathetic nervous system

cardiac efficiency, the normal heart maintains a balance of 60% to 80% fatty acid oxidation and 20% to 40% pyruvate oxidation; the heart derives approximately equal amounts of pyruvate from glycolysis and lactate metabolism. The heart also utilizes ketones, depending on their availability (3).

The diabetic state induces profound changes in cardiac metabolism. Myocardial glucose transport is reduced as a result of decreased glucose transporter 4 translocation, and decreased total glucose transporter 4 protein and messenger RNA levels (3). In contrast, fatty acid delivery to the heart from the coronary lumen by the enzyme lipoprotein lipase, and its subsequent uptake by fatty acid transporters, is increased (4).

High rates of fatty acid oxidation increase the ratios of NADH/NAD⁺ and acetyl coenzyme A (CoA)/free CoA, both of which feed back and inhibit glucose oxidation by decreasing flux through pyruvate dehydrogenase (4). High rates of fatty acid oxidation also increase citrate production. Citrate inhibits glycolysis by inhibiting the key glycolytic enzyme phosphofructokinase. This is known as the Randle cycle. It leads to an intracellular accumulation of intermediate products of glucose metabolism. Conversely, high rates of glycolysis and glucose oxidation can feed back to inhibit fatty acid oxidation.

The heavy reliance of the diabetic heart on fatty acids is harmful. It decreases myocardial efficiency; furthermore, although fatty acid oxidation increases dramatically in the

diabetic state, the delivery of free fatty acids into the cardiomyocyte exceeds its capacity to metabolize and store them. Lipids therefore accumulate in the cytoplasm, mainly in the form of long-chain acyl CoAs (4). Long chain acyl CoAs are converted into ceramide, a toxic substance that induces reactive oxygen species (ROS) and cardiomyocyte apoptosis (5). Further evidence for the involvement of lipotoxicity is provided by the observation that increasing fatty acid influx to the cardiomyocyte by overexpression of long-chain acyl CoA synthetase, fatty acid transport protein-1 or lipoprotein lipase produces a phenotype similar to that seen in diabetic cardiomyopathy (4).

Fatty acids can bind and activate peroxisome proliferator-activated receptors (PPARs), of which PPAR- α is the most important isoform in the heart. PPAR- α is a regulator of cardiac energy metabolism. It acts as a 'lipostat', inducing genes involved in fatty acid metabolism (6). Although PPAR- α can upregulate enzymes at every step of the fatty acid oxidation pathway, it controls fatty acid oxidation principally at the point of entry into the mitochondria (7). Overexpression of PPAR- α induces a phenotype similar to that seen in diabetic cardiomyopathy, and worsens the phenotype seen in the diabetic state (4). Conversely, PPAR- α -null mice are protected against the development of diabetic cardiomyopathy (4). These data indicate that activation of PPAR- α is essential to the

pathogenesis of diabetic cardiomyopathy. What is unclear, however, is whether PPAR- α activation is a consequence or a cause of increased fatty acid oxidation.

One aspect of metabolism that is seldom considered in the diabetic heart is amino acid metabolism. Protein synthesis in the diabetic heart is inhibited because RNA levels are decreased and protein synthesis itself is less efficient. Hyperglycemia produces a marked arteriovenous difference of branch-chained amino acids across the myocardium. The catabolism of amino acids may therefore be increased in the diabetic heart. This would decrease the availability of amino acids for protein synthesis. This, in turn, could produce qualitative and quantitative decreases in the amount of contractile protein present (3). In addition, uptake of the circulating amino acid homocysteine is of pathophysiological significance because it induces oxidative stress and activates perivascular matrix metalloproteinases (8).

Hyperglycemia can produce glucotoxicity through an increase in ROS formation (9). Hyperglycemia, coupled with the marked decrease in glucose oxidation, increases the flux of glucose through alternative pathways. Increased flux through the polyol pathway increases the NADH/NAD⁺ ratio, just as increased fatty acid oxidation does. This further inhibits glycolysis, and glycolytic intermediates can contribute to further de novo synthesis of diacylglycerol and activation of protein kinase C (PKC). This pathway also consumes NADPH, which is needed to form reduced glutathione, a major antioxidant defence of the cardiomyocyte (9).

Increased flux of glucose through the hexosamine biosynthetic pathway increases protein glycosylation, which in turn increases the transcription of various proinflammatory genes. Formation of AGEs, discussed above, increases the formation of ROS and increases the transcription of proinflammatory genes by interacting with their own receptors, receptors for AGE. The formation of AGEs is, in turn, enhanced in the presence of oxidative stress (9).

Nitric oxide is an important regulator of cardiac function, and its production is increased in the diabetic heart with deleterious consequences. Nitric oxide rapidly and spontaneously reacts with superoxide anion to form peroxynitrite, which is a very powerful oxidant and cytotoxic agent. In addition, excessive production of nitric oxide may depress cardiovascular function (9).

Increased de novo synthesis of diacylglycerol, either by increased polyol flux or by receptors for AGE activation, leads to activation of PKC isoforms. Stress signalling pathways such as the mitogen-activated protein kinase and c-jun NH(2)-terminal kinase pathways are also activated by the polyol pathway and oxidative stress (9). These pathways increase the transcription of proinflammatory and profibrotic genes and stimulate apoptosis.

OTHER SIGNALLING PATHWAYS

Alterations in G protein levels and/or function, notably G_i and G_q, have also been implicated in the cardiac dysfunction of diabetes (10). RhoA is a small-molecular-weight monomeric G-protein that activates Rho-kinase. Activation of the RhoA/Rho-kinase pathway plays a role in the induction of cardiac hypertrophy. Increased α -1-adrenoceptor stimulation, as well as stimulation by endothelium-derived vasoconstrictors (endothelin-1, thromboxane A₂) may all contribute to RhoA/Rho-kinase activation.

Cardiac dysfunction leads to the activation of the tissue renin-angiotensin system, the sympathetic nervous system and other neurohormonal regulatory systems in an effort to maintain systemic perfusion. Activation of the sympathetic nervous system increases apoptosis and necrosis predominantly through stimulation of β -1-adrenoceptors (11), and fibrosis through activation of α -1-adrenoceptors. Activation of the tissue renin-angiotensin system in the heart increases ROS generation in the cardiomyocyte (9).

EXCITATION-CONTRACTION COUPLING

At the level of the cardiomyocyte, the action potential is prolonged and calcium efflux is slowed, resulting in slowed myocyte shortening and lengthening (12). Cardiac contractile protein ATPase is markedly depressed in the diabetic heart. Induction of the so-called 'fetal gene program' results in a shift from the fast V₁ isomyosin pattern seen in the normal heart to a predominantly V₃ pattern in the diabetic heart (3). Due to reduced RNA levels and inefficient protein synthesis, total contractile protein levels may also be decreased.

Sarcoplasmic reticulum calcium ATPase and sodium-calcium exchanger expression and function are decreased, leading to disturbances in calcium handling. Calcium uptake, binding to the sarcolemma and intake by myofibrillar calcium-ATPase activity are all decreased in the diabetic heart. Increased activation of PKC increases the calcium sensitivity of myofilaments. Regulation of excitation-contraction coupling is impaired due to a decrease in β -adrenergic responsiveness (9) and autonomic neuropathy (3). As diabetic cardiomyopathy progresses to symptomatic heart failure, downregulation of myocyte enhancer factor-2 and its target genes occurs, resulting in a more severe contractile dysfunction (13).

STRUCTURAL AND ULTRASTRUCTURAL CHANGES

Left ventricular mass, thickness and size progressively increase as diabetic cardiomyopathy becomes more severe (14). The most prominent histopathological finding in the diabetic heart is fibrosis. This can be perivascular, interstitial or both. Progression of the disease is associated with myocyte cell death and replacement fibrosis (14). Myocyte cell death is caused both by apoptosis, a genetically controlled process for removing unwanted cells, and necrosis, in which cardiomyocytes are destroyed by biochemical damage. Only necrotic cell death stimulates fibrosis (14).

Interstitial fibrosis decreases the compliance of the heart. Perivascular fibrosis, in addition to this, has functional consequences. In the normal heart, extracellular matrix provides a functional link between the endothelium and the cardiomyocytes. In the diabetic heart, activation of matrix metalloproteinases disconnects the endothelium from the cardiomyocytes, impairing diastolic relaxation (8).

Diabetic cardiomyopathy is associated with microangiopathy which is also proposed to contribute to fibrosis. Whether focal microangiopathy can account for the diffuse fibrosis seen in the diabetic heart is controversial (see Fang et al [14] for review). However, a recent study (15) demonstrated that restoration of microvascular homeostasis by replenishment of vascular endothelial growth factor improved cardiac function in diabetic cardiomyopathy.

A number of ultrastructural changes have been reported in cardiomyocytes (3). These include alterations in myofibrillar

TABLE 1
Progression of diabetic cardiomyopathy

Stage	Pathophysiological changes	Structural changes	Functional changes	Detection by echocardiography
Early	Metabolic changes Oxidative stress Abnormal Ca ²⁺ handling Endothelial dysfunction	Ultrastructural changes only	Normal/mildly impaired diastolic function Normal systolic function	Sensitive methods only
Middle	Apoptosis/necrosis Fibrosis Hypertrophy RAS activation Autonomic neuropathy (mild)	Small increase in LV mass, wall thickness and size	Mildly impaired diastolic function Normal or mildly impaired systolic function	Sensitive methods or conventional echocardiography
Late	Microvascular disease Autonomic neuropathy (severe) Frequently associated with hypertension and onset of ischemic heart disease	Large increase in LV mass, wall thickness and size	Impaired diastolic function Impaired systolic function	Conventional echocardiography

Data from reference 14. LV Left ventricle; RAS Renin-angiotensin system

arrangements, disrupted mitochondria (linked to oxidative stress and impaired mitochondrial function) and increased cytoplasmic area with increased cytoplasmic lipid content and increased collagen fibre cross-sectional area. These changes are consistent with processes leading to decreased contractility, oxidative stress, lipotoxicity and fibrosis, as discussed above.

CONCLUSION

Diabetic cardiomyopathy is a complex multifactorial disorder initiated by hyperglycemia and changes in myocardial energy metabolism (Figure 1). Both processes increase oxidative stress and stimulate the PKC and stress pathways, leading to

myocardial apoptosis, fibrosis and inflammation. Biochemical damage also induces cardiomyocyte necrosis which, in turn, stimulates further fibrosis. Abnormal calcium handling and shifts in myofibril expression impair excitation-contraction coupling. Autonomic neuropathy and decreased beta-adrenergic responsiveness lead to impaired regulation of excitation-contraction coupling. These changes are associated with extensive structural abnormalities. Clinically, this process manifests as an asymptomatic diastolic dysfunction, which progresses to symptomatic combined diastolic and systolic dysfunction (Table 1). Future studies need to further elucidate these mechanisms and develop treatment strategies for this important diabetic complication.

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