

REVIEW

Diabetic cardiomyopathy: mechanisms, diagnosis and treatment

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ABSTRACT

Independent of the severity of coronary artery disease, diabetic patients have an increased risk of developing heart failure. This clinical entity has been considered to be a distinct disease process referred to as 'diabetic cardiomyopathy'. Experimental studies suggest that extensive metabolic perturbations may underlie both functional and structural alterations of the diabetic myocardium. Translational studies are, however, limited and only partly explain why diabetic patients are at increased risk of cardiomyopathy and heart failure. Although a range of diagnostic methods may help to characterize alterations in cardiac function in general, none are specific for the alterations in diabetes. Treatment paradigms are very much limited to interpretation and translation from the results of interventions in non-diabetic patients with heart failure. This suggests that there is an urgent need to conduct pathogenetic, diagnostic and therapeutic studies specifically in diabetic patients with cardiomyopathy to better understand the factors which initiate and progress diabetic cardiomyopathy and to develop more effective treatments.

INTRODUCTION

The epidemic of obesity and sedentary lifestyle is projected to result in over 300 million people with diabetes mellitus by 2025 [1]. Cardiovascular disease is responsible for 80 % of deaths among diabetic patients much of which has been attributed to CAD (coronary artery disease). However, there is an increasing recognition that diabetic patients suffer from an additional cardiac insult termed

'diabetic cardiomyopathy'. This entity was originally described in 1972 on the basis of observations in four diabetic patients who presented with HF (heart failure) without evidence of hypertension, CAD, valvular or congenital heart disease [2]. The increasing recognition of this additional cardiac insult is supported by data from epidemiological, molecular and more refined diagnostic studies.

Key words: diabetic cardiomyopathy, diagnosis, echocardiography, molecular mechanism, treatment.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AGE, advanced glycation end-product; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; CAC, coronary artery calcification; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CVI, cyclic variation index; *E/A* ratio, ratio of early to late peak mitral filling wave velocities; ET, endothelin; HbA_{1c}, glycated haemoglobin; HF, heart failure; HIF-1, hypoxia-inducible factor-1; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; LV, left ventricular; LVET, LV ejection time; LVH, LV hypertrophy; MFR, myocardial flow reserve; MHC, myosin heavy chain; MI, myocardial infarction; MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging; NEFA, non-esterified fatty acid; NF- κ B, nuclear factor κ B; NO, nitric oxide; PEP, pre-ejection period; PKC, protein kinase C; PARP, poly(ADP-ribose) polymerase; PPAR, peroxisome-proliferator-activated receptor; RAS, renin-angiotensin system; ROS, reactive oxygen species; RR, relative risk; SERCA2a, sarcoplasmic/endoplasmic-reticulum Ca²⁺-ATPase 2a; SPECT, single photon emission CT; statin, hydroxymethylglutaryl CoA reductase inhibitor; SNS, sympathetic nervous system; TDI, tissue Doppler echocardiographic imaging; TZD, thiazolidinedione; VEGF, vascular endothelial growth factor.

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EPIDEMIOLOGY

The Framingham study demonstrated the increased incidence of congestive HF in diabetic males (2.4:1) and females (5:1) independent of age, hypertension, obesity, CAD and hyperlipidaemia [3]. Other prospective studies also show that diabetic patients have a significantly increased lifetime risk of developing HF [4], and increased mortality from both Q-wave and non-Q-wave MI (myocardial infarction) [5,6]. This suggests that there is an additional insult to diabetic myocardium which predisposes it to more extensive damage and subsequent failure. Bertoni et al. [7] have shown a link between idiopathic cardiomyopathy and diabetes.

In contrast with the 4–6% prevalence of diabetes in the community, the overrepresentation of diabetic patients in HF trials such as SOLVD (Studies Of Left Ventricular Dysfunction; 26%) [8], ATLAS (Assessment Trial of Lisinopril And Survival; 19%) [9] and V-HeFT II (Vasodilator-Heart Failure Trial II; 20%) [10] attests to the increased prevalence of this condition among diabetic patients.

PATHOLOGY

Fatal and non-fatal CAD is increased 2–4-fold in patients with diabetes [11–13], and autopsy studies have shown that diabetic patients have more extensive CAD than non-diabetic patients with CHD (coronary heart disease) [14,15]. Angiographic studies show more severe proximal and distal CAD [16–19]. Mortality from CHD is increased 3–7-fold in patients [20–22] with diabetes mellitus, and 80% of deaths among diabetic patients are from CHD [23]. Immediate and long-term post-MI mortality is increased 1.5–2-fold among diabetic patients. Furthermore, Type II diabetic patients without a previous MI have as high a risk of MI as non-diabetic patients who have already had an MI [24]. Similarly, the OASIS registry results of patients hospitalized for unstable angina suggested that diabetic patients with no previous cardiovascular disease had the same long-term morbidity and mortality as non-diabetic patients with established CAD [25]. Furthermore, despite a comparable infarct size, diabetic patients have a far greater risk of developing HF post-MI compared with non-diabetic patients [26–28]. Following MI, the surviving myocardium of non-diabetic patients becomes hyperkinetic to compensate for non-viable infarcted myocardium in an attempt to maintain cardiac output. However, in diabetic patients, these areas of myocardium cannot achieve this compensatory enhancement in function due to a complex set of intra- and extra-myocardial factors superimposed on an already reduced coronary artery flow reserve [29–31]. Furthermore, endomyocardial samples from diabetic patients show enhanced thickening of capillary basement membrane, myocellular atrophy and

hypertrophy with myocardial and interstitial fibrosis, which further reduce myocardial function [32–34].

DEFINITIONS

Diabetic cardiomyopathy refers to a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities eventually leading to LVH [left ventricular (LV) hypertrophy] and diastolic and systolic dysfunction or a combination of these. The concept of diabetic cardiomyopathy is based upon the idea that diabetes is the factor which leads to changes at the cellular level, leading to structural abnormalities as outlined above. We know that diabetic patients are at increased risk of hypertension and CAD; however, the idea of the existence of a diabetic cardiomyopathy suggests that changes can occur and be detected without the presence of these other factors. Therefore patients with hypertension and CAD may well have myocardial changes related to these disease processes, but a specific cardiomyopathy may also affect the myocardium secondary to diabetes causing a synergistic adverse effect as seen with a combination of diabetes and hypertension [32]. Diabetic cardiomyopathy can be subclinical or apparent depending on the presence of symptoms and signs. There appears to be a long subclinical course in most patients before the development of symptoms.

STRUCTURAL CHANGES

It is important to understand what is meant by LVH and systolic and diastolic dysfunction and the prognostic implications in the context of diabetic cardiomyopathy.

LVH

As LV mass is a continuous variable, the threshold value for LVH is arbitrary; however, LVH is often defined as the upper 5% of the distribution of LV mass in the population. Although there is no clear consensus on the cut-off values used to define LVH, the 2003 ESC (European Society of Cardiology) guidelines proposed that LVH on echocardiography should be defined by an LV mass > 125 g/m² for men and 110 g/m² for women (Figure 1). Alternatively, the 12-lead ECG remains a useful qualitative screening technique for LVH. Among the most accurate criteria are the QRS voltage duration product [men: (RaVL + SV3) × QRS duration > 2440 mm × ms; women: (RaVL + SV3 + 8) × QRS]. The presence of LVH on the ECG is a poor prognostic indicator as seen by the results of the Framingham study [35]. Similarly, echocardiographic assessment of LVH in 3222 subjects enrolled in the Framingham study showed that the risk-factor-adjusted relative risk of cardiovascular disease was 1.49 for each increment of 50 g/m in LV mass for men and 1.57 for women [35]. The presence of LVH has been

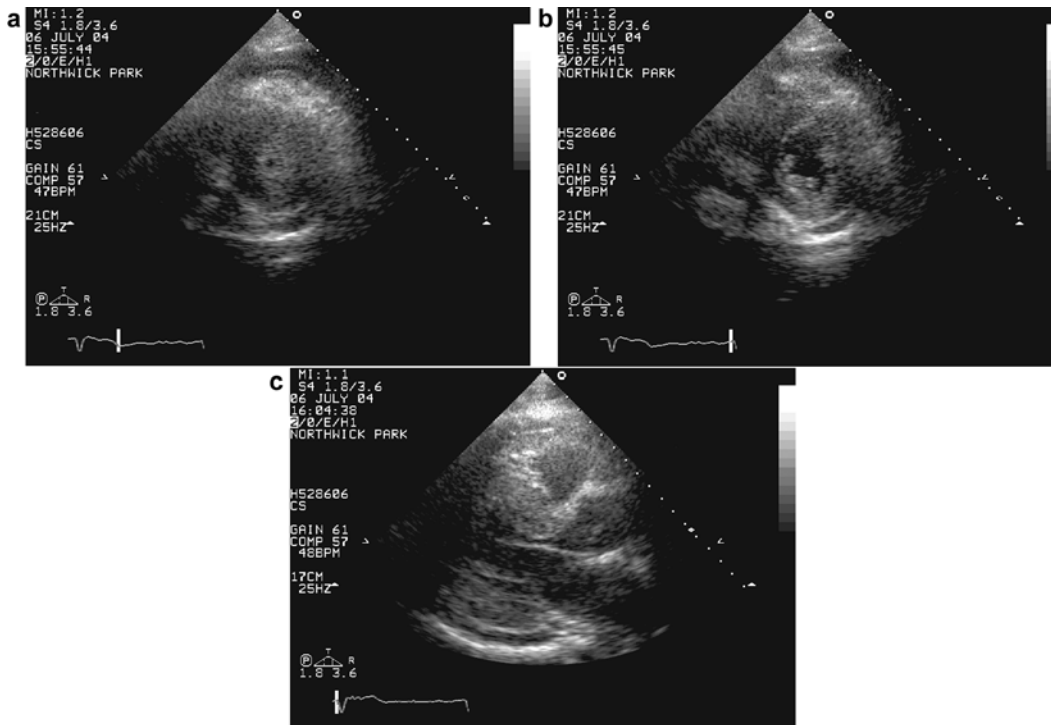


Figure 1 Parasternal short-axis view in systole (a) and diastole (b) and parasternal long-axis view (c) in a patient with severe concentric LVH

linked with increased markers of systemic inflammation [fibrinogen and CRP (C-reactive protein)] and microalbuminuria and, in a study of 1299 Type II diabetic patients, increased albuminuria was a marker of endothelial damage and increased atherothrombotic risk [36].

FUNCTIONAL CHANGES

Systolic dysfunction

The definition of systolic dysfunction is an impairment in the ability of the heart to eject blood; this is different from systolic HF where symptoms and signs of HF are developed secondary to systolic dysfunction. Although the principle hallmark of systolic dysfunction is a depressed LV ejection fraction, recent studies have shown that standard 2D (two-dimensional) echocardiography may actually miss subtle LV dysfunction, since circumferential LV function is assessed and longitudinal function overlooked [37]. In the context of diabetic cardiomyopathy, systolic dysfunction occurs late, often when patients have already developed significant diastolic dysfunction. The prognosis in patients with depressed systolic dysfunction is poor with an annual mortality of 15–20%.

Diastolic dysfunction

Traditionally diastole is defined as the period in the cardiac cycle from the end of aortic ejection until the onset of ventricular tension and development of the succeeding

beat [38]. A more accurate definition as described by Brutsaert et al. [39] is that diastole is the time period where the myocardium is no longer generating force and subsequently returns to an unstressed length and force. Diastolic dysfunction occurs when there is prolongation and slowing of this process. Diastolic function can be assessed using cardiac catheterization where LV relaxation rate and timing of diastolic filling can be assessed [40]; however, this is an invasive technique and not without risk. Alternative non-invasive methods include standard echocardiography and tissue Doppler echocardiography. Diastolic function can be defined by examining trans-mitral and trans-pulmonary flow rates [41]. An important limitation in using trans-mitral flow alone as a marker of diastolic dysfunction is related to the rise in left atrial pressure which occurs with diastolic dysfunction, leading to a pseudo-normalization of the mitral inflow pattern. Thus, although there is progressive diastolic dysfunction, the mitral inflow pattern appears normal. Furthermore, it has been shown that diastolic dysfunction is not just a defect in active relaxation, but also in passive stiffness of the left ventricle [42]. Thus diastolic dysfunction alone refers to echocardiographic features of an abnormal LV relaxation pattern without clinical HF. Diastolic HF refers to a clinical syndrome of HF with a preserved LV ejection fraction. Little work has been done to assess the prognosis of asymptomatic isolated diastolic dysfunction, but there is one study [43] which shows that echocardiographic

Table 1 Summary of the major molecular abnormalities and their consequence in the pathogenesis of diabetic cardiomyopathy

Cause	Mechanism
Hyperglycaemia	Excess AGE and ROS formation with deactivation of NO, myocardial collagen deposition and fibrosis [49–55].
Fatty acids	Impaired glycolysis, pyruvate oxidation, lactate uptake results in apoptosis [63], and perturbation of myocardial bioenergetics and contraction/relaxation coupling [62,64].
PKC	Activation of DAG/PKC signal transduction pathway leads to reduction in tissue blood flow, increased vascular permeability, alterations in neovascularization and enhanced extracellular matrix deposition [67].
RAS	Cardiomyocyte hypertrophy and apoptosis [69–71].
Aldosterone-induced fibrosis	Myofibroblast growth with interstitial and focal perivascular accumulation of collagen.
HIF-1/VEGF	HIF-1 α activation via hypoxia/free radicals [84] induces angiopoietin, PGF, PDGF- β and VEGF [85,86] but, in diabetes, VEGF and its receptors, VEGF-R1 and VEGF-R2, are decreased significantly [89], leading to impaired angiogenesis.
Endothelial dysfunction	Impaired endothelial NO production and increased vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules and platelet and vascular growth factors enhance vasomotor tone and vascular permeability and limit growth and remodelling [100–102].
Arterial stiffness	Increased central aortic pressure and left ventricular afterload and lowered central diastolic and coronary perfusion pressures, leading to subendocardial ischaemia and interstitial fibrosis [104–106].
Autonomic neuropathy	Decreased sympathetic/parasympathetic myocardial innervation with impaired coronary resistance vessel vasodilator response and impaired ventricular diastolic filling [107–113].

evidence of subclinical contractile dysfunction and diastolic filling abnormalities are both predictive of subsequent CHF (chronic HF). Furthermore, patients with diastolic HF have a significantly increased mortality of 5–8% annually compared with 1% for aged-matched controls [44]. The underlying cause is important with regard to mortality since, if CAD is excluded, then mortality is reduced to 2–3% [45,46]. The outcomes from systolic dysfunction are much worse in terms of mortality but comparable for morbidity [47,48]. In the course of diabetic cardiomyopathy, a spectrum of myocardial abnormalities develop and progress which include LVH and diastolic and systolic dysfunction. It is thus incumbent upon clinicians to identify these abnormalities, since early detection and appropriate treatment can prevent worsening of this condition to overt HF.

MOLECULAR BASIS FOR DIABETIC CARDIOMYOPATHY

Hyperglycaemia, hyperlipidaemia and increased ROS (reactive oxygen species) induce alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function and myocardial compliance. These effects are summarized in Table 1.

Hyperglycaemia

Hyperglycaemia may mediate its damaging effects through a series of secondary transducers. One of the principle abnormalities is the excess generation of AGEs (advanced glycation end-products), which deactivate NO (nitric oxide) and impair coronary vasodilation. Sustained

hyperglycaemia causes excess formation of mitochondrial ROS [49], which affects transcription, leading to contractile dysfunction [50]. An increase in ROS decreases NO levels, which leads to myocardial inflammation and endothelial dysfunction via PARP [poly (ADP-ribose) polymerase], inhibition of which has been shown to reverse diabetic endothelial dysfunction [51]. The severity of diastolic dysfunction correlates with HbA_{1c} (glycated haemoglobin) levels [52] and the likely cause is AGE-induced [53] formation of ROS, resulting in myocardial collagen deposition and fibrosis [54,55]. Enhanced expression of metallothionein, a potent antioxidant, limits the development of diabetic cardiomyopathy [56], and breaking collagen cross-links improves diastolic function [57,58]. Recently, the process of advanced glycation has been related directly to alterations in myocardial calcium handling and hence contractility [59,60]. SERCA2a (sarcolemmal/endoplasmic-reticulum Ca²⁺-ATPase 2a) is responsible for replenishing intracellular calcium stores following release; this results in the termination of contraction thus playing an integral part in cardiac relaxation. SERCA2a is a P-type ATPase that utilizes energy from the hydrolysis of the terminal phosphate bond of ATP to pump calcium against its electrochemical gradient [59,60]. The turnover rate of SERCA2a is low, which makes it susceptible to post-translational modification, especially in a chronic condition like diabetes. Thus advanced glycation of SERCA2a has been shown to lead to a decrease in its activity and a prolongation of cardiac relaxation [61].

Fatty acids

Independent of the effects of hyperlipidaemia on coronary artery endothelial function, the increase in and dependence of diabetic myocardium on fatty acid supply

results in several major cellular metabolic perturbations. Thus there is increased β -oxidation and mitochondrial accumulation of long-chain acyl carnitines, leading to uncoupling of oxidative phosphorylation [62]. Enhanced fatty acid oxidation decreases glucose and pyruvate utilization by inhibiting pyruvate dehydrogenase. Pyruvate oxidation is reduced further by *pdk4* and activated by PPAR (peroxisome-proliferator-activated receptor). The net result is an excess of glycolytic intermediates and increased synthesis of ceramide leading to apoptosis, which can be prevented by the PPAR- α and - γ agonist troglitazone [63].

Thus impaired glycolysis, pyruvate oxidation, lactate uptake and a greater dependence on fatty acids as a source of acetyl CoA leads to a perturbation of myocardial bioenergetics and contraction/relaxation coupling [64]. Classic pharmacotherapy is aimed at restoring the balance between ATP synthesis and breakdown by increasing oxygen delivery (i.e. long-acting nitrates or Ca^{2+} channel antagonist) or by decreasing cardiac power by reducing blood pressure and heart rate (Ca^{2+} channel antagonist or β -blocker). An alternative agent which may readdress the altered bioenergetics of diabetic cardiomyopathy is trimetazidine [1-(2,3,4-trimethoxybenzyl)-piperazine], as it partially inhibits myocardial fatty acid oxidation, increases carbohydrate oxidation and reduces lactate production [65]. Recently, in 32 Type II diabetic patients with ischaemic cardiomyopathy randomized to receive either trimetazidine or placebo for 6 months, a beneficial effect was observed on LV volumes and LV ejection fraction [66].

PKC (protein kinase C)

Increased activation of the DAG (diacylglycerol)-activated PKC signal transduction pathway has been identified in vascular tissues from diabetic animals and in vascular cells exposed to elevated glucose [67]. This has been shown to induce many of the changes in diabetic cardiomyopathy which include a reduction in tissue blood flow, enhanced extracellular matrix deposition, capillary basement membrane thickening and increased vascular permeability with alterations in neovascularization. LY333531, a PKC β isoform-specific inhibitor, has been shown to be efficacious in a number of phase II clinical trials in diabetic retinopathy, nephropathy, neuropathy and cardiac dysfunction. Phase III clinical trials are currently underway for a number of indications, including diabetic cardiomyopathy, and are expected to report in 2006.

RAS (renin-angiotensin system)

The activation of stretch receptors in the heart activates RAS and the SNS (sympathetic nervous system), leading to changes in myocardial structure and remodelling,

which impairs cardiac performance. In diabetes an up-regulation of RAS occurs despite minimal changes in myocardial loading [68]. An increased expression of angiotensin II in diabetic rats has been related to cardiomyocyte hypertrophy and apoptosis. IGF-1 (insulin-like growth factor-1) has been shown to down-regulate the binding of p53 DNA, leading to a reduction in the transcription of angiotensinogen and, thereby, angiotensin II, resulting in a reduction in cardiomyocyte apoptosis [69]. Similarly overexpression of the IGF-1 gene down-regulates the RAS system and inhibits the development of diabetic cardiomyopathy [70,71]. These findings provide a molecular platform for the increased benefits of ACE (angiotensin-converting enzyme) inhibition in diabetic patients in preventing and reversing diabetic cardiomyopathy.

Aldosterone-induced fibrosis

Clinical studies which have included small numbers of diabetic patients have demonstrated a reduction in cardiovascular mortality in patients with HF treated with aldosterone antagonists. In the RALES (Randomized Aldactone Evaluation Study) trial, patients with congestive HF treated with spironolactone added to standard therapy (ACE inhibitors, loop diuretics, digoxin, etc.) demonstrated a 30% reduction in mortality [72]. This effect was only significant in patients with elevated serum levels of collagen synthesis markers, suggesting limitation of excessive extracellular matrix turnover as one mechanism contributing to the beneficial effect of spironolactone [72]. It is known that angiotensin II and aldosterone are able to induce cardiac fibrosis, which is characterized by enhanced accumulation of collagen and increased fibroblast proliferation *in vivo* [73–75]. *In vitro*, angiotensin II and aldosterone increase the synthesis of collagen by human cardiac fibroblasts in a dose-dependent manner [76]. In addition, angiotensin II also stimulates the proliferation of human cardiac fibroblasts [77]. The existence of a local cardiac renin-angiotensin-aldosterone system comprising all components, including enzymes and receptors, has been demonstrated [78]. In addition, local aldosterone production has been demonstrated in the hearts of 2-month-old rats [79] and in the human foetus. Diffuse areas of fibrosis have been described throughout the myocardium as a result of alterations in the microvasculature of the heart in diabetic patients: changes defined as diabetic cardiomyopathy. Analysis of cardiac tissue, at post mortem, from diabetic patients demonstrated interstitial and focal perivascular accumulation of collagen, indicating fibrosis [80]. It has been suggested that aldosterone and glucose mediate cardiac fibrosis through stimulation of myofibroblast growth in patients with a dysregulated renin-angiotensin-aldosterone system especially with concomitant hyperglycaemia [81].

HIF-1 (hypoxia-inducible factor-1)/VEGF (vascular endothelial growth factor)

An inadequate angiogenic response to ischaemia in the myocardium of diabetic patients could result in poor collateral formation and hence an increased propensity to infarction with a reduced reparative response. Normally, vascular cells are quiescent, but are activated by various stimuli, particularly hypoxia, as occurs in ischaemia/infarction. The hypoxic stimulus is mediated chiefly through HIF-1, a transcriptional regulator complex which operates through a specific promoter motif [HRE (hypoxia response element)] present in many gene promoters, including VEGF [82]. Normally rapidly degraded through the proteasome machinery [83], HIF-1 α is stabilized by hypoxia and also by free radicals [84] and, thus, becomes transcriptionally active. It controls the expression of multiple angiogenic growth factors, including angiopoietin-1, -2 and -4, PGF (placental growth factor), PDGF- β (platelet-derived growth factor- β) and VEGF [85,86]. Several observations suggest that VEGF may play an important role in the response to cardiac injury. Thus, after MI, the expression of VEGF mRNA is increased markedly in the cardiac myocytes, arteriolar smooth muscle cells and infiltrating macrophages [87]. HIF-1 α mRNA is up-regulated in patients with acute ischaemia or early infarction, whereas VEGF transcripts are seen at a later stage in patients with evidence of evolving infarction [88]. In contrast, in diabetes, the expression of mRNA and protein for VEGF and its receptors, VEGF-R1 and VEGF-R2, has been shown to be decreased significantly (40–70%) in the myocardium of both diabetic and insulin-resistant non-diabetic rats, together with a 2-fold reduction in VEGF and VEGF-R2 in ventricles from diabetic patients compared with non-diabetic donors [89]. This suggests that, in diabetic patients, the normal molecular processes which regulate angiogenesis are impaired. Interestingly, TZDs (thiazolidinediones) have been shown to produce a 4-fold increase in circulating VEGF levels in diabetic patients and a 3-fold increase in VEGF mRNA in adipocytes [90]. Given that these compounds are now licensed to improve glycaemic control, they may also form a means of enhancing VEGF in myocardium and hence 'therapeutic angiogenesis'.

Gene expression

An alteration in gene expression has been observed for a number of key inducer or transducer molecules in diabetic cardiomyopathy. Enhanced myocardial gene expression for muscle carnitine palmitoyltransferase 1–8 and additional novel sequences predicted to play a role in signal conduction has been observed after 6 weeks of moderate hyperglycaemia in STZ (streptozotocin-induced) diabetic rats [91]. Oxidative damage to cardiomyocytes from diabetic animals has recently been

attributed to *de novo* methylation of the p53-inducible p21 (WAF1/CIP1) gene encoding a protein which binds to and inhibits a broad range of cyclin-CDK (cyclin-dependent kinase) complexes [92]. Sarcolemmal membrane abnormalities in Na⁺/K⁺ ATPase, Na⁺/Ca²⁺ exchange and Ca²⁺ pump activity have been proposed to lead to an overload of intracellular Ca²⁺ during the development of diabetic cardiomyopathy. A significant depression of the Na⁺/K⁺ ATPase α 1-subunit mRNA and an increase in Na⁺/Ca²⁺ exchanger mRNA has been observed in the ventricular myocardium of alloxan-induced diabetic rats [93]. A key electrophysiological abnormality in diabetic cardiomyopathy is enhanced arrhythmogenicity, which may be associated with a decrease of repolarizing K⁺ currents. RNase protection assay and Western blot analysis have demonstrated a reduction in mRNA expression and protein density of key cardiac K⁺ channel (Kv2.1, Kv4.2, and Kv4.3) genes in LV myocytes within 14 days of Type I diabetes in the rat [94].

Diabetic rats also show an induction of the foetal gene programme [95,96]. This refers to the re-expression of genes which were utilized during foetal life and down-regulated after birth. Members of this group include the contractile proteins β MHC (β -myosin heavy chain), atrial light chain 1 and α -skeletal actin, all of which are increased in cardiac failure and hypertrophy. There is also a down-regulation of α MHC (fast) isoform (contains 3–4 times enzymic activity of β MHC). These changes lead to contractile dysfunction in diabetic animals, resulting in cardiac hypertrophy and atrophy [96]. Thus it appears that diabetes induces the same pattern of gene expression as that seen in failing hearts, which could explain the link between diabetes and HF. It is interesting to note that β -blockers can reverse foetal gene expression [55]. Similarly, etomoxir, an inhibitor of fatty acid metabolism and promoter of glucose metabolism, has been shown to reverse foetal gene expression in animals [97], and a single clinical study in patients with HF showed an improvement in systolic function [98].

Endothelial dysfunction

Endothelial dysfunction is a precursor to and an effect of atherosclerosis. Anatomical and functional abnormalities of the vascular endothelium are commonly associated with diabetes [99]. Both chronic hyperglycaemia and dyslipidaemia are known to contribute to endothelial dysfunction. Hyperglycaemia results in impairment of endothelial cell NO production [100], increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules and platelet and vascular growth factors, which cumulatively enhance vasomotor tone and vascular permeability, growth and remodelling. Endothelial dysfunction also includes the accelerated disappearance of capillary endothelium [101], weakening of intercellular junctions, altered protein synthesis and

altered expression/production of adhesion glycoproteins on endothelial cells promoting attachment of monocytes and leucocytes, as well as their transendothelial migration. Furthermore, hyperglycaemia enhances endothelial cell matrix production, which may contribute to basement membrane thickening [102]. The clinical implications of endothelial dysfunction are not limited to increased atherosclerosis. Endothelial cells also help form collateral circulation, which is reduced in patients with diabetes, and may explain the increased infarct extension and congestive HF after MI in these patients.

Arterial stiffness

It is well known that hypertension and diabetes lead to a rise in arterial stiffness [54,103] through endothelial-dysfunction-mediated fibrosis. Vinereanu et al. [104] demonstrated an association between conduit arterial stiffness and impaired LV function. Their results suggest that subendocardial function of the left ventricle may be depressed in patients with stiff and relatively non-compliant conduit arteries. Reduced compliance of the large arteries modifies the timing of wave reflections and thus is a factor affecting ventricular load. Ventricular ejection creates a forward pressure wave which is then reflected back by the arterial tree as a wave travelling back towards the heart. In patients with increased arterial stiffness, the reflected wave returns early during LV ejection which leads to an increase in central systolic pressure and LV afterload, resulting in decreased central diastolic and coronary perfusion pressures [105]. The net effect of these haemodynamic changes is ischaemia, especially in the subendocardium, which, if chronic, can lead to interstitial fibrosis and the development of HF [106].

Autonomic neuropathy

CAN (cardiac autonomic neuropathy) may contribute to impaired diastolic function and is associated with an increased cardiovascular risk in diabetic patients. Diabetic autonomic neuropathy was associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation [107]. Twenty-one percent of patients with Type I diabetes without ischaemic heart disease have abnormal diastolic filling which is associated with the severity of CAN [108]. Similarly ventricular filling abnormalities are most prominent in patients with autonomic neuropathy [109]. Mustonen et al. [110] have shown a correlation between myocardial sympathetic innervation derived from scintigraphy and the *E/A* ratio (ratio of early to late peak mitral filling wave velocities) in Doppler echocardiography, providing evidence that an abnormal sympathetic innervation of the heart may contribute to a disturbance in LV filling. Sympathetic dysfunction has been related to both systolic and diastolic dysfunction in Type II diabetes [111]. An abnormal systolic blood pressure response to standing

was correlated significantly with a reduced mitral *E/A* ratio. Studies also reflect an association between parasympathetic and cardiac dysfunction as evidenced by the association between significantly lower mean heart rate variation during deep breathing and abnormal diastolic peak filling rate in diabetic patients [112]. The mitral *E/A* ratio has been shown to be significantly reduced in patients with autonomic neuropathy and a significant correlation was observed between the *E/A* ratio and autonomic neuropathy [113].

DIAGNOSTIC METHODS

Thus it is clear from the discussion above that a range of molecular changes may underlie the development of diabetic cardiomyopathy. Of clinical relevance is the means by which clinicians diagnose and characterize this problem, perhaps prior to it becoming clinically manifest. This is important as it may allow intervention at a point where significant cardiac dysfunction has not yet ensued.

Echocardiography

Clinically apparent diabetic cardiomyopathy may take several years to develop, but echocardiography can detect significant abnormalities well before the onset of symptomatic HF. There are different types of echocardiography which are used in diagnosing LV dysfunction.

Conventional echocardiography

Early abnormalities are defined by a preserved LV ejection fraction with reduced early diastolic filling, prolongation of isovolumetric relaxation and increased atrial filling, the presence of which confirms diastolic dysfunction (Figure 2). A reduction in LV distensibility is characterized by an increased PEP (pre-ejection period) and shorter LVET (LV ejection time), resulting in an increased PEP/LVET ratio. Such abnormalities have been demonstrated in a group of normotensive diabetic patients without overt microvascular or macrovascular complications [114].

Galderisi et al. [115] found a 22% increase in LV mass in diabetic women and, recently, LVH was demonstrated in one-third of patients with Type II diabetes independent of blood pressure or ACE inhibitor use [116]. Similarly Kimball et al. [117] found increased LV mass and performance in Type I diabetic patients with microalbuminuria. Framingham showed an association between diabetes mellitus and increased LV mass independent of conventional risk factors in women, but not in men [3,4]. A large echocardiography study of American Indians with diabetes found a reduction in LV systolic chamber size and LV function, despite increased LV mass in both sexes [54]. It has been suggested that aortic stiffness may contribute to the development of LVH and diastolic dysfunction in diabetic patients by increasing end-systolic wall stress. Eren et al. [118]

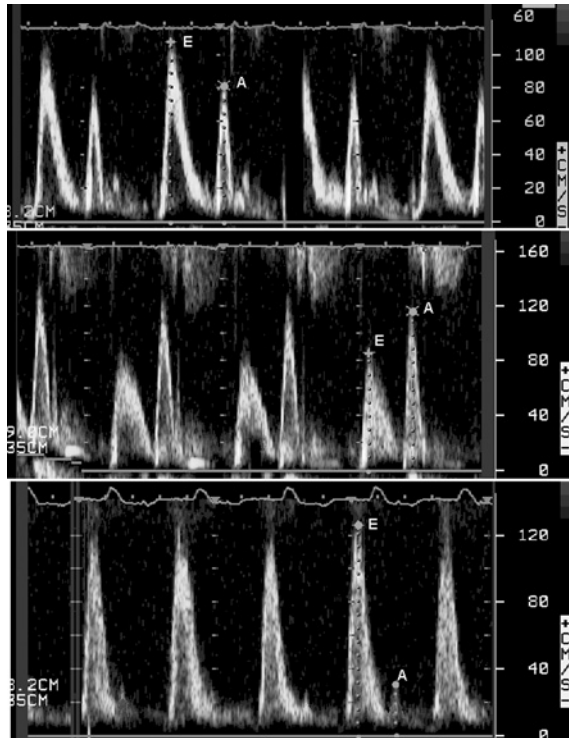


Figure 2 Trans-mitral valve spectral Doppler flow pattern in a normal subject (upper panel), in a patient with mild diastolic dysfunction (abnormal relaxation; middle panel), and in a patient with severe (restrictive) diastolic dysfunction (lower panel)

In the upper panel, the E/A wave ratio is approx. 1.5 to 1.0, and in the middle panel the E/A wave ratio is < 1.0 . In the lower panel, the E/A wave ratio is abnormally high and A wave velocity is very low.

also found an association between aortic stiffness and diastolic dysfunction in patients with either hypertension or diabetes or both. Earlier Doppler studies have been criticized for underestimating the degree of diastolic dysfunction since they failed to account for pseudo-normal filling patterns, which have been observed in up to 60% of normotensive diabetic patients. This suggests that up to 50% of patients with diastolic dysfunction could be missed on standard echocardiography. Pseudo-normalized filling patterns can be picked up by asking patients to perform the Valsalva manoeuvre whilst assessing trans-mitral and pulmonary Doppler signals [119,120]. Therefore echocardiography is a useful non-invasive tool to assess for the presence of LVH and systolic and diastolic dysfunction and can provide prognostic information in diabetic patients suspected of having cardiomyopathy.

Tissue Doppler echocardiography

In standard echocardiography, a high-velocity low-amplitude filter looks solely at blood flow through the heart to define valvular function. Newer technologies such as

TDI (tissue Doppler echocardiographic imaging) look promising as they apply a high-velocity low-amplitude filter to the myocardium enabling an assessment of myocardial tissue velocities. The advantage over standard Doppler echocardiography is that the results are independent of changes in pre-load. This provides a particularly useful tool for defining subtle systolic and diastolic dysfunction. In a recent study, although there was a significant reduction in resting S_m (peak myocardial systolic velocity) and E_m (early diastolic velocity) in diabetic patients, the response to dobutamine stress did not differ from control subjects, suggesting that ischaemia due to small-vessel disease may not be important in early diabetic heart muscle disease [121]. TDI also quantifies both longitudinal and circumferential cardiac contraction. Longitudinal (long-axis) contraction of the left ventricle is dependent on the integrity of longitudinal subendocardial myocardial fibres, whereas radial (short-axis) contraction depends on integrity of the circumferential fibres. The former is more susceptible to ischaemia and fibrosis which may result in a relative increase in short-axis velocity compared with a decrease in long-axis function due to compensatory ventricular remodelling. Thus, in 53 patients with diabetes but no LV hypertrophy, normal ejection fraction and no ischaemia on dobutamine echocardiography, radial contractility was increased and appeared to compensate for reduced longitudinal contractility [122]. In a recent study of 35 patients with Type II diabetes, the presence of regional systolic abnormalities in patients with an apparently normal ejection fraction questions the concept of isolated diastolic dysfunction [123].

TDI does not differentiate between active contraction and passive movement of a myocardial segment. Thus rotation and translation movements of the whole heart, as well as active contraction of segments adjacent to the analysed segment, may affect the determined velocity. Strain and strain rate echocardiography is a technique for assessing myocardial systolic and diastolic function. This modality has improved the quantitative assessment of regional wall motion and the accuracy and reproducibility of test readings. Myocardial strain and strain rate can detect inducible ischaemia and at earlier stages than visual estimation of wall motion or wall thickening parameters. Changes in systolic strain rate and strain have the potential to discriminate between different myocardial viability states. Measurement of the diastolic rate of deformation can differentiate physiological from pathological hypertrophy and restrictive from constrictive cardiomyopathy. Strain rate assessment has also been implemented in 3D (three-dimensional) echocardiography with promising results [124].

Doppler acoustics

Fibrosis alters the acoustic properties of the heart in animals and humans, and the magnitude of cyclic

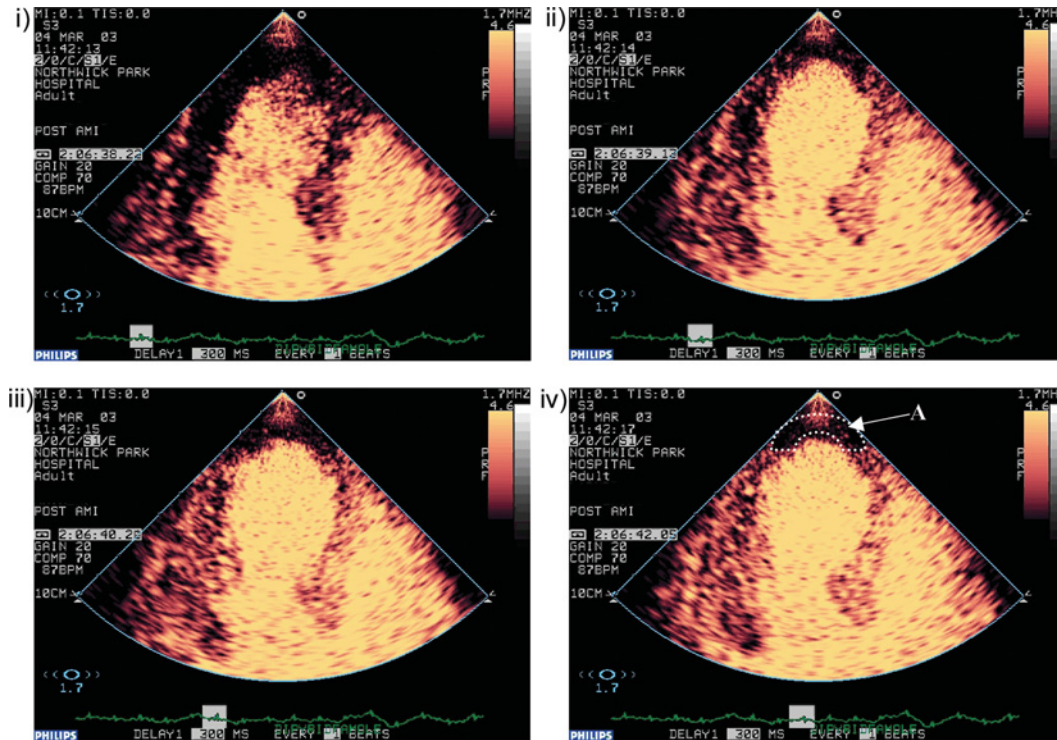


Figure 3 Contrast echocardiographic sequence with microbubble contrast agent defining myocardial perfusion within different myocardial segments

Frame i) is immediately following a high power ultrasound flash which destroys the micro-bubbles within the myocardium. Frames ii)–iv) show replenishment of micro-bubbles in the septum and lateral walls within 2 heartbeats. A clear apical perfusion defect (A) is demonstrated which persists.

variation of myocardial ultrasound integrated backscatter and its phase delay with respect to the onset of the cardiac cycle can be quantified via defining alteration in Doppler acoustics. In 54 diabetic patients with normal ventricular systolic function, the cyclic variation of backscatter in the septum and posterior wall of the left ventricle was significantly reduced and was related to the presence of neuropathy, retinopathy and nephropathy [125]. This technique has evolved in the form of video-densitometry which uses Doppler echocardiography to digitize images of the septum and posterior wall of the left ventricle and estimates the percentage CVI (cyclic variation index). Subjects with high LV masses and concentric hypertrophy demonstrate an increased CVI [126]. This has not yet been applied to diabetic patients.

Intravenous contrast echocardiography

During the last decade, the use of contrast echocardiography has gained considerable interest because it provides a non-invasive means of assessing integrity of the coronary microcirculation and myocardial perfusion as well as improving assessment of LV function. Contrast echocardiography relies on resonance of microbubble contrast agents when excited by diagnostic ultrasound frequencies, thus producing an increased ultrasound backscatter from the blood [127,128] (Figure 3).

These agents are used to enhance visualization of the blood–endocardial interface to assess myocardial perfusion. Furthermore, the proper delineation of the endocardial border observed after contrast administration increases the clarity of the images and improves the results provided by the algorithms orientated to the assessment of ventricular motion [129].

Direct assessment of myocardial blood flow and flow reserve is possible, as microbubble contrast agents remain entirely within the intravascular space and their presence in any myocardial segment denotes the status of microvascular perfusion within that region [130,131]. In a study by Senior and Swinburn [132], the sensitivity and negative predictive value of dobutamine echocardiography for the prediction of recovery of dysnergistic segments improved significantly from 59% to 79% and 88% to 95% when contrast opacification was observed in the dobutamine non-response segments. Thus contrast LV opacification studies allow more accurate measurements of LV size and mass, and myocardial contrast echocardiography provides an alternative non-invasive assessment of CAD.

3D Echocardiography

Conventional 2D echocardiography only provides partial information about cardiac function. Although multiple

studies have validated the superiority of 3D over 2D echocardiography to assess LV function, 3D methods have not been embraced in clinical practice because of the cumbersome methodology used until recently for data acquisition and analysis. In contrast with 2D echocardiography, 3D echocardiography does not rely on geometric assumptions to calculate LV volumes. This constitutes a real advantage in ventricles with odd shapes, wall motion abnormalities and in patients with cardiomyopathy. Similarly, the unique shape of the right ventricle has precluded accurate quantification using traditional echocardiography. Transthoracic 3D echocardiography has the potential to overcome these limitations resulting in precise measurements of right ventricular size and function [133,134]. Real-time 3D echocardiography is based on the design of an ultrasound transducer with a matrix array that instantaneously acquires the image contained in a pyramidal volume. The concurrent display of multiple tomographic images allows the anatomically correct examination of any structure contained within the volumetric image. The development of new software and the use of high-performance computers now allows rapid mapping of the volumetric image, and it is possible to simultaneously visualize multiple superimposed planes in an interactive manner. Real-time 3D echocardiography is being used in conjunction with strain rates to evaluate further both regional LV systolic dysfunction and diastolic dysfunction. An area where it looks especially promising is in predicting the response to biventricular pacing in patients with HF and interventricular conduction delay [135].

CT (computed tomography)

The CAC (coronary artery calcification) score, derived originally from electron-beam CT but more recently from multi-slice CT, has been shown to correlate strongly with the presence and severity of histological and angiographic evidence of coronary atherosclerosis and conventional CHD risk factors, in particular CRP, reflecting stable and unstable plaques [136]. In 10 377 asymptomatic patients, coronary calcium has been shown to provide independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality [137]. Of 101 patients aged 17–28 years with Type I diabetes and duration of diabetes over 5 years, 10.9% demonstrated CAC [138]. Similarly CAC was significantly increased in asymptomatic patients with Type II diabetes compared with non-diabetic subjects [139]. Although the CAC score correlates well with CAD, there are no studies to date which show an association with diabetic cardiomyopathy.

MRI (magnetic resonance imaging)

MFR (myocardial flow reserve) is not routinely assessed in MPI (myocardial perfusion imaging) studies, but it has been hypothesized to affect test accuracy when assessing

disease severity by coronary vessel lumenography. MRI is an emerging diagnostic technique that can both perform MPI and assess MFR [140]. Furthermore, MRI is also a very useful tool to assess diastolic function accurately without the drawbacks observed with echocardiographic assessment of diastolic function [141].

SPECT (single photon emission CT)

Quantitative myocardial perfusion SPECT has advanced significantly over the last few years providing a competitive advantage to nuclear cardiology compared with other higher-resolution non-invasive imaging modalities for the detection of CAD. In particular, gating has provided both perfusion and functional information and attenuation correction SPECT has improved perfusion information [142,143].

TREATMENT

Glycaemic control

Poor glycaemic control has been associated with an increased risk of cardiovascular mortality, with an increase of 11% for every 1% rise in HbA_{1c} levels [144], and a recent study has shown a link between HbA_{1c} and HF [52]. Thus it has been assumed that improving glycaemic control should have a beneficial effect on cardiovascular morbidity and mortality and that achieving this should be the *raison d'être* of every diabetologist. However, the UKPDS (UK Prospective Diabetes Study) failed to show a significant benefit of intensive blood glucose control using either sulphonylureas or insulin on the risk of developing macrovascular disease in patients with Type II diabetes [145].

It is important to note that there were significant methodological limitations in the UKPDS which merit consideration when interpreting the results [146]. These include that the study was unblinded and continued when no difference was observed at the initial agreed time point for analysis, patients in the diet-only group actually received drug treatment if the fasting plasma glucose was > 15 mmol/l, and at 9 years only 25% of patients were on monotherapy; however, significant benefits were observed in the subgroup of overweight patients treated with metformin, including diabetes-related mortality (42%), all-cause mortality (36%) and MI (39%). Again these data should be interpreted with caution as they are derived from a highly selected subgroup (patients with overt cardiovascular disease were excluded) of only 753 (342 on metformin compared with 411 on diet only) overweight (> 120% ideal body weight) patients. These data have, however, laid to rest the concerns raised by the findings of the NIH (National Institutes of Health)-funded UGDP (University Group Diabetes Program) study which had reported increased cardiovascular mortality with the sulphonylurea, tolbutamide [147].

The clinical relevance of this observation is based on the mechanism of action of sulphonylureas which close K^+ ATP channels in β cells to augment insulin release. Paradoxically, they also do this in cardiomyocytes and vascular smooth muscle cells which, at least theoretically, may have a detrimental impact on ischaemic preconditioning and vasodilatation.

In DCCT (Diabetes Control and Complications Trial), 1441 Type I diabetic patients were randomly assigned to conventional or intensive glycaemic control over 6.5 years. The number of combined major macrovascular events was 40 in the conventionally treated group compared with 23 in the intensive-treatment group, but the difference was not statistically significant, despite improvements in the lipid profile [148].

β -Blockers

Chronic stimulation of the SNS leads to increased heart rate and altered gene expression, resulting in cardiac remodelling in both HF [149] and diabetes [150]. Traditionally, there has been a reluctance to use β -blockers in patients with diabetes for fear of adverse effects on insulin resistance and an unawareness of hypoglycaemia. However, with the recent advances in the understanding of HF and the realization of the importance of the SNS in the release of vasoactive substances, they have become an essential treatment for HF [151]. Thus β -blockers have been shown to prevent and even reverse cardiac remodelling, resulting in improved LV function and a reduction in mortality [151]. Earlier studies of β -blockers recruited patients with advanced HF and, although LV function improved, mortality did not [152,153]. However, CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and MERIT-HF (Metoprolol Controlled-release Randomised Intervention Trial in Heart Failure) enrolled patients with mild-to-moderate HF and showed significant reductions in mortality of 32% and 34% respectively [154,155]. Carvedilol, a third generation β -blocker which antagonizes both α and β receptors, has been shown to have a highly significant effect on both morbidity and mortality (67% reduction) [156]. In a more recent trial, the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study group showed a significant reduction in mortality in patients with severe HF treated with carvedilol [157]. There has only been one large retrospective study which assessed the benefits of bucindolol in diabetic patients with HF. Patients with ischaemic cardiomyopathy had a worse prognosis compared with patients without ischaemic aetiology [158] and both diabetic and non-diabetic patients benefited from β -blockade [158]. A meta-analysis of the six main β -blocker HF trials [CIBIS-II, BEST (β -Blocker Evaluation of Survival Trial), ANZ (Australia and New Zealand)-Carvedilol, Carvedilol U.S. Trials, COPERNICUS and MERIT-HF] [159] has

subgroup data available which has enabled analysis of the diabetic cohort. Of 13 129 patients with chronic HF, 24.6% had diabetes. The results showed that the presence of diabetes was associated with a significant increase in mortality compared with subjects without diabetes mellitus among all patients studied {pooled RR (relative risk), 1.25; 95% CI (confidence interval), 1.15–1.36; $P < 0.001$ [146]}. In the placebo group only, the RR for mortality in patients with diabetes mellitus was 1.19 (95% CI, 1.06–1.33; $P < 0.002$). Similarly, in patients receiving β -blockers in these studies, there was an increase in mortality among diabetic patients (RR, 1.33; 95% CI, 1.17–1.51; $P < 0.001$) for all patients studied. The pooled RR of mortality in patients with diabetes mellitus and CHF on β -blocker treatment compared with placebo was 0.84 (95% CI, 0.73–0.96; $P < 0.011$). However, the relative risk reduction in non-diabetic patients on β -blockers compared with placebo was much greater (RR, 0.72; 95% CI, 0.65–0.79; $P < 0.001$).

In summary, β -blockers should be given to all diabetic patients with any evidence of HF, unless specifically contra-indicated. This will result in an RR reduction in mortality; however, the effect is not as pronounced as the introduction of β -blockers in non-diabetic patients, but both groups derive significant prognostic benefit.

ACE inhibitors

ACE inhibitors form the cornerstone for treatment of HF. The captopril multi-centre study demonstrated a significant improvement in exercise capacity and symptoms of HF without an effect on mortality [160]. The CONSENSUS study group was the first to show a significant reduction in mortality with enalapril in patients with severe HF [161]. The SOLV-D investigators confirmed these findings [162] and also showed that enalapril was able to prevent onset of new HF [163]. A number of post-MI trials have shown a reduction in mortality and morbidity with ACE inhibitors compared with placebo [164–166]. Significant benefits were obtained for both cardiovascular morbidity and mortality in the HOPE (Heart Outcomes Prevention Evaluation) study with ramipril in 9297 high-risk patients [167], but this benefit was even more impressive in the diabetic patients [168] (Table 2). Furthermore, HOPE demonstrated a 33% reduction in the rate of development of new HF [169] and a 44% reduction in the risk of developing Type II diabetes [170].

Angiotensin II receptor antagonists

Angiotensin II is considered to be a major player in the development of cardiac dysfunction. The ELITE (Evaluation of Losartan in the Elderly) study compared losartan with captopril in elderly patients with HF and found losartan to be as safe as captopril with a lower

Table 2 Cardiovascular morbidity and mortality in the HOPE study, illustrating a greater benefit in the diabetic patients

	All patients	Diabetic patients
Death from cardiovascular causes	26 %	37 %
MI	20 %	22 %
Stroke	32 %	33 %
All-cause mortality	16 %	24 %
Revascularization	15 %	17 %

secondary end point of combined mortality from hospital admission for HF [171]. However, although the ELITE II study confirmed better tolerability of losartan over captopril, it did show a slightly higher mortality [172]. ARBs (angiotensin II type 1 receptor blockers) have been proposed to have additive effects on haemodynamic measurements, neurohumoral activity and LV remodelling when added to ACE inhibitors in patients with chronic HF. Val-HeFT (Valsartan Heart Failure Trial) was the first study designed to measure morbidity and mortality in patients with HF compared with conventional therapy and as add-on therapy to conventional treatment [173]. Although a benefit was observed in patients not taking ACE inhibitors, an increase in mortality was observed in patients on ACE inhibitors and β -blockers [173]. In the OPTIMAAL (Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan) study, losartan was shown to be slightly less effective than captopril in post-MI patients [174]. The more recent VALIANT (Valsartan in Acute Myocardial Infarction Trial) assessed the use of a combination of ACE inhibitors and the ARB valsartan post-MI, and found no extra benefit in mortality but with a greater number of adverse reactions [175]. This was in contrast with the lack of further benefit observed in Val-HeFT [173] and, more recently, the CHARM (Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality)-Added trial [176]. Again, candesartan reduced the risk of developing Type II diabetes [176].

Ca²⁺ channel antagonists

An early animal study demonstrated an improvement in diabetic cardiomyopathy with verapamil [177]; however, trials of verapamil, diltiazem and nifedipine have shown a detrimental effect in HF [178]. Amlodipine and felodipine were investigated in the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) [179] and Val-HeFT III [180] trials respectively, and no significant benefit was observed over conventional treatment. A short-term improvement in ejection fraction was observed with felodipine, but this was not sustained at long-term follow-up. With amlodipine there was a reduction

of combined fatal and non-fatal events and decreased risk of death in the non-ischaeamic subgroup but, in view of the small numbers of patients, a further study is currently underway (PRAISE II).

Statins (hydroxymethylglutaryl CoA reductase inhibitors)

The ability of statins to lower serum cholesterol and reduce CHD end points has confirmed portions of the lipid hypothesis. However, the time to benefit and increased benefit in overlapping populations, in particular diabetic patients, have suggested that they induce pleiotropic effects. Thus, in addition to the direct effect on cholesterol metabolism, they may have a range of additional benefits, including inhibiting isoprenoid intermediates, modifying GTP-binding proteins such as Rho, augmenting collateral blood flow downstream of activated plaques, enhancing endothelial cell NO synthase activity, preventing AGE-induced NF- κ B (nuclear factor κ B)-induced protein-1 activation and preventing the up-regulation of VEGF mRNA [181,182]. The landmark 4S (Scandinavian Simvastatin Survival Study) demonstrated a significant reduction in CHD events following intervention with simvastatin, and firmly established the role of these drugs in the secondary prevention of CHD [183]. Moreover, recent analyses of the placebo data from 4S and AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) have demonstrated a 1.5- and 1.4-fold increased long-term relative risk of major coronary events in patients who have metabolic syndrome [184]. Thus it is not surprising that even greater benefits have been observed in patients with impaired glucose tolerance and diabetes [185]. In the HPS (Heart Protection Study), among the 5963 diabetic patients there was a 22 % reduction in the vascular event rate. Furthermore, among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease the reduction in event rate was 33 %. Alarmingly, it was 27 % among the 2426 diabetic patients who had pretreatment LDL (low-density lipoprotein)-cholesterol concentrations below 3.0 mmol/l [186]. This therefore argues for treating all Type II diabetic patients with a statin independent of their LDL levels. One can also envisage eventual clinical paradigms of the use of higher doses of statins to enhance pleiotropic effects and treatment, even when lipid markers are within guidelines.

Although statins have shown highly significant benefits in patients with CHD, there has been little data on the effect of statin therapy in HF. However, results of a recently published study do provide support for the use of statins in non-ischaeamic HF. Mozaffarian et al. [187] investigated whether statin therapy was associated with decreased mortality among patients with severe HF enrolled in the PRAISE study, the primary results of which have been published previously [177]. Even following

adjustment for age, gender, smoking, HF aetiology, diabetes, NYHA (New York Heart Association) class and ejection fraction, statin therapy was associated with a 62 % lower risk of death (RR 0.38; 95 % CI, 0.23–0.65). Recently, 551 patients with advanced HF of varying aetiologies (45 % with ischaemic HF, 25 % with idiopathic HF and 30 % with valvular, alcoholic and peripartum HF) were enrolled in an intervention trial with a statin. A proportion (45 %) of the cohort were already on a statin, including 73 % and 22 % of ischaemic and non-ischaemic HF patients respectively. Statin therapy was associated with significantly improved survival free from urgent transplantation (84 % in the statin group and 70 % in patients not on statins after 1 year). Decreased mortality has been observed in mice and rats treated with statins following the induction of LV dysfunction after coronary artery ligation [188,189]. Trials (CORONA; Controlled Rosuvastatin Multinational Study in Heart Failure) are currently underway to assess the efficacy of statins in HF. The recent analysis of the PRAISE data has demonstrated the safety and efficacy of statin therapy in patients with moderate-to-severe HF [190]. There is a significant reduction in mortality in patients with a non-ischaemic HF, adding further support to the additional effects of statins beyond their reduction in cholesterol and prevention of progression of CAD [190]. There is a need for a large randomized, blinded, placebo-controlled trial to evaluate further the benefits in patients with HF.

TZDs

TZDs are a new class of compounds for treating patients with Type II diabetes mellitus, which act by increasing insulin sensitivity in skeletal muscle and adipose tissue through binding and activation of PPAR- δ , a nuclear receptor that has a regulatory role in differentiation of cells. Additionally they also act on PPAR- α and increase serum HDL (high-density lipoprotein)-cholesterol, decrease serum triacylglycerols (triglycerides) and increase LDL-cholesterol levels marginally (pioglitazone to a lesser extent) [191]. To generate sufficient energy to sustain cardiac contractility, myocardial metabolism utilizes a range of substrates including NEFAs (non-esterified fatty acids), glucose and lactate. However, in Type II diabetes, as a consequence of insulin resistance, glucose is underutilized and NEFA metabolism, is increased impairing contractility. The TZDs, apart from insulin-sensitizing fat and skeletal muscle, increase the expression and function of glucose transporters in the heart, leading to improved glucose metabolism, and reduce NEFA utilization by the myocardium [192]. The consequences of this are that they protect against myocardial injury associated with ischaemia and improve recovery of function following ischaemia. However, caution should be taken in extrapolating these principally experimental findings to patients with diabetic cardiomyopathy as there are con-

cerns regarding the use of the TZDs in patients with HF [193]. Clinical trials with both rosiglitazone and pioglitazone are currently underway in diabetic patients with HF and are expected to report in 2007.

NEW THERAPEUTIC DIRECTIONS

PARP inhibitors

PARP-1 is a member of the PARP enzyme family and is one of the most abundant nuclear proteins which functions as a DNA-nick-sensor enzyme [194]. Recently in endothelial cells, hyperglycaemia-induced overproduction of mitochondrial superoxide has been shown to cause DNA strand breaks, leading to an activation of PARP which inhibits GAPDH (glyceraldehyde-3-phosphate dehydrogenase). This leads to the accumulation of glucose and other glycolytic intermediates prior to their entry into the Krebs cycle. These intermediaries activate a number of major transducers of hyperglycaemic damage (polyol pathway, AGE formation and PKC β activation) [195]. In addition to the direct cytotoxic pathway regulated by DNA injury and PARP activation, PARP also modulates the course of cardiovascular inflammation and injury by regulating the activation of NF- κ B [194] and inducing over-expression of ET (endothelin)-1 and ET receptors [196]. Blocking PARP activity with two different competitive PARP inhibitors provides a 'magic bullet' approach as it blocks activation of all the major pathways thought to mediate tissue damage in diabetes [195]. Thus far, PARP activation has been shown to occur in subjects at risk of developing diabetes as well as in those with Type II diabetes. Furthermore, it has been associated with impaired reactivity in the skin microcirculation of these subjects [197].

CONCLUSIONS

There is a large body of evidence to suggest that diabetic patients are prone to significant perturbations at the cellular level causing functional and structural abnormalities in the myocardium, leading to 'diabetic cardiomyopathy'. There remains considerable controversy over which are the most relevant cellular and molecular mechanisms underlying this process. In particular, there is a sparsity of clinical/translational studies in diabetic cardiomyopathy. The lack of consensus as to how best to diagnose and monitor this condition limits our understanding of the clinical and physiological characteristics of this condition. Furthermore, clinical trials have only enrolled limited numbers of patients with diabetic cardiomyopathy and much of our clinical practice is based on limited sub-analyses. However, the future holds promise, especially from data currently being generated from detailed molecular studies in tissue-specific knockout and transgenic models of cardiomyopathy. These and other more

clinically relevant translational studies may help to unravel the mechanisms behind diabetic cardiomyopathy. In so doing this offers a means to provide more precise therapeutics which, together with more advanced diagnostics, may allow effective intervention at much earlier stages of the disease.

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