HEART REVIEW

Diabetic heart disease

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Diabetes mellitus is responsible for a spectrum of cardiovascular disease. The best known complications arise from endothelial dysfunction, oxidation, inflammation, and vascular remodelling and contribute to atherogenesis. However, the effects on the heart also relate to concurrent hypertensive heart disease, as well as direct effects of diabetes on the myocardium. Diabetic heart disease, defined as myocardial disease in patients with diabetes that cannot be ascribed to hypertension, coronary artery disease, or other known cardiac disease, is reviewed.

Diabetes mellitus is responsible for a spectrum of cardiovascular disease. The best known complications arise from endothelial dysfunction, oxidation, inflammation, and vascular remodelling and contribute to atherogenesis.[1] However, the effects on the heart also relate to concurrent hypertensive heart disease, as well as direct effects of diabetes on the myocardium (fig 1). Despite the description of diabetic cardiomyopathy by Rubler *et al*[2] over three decades ago, the existence of this entity has been the source of ongoing controversy. For the purposes of this discussion, diabetic heart disease is defined as myocardial disease in patients with diabetes that cannot be ascribed to hypertension, coronary artery disease, or other known cardiac disease.

CLINICAL SIGNIFICANCE OF HEART FAILURE IN DIABETES

Many epidemiological and clinical trials have shown that heart failure is associated with diabetes mellitus. Within populations of patients with heart failure, diabetes is twice as common as in matched controls.[3] This increased prevalence is particularly seen in patients presenting with heart failure and normal systolic function.[4] Conversely, diabetes has been shown to be a risk factor for the development of heart failure.[5 6] In diabetic men, the Framingham study showed a 2.4-fold increased incidence of heart failure, with this rising to a 5.1-fold increased incidence in diabetic women.[7]

Not only are diabetes and heart failure associated, but their presence together portends an extremely adverse outcome. This is particularly so in patients with ischaemic cardiomyopathy.[8] Indeed, coronary artery disease has an important role in this association between diabetes and heart failure, and patients with diabetes are more likely than non-diabetic subjects to develop heart failure after myocardial infarction.[9] Many authors feel that the worse impact of myocardial injury in diabetic patients attests to the role of pre-existing subclinical left ventricular dysfunction.[10]

EVIDENCE FOR PRECLINICAL DIABETIC HEART DISEASE

Diastolic dysfunction

In apparently healthy, asymptomatic patients with diabetes mellitus, diastolic dysfunction is extremely common. Impaired relaxation has been reported in 26% of young, normotensive, and well controlled patients with diabetes.[11] However, with the performance of more sophisticated steps for the detection of pseudonormal filling, including the Valsalva response, tissue Doppler, and flow propagation analysis, abnormalities have been identified in 75% of apparently healthy asymptomatic normotensive diabetic patients with a negative stress echocardiogram.[12] Even after exclusion of patients with left ventricular hypertrophy or ischaemia, abnormal myocardial characteristics are present in about a third of the remaining patients (fig 2).[13]

Although these patients are often labelled as having diastolic dysfunction, to a large extent this is an artefact of the insensitivity of conventional systolic parameters. When, for example, systolic velocities are examined, patients with diastolic dysfunction and diastolic heart failure have abnormalities of sensitive indices of long axis ventricular function.

Systolic function

Evidence of systolic dysfunction in diabetic heart disease has been obtained from epidemiological data, as well as animal and human studies.

Abnormal systolic characteristics have been reported in isolated papillary muscle preparations and in diabetic mice.[14] Systolic dysfunction has been more difficult to find in human studies because of the insensitivity of standard parameters of systolic function (for example, ejection fraction), although even with these parameters, systolic dysfunction may be uncovered with exercise. More recently, sensitive indices of long axis function have provided evidence of disturbances of systolic function, initially compensated by preservation of radial function.[15–17] This implies that the problem may start in the subendocardium and accounts for the initial preservation of left ventricular volumes and ejection fraction.[18]

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Abbreviations: BNP, brain natriuretic peptide; HOPE, heart outcomes prevention evaluation; HOT, hypertension optimal treatment; LIFE, losartan intervention for endpoint reduction in hypertension; UKPDS, UK prospective diabetes study

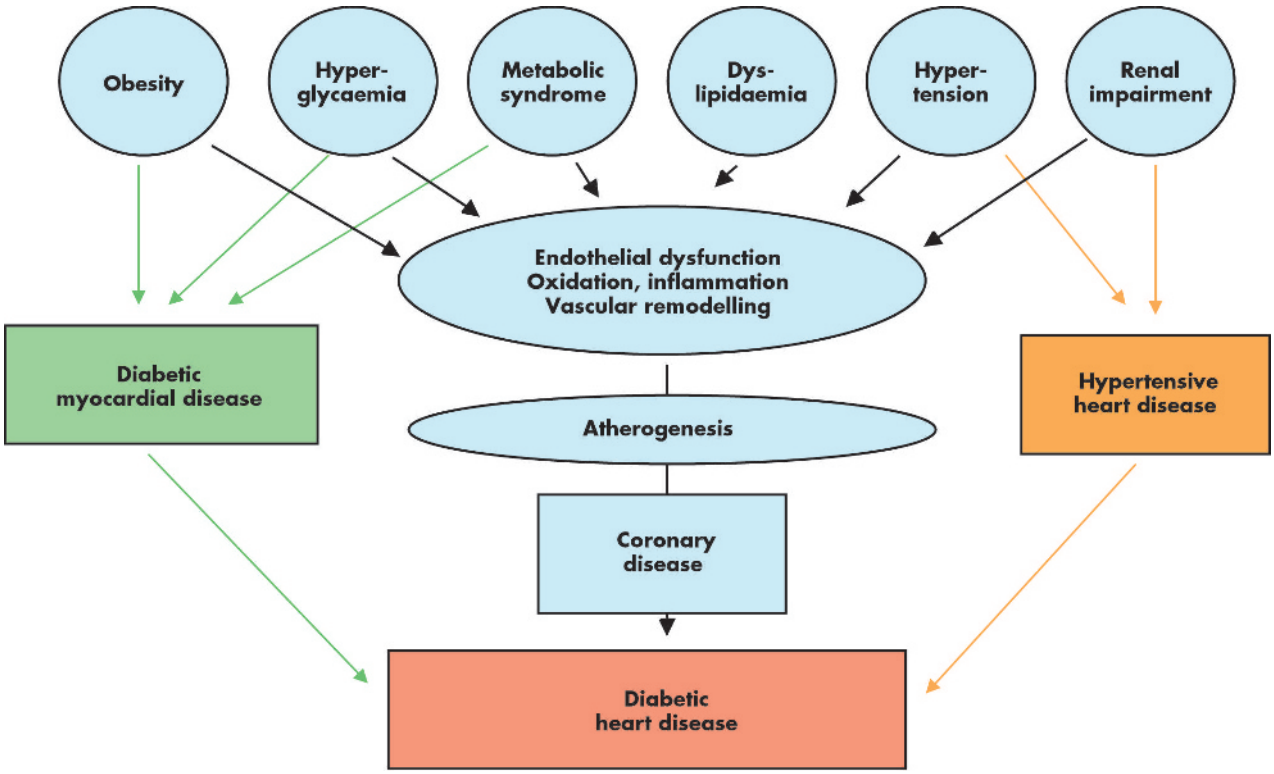

Figure 1 Contributors to and causes of diabetic heart disease.

Structural changes

Structural changes have been identified in the diabetic myocardium of animal models and humans.[14] These include increases in the extracellular space, including extracellular fibrosis, myocyte atrophy, and apoptosis. Although biopsy studies have been restricted to animal models, myocardial backscatter—which has been shown in validation studies to correspond to fibrosis—is abnormal in diabetic heart disease.

Role of co-morbid disease

Some of the controversy about the existence of a discrete entity of diabetic cardiomyopathy is based on the argument that the reported abnormalities are evidence of co-morbid disease. Although it is certainly true that the prevalence of hypertension is increased in patients with diabetes, the evidence supports an independent effect of diabetes on left ventricular function. In the Strong heart study, similar abnormalities were identified in the transmitral flow characteristics of patients with hypertension or diabetes alone but these effects were additive in those patients with both diseases, and the influence of diabetes on abnormal filling was identified as independent of age, blood pressure, left ventricular mass, and left ventricular function.[19] Similarly, by using myocardial strain and strain rate as well as integrated backscatter, Fang *et al*[15] identified similar abnormalities in patients with diabetes and left ventricular hypertrophy, but the combination of both diabetes and hypertrophy caused incremental changes. Not only did these observations pertain to left ventricular systolic function but also each group had abnormal integrated backscatter, probably portraying increased myocardial reflectivity due to fibrosis.

CLINICAL PRESENTATION OF DIABETIC HEART DISEASE

The typical presentation of subclinical diabetic myocardial disease is in an apparently well patient, perhaps with some

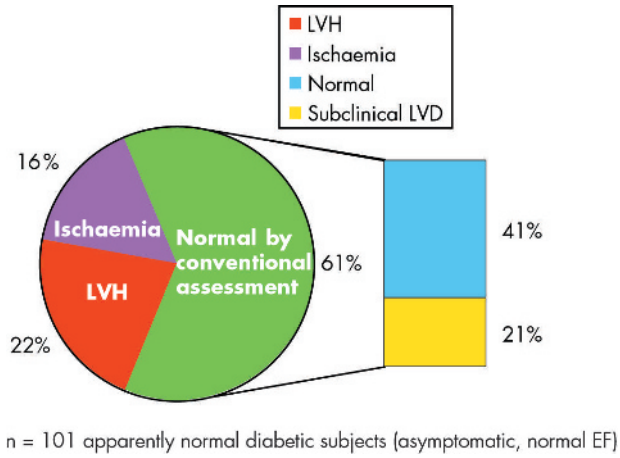

Figure 2 Prevalence of cardiac disorders in asymptomatic patients with diabetes mellitus. EF, ejection fraction; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy.

exercise limitation, with mild diastolic dysfunction, typically a delayed relaxation pattern. Paradoxically, more severe diastolic impairment is often not identified in patients whose transmitral flow has pseudonormalised due to raised left atrial pressure. This condition can be recognised by the presence of left atrial enlargement, alteration of the filling pattern following a Valsalva manoeuvre, and examination of pulmonary venous flow, flow propagation, or tissue Doppler.[20]

Echocardiography is the test of choice for identifying subclinical left ventricular dysfunction. Whereas brain natriuretic peptide (BNP) is a useful marker for heart failure, its role as a screening test for systolic left ventricular impairment is debated. We have not found BNP to be useful

for the detection of subclinical disease, probably reflecting normal transmural wall stress in these patients.[13]

Patients with non-insulin dependent diabetes often have a reduced exercise capacity, manifest both by a reduction in peak oxygen consumption and by oxygen consumption at submaximal levels of exercise.[21] Although age and obesity, indicators of exercise capacity, are as expected, diastolic myocardial tissue velocity is also predictive.[22] Thus, the causes of reduced exercise capacity include diabetic myocardial disease, as well as abnormalities of skeletal muscle and diabetic lung disease.

MECHANISMS

Diabetic myocardial disease is undoubtedly multifactorial (fig 3). However, there appear to be four significant contributors.

Metabolism

The association of abnormal myocardial disease with abnormal metabolism has been identified in patients with impaired glucose tolerance, obesity, and the metabolic syndrome, as well as in patients with diabetes. Patients with impaired glucose tolerance have left atrial enlargement—a good marker of abnormal ventricular filling.[23] Likewise, obese patients (many of whom have insulin resistance) have abnormalities of left ventricular systolic function (strain), diastolic function (tissue diastolic velocity), and reflectivity (backscatter), and these changes are related to the severity of obesity.[24]

Substrate metabolism is altered in diabetes, with reduced glucose and pyruvate utilisation, increased free fatty acid oxidation, accumulation of non-chain acylcarnitines, and reduced GLUT4 expression. All of these features combine to uncouple oxidative phosphorylation and myocardial oxygen demand, with consequences on myocardial performance as well as morphological changes and apoptosis.[25] Myocyte bioenergetics are compromised by reduced myosin, and reduced sodium-potassium and sodium-calcium ATPase.

Despite this evidence, however, the relation between glycaemic control and diabetic myocardial abnormalities has been variable and contradictory, with roughly equal numbers of studies suggesting that glycaemic control is important, as there are studies showing lack of relation to glycaemic control. The Strong heart study found higher concentrations of haemoglobin A_{1c} in patients with abnormal relaxation.[19] More recent work with tissue Doppler parameters has shown poor control to be associated with higher filling pressures.[17] In our experience, lower levels of systolic strain are associated with higher concentrations of haemoglobin A_{1c}, and patients taking oral hypoglycaemic agents are more likely to have impaired diastolic tissue velocity.[26]

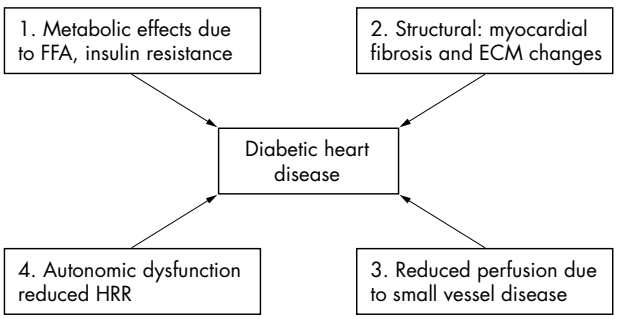

Figure 3 Pathogenesis of diabetic heart disease. CAD, coronary artery disease; ECM, extracellular matrix; FFA, free fatty acids; HRR, heart rate recovery.

Structural changes in the myocardium

Structural changes have been shown in both necropsy and biopsy studies of animals and humans. Increased fibrosis may be attributable to increases of both angiotensin II receptors and angiotensin II, which induces myocyte fibrosis. As age itself is responsible for increased stiffness and fibrosis in the heart, the contribution of the duration of diabetes is difficult to define in humans, as patients with a longer duration of non-insulin dependent diabetes are usually older.

Protein glycation may be a common pathway to myocardial damage in diabetes. Advanced glycation products bind to their receptor with activation of protein kinase C, which induces nuclear factor and proinflammatory cytokines, inflammation, growth factor release, and fibrosis. Extracellular changes are believed to be a consequence of increased vascular permeability (itself due to glycation of proteins of the basement membrane), which also contributes to angiogenesis. This process appears to underlie the nephropathy of diabetes, its contribution to atherogenesis, and very likely its role in diastolic dysfunction.[27] Myocyte apoptosis is related directly to glucose concentrations, angiotensin II concentrations, and reduction of insulin-like growth factor, which is anti-apoptotic.

The importance of collagen cross linking has been defined in animal experiments where the upregulation of BNP gene expression and other left ventricular disturbances appear to be reversed by cross link breakers, which have been shown histologically to result in smaller amounts of collagen-free staining.[28]

Microvascular disease

Analogies have been identified between myocardial changes and the changes in glomeruli, including increased thickness of the basement membrane, reduction of capillary density, and increased permeability with consequent increases of extracellular volume. The consequent increased oxygen diffusing distance to mitochondria is believed to contribute to myocyte apoptosis and fibrosis. In addition, functional changes occur in the microvasculature relating to reduction of endogenous nitric oxide production and protein kinase C activation.

Despite the contribution of diabetes to this pathological picture, however, the clinical importance of these vascular changes in diabetic heart disease is unknown. The Strong heart study showed an association between both abnormalities of mid-wall shortening and diastolic function and the degree of albuminuria, although the role of co-morbidity could not be excluded, as patients with micro- and macroalbuminuria have a greater tendency towards coronary disease, longer duration of diabetes, and associations with hypertension, left ventricular hypertrophy, and renal impairment.[29] Although abnormalities of coronary flow reserve have been reported in apparently healthy diabetic hearts, we have been unable to show a relation between subclinical changes of myocardial perfusion reserve and the degree of disturbed function. Moreover, Fang *et al*[30] reported a normal myocardial response to dobutamine, albeit at a lower baseline velocity than in control subjects. In contrast, Vinereanu *et al*[17] showed that the functional reserve of patients with diabetes was impaired during dobutamine echocardiography and that the correlates of this stress response were haemoglobin A_{1c} and low density lipoprotein cholesterol concentrations. Clearly, more work on the relation between abnormal perfusion and function in diabetic hearts is justified.

Cardiac neuropathy

Cardiac neuropathy is associated with disturbances of both myocardial blood flow and myocardial function. Cardiac neuropathy is evidenced by attenuation of heart rate and blood pressure responses to breathing, Valsalva and posture,

reduction of heart rate variability, and reduction of heart rate recovery after exercise. More sophisticated approaches to the identification of cardiac neuropathy include single photon emission computed tomography and positron emission tomography showing evidence of denervation.

POTENTIAL THERAPEUTIC APPROACHES

Glycaemic control

Whereas some evidence points towards poor glycaemic control as a contributor to functional impairment, data suggesting that improvements in glycaemic control are therapeutic are limited. Hansen *et al*[31] showed that both myocardial function and myocardial blood volume were reduced in patients with insulin dependent diabetes, and after administration of C peptide a 12% improvement of function was seen in association with improvements of myocardial blood volume and flow. In a follow up clinical study, von Bibra *et al*[32] showed improvements of myocardial function and perfusion with insulin, and showed that the degree of both mechanical change and perfusion was related to the degree of change of fasting insulin with treatment.

Blood pressure control

No specific data related to changes of myocardial function in diabetes with improved blood pressure control are available. Nonetheless, the importance of blood pressure control in patients with diabetes was identified in the UKPDS (UK prospective diabetes study), with a 15% reduction of mortality for every 10 mm Hg reduction of systolic blood pressure.[33] The HOT (hypertension optimal treatment) study showed that benefits of blood pressure reduction appear to extend to within the normal range, and the risk reduction associated with blood pressure control is greater in diabetic than in non-diabetic patients.[34]

Treatment of fibrosis

Interestingly, in our observational data, the use of angiotensin converting enzyme inhibition is protective against the development of subclinical dysfunction, a finding consistent with the micro-HOPE (heart outcomes prevention evaluation) and LIFE (losartan intervention for endpoint reduction in hypertension) studies. Although there is no evidence yet that aldosterone blockade has a favourable effect on subclinical dysfunction in diabetic patients, such benefit has been identified in hypertensive heart disease.[35]

Cross link breakers

Limited animal and human data indicate benefit with cross link breakers. In studies of aging non-diabetic dogs, cross link breakers caused a reduction of left ventricular stiffness, which translates into an improvement of cardiac function.[36] In diabetic dogs, baseline assessment showed reduced systolic function, increased aortic stiffness, and increased myocardial collagen, all of which were reversed with cross link breakers.[37]

Insulin resistance

Insulin resistance may be a contributor to the direct metabolic affects of diabetes on the heart. Insulin sensitisers have been shown to have beneficial vascular effects but to date no studies of myocardial function have been reported. Our initial experience with exercise training suggests that improvements may be seen in the tissue diastolic velocity of treated patients, but the clinical significance of these changes awaits more complete study.

CONCLUSION

Pathological, experimental, and clinical evidence points towards the existence of a diabetic cardiomyopathy, which influences systolic and diastolic function as well as being correlated with impaired exercise capacity. The origin of this problem appears to be multifactorial, with both direct metabolic contributions and consequences of protein glycation. The entity is very likely a contributor to the adverse consequences of combined diabetes and heart failure. Extensive study of glycaemic control, insulin sensitivity, antifibrotic agents, and cross link breakers will likely provide evidence for specific treatment strategies in the near future.

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IMAGES IN CARDIOLOGY

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The coronary ''echo-stenotic'' reflex

A 71 year old woman underwent coronary angiography for typical stable angina symptoms. A bicycle ECG stress test showed a 4 mm horizontal V2–V4 downshift at 75 W. An intermediate lesion was observed on the mid left anterior descending coronary (panel A), and intravascular ultrasound showed a significant plaque burden (panel B). She was treated with a drug eluting stent but returned after five months complaining of persisting symptoms. A new ECG stress test showed a 3.5 mm horizontal V2–V4 downshift of the ST segment again at 75 W. There was no intimal hyperplasia and no new coronary lesions (panel C). Coronary flow reserve as measured by the Radi PressureWire system in response to intracoronary infusion of 15 mg papaverine showed a value of 1.3 (normal 3–6, pathologic < 2) (panel D). Resistance vessel disease (coronary syndrome X) was diagnosed and treatment with calcium antagonists was initiated.

The expression ''oculostenotic reflex'' refers to the tendency to overestimate the functional importance of intermediate coronary artery lesions, an effect that is emphasised by intravascular ultrasound. The case described here shows that functional assessment of plaque severity and small vessel function using recently developed techniques is particularly useful in order to avoid inappropriate revascularisation procedures.

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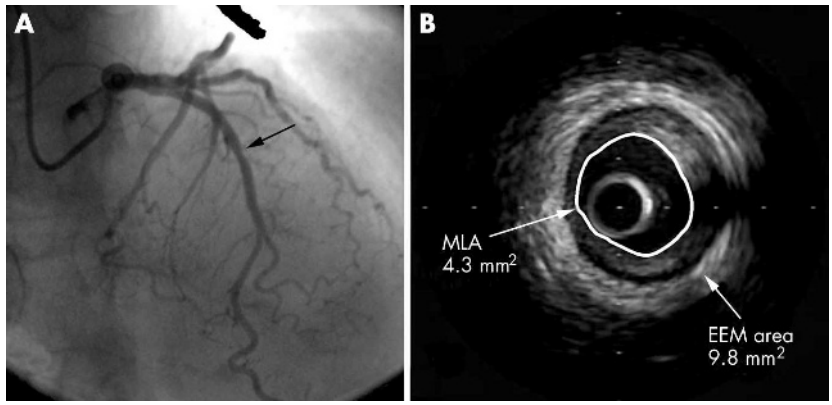
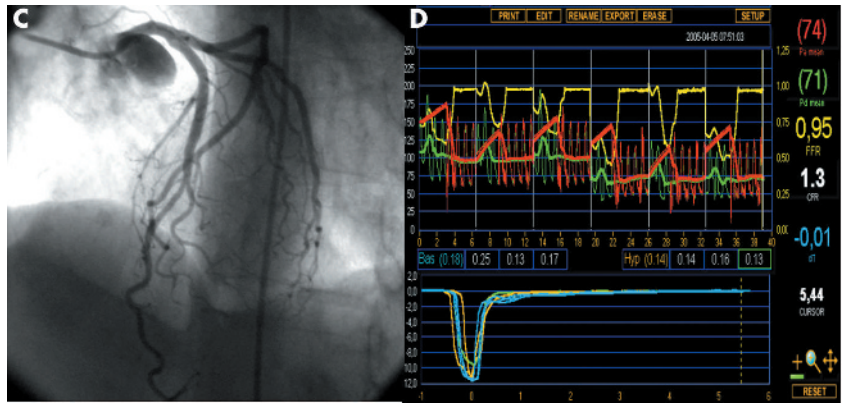


(A) Baseline angiography. An intermediate lesion is evident in the left anterior descending coronary (arrow). (B) Intravascular ultrasound shows a minimum lumen area (MLA) of 4.3 mm^2, with an external elastic membrane (EEM) area of 9.8 mm^2.



(C) Follow up angiography showed no coronary (re)stenosis. (D) Coronary flow reserve measurement showing resistance small vessel disease.