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,

preferably with agents that reduce insulin resistance, is essential. In the future, the availability of agents that prevent or reverse glycosylation and cross-linking of collagen or decrease lipotoxicity or its effects will be helpful. At the present time, we know that β-blockers and thiazolidinediones shift the metabolism of the myocardium from the use of FFAs to that of glucose (23,24). In addition, thiazolidinediones have been shown in animals to decrease myocardial FFA content and their toxic metabolites and improve ventricular function (25). The initial definitive therapy should be the use of ACE inhibitors, which decrease left ventricular hypertrophy and myocardial fibrosis, prevent myocardial remodeling, improve endothelial function, and lower insulin resistance (26). Because the new diagnostic criteria for heart failure regard the presence of diabetes as stage 1 heart failure, even the addition of a β-blocker at this early stage to prevent or reverse any present myocardial remodeling is appropriate (27). Use of a third-generation β-blocker such as carvedilol, which through its α1 blockade has the advantages of vasodilatation and lowering of insulin resistance in addition to its proven efficacy in heart failure, provides a distinct advantage in the diabetic patient (28). Either spironolactone or eplerenone because of antifibrotic effects in the myocardium, also seem to be a logical therapy, but they are unproven in diabetic cardiomyopathy (29).

Therefore, the prevalence of diabetic cardiomyopathy in the type 2 diabetic patient is higher than was previously believed, and diabetic cardiomyopathy is due to diastolic dysfunction caused by myocardial fibrosis, which occurs in response to hyperglycemia. A definitive diagnosis of diabetic cardiomyopathy can be made by echocardiographic techniques, and echocardiographic screening for asymptomatic diabetic cardiomyopathy should be performed in all asymptomatic diabetic subjects with microalbuminuria. Identification of diabetic cardiomyopathy should result in the initiation of therapies to prevent the progression of diabetic cardiomyopathy to CHF.

DAVID S.H. BELL, MB, FACE

From the University of Alabama School of Medicine, Birmingham, Alabama.

Address correspondence to David S.H. Bell, MB, FACE, Faculty Office Tower, Room 702, 510 South 20th St., Birmingham, AL 35294-3407. E-mail: dbell@endo.dom.uab.edu.

D.S.H.B. has served as a consultant for and received honoraria from Abbott Laboratories and GlaxoSmithKline Pharmaceuticals.

References

1. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30: 595–602, 1972
2. Bell DSH: Diabetic cardiomyopathy: a unique entity or a complication of coronary artery disease? *Diabetes Care* 18:708–714, 1995
3. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE: Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. *Cardiology* 98:33–39, 2002
4. Di Bonito P, Cuomo S, Moio N, Sibilio G, Sabatini D, Quattrin S, Capaldo B: Diastolic dysfunction in patients with non-insulin-dependent diabetes mellitus of short duration. *Diabet Med* 13:321–324, 1996
5. Beljic T, Miric M: Improved metabolic control does not reverse left ventricular filling abnormalities in newly diagnosed non-insulin-dependent diabetes patients. *Acta Diabetol* 31:147–150, 1994
6. Nicolino A, Longobardi G, Furgi G, Rossi M, Zoccolillo N, Ferrara N, Rengo F: Left ventricular diastolic filling in diabetes mellitus with and without hypertension. *Am J Hypertens* 8:382–389, 1995
7. Redfield MM, Jcobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ: Burden of systolic and diastolic ventricular dysfunction in the community. *JAMA* 289:194–202, 2003
8. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 24:5–10, 2001
9. Bertoni AG, Tsai A, Kasper EK, Francati FL: Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. *Diabetes Care* 26:2791–2795, 2003
10. Galderisi M, Anderson KM, Wilson PW, Levy D: Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 68:85–89, 1991
11. Struthers AD, Morris AD: Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. *Lancet* 359:1430–1432, 2002
12. Phillips RA, Krakoff LR, Dunaif A, Finegood DT, Gorlin R, Shimabukuro S: Relation among left ventricular mass, insulin resistance, and blood pressure in nonobese subjects. *J Clin Endocrinol Metab* 83: 4284–4288, 1998
13. Shehadeh A, Regan TJ: Cardiac consequences of diabetes mellitus. *Clin Cardiol* 18:301–305, 1995
14. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV: Impact of diabetes on cardiac structure and function: the Strong Heart Study. *Circulation* 101:2271–2276, 2000
15. Bauters C, Lamblin N, McFadden EP, Van Bell E, Millaire A, DeGroote P: Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol* 2:1–16, 2003
16. Candido R, Forbes JM, Thomas MC, Thallas V, Dean RG, Burns WC, Tikellis C, Ritchie RH, Twigg SM, Cooper ME, Burrell LM: A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. *Circ Res* 92:785–792, 2003
17. Ziegelhoffer A, Ravingerova T, Styk J, Sebokova J, Waczulikova I, Breier A, Dzurba A, Volkovova K, Carsky J, Turecky L: Mechanisms that may be involved in calcium tolerance of the diabetic heart. *Mol Cell Biochem* 176:191–198, 1997
18. Wakasaki H, Koya D, Schoen FJ, Jirousek MR, Ways DK, Hoit BD, Walsh RA, King GL: Targeted overexpression of protein kinase C beta2 isoform in myocardium causes cardiomyopathy. *Proc Natl Acad Sci U S A* 94:9320–9325, 1997
19. Szabo C: PARP as a drug target for the therapy of diabetic cardiovascular dysfunction. *Drug News Perspect* 15:197–205, 2002
20. Young ME, McNulty P, Taegtmeyer H: Adaptation and maladaptation of the heart in diabetes. Part II. Potential mechanisms. *Circulation* 105:1861–1870, 2002
21. Liu JE, Robbins DC, Palmieri V, Bella JN, Roman MJ, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB: Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the Strong Heart Study. *J Am Coll Cardiol* 42:2022–2028, 2003
22. Arnold JM, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, Lonn E, Pogue J, Bosch J, HOPE Investigators: Prevention of heart failure in patients in the Heart Outcome Prevention Evaluation (HOPE) study. *Circulation* 107:1284–1290, 2003
23. Bell DSH: Use of beta blockers in patients with diabetes. *Endocrinologist* 13:116–123, 2003
24. Nuttila P, Hallsten K, Kirsi A, Virtanen F, Lonnqvst F, Vitcari J, Ronnemaa T, Knutti J: Rosiglitazone but not metformin enhances insulin stimulated glucose uptake

in patients with type 2 diabetes (Abstract). *Diabetes* 51 (Suppl. 2):A142, 2002
25. Zhou Y-T, Graburn P, Karim A, Shimabukuro M, Higa M, Baeters D, Orci L, Unger H: Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 97:1784–1789, 2000
26. Kambara N, Holycross BJ, Wung P, Schanbacher B, Ghosh S, McCune SA, Bauer JA, Kwiatowski P: Combined effects of low-dose oral spironolactone and captopril therapy in a rat model of spontaneous hypertension and heart failure. *J Cardiovasc Pharmacol* 41:830–837, 2003
27. Hunt SA Baker DN, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr, American College of Cardiology/American Heart Association: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 38:2101–2113, 2001
28. Bell DSH: Treatment of heart failure in patients with diabetes: clinical update. *Ethn Dis* 12:S1–S8, 2002
29. Hagashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, Fuji M, Tanigachi A, Hamatani T, Nozato Y, Kataoka K, Morigami N, Ohnishi M, Kinoshita M, Horie M: Immediate administration of mineraldocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 107:2559–2565, 2003