# Diabetic Cardiomyopathy

## A unique entity or a complication of coronary artery disease?

DAVID S.H. BELL, MB, FACP

The increased incidence of congestive heart failure and the increased mortality and morbidity in the diabetic patient following myocardial infarction or coronary artery bypass graft can be explained by the presence of diabetic cardiomyopathy. Noninvasive studies in young diabetic patients show no cardiac abnormality, but in older diabetic patients mild cardiac diastolic dysfunction is detectable. This mild cardiomyopathy can become clinically detectable in the presence of hypertension and can be severe in the presence of myocardial ischemia. Microvascular disease is unlikely to cause diabetic cardiomyopathy. Cellular changes, including defects in calcium transport and fatty acid metabolism, may lead to myocellular hypertrophy and myocardial fibrosis, initially causing diastolic dysfunction that may advance to systolic dysfunction. Glycemic control, energetic detection and treatment of hypertension with appropriate antihypertensive agents, and early detection and treatment of ischemic heart disease are essential in preventing and treating diabetic cardiomyopathy.

There is a threefold increase in the death rate for people with diabetes compared with age- and sex-matched nondiabetic control subjects (1). Patients with diabetes show an increase in relative mortality from all cardiovascular causes, and this relative mortality is greatest in women who use insulin. Although patients with diabetes tend to have a higher prevalence of hyperlipidemia, hypertension, and obesity, these factors do not entirely account for the increased mortality (2). Thus, the presence of diabetes is in itself a risk factor for cardiovascular disease.

The three major factors in diabetic heart disease are coronary artery disease, autonomic neuropathy causing cardiac denervation, and diabetic cardiomyopathy. The factors that play a role in the etiology of these disorders include obesity, hypertension, dyslipidemia, glycemic control, insulin resistance, glycosylation of proteins, and presence of long-term diabetic complications—particularly diabetic nephropathy, enhanced platelet aggregation, rheological factors, and diabetic coagulopathy (3).

The term cardiomyopathy means disease of heart muscle. As long ago as 1881, diabetes was reported to be associated with cardiomyopathy (4). Further evidence for an association of cardiomyopathy with diabetes was not published until 1972, when autopsies on four diabetic patients with diabetic nephropathy and congestive heart failure showed the absence of coronary atherosclerosis (5). This led to several further reports on the association of diabetes and cardiomyopathy, including a report of an increased incidence of diabetes in patients with idiopathic cardiomyopathy (6). The publication of the high frequency of congestive heart failure in the diabetic population of Framingham, Massachusetts (1), led to the belief that this cardiomyopathy was associated with diabetic microvascular disease. However, later studies suggested that this was not the case and that the etiology was metabolic rather than vascular.

Autopsy, experimental animal studies, and clinical noninvasive and invasive human cardiac studies have provided evidence for the existence of a separate diabetic cardiomyopathy that is not due to coronary atherosclerosis. However, the exact nature of the etiology of this condition remains controversial because of the multiple abnormalities that occur in association with diabetes.

**AUTOPSY STUDIES** — There is little doubt that diabetes is an independent risk factor for coronary artery disease. Most studies have confirmed this impression by showing a higher frequency of coronary artery disease, which was more diffuse and involved a greater number of vessels, especially distal vessels, when diabetic patients were compared with age- and sex-matched control subjects (7,8). In addition, more collaterals had opened and there were more myocardial infarcts. However, the extent and severity of the atherosclerosis was unrelated to the duration or severity of the diabetes. On the other hand, two autopsy studies have noted no difference in the number of vessels with >75% obstruction in diabetic patients with or without a history of congestive heart failure (9,10). Similarly, the proximal and distal arteries of patients with a clinical history of coronary artery

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

Address correspondence and reprint requests to David S.H. Bell, MB, 2000 6th Ave. South, Birmingham, AL 35233.

Received for publication 4 May 1994 and accepted in revised form 13 January 1995.

ACE, angiotensin-converting enzyme.

disease did not differ from those of diabetic patients without a clinical history of coronary heart disease. In another study of diabetic patients, apical scarring of ~2 × 1.5 cm was found without evidence of arterial obstruction but instead with accumulation of interstitial collagen, which is the probable cause of ventricular wall stiffness and apical scarring and suggests the presence of a congestive and/or a restrictive cardiomyopathy (11). Thus, coronary artery disease by itself cannot explain the high frequency of congestive heart failure in diabetic patients, suggesting that another myocardial pathology may be at least partially responsible.

**ANIMAL STUDIES** — When mild non-insulin-requiring diabetes without fasting hyperglycemia was induced in dogs with low doses of alloxan, left ventricular end-diastolic and stroke volumes decreased after 11 months in spite of end-diastolic pressures similar to those in control animals (12). These changes were thought to be due to the accumulation of a *p*-aminosalicylic acid–positive material among the muscle fibers. Coronary arteries and coronary blood flow were normal. Later studies in dogs and monkeys showed an increase in collagen-like material in the myocardium and an accumulation of cholesterol and triglycerides in the myocardium (13–15). These changes were not reversed with correction of hyperglycemia. Coronary artery occlusion in these animals resulted in a greater increase in left ventricular end-diastolic pressure than in nondiabetic dogs. Other studies have shown partial reversal of cardiac function with correction of hyperglycemia (16).

In diabetic dogs, coronary artery occlusion results in more myocardial damage than in nondiabetic dogs (17), which corresponds to the increased morbidity and mortality seen in the diabetic human patient with myocardial infarction (see below).

In diabetic rats, actomyosin ATPase activity and utilization of calcium by the sarcoplasmic reticulum are reduced, but in the absence of hypertension, anatomic changes do not accompany these pathophysiological changes (18).

**CLINICAL STUDIES** — There is higher mortality and morbidity after myocardial infarction in the diabetic patient. In 1974, the early days of coronary care units, Soler et al. (19) reported that mortality after a myocardial infarct was increased in the diabetic patient (35.5 vs. 18.1%) when compared with nondiabetic control subjects and also that half of these deaths occurred in the first 4 days. Mortality was not increased in those patients whose diabetes was controlled by diet alone but was equally increased in diabetic patients who used oral hypoglycemic agents and diabetic patients who used insulin. While 70% of the diabetic patients with myocardial infarcts developed left ventricular failure, only 6% had cerebrovascular accidents, 3% pulmonary emboli, and 15% ventricular fibrillation. Thus, the major cause of mortality in the diabetic patient with a myocardial infarct was ventricular failure.

Later, Stone et al. (20) reported that in spite of smaller-sized myocardial infarcts as judged by peak creatine phosphokinase (CPK) levels, the area of CPK under the curve, and a decrease in the percentage of patients developing Q waves, diabetic patients who had a myocardial infarct had a much worse prognosis than nondiabetic patients with larger myocardial infarcts. Ten days after myocardial infarction, there was a significant decrease in left ventricular ejection fraction (44.2 vs. 48.7%) that was not present at the time of the infarction. In survivors, there was no significant difference in ejection fraction after 3 months, in spite of a higher frequency of congestive heart failure in diabetic patients. This suggests that diastolic dysfunction accounts for the increased frequency of congestive heart failure in diabetic patients who have had a myocardial infarction. In addition, there was an almost twofold increase in the incidence of congestive heart failure and a significant increase in infarct extension, frequency of postinfarction angina, and development of intraventricular conduction delay. Despite an increased incidence of premature ventricular contractions in the nondiabetic patient after myocardial infarction, the immediate mortality rate in the diabetic population was higher, again emphasizing the increased frequency of ventricular dysfunction in the diabetic patient. Long-term studies of diabetic patients with myocardial infarction have shown a consistent increased mortality, especially in women (21,22). Many of these postinfarction complications may be due to the presence of diabetic cardiomyopathy.

Diabetes has greater impact on the incidence of congestive heart failure than on the incidence of coronary artery disease, especially in women. Congestive heart failure is twice as common in diabetic men and five times more common in diabetic women in the range of 45–74 years of age when compared with age-matched control subjects (1). Congestive heart failure is twice as common in diabetic women as in diabetic men, and overall, death due to congestive heart failure is 30% more common in diabetic patients (7,23). In addition, diabetes is an independent risk factor for a left ventricular mass in diabetic women (24), and diabetic patients have an increased mortality after percutaneous transluminal coronary angioplasty (25) and coronary artery bypass grafting (26). Furthermore, when subjected to coronary angiography, diabetic patients with and without congestive heart failure showed no differences in the severity of coronary atherosclerosis (27). Thus, the increase in the frequency of congestive heart failure in the diabetic patient is more likely to be due to cardiomyopathy than to ischemic heart disease.

**NONINVASIVE AND INVASIVE HUMAN CARDIAC STUDIES** — Evidence of diabetic cardiomyopathy can be found in symptomatic and asymptomatic diabetic patients with heart rates and blood pres-

sures similar to nondiabetic control subjects and also in the infants of mothers with poorly controlled diabetes. In diabetic patients, left ventricular ejection time is decreased, the length of the pre-ejection period is increased, and the ratio of pre-ejection period to left ventricular ejection time is increased (28,29). These findings are not related to the duration or form of treatment of diabetes and are consistent with both diastolic and systolic dysfunction (11). Other studies of asymptomatic diabetic patients have found that while the pre-ejection period: left ventricular ejection time ratio is not increased at rest, it can be increased by increasing the cardiac workload with exercise or alcohol (30,31). However, echocardiography and radionucleotide scanning have shown that the isovolumic relaxation time and left ventricular diastolic filling time are prolonged in asymptomatic diabetic patients with cardiac denervation (32,33), indicating that some or all of these changes could be due to cardiac denervation. Support for this theory can be found in studies of diabetic children and young adults in which no evidence of diabetic cardiomyopathy was found when diabetes was not accompanied by cardiac denervation, hypertension, or ischemic heart disease (34–37).

In diabetic patients with suspected cardiomyopathy, myocardial fibrosis can be documented using ultrasonic techniques and the presence of fibrosis has been shown to be associated with the long-term complications of diabetes, i.e., neuropathy, nephropathy, and retinopathy (38). In clinical practice, diabetic patients present with cardiac symptoms that are assumed to be attributable to ischemic heart disease, but upon angiography, they are found to have nonobstructive coronary artery disease or normal coronary arteries. In such a group of patients without significant coronary artery disease and with normal left ventricular mass, left ventricular end-diastolic pressure was elevated, left ventricular end-diastolic volume was normal, and stroke volume was decreased when compared with control subjects (11). The ratio of left ventricular end-diastolic pressure to volume, which is a measure of wall stiffness, was increased. In addition, the ejection fraction was low and in most patients there was diffuse ventricular hypokinesis (11). On the other hand, in contrast to other studies (27), a matched-pair analysis of randomly selected diabetic and nondiabetic patients with coronary artery disease in whom angiography had been performed showed an increased prevalence of cardiomyopathy that was related to the extent of proximal coronary artery disease and myocardial damage (39). The question as to whether low ejection fraction congestive heart failure in diabetic patients with coronary artery disease can be explained by more extensive coronary artery disease and more frequent myocardial infarction is unresolved.

Thus, when diabetes is not complicated by neuropathy, nephropathy, retinopathy, hypertension, or ischemic heart disease, little or no myocardial dysfunction can be detected. However, with the addition of untreated hypertension and/or myocardial ischemia, the mild subclinical cardiomyopathy of diabetes may rapidly advance to clinically obvious diastolic dysfunction and later systolic dysfunction.

## ETIOLOGY OF DIABETIC CARDIOMYOPATHY

— If obstructive coronary artery disease is not present but widespread microvascular disease is, then the myocardial fibrosis found with diabetic cardiomyopathy could still be attributed to ischemia. In favor of this hypothesis are studies that show thickened intima of arteries (40), microaneurysms of myocardial arterioles with the microaneurysms being more frequent in areas of myocardial degeneration (41), and increased capillary basement membrane thickening in patients with diabetes and glucose intolerance undergoing coronary artery bypass grafts (42). On the other hand, other autopsy studies have not shown a difference in small vessel pathology between diabetic and nondiabetic subjects (43). In addition, myocardial biopsies in diabetic patients with cardiac failure and no significant coronary artery disease have not shown microangiopathy (44), and in a group of patients exposed to atrial pacing during cardiac catheterization, no increase in lactate production was found after an increase in the heart rate, which would indicate the absence of myocardial ischemia (45). While this evidence suggests that occlusive disease of the small vessels is not the cause of diabetic cardiomyopathy, the possibility that an imbalance in endothelial factors leading to arterial spasm and subsequent reperfusion injury to the myocardium that may eventually lead to diabetic cardiomyopathy cannot be excluded (28). In addition, in diabetic patients there may be inadequate reactive angiogenesis in the presence of ischemia (46). It is also possible that the abnormal permeability seen in diabetic small-vessel disease could lead to interstitial edema, fibrosis, and diabetic cardiomyopathy (47).

If microvascular and macrovascular disease are not responsible or are only partially responsible for the myocardial dysfunction seen in some diabetic patients, then what is the etiology and pathogenesis of their cardiomyopathy? Unlike other restrictive cardiomyopathies, diabetic cardiomyopathy is characterized by myocellular hypertrophy and myocardial fibrosis (45). Studies in dogs, monkeys, and rabbits have shown that experimentally induced diabetes causes defects in cellular calcium transportation (48), which may be reversible with Verapamil (49), defects in myocardial contractile protein (50), and an increase in collagen formation (14), which results in minor anatomic and physiological changes in the myocardium. More recent studies have suggested that increased utilization of fatty acids accompanied by a decrease in glucose utilization leads to an accumulation of toxic fatty acid intermediates that further inhibit glucose utilization by the myocardium. This may lead to ATP depletion, prevention of lactate pro-

duction, and increased myocardial oxygen consumption, all of which lead to impaired myocardial performance (51).

The addition of hypertension, to which the diabetic patient is more vulnerable, will cause further damage to the myocardial contractile proteins, induce myocardial fibrosis, and worsen the anatomical and physiological changes caused by diabetes (52). The addition of ischemia to a mildly dysfunctional diabetic myocardium or to a moderately dysfunctional myocardium due to the combined effects of diabetes and hypertension has the potential to precipitate a severe and even terminal cardiomyopathy (39). Diabetes, hypertension, and ischemia all lead to accumulation of fibrous tissue, which causes myocardial stiffness and diastolic and systolic dysfunction (20). Furthermore, if fibrosis involves the papillary muscles, valvular dysfunction can occur, adding a mechanical problem to the myocardial dysfunction.

**TREATMENT OF DIABETIC CARDIOMYOPATHY**— In preventing and treating diabetic cardiomyopathy, glycemic control is essential. In animals, insulin therapy can prevent or improve diabetic cardiomyopathy (53,54). On the other hand, in animal studies, first-generation sulfonylureas have been reported to worsen diabetic cardiomyopathy in spite of improved glycemic control (13).

Since the combination of diabetes and hypertension has an adverse effect on the myocardium, the control of hypertension with the appropriate antihypertensive agents, in addition to glycemic control, is essential in preventing, delaying the onset of, or ameliorating the development of myocardial disease. This particularly applies to the African-American population, which has a high prevalence of diabetes and hypertension. In treating the hypertension associated with diabetes, the use of thiazide diuretics, especially in combination with β-blockers, should be avoided whenever possible (55). Thiazide diuretics increase insulin resistance (56), decrease insulin release, worsen hyperglycemia, cause and worsen impotence and hyperlipidemia (55), and have been associated with an increase in mortality in diabetic patients with and without proteinuria (57).

β-blockers, when not needed to prevent cardiac arrhythmias or treat myocardial ischemia, should not be used in diabetic patients. β-blockers increase insulin resistance and decrease insulin release from the islet cells of the pancreas, especially when used in combination with thiazide diuretics, so that glycemic control often deteriorates to the point that insulin may be required (55,57–59). By blocking glucose production by the liver, β-blocker use results in more frequent hypoglycemia and delay in recovery from hypoglycemia, and because of the β-blockade, hypoglycemia may not be recognized and accelerated hypertension may occur during hypoglycemia (60,61). Hyperlipidemia, impotence, and peripheral vascular disease may also be worsened by β-blockers (55,62–64).

Therefore, the ideal antihypertensive agent would not worsen hyperglycemia in the diabetic patient, cause or worsen hypoglycemia, hyperlipidemia, impotence, postural hypotension, or peripheral vascular disease, and would have a protective effect on the kidney (56,65). The antihypertensive medications that most nearly meet these criteria are the angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and $\alpha_1$-blockers. None of these medicines will worsen hyperglycemia, hypoglycemia, hyperlipidemia, impotence, or peripheral vascular disease, and hypotension is usually only an initial and transient problem (55,66,67). In addition, ACE inhibitors have a protective effect on the kidney (68–70), reduce insulin resistance (71), and are useful in the treatment of congestive heart failure (72). Furthermore, calcium-channel blockers and ACE inhibitors may prevent the development of left ventricular hypertrophy (73) and its associated problems of myocardial ischemia, cardiac arrhythmias, deterioration of diastolic and systolic ventricular function, and sudden death (74).

Since animal studies have shown a defect in calcium transport in myocardial cells in diabetic cardiomyopathy, which is reversed with Verapamil (33), the use of this or other calcium-channel blockers would seem even more logical. Since calcium-channel blockers may worsen ventricular function in congestive heart failure, they should be used cautiously. In addition, ACE inhibitors, with a documented beneficial effect on myocardial contractility, coronary vasoconstriction, myocardial cell growth, hypertrophy, and reperfusion injuries, are another logical choice for antihypertensive agents that have cardioprotective effects in the diabetic patient (75).

Because myocardial ischemia has the potential to precipitate a severe and even terminal cardiomyopathy (38), the presence of significant obstructive coronary artery disease and ischemia should be diagnosed early and treated energetically in the diabetic patient. Though it is not universally accepted, most diabetologists believe that silent myocardial ischemia in the diabetic patient is much more common (76–78), is associated with cardiac denervation, and ideally should be recognized before a sudden and unexpected cardiac decompensation occurs. Evidence of cardiac denervation may be obtained by measurement of variation in the R-R interval (79). If the variation is abnormal, noninvasive testing by stress test, with or without echocardiography, or ambulatory Holter monitoring is recommended to rule out silent ischemia. If myocardial ischemia is diagnosed clinically or by noninvasive testing, its extent should be documented and corrected or treated aggressively. In this way, further advancement of diabetic cardiomyopathy due to the myocardial ischemia can be halted.

**SUMMARY**— Increased mortality from cardiac disease in the diabetic population is not entirely attributable to ischemic heart disease and may well be

caused by diabetic cardiomyopathy. Animal, autopsy, clinical, and electrophysiological studies have documented the presence of a distinct cardiomyopathy. In the presence of diabetes alone, the cardiomyopathy is mild, but with the addition of hypertension or ischemic heart disease, the cardiomyopathy can become severe. Diabetic cardiomyopathy is characterized by myocellular hypertrophy, myocardial fibrosis, and, at the cellular level, defects in calcium transportation, myocardial contractile protein collagen formation, and fatty acid metabolism. Diabetic cardiomyopathy is unlikely to be caused by microvascular disease. Clinically, diabetic cardiomyopathy has the characteristics of a restrictive cardiomyopathy, the most common noninvasive finding being diastolic dysfunction. Treatment of diabetic cardiomyopathy should include glycemic control, use of appropriate antihypertensive therapy, and early detection and correction of myocardial ischemia.

## References


1. Garcia MJ, McNamara PM, Gordon T, Kannell WB: Morbidity and mortality in diabetics in the Framingham population: sixteen year follow-up study. *Diabetes* 23: 105–111, 1974
2. Fuller JH, Shipley MJ, Rose G, Jarret RJ, Keen H: Coronary heart disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* i:1373–1376, 1980
3. Colwell JA, Lopes-Virella M, Halushka PV: Pathogenesis of atherosclerosis in diabetes mellitus. *Diabetes Care* 4:121–133, 1981
4. Leyden E: Asthma and diabetes mellitus. *Klin Med* 3:358–364, 1981
5. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grisham A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30: 595–602, 1972
6. Zoneraich S, Silverman G, Zoneraich Q: Small coronary artery disease in diabetes mellitus. *Circulation* 55:111–124, 1977
7. Bell ET: A post-mortem study of vascular disease in diabetics. *Arch Pathol* 53:444–455, 1952
8. Roberson WB, Strong JP: Atherosclerosis in persons with hypertension and diabetes. *Lab Invest* 18:538–551, 1968
9. Waller BF, Palumbo PJ, Lei JT, Roberts WC: Status of the coronary arteries at necroscopy in diabetes mellitus with onset after age 30 years: analysis of 229 diabetic patients with and without clinical evidence of coronary heart disease and comparison to 183 control subjects. *Am J Med* 69:498–506, 1980
10. Vigorita VJ, Moore GW, Hutchins GM: Absence of correlation between coronary arterial sclerosis and severity or duration of diabetes mellitus of adult onset. *Am J Cardiol* 46:535–542, 1980
11. Regan TJ, Lyons MM, Ahmed GS: Evidence of cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 60:885–899, 1977
12. Regan TJ, Ettinger PO, Kahn MI, Jesrani MU, Lyons MM, Oldewurtel HA, Weber M: Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. *Circ Res* 35: 222–237, 1974
13. Wu CF, Haider B, Ahmed SS, Oldewurtel HA, Lyons MM, Regan TJ: The effect of tolbutamide on the myocardium in experimental animals. *Circulation* 55:200–255, 1973
14. Regan TJ, Wu CF, Oldewurtel HA, Haider B: Myocardial composition and function in diabetes: the effects of chronic insulin use. *Circ Res* 49:1268–1277, 1981
15. Haider B, Yeh CK, Thomas G, Oldewurtel HA, Lyons MM, Regan TJ: Influence of diabetes on the myocardium and coronary arteries of rhesus monkeys fed an atherogenic diet. *Circ Res* 49:1278–1288, 1981
16. Pogatsa G, Bihari-Vargas M, Szinay G: Effect of diabetes therapy on the myocardium in experimental animals. *Acta Diabetol Lat* 16:129–138, 1979
17. Palik I, Koltai ZS, Kolonies I: Effects of coronary occlusion and norepinephrine on the myocardium of alloxan-diabetic dogs. *Basic Res Cardiol* 77:499–506, 1982
18. Fein FS: Diabetic cardiomyopathy. *Prog Cardiovasc Dis* 27:255–270, 1985
19. Soler NG, Bennett MA, Lamb P, Pentecost BL, Fitzgerald MG, Mullins JM: Coronary care for myocardial infarction in diabetics. *Lancet* i:475–477, 1974
20. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Srauss HW, Willerson JT, Robertson T, Braunwald E, Jaffe AS, MILIS Study Group: The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. *J Am Coll Cardiol* 14:49–57, 1989
21. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S, the Israeli SPRINT investigators: In-hospital and 1-year mortality in 1524 women after myocardial infarction: comparison with 4,315 men. *Circulation* 83:484–491, 1991
22. Sprafka JM, Burke GL, Folsom AR, McGovern PG, Hahn LP: Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. *Diabetes Care* 14: 537–543, 1991
23. Kannel WB, McGee DL: Diabetes and cardiovascular disase: the Framingham Study. *JAMA* 241:2035–2038, 1979
24. Galderisi M, Anderson KM, Wilson PW, Levy D: Echocardiographic evidence for existence of a distinct diabetic cardiomyopathy (The Framingham Heart Study). *Am J Cardiol* 68:85–89, 1991
25. Simpfendorfer C, Platko W, Divernois J, Dorosti K, Pranco I, Hollman J, Whitlow P: Coronary angioplasty in insulin-dependent diabetics: immediate and long-term results (Abstract). *Eur Heart J* 11 (Suppl.):87, 1990
26. Lawrie GM, Morris GO, Glaeser DJ: Influence of diabetes mellitus on the results of coronary bypass surgery: follow-up of 212 diabetic patients ten to fifteen years after surgery. *JAMA* 256:2967–2971, 1986
27. Wilson CS, Gau GT, Fulton RE, Davis GD: Coronary artery disease in diabetic and non-diabetic patients: a clinical and angiographic comparison. *Clin Cardiol* 6:440–446, 1983
28. Ahmed SS, Jaferi GA, Narang RM, Regan TJ: Preclinical abnormality of left ventricular function in diabetes mellitus. *Am Heart J* 89:153–158, 1975
29. Mehta S, Nuamah I, Kalhan S: Altered di-

astolic function in asymptomatic infants of mothers with gestational diabetes. *Diabetes* 40 (Suppl. 2) 56–60, 1991
30. dei Cas L, Zuliani U, Manca C, Zonca A, Bernardini B, Mansour M, Barilli AL: Non-invasive evaluation of left ventricular performance in 294 diabetic patients without clinical heart disease. *Acta Diabetol Lat* 17:145–152, 1980
31. Rubler S, Sajadi RM, Araoye MA, Holford FD: Non-invasive estimation of myocardial performance in patients with diabetes: effect of alcohol administration. *Diabetes* 27:127–134, 1978
32. Shapiro LM: Echocardiographic features of impaired ventricular function in diabetes mellitus. *Br Heart J* 47:439–446, 1982
33. Kahn JK, Zola B, Jani JE, Vinik AI: Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 7:1303–1309, 1986
34. Rowland TW, Martha PM Jr, Reiter EO, Cunningham LN: The influence of diabetes mellitus on cardiovascular function in children and adolescents. *Int J Sports Med* 13:431–435, 1992
35. Mathew P, John L, Jose J, Krishmaswami S: Assessment of left ventricular diastolic function in young diabetics: a two-dimensional echo Doppler study. *Indian Heart J* 44:29–32, 1992
36. Erbas T, Erbas B, Gedik O, Biberolgu S, Bekdik CF: Scintigraphic evaluation of left ventricular function in correlation with autonomic cardiac neuropathy in diabetic patients. *Cardiology* 81:14–24, 1992
37. Borrow KM, Jaspan JB, Williams KA, Neumann A, Wolinski-Walley P, Lang RM: Myocardial mechanics in young adult patients with diabetes mellitus: effects of altered load, ionotropic state and dynamic exercise. *J Am Coll Cardiol* 15: 1508–1517, 1990
38. Perez JE, McGill JB, Santiago JV, Schectman KB, Waggoner AD, Miller JG, Sobel BE: Abnormal myocardial acoustic properties in diabetic patients and their correlation with the severity of the disease. *J Am Coll Cardiol* 19:1154–1162, 1992
39. Dash H, Johnson RA, Dinsmore RE, Francis CK, Harthorne JW: Cardiomyopathic syndrome due to coronary heart disease: increased prevalence in patients with diabetes mellitus: a matched pair analysis. *Br Heart J* 39:740–747, 1977
40. Blumenthal HT, Alex M, Goldenberg S: Study of lesions of the intramural coronary artery branches in diabetes mellitus. *Arch Pathol* 70:13–28, 1960
41. Factor SM, Okun EM, Minase T: Capillary microaneurysms in the human diabetic heart. *N Engl J Med* 302:384–388, 1980
42. Fischer VW, Barner HB, Larose LS: Pathomorphologic aspects of muscular tissue in diabetes mellitus. *Hum Pathol* 15:1127–1136, 1984
43. Sunni S, Bishop SP, Kent SP, Greer JC: Diabetic cardiomyopathy. *Arch Pathol Lab Med* 110:375–381, 1988
44. Shirey EK, Proudfit WL, Hawk WA: Primary myocardial disease: correlation with clinical findings, angiographic and biopsy diagnosis: follow-up of 139 patients. *Am Heart J* 62:251–254, 1980
45. Genda A, Mizuno S, Nunoda S, Nakayama A, Igarashi Y, Sugihara N, Namura M, Takeda R, Bunko H, Hisada K: Clinical studies on diabetic myocardial disease using exercise testing with myocardial scintigraphy and endomyocardial biopsy. *Clin Cardiol* 9:375–382, 1986
46. Yarom R, Zirkin H, Stammler G, Rose AG: Human coronary microvessels in diabetes and ischemia: morphometric study of autopsy material. *J Pathol* 166:265–270, 1992
47. Cho S, Fein FS, Factor SM, van Hoeven KH: Microangiopathy and focal myocardial injury: their role in the development of diabetic cardiomyopathy. In *The Diabetic Heart*. Nagano M, Dhalla NS, Eds. New York, Raven, 1991, p. 89–101
48. Ganguly PK, Pierce GN, Dhalla KS, Dhalla NS: Defective sarcoplasmic reticular calcium transport in diabetic cardiomyopathy. *Am J Physiol* 244:E528–E535, 1983
49. Afzal N, Garguly PK, Dhalla KS, Pierce GN, Singall PK, Dhalla NS: Beneficial effects of Verapamil in diabetic cardiomyopathy. *Diabetes* 37:936–942, 1988
50. Giacomelli F, Weiner J: Primary myocardial disease in the diabetic mouse: an ultrastructural study. *Lab Invest* 40:460–473, 1979
51. Rodrigues B, McNeill JH: The diabetic heart: metabolic causes for the development of a cardiomyopathy. *Cardiovasc Res* 26:913–922, 1992
52. Factor SM, Minase T, Sonnenblick EH: Clinical and morphological features of human hypertensive diabetic cardiomyopathy. *Am Heart J* 99:446–458, 1980
53. Tahiliani AG, Vadlamudirv SV, McNeill JH: Prevention and reversal of altered myocardial function in diabetic rats by insulin treatment. *Can J Physiol Pharmacol* 61:516–523, 1983
54. Fein FS, Miller-Green B, Dola B, Sonnenblick EH: Reversibility of diabetic cardiomyopathy in rabbits. *Am J Physiol* 250: H108–H113, 1986
55. Bell DSH: Hypertension in the person with diabetes. *Am J Med Sci* 297:228–232, 1989
56. Pollare T, Lithell M, Selinas T, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 321:868–873, 1989
57. Warram JH, Laffel LMB, Valsania P, Christlieb AR, Krolewski AS: Excess mortality associated with diuretic therapy in diabetes mellitus. *Arch Intern Med* 151: 1350–1356, 1991
58. Pollare T, Lithell H, Selinas I, Berne C: Sensitivity to insulin during treatment with atenolol and metoprolol: a randomized double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *Br Med J* 297:1152–1157, 1989
59. Dornhorst A, Powell SH, Pensky J: Aggravation by propranolol of hyperglycemic effect of hydrochlorothiazide in type II diabetics without alteration of insulin secretion. *Lancet* i:123–126, 1985
60. Popp DA, Tse TF, Shah SP, Clutter WE, Cryer PE: Oral propranolol and metoprolol: both impair glucose recovery from insulin-induced hypoglycemia in insulin-dependent diabetes mellitus. *Diabetes Care* 7:243–247, 1984
61. McMurry RJ: Propranolol, hypoglycemia and hypertensive crisis. *Ann Intern Med* 80:669–670, 1974
62. Roberts DH, Tsa OU, McLoughlin GA, Breckenridge A: Placebo-controlled comparison of captopril, atenolol, labetolol and pindolol in hypertension compli-

cated by intermittent claudication. *Lancet* ii:650–653, 1987
63. Goldman AI, Steel BW, Schnaper HW, Fitz AE, Frohlich E, Perry HM: Serum lipoprotein levels during antihypertensive therapy. *JAMA* 224:1691–1695, 1980
64. Weinberger MH: Antihypertensive therapy and lipids: incidence, mechanisms, and implications. *Arch Intern Med* 145: 1103–1105, 1985
65. Kaplan NN, Rosenstock J, Raskin P: A differing view of the treatment of hypertension in patients with diabetes mellitus. *Arch Intern Med* 147:1160–1162, 1987
66. Pollare T, Lithell H, Selinas I, Bearne C: Application of prazosin is associated with an increase of insulin sensitivity in obese patients with hypertension. *Diabetologia* 31:415–420, 1988
67. Pollare T, Lithell H, Morlin C, Pranture H, Hvarfner A, Ljunghall S: Metabolic effects of diltiazem and atenolol: results from a randomized double-blind study with parallel groups. *J Hypertens* 7:551–559, 1989
68. Ajorck S, Gundrun N, Mulec H, Granerus G, Herlitz H, Aurn M: Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *Br Med J* 293:471–476, 1986
69. Zutz R, Dunn BR, Meyer TW, Anderson S, Renneker H, Brenner BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
70. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993
71. Berne C, Pollare T, Lithell H: Effects of antihypertensive treatment on insulin sensitivity with special reference to ACE inhibitors. *Diabetes Care* 14 (Suppl. 4): 39–47, 1991
72. The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325: 293–302, 1991
73. Frohlich ED, Sasaki O: Dissociation of changes in cardiovascular mass and performance with angiotensin-converting enzyme inhibitors in Wistar-Kyuro and spontaneously hypertensive rats. *J Am Coll Cardiol* 16:1492–1497, 1990
74. Messerli FH, Soria F: Hypertension, left ventricular hypertrophy, ventricular ectopy and sudden death. *Am J Med* 93(2A): 21S–26S, 1992
75. ACE inhibitors and tissue binding (Editorial). *Lancet* i:718–720, 1990
76. Margolis JR, Kannel WB, Feinleib M, Dawber TR, McNamara PM: Clinical features of unrecognized myocardial infarction: silent and symptomatic. *Am J Cardiol* 32:1–7, 1973
77. Chiariello M, Indolfi C, Cotecchia MR, Sifola C, Romano M, Condorelli M: Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. *Am Heart J* 110:529–534, 1985
78. Airaksinen KEJ, Koistinen MJ: Association between silent coronary artery disease, diabetes, and autonomic neuropathy. *Diabetes Care* 15:288–292, 1992
79. Ewing DJ, Martyn CN, Young RJ, Clarke BF: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 8:491–498, 1985