Ventricular dysfunction in early diabetic heart disease: detection, mechanisms and significance

ABSTRACT

The detection of preclinical heart disease is a new direction in diabetes care. This comment describes the study by Vinereanu and co-workers in this issue of Clinical Science in which tissue Doppler echocardiography has been employed to demonstrate subtle systolic and diastolic dysfunction in Type II diabetic patients who had normal global systolic function and were free of coronary artery disease. The aetiology of early ventricular dysfunction in diabetes relates to complex intramyocardial and extramyocardial mechanisms. The initiating event may be due to insulin resistance, and involves abnormal myocardial substrate utilization and uncoupling of mitochondrial oxidative phosphorylation. Dysglycaemia plays an important role via the effects of oxidative stress, protein kinase C activation and advanced glycosylation end-products on inflammatory signalling, collagen metabolism and fibrosis. Extramyocardial mechanisms involve peripheral endothelial dysfunction, arterial stiffening and autonomic neuropathy. The clinical significance of the ventricular abnormalities described is unknown. Confirmation of their prognostic importance for cardiac disease in diabetes would justify routine screening for presymptomatic ventricular dysfunction, as well as clinical trials of novel agents for correcting causal mechanisms. These considerations could also have implications for patients with obesity and the metabolic syndrome.

Type II diabetes is frequently associated with heart failure, a common cause of cardiac death in diabetic patients [1]. Hence an important new direction in the management of diabetes is the screening for and treatment of preclinical ventricular abnormalities [2]. The rationale behind this new strategy is the assumption that medical therapies can prevent progression of ventricular dysfunction to structural and symptomatic cardiac disease. Central to this is the concept of a specific diabetic cardiomyopathy.

In the present issue of Clinical Science, a small case-control study [3] has identified dysfunction of the left ventricle in Type II diabetic patients compared with non-diabetic controls. The detection of ventricular abnormalities relied on the use of tissue Doppler echocardiographic imaging, a relatively new methodology that permitted the quantification of longitudinal (base-apex) contraction [4,5], a sensitive marker of systolic dysfunction. Long-axis contraction of the left ventricle is dependent on the integrity of longitudinal subendocardial myocardial fibres, which are particularly susceptible to the adverse effects of ischaemia and fibrosis. By contrast, short-axis (radial) contraction of the left ventricle reflects the integrity of circumferential fibres within the myocardium, which are less susceptible to ischaemic damage. The increase in short-axis velocity that accompanied the reciprocal depression in long-axis function may be due to compensatory ventricular remodelling, a notion supported by the increase in ventricular mass index. Such an adaptive response may also explain the preservation of global systolic function, as measured by the ejection fraction. In the present study by Vinereanu et al. [3], systolic dysfunction was detected in diabetic patients with an ejection fraction $\geq 50\%$ and abnormal ventricular relaxation who, on the basis of the conventional criteria, would have been diagnosed as having pure diastolic dysfunction [6]. Apparent diastolic dysfunction alone has been well described in Type II diabetes by others [5,7,8]. The finding by Vinereanu et al. [3] of regional systolic abnormalities, however, questions whether diastolic dysfunction can, in principle, occur as an isolated abnormality, or whether it may in fact be a secondary response to primary systolic dysfunction, as postulated recently [9,10].

The aetiology of early ventricular functional abnormalities in diabetes is complex and multifactorial. It involves both intramyocardial and extramyocardial mechanisms (Table 1). The clinical correlates of systolic and diastolic dysfunction reported in this study by Vinereanu et al. [3] point to aetiological roles of poor glycaemic control, dyslipidaemia and diastolic hypertension

Key words: diabetes mellitus, stress echocardiography, tissue Doppler, ventricular function.
Table 1  Summary of several mechanisms that could contribute to early ventricular dysfunction and cardiomyopathy in Type II diabetes mellitus

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Cause</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Intramyocardial</td>
<td>Latent macroangiopathy</td>
<td>Dysglycaemia, dyslipidaemia, hypertension, coagulopathy, inflammation</td>
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<td>Microangiopathy/endothelial dysfunction</td>
<td>Risk factor effect on bioavailability of NO and endothelin</td>
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<td>Altered cardiomyocyte substrate metabolism</td>
<td>Decreased glucose and pyruvate utilization</td>
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<td>Enhanced fatty acid β-oxidation and mitochondrial accumulation of long-chain acyl carnitines</td>
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<td>Depressed cardiomyocyte bioenergetics/dynamics</td>
<td>Uncoupled oxidative phosphorylation and increased O₂ demand</td>
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<td>Insulin resistance/dysglycaemia</td>
<td>Decreased myosin, Na⁺/K⁺ and Ca²⁺-ATPases</td>
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<td>Increased ADP/ATP ratio</td>
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<td>Altered collagen metabolism/inflammation/fibrosis</td>
<td>Decrease in NO depresses cardiomyocyte cGMP and cAMP levels</td>
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<td>Oxidative stress and PKC activation</td>
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<td>Glycation of matrix and contractile proteins (AGEs)</td>
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<td>Oxidative stress, AGEs and activated PKC induce NF-κB and pro-inflammatory cytokines</td>
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<td>RAAS activation</td>
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<td>Formation of fibrillar collagen and collagen cross-linking</td>
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<td></td>
<td>Extramyocardial</td>
<td>Increased central aortic pressure and left ventricular afterload</td>
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<td></td>
<td>Endothelial dysfunction and arterial stiffening</td>
<td>Lowered central diastolic and coronary perfusion pressures</td>
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<td></td>
<td>Cardiovascular autonomic neuropathy</td>
<td>Decreased sympathetic myocardial innervation</td>
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<tr>
<td></td>
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<td>Altered ventricular preload and afterload</td>
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</table>

in the development of early diabetic cardiomyopathy. These variables, however, only accounted for approx. 35 % of the variance in ventricular dysfunction, suggesting alternative, related and/or more fundamental mechanisms.

Although all patients in the study by Vinereanu et al. [3] had normal stress echocardiograms, this does not strictly exclude coronary artery disease as an aetiological factor in cardiomyopathy, given the small but significant false-negative test rate. Latent coronary atherosclerosis may indeed explain similar observations in normotensive Type II diabetes [11]. Myocardial contractility and relaxation may be impaired in diabetes as a consequence of reduced myosin, Na⁺/K⁺ and Ca²⁺-ATPase activities, Ca²⁺ transients and nitric oxide (NO) bioavailability [1,12–16]. Disturbances in myocardial NO metabolism may be particularly critical, since the paracrine release of NO from coronary microvascular endothelium may have an inotropic effect via modulation of cardiomyocyte cGMP and cAMP levels, as well as a lusitropic effect by activating sarcoplasmic release of Ca²⁺ [13,16]. This may form the basis of the well recognized association between microangiopathy and diastolic dysfunction in diabetes [1]; however, ventricular abnormalities have been described in Type II diabetics without microalbuminuria [11], a marker of microangiopathy and endothelial dysfunction. Experimental studies have suggested that in diabetes, increased fatty acid supply to the myocardium increases the rate of β-oxidation and the mitochondrial accumulation of long-chain acyl carnitines that uncouple oxidative phosphorylation [13]. The dependence of diabetic myocardium on fatty acid oxidation also decreases glucose and pyruvate utilization by inhibiting pyruvate dehydrogenase, with the collective effect of increasing myocardial oxygen consumption. Uncoupling of mitochondrial oxidative phosphorylation may therefore be a primary mechanism whereby diabetes perturbs myocardial bioenergetics and contraction/relaxation coupling [14]. Importantly, a recent study in Type II diabetic patients employing positron-emission tomography [17] has suggested that insulin resistance may contribute to this by mismatching myocardial blood flow and glucose utilization.

There are also additional intramyocardial pathways that can contribute to cardiomyopathy, including an effect of hyperglycaemia that induces oxidative stress, activates protein kinase C (PKC) and increases formation of advanced glycosylation end-products (AGEs) [1]. These processes may also increase the expression of nuclear factor κB (NF-κB) in the myocardium [18]. Activation of NF-κB is a critical trigger for a cascade of pro-inflammatory cytokines which could,
in turn, induce collagen synthesis and fibrosis and have a direct negative inotropic effect on myocardial contractility. Neurohormonal activation, especially of the renin–angiotensin–aldosterone system (RAAS), is well recognized to occur in diabetes. Together with accumulation of AGEs, this constitutes another important trigger that alters collagen metabolism in the extracellular matrix and results in reduced ventricular compliance [12]. The inverse correlation reported by Vinereanu et al. [3] between ventricular dysfunction and plasma low-density lipoprotein (LDL)–cholesterol concentration is a new finding that may, in part, reflect the effect of lipid accumulation in myocardial membranes with impairment of Ca^{2+} homoeostasis and thermodynamics. This correlation may, however, simply reflect other related processes, including undetected coronary artery disease.

Extramyocardial mechanisms may also decrease ventricular compliance and contractility in diabetes. These include endothelial dysfunction and arterial stiffening of the peripheral circulation [19], which together increase central systolic aortic pressure and left ventricular afterload and reciprocally lower central diastolic and coronary perfusion pressures. These haemodynamic effects could also contribute to the selective development of subendocardial ischaemia and to ventricular remodelling, which may account for both the systolic and diastolic abnormalities reported by Vinereanu et al. [3]. Increased peripheral arterial stiffness in the absence of hypertension may possibly explain the reduction in left ventricular longitudinal contraction described recently in normoalbuminuric patients with Type II diabetes [11]. Cardiovascular autonomic neuropathy occurs in long-standing diabetes and may also lead to ventricular dysfunction by altering ventricular preload and afterload and limiting sympathetic myocardial innervation [20,21]. The precise contributory roles of the various intramyocardial and extramyocardial mechanisms referred to above (see Table 1) to the development of early cardiomyopathy and the echocardiographic changes reported by Vinereanu et al. [3] remain unclear and require further investigation. We postulate that the initiating event in the complex web of causality relates to abnormal myocardial substrate utilization that increases oxygen demand and uncouples oxidative phosphorylation, and that this is primarily a consequence of insulin resistance.

The clinical significance of the ventricular abnormalities described by Vinereanu et al. [3] for diabetic patients is also unknown. Longitudinal systolic abnormalities carry a poor prognosis, but this has only been demonstrated in non-diabetic subjects with clinical heart failure [6,10]. Isolated diastolic dysfunction in well-controlled diabetic patients has been associated with poor exercise tolerance and is therefore clinically significant [22]. The co-existence of ventricular and diastolic abnormalities is likely to have more adverse clinical implications than diastolic dysfunction alone [11]. As noted earlier, increased arterial stiffness and endothelial dysfunction may be aetiologically related to early cardiomyopathy and have both been shown to be predictive of adverse cardiovascular outcomes [23,24]. Hence it would be anticipated that the ventricular abnormalities described by Vinereanu et al. [3] indicate poor cardiac prognosis. This is more likely in the presence of other cardiovascular risk factors [25], such as hypertension, dyslipidaemia, proteinuria, and/or ventricular hypertrophy, but this will have to be formally demonstrated.

Having established the prognostic significance of these presymptomatic echocardiographic abnormalities in diabetes, clinical trials testing the effects of therapies that target the underlying causal mechanisms of ventricular dysfunction would be well justified. In addition to conventional approaches that regulate insulin resistance, dyslipidaemia, dysglycaemia and hypertension, novel therapies should be considered for preventing or reversing of the early stages of diabetic cardiomyopathy. As suggested earlier, these could include agents that may favourably regulate myocardial Ca^{2+} homoeostasis and bioenergetics, fatty acid and pyruvate oxidation, pro-inflammatory responses, turnover of AGEs, collagen metabolism and myocardial fibrosis.

Beyond Type II diabetes, asymptomatic abnormalities in ventricular systolic and diastolic function have also been described in patients with obesity [26,27], a growing problem in our communities. The aetiology of cardiomyopathy in obesity may share a ‘common soil’ with Type II diabetes through inter alia the effects of insulin resistance, hypertension, dyslipidaemia, inflammation and oxidative stress on myocardial dynamics and energetics. As with diabetes, the prognostic significance and response to therapy of the early echocardiographic abnormalities in obesity also require vigorous research.

Finally, although echocardiography is at present the preferred investigation for detecting diabetic myocardial disease, the requirement of sophisticated new imaging techniques will limit the ability to make this diagnosis. Simpler primary tests, such as screening for elevated plasma levels of brain natriuretic peptide (BNP) [28], followed by selective echocardiography may afford the most cost-effective approach for detecting early diabetic cardiomyopathy. As with the mechanistic and therapeutic challenges referred to earlier, the efficacy of this detection strategy will also need to be evaluated.

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Received 23 June; accepted 9 July 2003
Published as Immediate Publication 9 July 2003, DOI 10.1042/CS20030211