

Diabetic Cardiomyopathy

It has been over 30 years since Rubler et al. (1) described four diabetic patients with congestive heart failure (CHF), normal coronary arteries, and no other etiologies for CHF and proposed that it was due to diabetic cardiomyopathy. Eight years ago, I reviewed the evidence for diabetic cardiomyopathy as a unique entity unassociated with coronary artery disease and concluded that diabetic cardiomyopathy was a distinct entity characterized by diastolic dysfunction, which was rarely clinically apparent unless associated with hypertension (when it was likely to become clinically apparent) and/or with myocardial ischemia (when it was likely to present with severe clinical manifestations) (2). At that time the evidence also suggested that diastolic dysfunction was due to myocellular hypertrophy and myocardial fibrosis, and at the cellular level there were defects in calcium transportation, myocardial contractile protein collagen formation, and fatty acid metabolism (2). Since then we have learned that diabetic cardiomyopathy is not a rare condition but instead a very common one, and that its etiology is largely due to hyperglycemia with contributions from the insulin resistance syndrome that cause left ventricular hypertrophy.

Left ventricular diastolic dysfunction is characterized by impairment in early diastolic filling, prolongation of isovolumetric relaxation, and increased atrial filling, and these characteristics have even been documented in young type 1 diabetic patients (3). Older studies (4–6) of well-controlled type 2 diabetic subjects showed that 30% had diastolic dysfunction. However, this prevalence was based on standard echocardiography testing, in which mild and early diastolic dysfunction is not detectable in approximately one-third of subjects. When more rigorous Doppler methods are used, early and mild diastolic dysfunction can be diagnosed. Using these methods in Olmstead County, Minnesota, 52% of diabetic subjects were shown to have diastolic dysfunction (7). Using similarly sensitive methods, Porier et al. (8) showed the prevalence of diastolic dysfunction to be

60% in well-controlled type 2 diabetic patients. Therefore, it is not surprising that in this issue of *Diabetes Care*, Bertoni et al. (9) have documented that the diagnosis of idiopathic cardiomyopathy is more common in the diabetic patient.

While these studies of diastolic dysfunction were performed in diabetic patients with a normal left ventricular mass, left ventricular hypertrophy is more prevalent in type 2 diabetic patients and contributes to ventricular dysfunction. In the Framingham Heart study, diabetic women had a left ventricular mass 10% greater than that of their nondiabetic peers; and in the Tayside Study, left ventricular hypertrophy was present in 32% of normotensive type 2 diabetic subjects who were not utilizing ACE inhibitors and had no known coronary artery disease (10, 11). Unlike myocardial fibrosis, which is likely due to hyperglycemia, left ventricular hypertrophy is most likely related to the insulin resistance syndrome (12).

The high prevalence of diastolic dysfunction is due to myocardial fibrosis, and in the Strong Heart Study, the extent and frequency of diastolic dysfunction was directly proportional to the HbA_{1c} level (13,14). The most likely reason for this intimate association is the accumulation of advanced glycosylation end products (AGEs) in the myocardium (15). In animal studies the presence of diabetes results in increased myocardial AGE receptor expression, increased cross-linking of collagen, and myocardial fibrosis. With lysis of the collagen cross-links, there was a decrease in myocardial fibrosis and an improvement in diastolic dysfunction (16). Intracellular myocardial glycation also alters calcium homeostasis, leading to myocardial dysfunction, which can be reversed with an aminoguanidine-induced reduction in glycosylation (17). In animal studies, activation of protein kinase C (PKC)- β activity by hyperglycemia has resulted in myocardial necrosis and fibrosis and ventricular dysfunction, which again improved with the inhibition of PKC- β (18). Hyperglycemia also increases the myocardial content of free radicals and oxidants, which decrease nitric oxide levels, worsen endothelial function,

and induce myocardial inflammation through stimulation of poly(ADP-ribose) polymerase-1; yet poly(ADP-ribose) polymerase-1 inhibition prevents and reverses these effects (19). Lipotoxicity due to the elevation of free fatty acids (FFAs) associated with hyperglycemia and/or insulin resistance may also be a factor because FFAs and their oxidation products may be directly toxic to the myocardium and contribute to the development of diabetic cardiomyopathy (20).

Since diabetic cardiomyopathy is now known to have a high prevalence in the asymptomatic type 2 diabetic patient, screening for its presence at the earliest stage of development would be appropriate in order to prevent the progression to CHF. The most sensitive test for that is a standard echocardiogram with pulsed-wave Doppler examinations during the second stage of the Valsalva maneuver (7,8). However, the cost of this screening is prohibitive, and a less expensive prescreening method needs to be devised. Fortunately, detection of microalbuminuria, which should be performed annually in all diabetic patients, is an adequate prescreening test. The Strong Heart Study (21) showed that the degree of diastolic dysfunction was proportional to the level of microalbuminuria, even after adjusting for age, sex, BMI, systolic blood pressure, duration of diabetes, left ventricular mass, and presence of coronary artery disease. Furthermore, the Heart Outcomes Prevention Evaluation (HOPE) (22) study showed that the presence of microalbuminuria was associated with significant risk for CHF. Because microalbuminuria is a marker of endothelial dysfunction in the glomerulus, which is an arteriole, it is logical to postulate that endothelial dysfunction in the myocardium leads to increased ventricular scarring and stiffness (2). Therefore, the presence or development of microalbuminuria warrants the cost of echocardiography with pulsed-wave Doppler evaluation, even in the asymptomatic diabetic patient.

Documentation of diastolic dysfunction should result in the initiation of therapy to prevent advancement to heart failure. Achievement of glycemic control,

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