Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 8, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.033

VIEWPOINT

Diastolic Dysfunction and Diabetic Cardiomyopathy

Evaluation by Doppler Echocardiography

Maurizio Galderisi, MD
Naples, Italy

Doppler echocardiography has largely contributed to show the existence of a distinct diabetic cardiomyopathy. Several studies have pointed out the evidence of left ventricular (LV) remodeling and hypertrophy in alterations of both midwall systolic mechanics and LV diastolic filling in diabetes mellitus (DM), independent of the coexistence of concomitant risk factors. Further progress will be provided by new ultrasound technologies in this clinical setting. The combination of pulsed tissue Doppler study of mitral annulus with transmitral inflow may be clinically valuable for obtaining information about left ventricular filling pressure (LVFP) and unmasking Doppler inflow pseudonormal pattern, a hinge point for the progression toward advanced heart failure. In the absence of epicardial coronary artery stenosis, the ultrasound assessment of coronary flow reserve (CFR) may identify the dysfunction of coronary microcirculation, in relation with glycemic levels, insulin resistance, sympathetic overdrive, endothelial dysfunction, abnormalities of the angiotensin-renin system, and LV remodeling/hypertrophy. Diastolic dysfunction and impairment of CFR may be associated in DM, with a likely common origin. In this view, a comprehensive transthoracic Doppler evaluation of diabetic patients should include the assessment of diastolic function and estimation of LVFP by tissue Doppler, and coronary microvascular function by CFR test. Additional analysis of regional wall motion during a stress test would be required in patients with suspected coronary artery disease, another cause of diastolic dysfunction. (J Am Coll Cardiol 2006;48:1548–51) © 2006 by the American College of Cardiology Foundation

The demonstration of a distinct diabetic cardiomyopathy has represented a major challenge to echocardiography (Table 1). The journey began in the early 1990s when the Framingham study showed an increase of left ventricular (LV) mass in diabetic women, independent of the effects of other traditional risk factors. In addition, by assessing the association of age with LV mass, the age coefficient for diabetic patients was observed to be higher than that for nondiabetic patients (1). Subsequent studies confirmed these results in both genders, highlighting associations of both diabetes mellitus (DM) and glucose intolerance with LV structure abnormalities (LV concentric remodeling/hypertrophy), independent of the influence of relevant covariates (2–7). Glucose intolerance and DM were also found to negatively affect midwall systolic mechanics (3,4,7) and diastolic filling (8), even in the presence of normal chamber function (4), with an impact amplified by the coexistence of hypertension (7,8). These findings have now been complemented by the ability of Doppler techniques to identify, categorize, and quantify diastolic dysfunction and abnormal coronary flow reserve.

Diabetes and LV diastolic dysfunction. Doppler pattern of impaired LV relaxation, characterized by reduced early and increased late diastolic flow, is an early sign of diastolic dysfunction (DD) (grade I). More advanced grades, manifested by predominant early diastolic filling and rapid velocity deceleration (restrictive filling patterns), are associated with the most severe LV decompensation (9). The hinge point of these grades is the intermediary, pseudonormal pattern, which occurs when LV filling pressure (LVFP) rises to maintain normal cardiac output and increases the early filling caused by impaired relaxation. Pseudonormal and normal patterns cannot be distinguished by transmitral inflow because of its preload dependence (9). Accordingly, the transmitral E/A ratio was found to show a U-shaped prognostic behavior: subjects with values <0.6 (abnormal relaxation) and >1.5 (likely restrictive pattern) were both associated with increased mortality, but the intermediate range (0.6 to 1.5), encompassing patients with normal or unidentified pseudonormal patterns, had no significant prognostic impact (10).

These dynamics are of fundamental importance in studying diabetic patients without coronary artery disease (CAD), who often manifest abnormal LV relaxation while systolic function is still normal. When dyspnea becomes overt, these abnormalities characterize "isolated" diastolic heart failure. Myocardial fibrosis and apoptosis (11) are likely the basis of these changes. Over time, diabetic patients may transition to a pseudonormal pattern. At this stage, accurate evaluation of DD requires additional analysis of Valsalva maneuver, pulmonary venous flow, and/or left

From the Echocardiography Laboratory, Division of Cardioangiology, Department of Clinical and Experimental Medicine, Federico II University Hospital, Naples, Italy.

Manuscript received September 27, 2005; revised manuscript received May 30, 2006, accepted June 22, 2006.

Abbreviations and Acronyms

CAD = coronary artery disease
CFR = coronary flow reserve
DD = diastolic dysfunction
DM = diabetes mellitus
LV = left ventricular
LVFP = left ventricular filling pressure

atrial volume determination. In a population of 140 adults (16% diabetic), left atrial volume index was associated with the degree of DD, independent of ejection fraction, age, gender, and cardiovascular risk score (12). A pseudonormal pattern was unmasked in 28% of diabetic patients by Valsalva maneuver (E/A ratio decrease ≥25%) and/or pulmonary venous flow (atrial reverse velocity duration longer than mitral A duration) (13). In this context, the combination of pulsed tissue Doppler with transmitral inflow may be extremely useful for characterizing DD and LVFP because early diastolic peak velocity (E′) of the mitral annulus reflects the rate of myocardial relaxation and is relatively insensitive to preload effects (14). The ratio E/E′ (E′ as average of medial and lateral annulus) has been validated as reliable index of LVFP (15). A reduction of annular E′ was shown in recent-onset type 2 DM (16). In 25 type 1 diabetic patients, an increased E/E′ ratio was associated with left atrial enlargement and correlated independently with glycosylated hemoglobin (17), thus confirming the association between level of glycemic control and DD (8). The E/E′ ratio therefore may be used to detect and follow up the progression of DD in DM.

Diabetes and coronary microvascular dysfunction. Novel techniques open intriguing applications for cardiac ultrasound in DM. The alterations of myocardial composition and, thus, of diastolic properties and LVFP might be mediated by changes in the coronary microcirculation. Microvascular damage experienced by the diabetic heart (18) may lead to myocardial cell injury and reactive fibrosis/hypertrophy. Although focal microvascular alterations have not seemed sufficient to account for diffuse interstitial fibrosis (19), these observations looked at structure but not dynamics of coronary microvessels. Today, the function of coronary circulation may be evaluated by transthoracic echocardiography, by visualizing the distal left anterior descending artery (20–22), and by measuring coronary flow reserve (CFR) as hyperemic to the resting velocities ratio (20–22). The CFR has excellent concordance with intracoronary Doppler flow wire-derived CFR (20), high feasibility (21), and reproducibility (21). In the absence of epicardial coronary stenosis, impaired CFR indicates coronary microvascular dysfunction (22). A reduction of CFR has been documented in both type 1 and type 2 DM and seems to be a direct consequence of elevated glycemia (23,24). An alternative explanation is insulin resistance, which alters CFR during a cold pressure test, a completely endothelium-dependent stimulus (25). Endothelial function, another possible determinant of CFR, is impaired in early DM (26). Also, increased cardiac sympathetic activity may account for abnormal CFR in diabetic patients (27).

The link between coronary microvascular and diastolic dysfunction in diabetes. Diastolic dysfunction is evident in type 1 diabetic patients free of CAD when CFR impairment is also detectable (27). A similar relationship between the magnitude of CFR reduction and the degree of myocardial DD was found in uncomplicated hypertension (28), another condition characterized by impaired coronary microcirculation. This association is not surprising because coronary flow occurs predominantly during diastole. A change in the time constant of LV isovolumic pressure fall (τ), measured by catheterization, is associated with decreased coronary flow even in patients without CAD (29). Both reduced CFR and DD are associated with insulin resistance (26,30), with LV concentric remodeling/hypertrophy (8,31), with disorders of the sympathetic ner-

Table 1. Main Echocardiographic, Population-Based Studies on Diabetic Cardiomyopathy

Findings	Population Sample (n)	Authors	Year
Increase of LVM in women	111 DM 381 IGT	Galderisi et al. (1) Framingham Heart Study	1991
Increase of LVM in both genders	2,697 DM or IGT >65 yrs	Lee et al. (2) Cardiovascular Health Study	1997
Increase of LVM, reduction of EFS and MFS	1,810 DM	Devereux et al. (3) Strong Heart Study	2000
Increase of LVM and RWT, reduction of MFS	386 DM + HTN	Palmeri et al. (4) HyperGEN Study	2001
Increase of LVM and RWT	457 IGT	Ilercil et al. (5) Strong Heart Study	2001
Progressive increase of LVM and reduction of EFS and MFS in DM and DM + HTN	642 DM 874 DM + HTN	Bella et al. (7) Strong Heart Study	2001
Progressive reduction of E/A ratio and prolongation of DT in DM and DM + HTN	616 DM 671 DM + HTN	Liu et al. (8) Strong Heart Study	2001
Progressive increase of LVM, RWT, and LA in IGT and DM	186 DM 343 IGT	Rutter et al. (6) Framingham Heart Study	2003

DM = diabetes mellitus; EFS = endocardial fractional shortening; HTN = hypertension; IGT = impaired glucose tolerance; LA = left atrium; LVM = left ventricular mass; MFS = midwall fractional shortening; RWT = relative wall thickness.

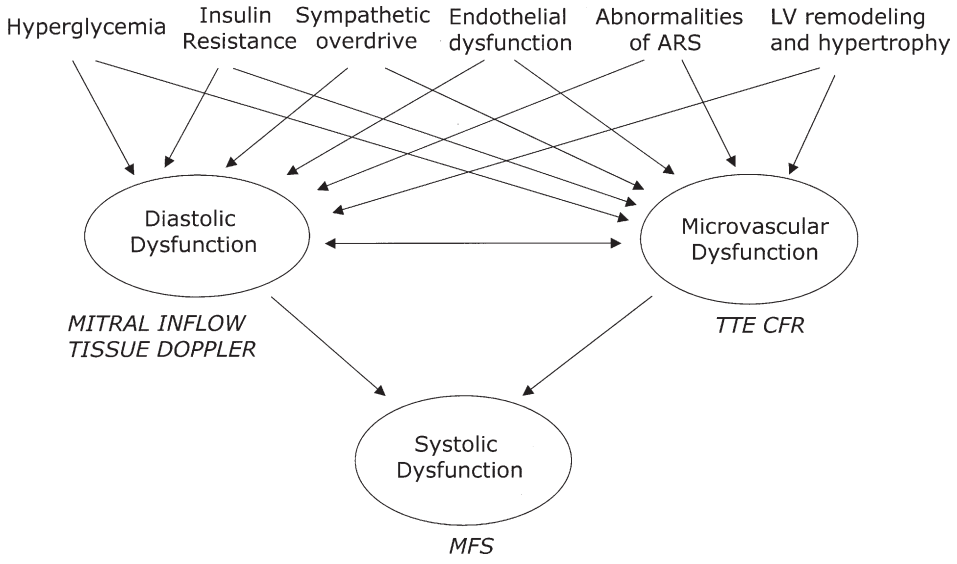

Figure 1. The hypothetical link of metabolic alterations to left ventricular (LV) function and coronary microcirculation in diabetes mellitus. Hyperglycemia, insulin resistance, sympathetic overdrive, endothelial dysfunction, abnormalities of the angiotensin-renin system (ARS), and LV remodeling/hypertrophy may induce diastolic dysfunction (DD) and impairment of the coronary microcirculation. The microvascular alterations may induce DD or vice versa. The LV systolic involvement appears subsequent to DD and/or coronary microvascular dysfunction. Ultrasound technology may detect DD and increased LV filling pressure (Doppler mitral inflow + mitral annular tissue Doppler) and impairment of coronary microcirculation (CFR) and of midwall systolic function. CFR = coronary flow reserve; MFS = midwall fractional shortening; TTE = transthoracic echocardiography.

vous system (27), with abnormalities of the angiotensin-renin system (32), and with endothelial dysfunction (33). We can, therefore, suppose that coronary microvascular damage plays a mechanistic role for DD (34) or even vice versa, considering DD as the main expression of myocardial fibrosis. Determinants of microvascular dysfunction in DM, such as hyperglycemia and insulin resistance, and factors including sympathetic overdrive, endothelial dysfunction, and LV concentric remodeling, also contribute to the development of DD. Systolic failure may be a further consequence because of impairment of both diastolic properties and coronary microcirculation (Fig. 1). In my view, a comprehensive transthoracic Doppler evaluation of diabetic patients should include assessment of diastolic function with estimation of LVFP by tissue Doppler, and of coronary microvascular function by CFR test. Analysis of regional wall motion during stress would be required in patients with suspected CAD, another cause of DD. The detection of wall motion abnormalities cannot be ascribed to microvascular dysfunction but has to be considered a true expression of epicardial artery stenosis (macrovascular disease).

Clinical implications. The journey of Doppler echocardiography in the assessment of diabetic heart disease is not yet complete. Ultrasound identifies early diastolic involvement and progression toward more severe DD by detecting changes of LVFP. Future potential links between diastolic behavior and the state of coronary microcirculation will be examined by combined imaging of coronary flow dynamics and global/regional diastolic function. This will be useful for preclinical diagnosis, risk stratification, and therapeutic management of the cardiac involvement in diabetes mellitus. These findings may enable the value of cardiac drugs, such as angiotensin-converting enzyme inhibitors, selective blockers of angiotensin II type receptors, aldosterone antagonists, beta-blockers, and even statins, to be documented so that these agents may be applied more appropriately. The response to tight glycemic control by diet and new insulin-sensitizing agents could be followed up to determine whether a parallel reversal of myocardial and microvessel modifications could be achieved.

Reprint requests and correspondence: Dr. Maurizio Galderisi, Echocardiography Laboratory, Division of Cardioangiology, Department of Clinical and Experimental Medicine, Federico II University Hospital, Via S. Pansini 5, 80131 Naples, Italy. E-mail: mgalderi@unina.it.

REFERENCES

1. 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 1991;68:85–9.
2. Lee M, Gardin JM, Lynch JC, et al. Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women. The Cardiovascular Health Study. Am Heart J 1997;133:36–43.
3. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function: the Strong Heart Study. Circulation 2000;101:2271–6.
4. Palmieri V, Bella JN, Arnett DK, et al. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects. Hypertension Genetic Epidemioloy Network (HyperGEN) study. Circulation 2001;103:102–7.
5. Ilercil A, Devereux RB, Roman MJ, et al. Relationships of impaired glucose tolerance to left ventricular structure and function: the Strong Heart Study. Am Heart J 2001;14:992–8.
6. Rutter MK, Parise H, Benjamin EJ, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. Circulation 2003;107:448–54.

7. Bella JN, Devereux RB, Roman MJ, et al. Separate and joint effects of systemic hypertension and diabetes mellitus on left ventricular structure and function in American Indians (the Strong Heart Study). Am J Cardiol 2001;87:1260–5.
8. Liu JE, Palmieri V, Roman MJ, et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol 2001;37:1943–9.
9. Nishimura RA, Tajik J. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8–18.
10. Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults. The Strong Heart Study. Circulation 2002;105: 1928–33.
11. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. Circ Res 2000;87:1123–32.
12. Tsang TSM, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284–9.
13. Poirier P, Bogaty P, Garneau C, Marois L, Dumensnil JC. Diastolic dysfunction in normotensive men with well controlled type 2 diabetes 2. Diabetes Care 2001;24:5–10.
14. Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997;30:474–80.
15. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler catheterization study. Circulation 2000;102:1788–94.
16. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol 2004;93:870–5.
17. Shishehbor MH, Hoogwerf BJ, Schoenhagen P, et al. Relation of hemoglobin A1C to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. Am J Cardiol 2003;91:1514–7.
18. Kawaguchi M, Techigawara M, Ishihata T, et al. A comparison of ultrastructural changes on endomyocardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. Heart Vessels 1997;12:267–74.
19. Sunni S, Bishop SP, Kent SP, Geer JC. Diabetic cardiomyopathy. A morphological study of intramyocardial arteries. Arch Pathol Lab Med 1986;110:375–81.
20. Caiati C, Montaldo C, Zedda N, Bina A, Iliceto S. New invasive method for coronary flow reserve assessment. Contrast-enhanced transthoracic second harmonic echo Doppler. Circulation 1999;99: 771–8.
21. Pizzuto F, Voci P, Mariano E, Puddu PE, Sardella G, Nigri A. Assessment of flow velocity reserve by transthoracic Doppler echocardiography and venous adenosine infusion before and after left anterior descending coronary artery stenting. J Am Coll Cardiol 2001;38: 155–62.
22. Rigo F, Richieri E, Pasanisi E, et al. Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography. Am J Cardiol 2003;91:269–73.
23. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol 1997;30:1472–7.
24. Srinivasan M, Herrero P, McGill JB, et al. The effects of plasma insulin and glucose on myocardial blood flow in patients with type 1 diabetes mellitus. J Am Coll Cardiol 2005;46:42–8.
25. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med 2004:140:700–8.
26. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. Clin Sci 2005;109: 143–59.
27. Pop-Busui R, Kirkwood I, Schmid H, et al. Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol 2005;44: 2368–74.
28. Galderisi M, Cicala S, Caso P, et al. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. Am J Cardiol 2002;90:860–4.
29. Masuyama T, Uematsu M, Doy I, et al. Abnormal coronary flow dynamics at rest and during tachycardia associated with impaired left ventricular relaxation in humans: implication for tachycardia-induced myocardial ischemia. J Am Coll Cardiol 1994;24:1625–32.
30. Wisniacki N, Taylor W, Lye M, Wilding JP. Insulin resistance and inflammatory activation in older patients with systolic and diastolic heart failure. Heart 2005;91:32–7.
31. Schafer S, Kelm M, Mingers S, Strauer BE. Left ventricular remodelling impairs coronary flow reserve in hypertensive patients. J Hypertens 2002;20:1431–7.
32. Fiordaliso F, Leri A, Cesselli D, et al. Hyperglycemia activates p53 and p53-regulated genes leading to myocyte cell death. Diabetes 2001;50:2363–75.
33. Paulus WJ, Shah AM. NO and cardiac diastolic function. Cardiovasc Res 1999;43:595–606.
34. Strauer BE, Motz W, Vogt M, Schwartzkopff B. Impaired coronary flow reserve in NIDDM: a possible role for diabetic cardiomyopathy in humans. Diabetes 1997;46 Suppl 2:S119–24.