Diabetes

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Coronary artery disease is the leading cause of mortality and morbidity in patients with diabetes. Approximately one-half of deaths are attributed to coronary artery disease in diabetic patients, whose risk of myocardial infarction or cardiac death is two- to fourfold greater than in nondiabetic patients [1]. Moreover, cardiac events are as frequent in diabetic patients without evidence of coronary artery disease as in nondiabetic patients with known coronary artery disease [2]. Recent studies with electron beam computed tomography have shown that subclinical atherosclerosis is common in patients with diabetes, and studies with myocardial perfusion scintigraphy (with single-photon emission tomography) or stress echocardiography have demonstrated that between 25 and 50% of asymptomatic diabetic patients have ischemia during exercise or pharmacological stress and that a substantial proportion of these patients go on to develop major cardiovascular events within several years [2, 3]. The increased risk associated with diabetes calls for effective prevention and risk stratification strategies to optimize therapeutic interventions [3]. Clearly, asymptomatic diabetic patients include a subset of individuals at high risk of cardiovascular disease who would benefit from improved risk stratification beyond that possible with risk factor scoring systems alone [4]. Exercise testing is of limited value in the diabetic population because exercise capacity is often impaired by peripheral vascular [5] or neuropathic disease [6]. Furthermore, test specificity on electrocardiographic criteria is less than ideal because of the high prevalence of hypertension and microvascular disease [7]. Stress imaging, and in particular stress echocardiography, can play a key role in the optimal identification of the high-risk diabetic subset, also minimizing the economic and biologic costs of diagnostic screening, since stress echocardiography costs three times less than a perfusion scintigraphy and is a radiation-free technique without long-term oncogenic risks [8].

32.1 Pathophysiology

Diabetes mellitus can provoke cardiac damage at four levels: coronary macrovascular disease, autonomic cardiomyopathy, diabetic cardiomyopathy, and coronary microvascular disease (Fig. 32.1). These syndromes are rarely found in isolated form in individual patients, but

E. Picano, *Stress Echocardiography*,

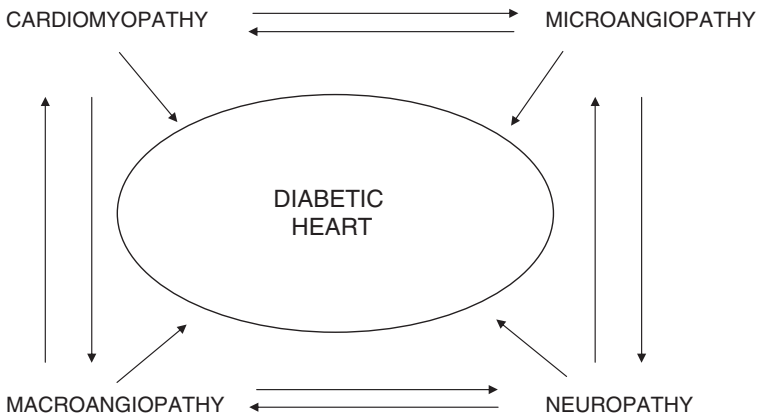

Fig. 32.1 The four aspects of damage in the diabetic heart: autonomic neuropathy, diabetic cardiomyopathy, coronary microangiopathy, coronary macroangiopathy. The four pathways – albeit pathogenetically distinct – cross-talk. For instance, microangiopathy may codetermine neuropathy – through vas nervorum involvement – and at the coronary level, may impair coronary flow reserve, amplifying the impact of an epicardial coronary artery stenosis

more often overlap and potentiate each other. In particular, diabetes mellitus induces coronary structural [9] and functional [10, 11] microvascular abnormalities, which are associated with coronary endothelial dysfunction and impairment in coronary flow reserve, even in the absence of epicardial coronary artery disease [12]. In young subjects with uncomplicated diabetes, there is a marked coronary microvascular dysfunction in response to adenosine infusion (primarily reflecting aberrant endothelium-independent vasodilation) and to the cold pressor test (primarily reflecting endothelium-dependent vasodilation) [13].

32.2 Diagnosis of Coronary Artery Disease

The coronary microangiopathy component can amplify the effects of coronary macroangiopathy, which is a major complication of diabetes. Coronary, cerebral, and peripheral vascular diseases are the causes of death in 75% of adult diabetic subjects. The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to stress echocardiography in the detection of coronary artery disease in asymptomatic (and symptomatic diabetic patients [14–21]). In fact, the typical behavior of microvascular disease during stress testing is the frequent induction of ST-segment depression and perfusion abnormalities, with true reduction in coronary flow reserve without regional or global wall motion changes [8]. In practical terms, this means that in patients with normal baseline ECG results, the negative predictive value of a maximal exercise ECG is satisfactory, but in all patients with positive or ambiguous ECG and/or chest pain findings, a stress echocardiography test is warranted. In diabetic

patients, stress echocardiography has shown a higher specificity than perfusion imaging but suffers from a higher rate of false-positive results, possibly due to the coexistence of cardiomyopathy in many patients [21].

32.3 Prognostic Stratification

Risk stratification of diabetic patients is a major objective for the clinical cardiologist, given their increased risk for coronary artery disease [1]. Resting echocardiography is already important for this purpose, since there is a distinct "cardiomyopathy cascade" (Fig. 32.2) with higher risk levels – and higher degrees of cardiomyopathic involvement – identified by left atrial dilatation [22], diastolic dysfunction [23], and impaired longitudinal function [24], which all may coexist with normal ejection fraction [25].

Stress echocardiography has shown powerful risk stratification capabilities in diabetics. In patients with overt resting ischemic cardiomyopathy, the presence of myocardial viability recognized by dobutamine echocardiography independently predicts improved outcome following revascularization in nondiabetics as well as in diabetic patients following revascularization [26]. Also in patients with normal resting left ventricular function, a clear refinement of prognosis can be obtained with stress echocardiography, first and foremost on the basis of classical wall motion abnormalities [27–32], which place the patients in a high-risk subset for cardiovascular events (Fig. 32.3). The incremental prognostic information pro-

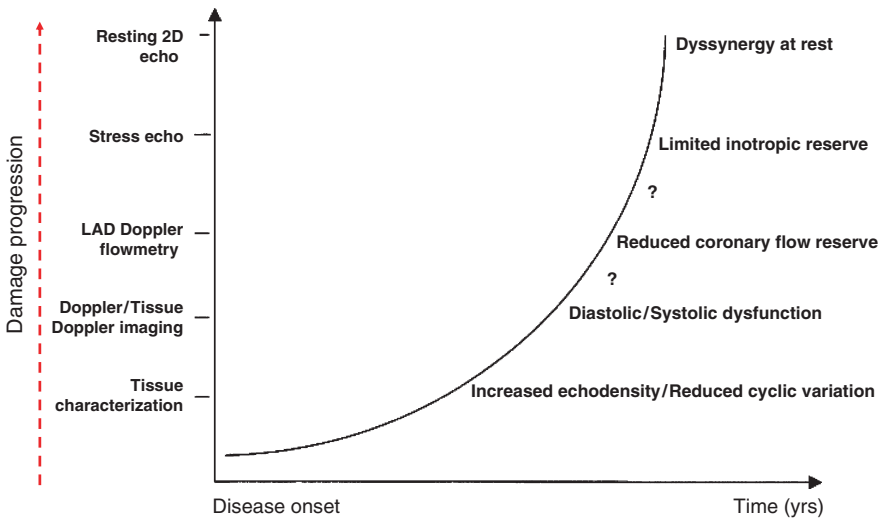

Fig. 32.2 Cardiomyopathy cascade. In the sequence of events, changes in diastolic function and alternations in longitudinal function of the left ventricle (such as reduction in mitral annulus plane systolic excursion by *M*-mode or reduction in systolic velocity by myocardial tissue Doppler or strain rate imaging) precede by years or decades the reduction of ejection fraction. (From [25])

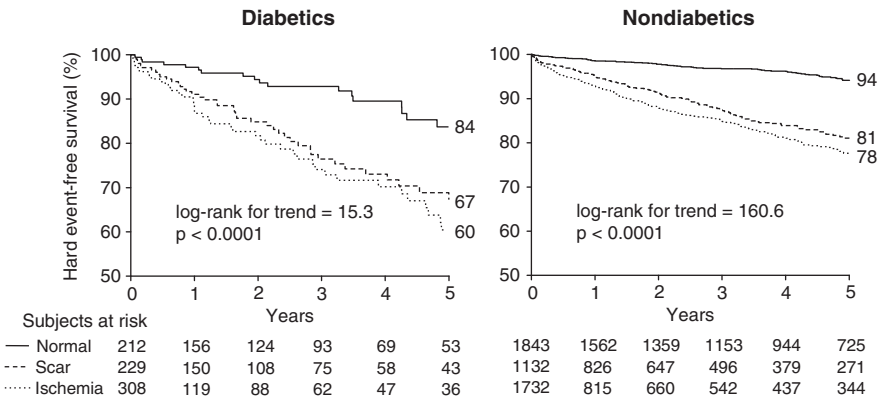

Fig. 32.3 Kaplan–Meier event-free survival curves in diabetics (*left*) and nondiabetics (*right*). In patients without scar and inducible wall motion abnormalities, the prognosis is excellent in nondiabetics, but still poor in diabetics in whom a better stratification is needed. (From [33])

vided by stress echocardiography is highest in patients with intermediate-to-high threshold positive exercise electrocardiography test results [33]. However, in diabetic patients – differently from nondiabetic subjects – a negative test result based solely on wall motion criteria is associated with less benign outcome in the presence of diabetes [32] (Fig. 32.3). In these patients, coronary flow reserve evaluated simultaneously with wall motion during vasodilation stress testing by transthoracic Doppler echocardiography adds independent prognostic information [34] (Fig. 32.4). In particular, a normal coronary flow reserve off therapy is associated with better and similar survival both in the diabetic and nondiabetic population. Explanations for reduced coronary flow reserve in the absence of stress-induced wall motion abnormalities include mild-to-moderate epicardial coronary artery stenosis, severe epicardial artery stenosis in presence of antiischemic therapy, and severe microvascular coronary disease in presence of patent epicardial coronary arteries [34].

32.4 The Diagnostic Flow Chart in Diabetics

The general diagnostic flow chart in diabetics (both symptomatic and intermediate-to-high risk asymptomatic) can be summarized as in Fig. 32.5. After the exercise stress test, a stress imaging test is often warranted. In the literature, strategies based on perfusion imaging (with thallium or sestamibi) have been proposed, even in guidelines and in young or middle-aged women. For instance, the Swiss Society of Endocrinology-Diabetology recommends screening for coronary artery disease for diabetic patients with two or more additional cardiovascular risk factors, and the recommended test for screening is either stress echocardiography or myocardial perfusion imaging [35]. Nearly 10 years ago, the American Diabetes Association recommended exercise tolerance testing alone in asymptomatic patients with two or more coronary artery disease risk factors or an abnormal resting electrocardiogram. However, the recommendation is not based on hard evidence but rather is the consensus of an

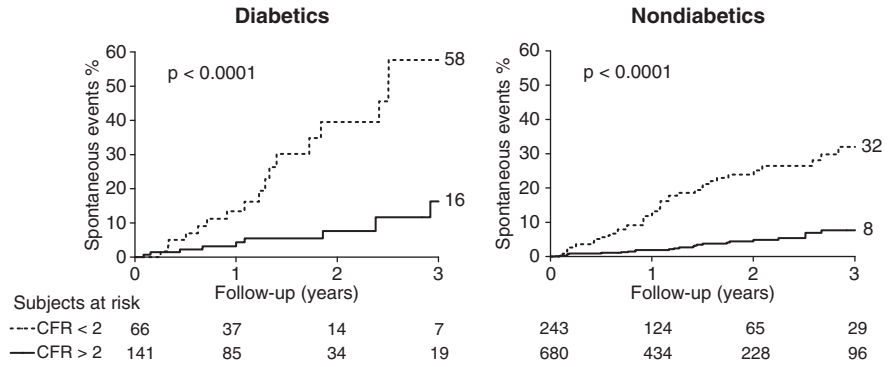

Fig. 32.4 Kaplan–Meier survival curve event rate for diabetic and nondiabetic patients with coronary flow reserve (*CFR*)>2 or ≤2, normal resting echocardiography, and negative stress echocardiography by wall motion criteria. (From [34])

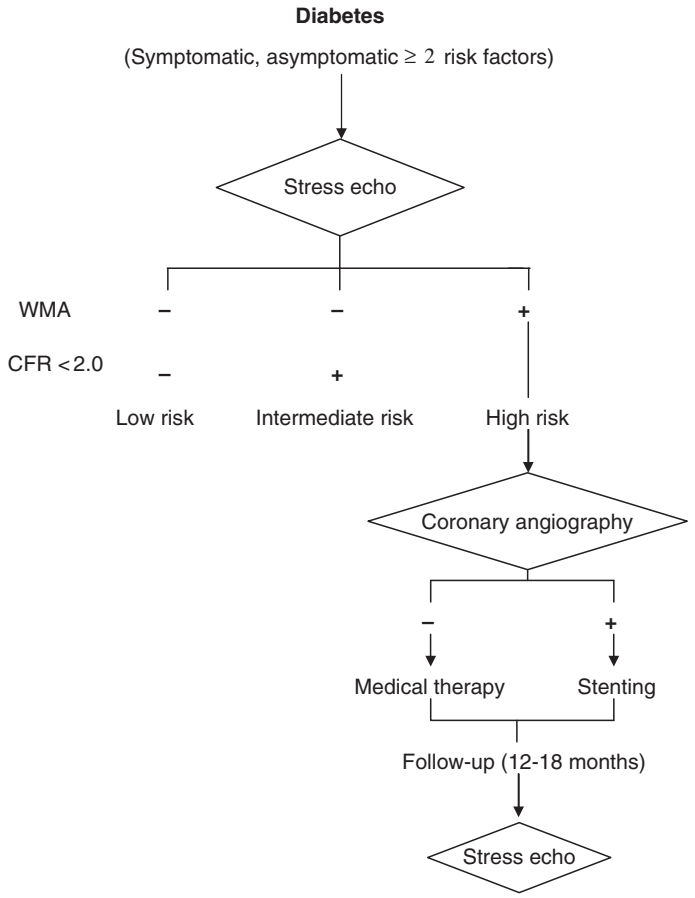

Fig. 32.5 The diagnostic flow chart in diabetics for recognition of coronary artery disease

expert panel. The recognized finding that 10–15% of asymptomatic diabetics indeed have coronary artery disease have led to proposing stress imaging for a more effective risk stratification [36]. However, the economic and long-term risk burden is especially important due to recent accumulation of suggestive evidence that percutaneous coronary revascularization may not provide additive benefit to intensive medical management in patients with stable coronary artery disease [4]. Therefore, we currently recommend that testing for atherosclerosis or ischemia be reserved for those in whom medical treatment goals cannot be met and for selected individuals in whom there is strong clinical suspicion of very-high-risk coronary artery disease [4]. Even in these individuals, techniques with substantial radiation exposure – albeit recommended by authorities – such as myocardial scintigraphy or cardiac computed tomography should be used with great wisdom and prudence, and stress echocardiography is by far a more sustainable option [8]. The information obtained with the two different approaches is more or less the same for the physician, but certainly not for the patient and society, since small individual risks multiplied by a million examinations translate into significant population risks [37]. The radiation dose is 500–1,500 chest X-rays for every scintigraphy or 50–1,500 chest X-rays for each cardiac computed tomography scan. The long-term risk of cancer for these procedures is not insignificant (1 in 500 for a single thallium scan), higher in women (1 in 350 for a 35-year-old woman) and cumulative: every test adds dose to dose, risk to risk, and cost to cost. In addition, patient acceptance of testing is higher when no radiation exposure is involved [38]. The issue of economic and biological sustainability is especially important in diabetic patients, since the results of testing are thought to no longer be valid after 12–18 months and serial examinations are regularly needed in these patients [39]. The same diagnostic efficacy can be achieved with stress echocardiography, if possible with combined wall motion and coronary flow reversible assessment simultaneously evaluated with a single stress (a “two birds with a stone” approach). Patients with wall motion abnormalities are at high risk and should be referred to coronary angiography for ischemia-driven revascularization. Patients without wall motion abnormalities and after reduction in coronary flow reserve are at intermediate risk and should be treated aggressively with tight metabolic control, maximal antiischemic therapy, and a more frequent follow-up by noninvasive stress testing [32]. Patients with neither wall motion abnormalities nor reduction in coronary flow reserve are at low risk and can be managed conservatively. These approaches will optimize the quality of screening for coronary artery disease but at the same time minimize the costs and the radiation burden of a diagnostic “carpet bombing” still of questionable benefit in asymptomatic diabetes.

References

1. Ryden L, Standl E, Bartnik M, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD) (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. Eur Heart J 28:88–136
2. Berry C, Tardif J-C, Bourassa MG (2007) Coronary heart disease in patients with diabetes. Part I: recent advances in prevention and non-invasive management. J Am Coll Cardiol 49:631–642
3. Bax JJ, Bonow RO, Tschöpe D, et al; Global Dialogue Group for the Evaluation of Cardiovascular Risk in Patients With Diabetes (2006) The potential of myocardial perfusion scintigra-

phy for risk stratification of asymptomatic patients with type 2 diabetes. J Am Coll Cardiol 48:754–760
4. Bax JJ, Young LH, Frye RL, et al; ADA (2007) Screening for coronary artery disease in patients with diabetes. Diabetes Care 30:2729–2736
5. Akbari CM, LoGerfo FW (1999) Diabetes and peripheral vascular disease. J Vasc Surg 30:373–384
6. May O, Arildsen H, Damsgaard EM, et al (2000) Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk o coronary heart disease in the general population. J Intern Med 248:483–491
7. Picano E, Pálinkás A, Amyot R (2001) Diagnosis of myocardial ischemia in hypertensive patients. J Hypertens 19:1177–1183
8. Picano E (2003) Stress echocardiography: a historical perspective. Am J Med 114:126–130
9. Factor SM, Okun EM, Minase T (1980) Capillary microaneurysms in the human diabetic heart. N Engl J Med 302:384–388
10. Strauer BE, Motz W, Vogt M, et al (1997) Evidence for reduced coronary flow reserve in patients with insulin-dependent diabetes. A possible cause for diabetic heart disease in man. Exp Clin Endocrinol Diabet 105:15–20
11. Nahser PJ Jr, Brown RE, Oskarsson H, et al (1995) Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation 91:635–640
12. Nitenberg A, Valensi P, Sachs R, et al (1993) Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. Diabetes 42:1017–1025
13. Di Carli MF, Janisse J, Grunberger G, et al (2003) Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol. 41:1387–1393
14. Bates JR, Sawada SG, Segar DS, et al (1996) Evaluation using dobutamine stress echocardiography in patients with insulin-dependent diabetes mellitus before kidney and/or pancreas transplantation. Am J Cardiol 77:175–179
15. Hennessy TG, Codd MB, Kane G et al (1997) Evaluation of patients with diabetes mellitus for coronary artery disease using dobutamine stress echocardiography. Coron Artery Dis 8:171–174
16. Elhendy A, Domburg RT van, Poldermans D, et al (1998) Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. Diabetes Care 21:1797–1802
17. Gaddi O, Tortorella G, Picano E, et al (1999) Diagnostic and prognostic value of vasodilator stress echocardiography in asymptomatic type 2 diabetic patients with positive exercise thallium scintigraphy: a pilot study. Diabet Med 16:762–766
18. Lin K, Stewart D, Cooper S, et al (2001) Pre-transplant cardiac testing for kidney–pancreas transplant candidates and association with cardiac outcomes. Clin Transplant 15:269–275
19. Penfornis A, Zimmermann C, Boumal D, et al (2001) Use of dobutamine stress echocardiography in detecting silent myocardial ischaemia in asymptomatic diabetic patients: a comparison with thallium scintigraphy and exercise testing. Diabet Med 18:900–905
20. Coisne D, Donal E,Torremocha F, et al (2001) Dobutamine stress echocardiography response of asymptomatic patients with diabetes. Echocardiography 18:373–379
21. Griffin ME, Nikookam K, Teh MM, et al (1998) Dobutamine stress echocardiography: false positive scans in proteinuric patients with type 1 diabetes mellitus at high risk of ischaemic heart disease. Diabet Med 15:427–430
22. Bangalore S, Yao SS, Chaudhry FA (2007) Role of left atrial size in risk stratification and prognosis of patients undergoing stress echocardiography. J Am Coll Cardiol 50:1254–1262
23. Galderisi M (2006) Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. J Am Coll Cardiol 48:1548–1551
24. Fang ZY, Najos-Valencia O, Leano R, et al (2003) Patients with early diabetic heart disease demonstrate a normal myocardial response to dobutamine. J Am Coll Cardiol 41:1457–1465

25. Picano E (2003) Diabetic cardiomyopathy: the importance of being earliest. Editorial comment. J Am Coll Cardiol 41:1465–1471
26. Cortigiani L, Sicari R, Desideri A, et al; VIDA (Viability Identification with Dobutamine Administration) Study Group (2007) Dobutamine stress echocardiography and the effect of revascularization on outcome in diabetic and non-diabetic patients with chronic ischaemic left ventricular dysfunction. Eur J Heart Fail 9:1038–1043
27. Elhendy A, Arruda AM, Mahoney DW, et al (2001) Prognostic stratification of diabetic patients by exercise echocardiography. J Am Coll Cardiol 37:1551–1557
28. Bigi R, Desideri A, Cortigiani L, et al (2001) Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. Diabetes Care 24:1596–1601
29. Kamalesh M, Matorin R, Sawada S (2002) Prognostic value of a negative stress echocardiographic study in diabetic patients. Am Heart J 2002 143:163–168
30. Marwick TH, Case C, Sawada S, et al (2002) Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. Diabetes Care 25:1042–1048
31. Sozzi F, Elhendy A, Rizzello V, et al (2007) Prognostic significance of myocardial ischemia during dobutamine stress echocardiography in asymptomatic patients with diabetes mellitus and no prior history of coronary events. Am J Cardiol 99(9):1193–1195
32. Cortigiani L, Bigi R, Sicari R, et al (2006) Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. J Am Coll Cardiol 47:605–610
33. Cortigiani L, Bigi R, Sicari R, et al (2007) Comparison of prognostic value of pharmacologic stress echocardiography in chest pain patients with versus without diabetes mellitus and positive exercise electrocardiography. Am J Cardiol 100:1744–1749
34. Cortigiani L, Rigo F, Gherardi S, et al (2007) Additional prognostic value of coronary flow reserve in diabetic and nondiabetic patients with negative dipyridamole stress echocardiography by wall motion criteria. J Am Coll Cardiol. 50:1354–1361
35. Hurni CA, Perret S, Monbaron D, et al (2007) Coronary artery disease screening in diabetic patients: how good is guideline adherence? Swiss Med Wkly 137:199–204
36. Heller GV (2005) Evaluation of the patient with diabetes mellitus and suspected coronary artery disease. Am J Med 118:9S–14S
37. Picano E (2004) Sustainability of medical imaging. Education and debate. BMJ 328:578–580
38. Picano E (2004) Informed consent and communication of risk from radiological and nuclear medicine examinations: how to escape from a communication inferno. BMJ 329:849–851
39. Picano E (2005) Economic and biological costs of cardiac imaging. Cardiovasc Ultrasound 3:13