EDITORIAL COMMENT

Diabetic Cardiomyopathy: The Importance of Being Earliest*

Eugenio Picano, MD, PhD, FESC
Pisa, Italy

Over the years, the existence of a diabetic cardiomyopathy distinct from ischemic injury has been confirmed (1), but the challenge of recognizing diabetic cardiomyopathy at an early stage, in a noninvasive way, still remains. In this issue of the Journal, Fang et al. (2) evaluated 41 diabetic patients and 41 matched control subjects with standard echocardiographic rest and dobutamine tissue Doppler-derived indices of systolic and diastolic left ventricular (LV) function. In that study, the diabetic patients, compared with control subjects at rest, showed an impairment of peak myocardial systolic velocity and early diastolic velocity. However, in the diabetic group and in the control group, the dobutamine-induced increases in both peak systolic and early diastolic velocity were similar. The study comes from a well-known laboratory and addresses an important, yet still elusive, clinical target: the pre-clinical objective identification of diabetic cardiomyopathy. The results obtained are interesting, as the study outlines a novel approach for the identification of early incipient diabetic cardiomyopathy, supporting the physician with suitable end points to test new preventive and therapeutic approaches in these patients.

Diabetic cardiomyopathy: a heterogeneous entity. Diabetes mellitus can provoke cardiac damage at different levels, leading to the conditions known as coronary macrovascular disease, autonomic dysfunction, diabetic cardiomyopathy, and coronary microvascular disease (3). These syndromes can be rarely found as isolated forms in individual patients but rather often overlap and potentiate each other. In particular, diabetes mellitus induces structural (4) and functional (5,6) coronary microvascular abnormalities that are associated with coronary endothelial dysfunction (7) and with impairment in coronary flow reserve, even in the absence of epicardial coronary artery disease. The coronary microangiopathy component can amplify the effects of coronary macroangiopathy, which is a major complication of diabetes and can be important also for the progression of cardiomyopathy (8). However, it can also be present independently of epicardial coronary artery stenoses (3)—as might have been the case in the population studied by Fang et al. (2), where a part had been screened with coronary angiography and showed normal coronary arteries. Sometimes the evidence of coronary microangiopathy is associated with signs of LV diastolic dysfunction in the absence of systolic dysfunction (5). Contractile impairment and heart dysfunction in chronic diabetes can be also due to subcellular remodeling and calcium-handling abnormalities, with defects in sarcoplasmatic reticulum and sarcolemmal calcium transport due to the accumulation of lipid metabolites in the membrane (9).

Diabetic microvascular disease and the alternative ischemic cascade. Fang et al. (2) described a normal hyperkinetic response during dobutamine stress in diabetic hearts. However, this evidence does not rule out small vessel disease in diabetic hearts. In fact—as counterintuitive as it might seem—it is now recognized that a pure "microvascular" disease leading to reduced coronary flow reserve with angiographically normal coronary arteries is associated with a supernormal LV function during stress (10). In diagnostic practice with stress imaging, not all patients follow the reassuring paradigm proposed by the classical "ischemic cascade." Electrocardiographic changes may often occur with typical chest pain, in the absence of echocardiographic changes, and can be accompanied by real, not artifactual, reversible perfusion defects (10–12). In fact, the typical behavior of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and also perfusion abnormalities without regional or global wall motion changes (10).

The sequence of events is therefore strikingly different from the classic ischemic cascade found during stress testing in the presence of a coronary stenosis. The LV is hyperdynamic during stress, despite the frequent occurrence of chest pain and ST-segment depression: "too good to be ischemic," at least when the usual pattern of classic ischemia due to coronary artery stenosis is considered. Thus, although few would argue that induced myocardial dysfunction is an accurate marker of regional ischemia, the presence of regional abnormal vasodilator reserve may or may not be associated with ischemia. Our monolithic view of ischemia mirrored in the classic ischemic cascade should be integrated by the awareness of the reverse or alternative ischemic cascade best describing microvascular disease, with echocardiographic changes usually being absent during physical or pharmacologic stress. Not all forms of myocardial ischemia are the same, and milder patchy degrees of myocardial ischemia—as those possibly induced in microvascular angina associated with diabetes (11,12)—remain silent in their mechanical functional manifestations and may represent a physiologic scotoma of stress echocardiography (10).

The diabetic "cardiomyopathy cascade." In diabetic patients, an integrated ultrasound assessment can identify different stages of disease well before clinical overt cardiomyopathy (Fig. 1). Early in the natural history of the disease, some metabolic damage can lead to abnormal
increased myocardial echodensity (detectable by tissue characterization) and to abnormal subendocardial function (detectable by cyclic backscatter variation) (13,14). This alteration can be associated with abnormal global systolic and diastolic indices, such as those derived by Doppler (15) or tissue Doppler imaging, when conventional two-dimensional echo still gives normal values of ejection fraction. At a more advanced stage, a reduced inotropic reserve can be observed during exercise (16). In an advanced stage, wall motion abnormalities—at first regional, and later global—occur at rest. Somewhere in between, a reduction in coronary flow reserve can be detected, usually in patients with some degree of diastolic or systolic dysfunction (5) and microangiopathic involvement (17).

Within this conceptual framework, stress tissue Doppler imaging was a reasonable candidate for providing a simple, quantitative marker of incipient diabetic cardiomyopathy. Unfortunately, it did not work (2). The baseline differences in peak myocardial and early diastolic velocity (18) disappeared during stress (2). This may be related to the type of index employed. Tissue Doppler imaging represents an attractive technique for quantifying stress echo because: 1) it permits subtle segmental assessment of myocardial function during cardiac cycle; 2) it compares well versus reference methods such as sonomicrometry; and 3) it is very sensitive to inotropic stimulation and ischemic challenge. However, tissue Doppler imaging does have limitations (19). Firstly, the amplitude of the estimated velocity is dependent on the angle at which the region is imaged. Secondly, overall heart motion, rotation, and contraction of adjacent myocardial segments will influence regional velocity estimates. Therefore, both the angle and motion of adjacent segments can change during dobutamine stress, diluting the information obtained by tissue Doppler imaging in this setting.

The results of Fang et al. (2) are therefore not in agreement with their very reasonable working hypothesis of finding an abnormal stress response in patients with baseline abnormalities, and this adds strength and value to their work. In the field of leading edge innovations, many new technologies are presented as the ultimate breakthrough before their inaccuracies are recognized. Due to the pro-technology bias of modern medicine, we, as physicians, are encouraged to trust and to use (and to buy) technologies long before their clinical incremental value has been shown. Illogically, technologies are first sold and only later assessed, sometimes with very disappointing results (20). The study

![Image: Hypothetical echocardiographic cascade of diabetic cardiomyopathy.](image.png)
of Fang et al. (2) is important also because of the negative finding, showing that there was a normal stress response detected with tissue Doppler imaging. But, it also has an equally important positive finding, showing that resting tissue Doppler signal is a very early event in diabetic cardiomyopathy (18), perhaps early enough to have a therapeutic impact.

Detection of diabetic cardiomyopathy: the importance of being earliest. Diagnosing pre-clinical diabetic cardiomyopathy early through cardiac ultrasound is not only important but also may turn out also to be essential for the appropriate clinical testing of new therapeutic approaches. In animal models, high concentrations of plasma glucose can induce a loss in number and hypertrophy of myocytes, leading to the cardiomyopathy, diastolic dysfunction, loss of heart mass, and cardiac insufficiency that accompany diabet es. In cardiac myocytes, hyperglycemia amplifies the presence of renin and angiotensin. Angiotensin II binds to its receptor, AT1, and induces apoptosis, which probably contributes to cardiac myopathy (21). Changes in cardiac systolic and diastolic function induced by diabetes can be well monitored by experimental echocardiography, which assesses the efficacy of therapeutic interventions such as restoring cardiac metabolism in transgenic diabetic mice with human glucose transporter 4 (22).

According to studies performed in humans, apoptosis of myocytes, endothelial cells, and fibroblasts in the diabetic heart was characterized by an 85-fold, a 61-fold, and a 26-fold increase, respectively (23). Diabetes upregulates the renin-angiotensin system, which may contribute to the development of a dilated cardiomyopathy, whereas locally, angiotensin II may lead to oxidative damage, activating cardiac cell death. These advances in the basic understanding of cellular mechanisms underlying diabetic cardiomyopathy might be relevant to therapy. Tight glycemic control could be a strategy to prevent cardiomyopathy, along with other pharmacologic treatment—for instance, angiotensin-converting enzyme inhibitors, selective blockers of angiotensin II type 1 receptors, or aldosterone antagonists at low non-diuretic doses (24).

Any clinical study aimed at assessing the prevention of dilated cardiomyopathy should probably have a target population of diabetic patients with early, incipient cardiomyopathy. Clinically overt dilated cardiomyopathy may already be beyond the point of no return of advanced structural myocardial alterations—hardly reversible with any form of treatment.

Conclusions. Ultrasound could provide the ideal probe for the early detection of subtle changes and monitoring of the natural history and the effects of therapeutic interventions over time. But still research goes on as the debate remains over which parameter is best: tissue characterization, non-invasively assessed coronary flow reserve, tissue Doppler, diastolic or systolic function, regional or global function, baseline assessment, or evaluation during stress. Nonetheless, the use of ultrasound will inevitably increase as it assesses, in a methodologically robust way, diabetic cardiomyopathy with a relatively inexpensive, ecologically sustainable, biohazard-free technology (25) that also can detect early and evaluate the efficacy of therapeutic interventions in these patients through serial follow-ups.

Reprint requests and correspondence: Dr. Eugenio Picano, CNR, Institute of Clinical Physiology, Via Moruzzi, 1, 56124, Pisa, Italy. E-mail: picano@ifc.cnr.it.

REFERENCES