HEART MUSCLE DISEASES — THE CARDIOMYOPATHIES
II. MYOCARDIUM IN DIABETES

By

S. SULTAN AHMED, M.D., FRCP(C)., FACP., FACC*

and

TIMOTHY J. REGAN, M.D., FACC**

From the earlier article it is obvious that many diseases affect the heart muscle either primarily or secondary to systemic disease (1). Among them some have attracted much attention in the past decade, these include idiopathic hypertrophic obstructive, diabetic, alcoholic and carbon monoxide cardiomyopathies. The latter three appear to require still moe emphasis for the medical community to take heed of. Being involved in the experimental and the initial clinical observations of these entities I will like to review them briefly.

Myocardium in Diabetes Mellitus

A relatively high incidence of cardiac disease appears to be an important cause of mortality in diabetes mellitus (2). Although accelerated atherosclerosis of the coronary arteries has previously been considered the major pathogenetic factor, more recent post mortem studies have questioned the significance of coronary artery disease as accounting for premature death in adult onset diabetes (3). Two separate studies found no greater degree of obstructive disease of the coronary arteries in diabetics compared to normal control subjects (4,5). This is supported by an epidemologic study suggesting that cardiac abnormalities in diabetics frequently occur without the usual risk factors associated with coronary atherosclerosis (6). Our own studies indicate that patients with cardiac symptomatology who are diabetic may have considerable malfunction of the ventricle as well as abnormal morphology and composition in the absence of significant large vessel occlusive disease (7,8). A recent report in the British Medical Journal has added support to the view that some patients with diabetes mellitus have myocardial alterations that may result in heart failure as the process develops fully (9). Obliterative disease of the small coronary arteries has been thought to be important in the pathogenesis of cardiac disease in diabetes in the form of thickened intramural arteries, with occasional bridging of endothelial cells (10). However, such lesions were

*Professor of Medicine and Director, Stress Testing Laboratory

**Professor of Medicine and Director, Division of Cardiovascular Diseases.

From the Department of Medicine, CMDNJ - New Jersey Medical School Newark, New Jersey 07103, U.S.A.

also observed in non-diabetics without evident effects on cardiac muscle (11). The failure to find demonstrable obstructive lesions of intramural vessels in the free wall of the left ventricle in prior studies of diabetics (4,7,8,12), suggests that small vessel lesions in diabetics may have little or no relation to the cardiac pathology.

Lactate production or a decrease in lactate extraction as well as ischemic ECG changes are regular, although non-uniform, features of the myocardial response to pacing in patients with classic angina associated with coronary artery disease (13). Neither of these responses were observed in the diabetic group without significant coronary occlusive disease (8). This is compatible with the response to the majority of non-diabetic patients who have anginal type pain without arterial disease (14). Thus, if abnormalities of the samll arteries or capillaries are present in diabetics with altered ventricular function, these are apparently insufficient to restrict myocardial perfusion (8).

For above mentioned reasons we have proposed that a portion of the cardiac diabetic population may have primary myocardial abnormalities analagous to the alteration of renal and retinal paranchyma (7,8,15-19). Following clinical observations and studies appear supportive.

Preclinical:

To test the hypothesis that a portion of the cardiac diabetic population may have asymptomatic myocardial abnormalities the status of the left ventricle was examined in 25 diabetic non-cardiac patients who ranged in age from 20 to 56 years. There were 15 males and 10 females (20). In none was there evidence of systemic disease that might potentially affect the heart. Subjects selected were either ambulatory, clinic patients or at least one week post recovery from an episode of ketoacidosis requiring hospitalization. None had cardiorespiratory symptoms at any time, nor any clinical, electrocardiographic, or x-ray evidence of cardiac abnormality. None exceeded ideal body weight by more than 15%; none had blood pressure over 140/90 mmHg, and there was no clinical evidence of renal, retinal, or neurologic complications. After careful interview, none were found to have a history of chronic alcoholism or heavy ciagrette smoking (more than one pack/day).

The diabetes was known to have been present in the subjects from 1-25 years. Seven were now diabetic patients and were not receiving hypoglycemic agents; eight received oral hypoglycemic agents and ten received insulin. While none had subjective symptoms suggestive of angina, those over 40 years of age had a stress test and were found to have normal, non-ischemic responses, with ST depressions not approaching 1 mm. Morning fasting blood glucose levels were between 126 and 240 mg/100 cc. Serum electrolytes, total protein, albumin and blood urea levels were within normal limits in each patient. Control subjects were 21 males and 16 females between 23 and 46 years of age with no history of diabetes in them or in their families.

To preclude the necessity for left ventricular catheterization in this group of normal volunteers and non-cardiac diabetic patients, the systolic time intervals were measured at least two hours after breakfast using the method and instrumentation described by Weissler and his associates (21). This non-invasive measurement is reported to provide information concerning

the contractile state of the left ventricle (22). The diabetic subjects had a shorter left ventricular ejection time, longer pre-ejection period, and a high ratio of pre-ejection period to left ventricular ejection time. The isovolumic time was also prolonged significantly in these subjects, while heart rate and arterial blood pressure were within normal limits. Abnormal function in these diabetics was independent of apparent duration and treatment by diet alone, insulin, or hypoglycemic agents.

In a more recent study of non-cardiac middle aged males, fractional shortening of the left ventricle was significantly reduced (9,23). An additional report supports the hypothesis that some patients with diabetes mellitus have preclinical myocardial alteration that may result in heart failure if the process develops fully (9). The study is of particular interest as 14 of 23 normotensive diabetics under 40 years of age without any clinical evidence of heart disease were shown to have echocardiographic abnormality during left ventricular diastole, an alteration which has been previously observed in patients with cardiomyopathy. These findings were interpreted to represent a diffuse myopathic process.

Clincial:

To further define the roles of factors like myocardial contractility and altered preload by direct invasive studies, the status of the left ventricle was examined in 17 chronic, uncomplicated, adult diabetics without hypertension or obesity but with a familial history. These were compared with nine controls of similar age (8).

Of the 17, 12 subjects had no significant occlusive lesions by coronary angiography. Eight with anginal type pain but without heart failure had a modest, but significant, elevation of left ventricular end-diastolic pressure. End-diastolic and stroke volumes were reduced, but ejection fraction and mean rate of fiber shortening were within normal limits. The left ventricular end-diastolic pressure/volume ratio was significantly higher than in the controls. Afterload increments evoked a significant increase of filling pressure compared to the normal without stroke volume response—a finding consistent with early cardiomyopathy. Those with prior heart failure had more extensive hemodynamic abnormalities. None had local dyskinesia by angiography and lactate production was not observed during pacing-induced tachycardia. Left ventricular biopsy in two patients without ventricular decompensation showed interestitial collagen deposition with relatively normal muscle cells. These findings suggested a myopathic process without ischemia.

Post mortem studies performed to evaluate more advanced state of diabetes indicated no significant obstructive disease of the proximal coronary arteries. The heart weight ranged from 300 to 500 grams. Gross scars measuring 1 cm^2 were visible in the free wall of the left ventricle of a few patients. Neither mural thrombi or systemic emboli were found. There was no evidence of inflammatory cell infiltrations, but accumulation of PAS-positive (for glycoprotein) material was present to a variable but enhanced extent in the left ventricular muscle of all diabetics. Those who succumbed in heart failure appeared to have more collagen by trichrome stain arranged about the intramural vessels, interspersed between myofibers and/or as replacement fibrosis (8,18). No structural changes were observed in micro-circulation on myocardial

biopsies in 12 diabetics with cardiac symptoms (18, 24).

Experimental:

Further evidence of such a myopathic process is provided by experimental studies (25-28). Ventricular function and compliance were observed to be abnormal associated with interstitial accumulation of PAS-positive glycoprotein and collagen in the myocardium of mongrel and monkeys with chronic experimental diabetes. A mild, stable form of diabetes was produced after three intravenous doses of alloxan at monthly intervals. Myocardial performance was studied 12-18 months after the onset of glucose intolerance and was compared with the performance of normal animals. Although the baseline hemodynamic values in these diabetic dogs and monkeys were not significantly different from those of the control animals, the ventricular function became abnormal when stresses in perload and afterload were applied. An increae in the afterload with moderate aortic pressure elevation elicited a significant rise in end-diastolic and stroke volumes in the normal controls. In diabetics despite a similar end-diastolic pressure response, the end-diastolic volume and the stroke volume responses were significantly less than those in the controls. During acute volume expansion of the ventricle with saline, the end-diastolic tension increment in diabetic animals was twice that of the controls. These responses were attributed to an increase in stiffness of the left ventricle, not associated with hypertrophy but which was apparently due to accumulation of glycoprotein observed in the myocardial interstitium (25) and also by the findings of increased amounts of of insoluble collagen (26). The former is reported to further limit the diastolic filling when experimental ischemia is produced in diabetic myocardium (27). Myocardial ischemia was excluded in experimental diabetes on the basis of patency of coronary arteries and normal coronary blood flow, myocardial CAT—ion content and myocardial morphology (25,26).

Conclusions:

On the basis of available morphologic data in human and experimental diabetic animals, it is concluded that chronic diabetes mellitus can alter myocardial composition and function independent .of vascular defects. The relative prominence of glycoprotein in the myocardial interstitium of both human and experimental animals suggests a basis for the diminished diastolic compliance in the diabetic heart. These myocardial abnormalities also appear to be the basis for the preclinical abnormality. It occurs in both sexes and is independent of age. The abnormal function is also independent of apparent duration and treatment by diet, insulin or hypoglycemic agents. The latter interestingly had been reported, despite improved glucose tolerance, to affect further reduction of left ventricular function and altered myocardial morphology at least in experimental canine diabetes (38). Whether the observed functional abnormality progresses to clinical heart failure may depend on intensification of the underlying pathophysiology of the myocardium or superimposition of complications such as hypertension, obesity and obstructive disease of the coronary vessels.

Though strict caloric restriction and moderate exercise program usually result in improved glucose tolerance, no control studies are available to indicate that this preventive intervention reduces

the incidence of cardiomyopathy. Cigarette use by general agreement should be interrelated. Treatment of hypertension and hyperlipidemia are as important as in the non-diabetic population. It remains an open question whether an individual with mild hyperglycemia may benefit from low dose insulin to strictly control blood glucose levels.

Acknowledgement:

We appreciate the technical assistance provided by many of our colleagues, cardiac fellows, RNs and technicians in the cardiac cath room and support laboratories. We thank Mrs. Charlotte Blocker for typing the manuscript.

References:

1. Ahmed S.S. Heart muscle diseases. Cardiomyopathies. I Introduction, Pakistan Heart Journal 13:30, 1980.
2. Goetz F.C. Prognosis in diabetes mellitus, in. Diabetes Mellitus: Diagngosis and Treatment. Hamiwi G.J., and Danowski T.J., editors. New York, 1967, American Diabetes Association, Inc., vol. 2, pp. 177-183.
3. Kessler I.I. Mortality experience of diabetic patients, Am. J. Med. 51:715, 1971.
4. Vihert A, Zhdanov V.S., Matova E.E. Atherosclerosis of the aorta and coronary vessels of the heart in cases of various diseases. Atherosclerosis Res 9:279, 1969.
5. Ledet T. Histological and histochemical changes in the coronary arteries of old diabetic patients. Diabetologia 4:268, 1968.
6. Kannel W.B., McGee D.L. Diabetes and cardiovascular disease. The Framingham Study. J. Am. Med. Assoc. 241:2035-2038, 1979.
7. Regan T.J., Ahmed S.S., Levinson E.G., Oldewurtel H.A., Ahmad M.R., Haider B., Lyons M.M. Cardiomyopathy and regional scar in diabetes mellitus. Transactions of the Association of American Physicians 88:217-223, 1975.
8. Regan T.J., Lyons M.M., Ahmed S.S., Levinson G.E., Oldewrutel H.A., Ahmad M.R., Haider B. Evidence for cardiomyopathy in familial diabetes mellitus. J. Clin Invest 60:885-899, 1977.
9. Sanderson J.E., Brown D.J., Rivellese A., Kohner E. Diabetic cardiomyopathy? An echocardiographic study of young diabetics. Br. Med. J. 1:404-407, 1978.
10. Blumenthal H.A., Goldenberg A., Goldenberg S. A study of lesions of the intramural coronary artery branches in diabetes mellitus. Arch Pathol 70:13-28, 1960.
11. Rubler S., Dlugash J., Yuceoglu Y.Z., Kumral T., Branwood A.W., Grishman A. A new type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J. Cardiol 30:595-601, 1972.
12. Roberts W.C. Coronary arteries in fatal acute myocardial infarction. Circulation 45:215-230, 1972.
13. Parker J.O., Chinog M.A., West R.O., Case R.B. Sequential alterations in myocardial lactate metabolism, S-T segments, and left ventricular function during angina induced by atrial pacing. Circulation 40: 113:-131, 1969.
14. Kemp H.G. Jr., Vokonas P.S., Cohn P.F., Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Am. J. Med. 54:735-742, 1973.

15. Ahmed S.S., Regan T.J. Diabetes mellitus and left ventricular function. Comp Therapy 2(11) 51-57, 1976.

16. Regan T.J., Ahmed, S.S., Haider B., Myons M.M. The myocardium and its vasculature in diabetes mellitus. Modern Concepts of Cardiovascular Disease 47:71-78, 1978.

17. Regan T.J., Weisse A.B. The question of cardiomyopathy in diabetes mellitus. Annals of International Medicine 89:1000-1002, 1978, (Editorial).

18. Regan T.J., Ahmed S.S. The heart in diabetes mellitus. Comp Therapy 5:36-42, 1979.

19. Regan T.J., Ahmed S.S. Diabetic cardiomyopathy. Cardiovascular Medicine (in press).

20. Ahmed S,S., Jaferi G.A., Narang R., Regan T.J. Preclinical abnormality of left ventricular function in diabetes mellitus. Am. Heart J. 89:153-158, 1975.

21. Weissler A., Harris W.S., Schoenfeld C.D. Bedside techniques for the evaluation of ventricular function in man. Am. J. Cardiol 23:577, 1969.

22. Ahmed S.S., Levinson F.E., Schwartz C.J., Ettinger P.O. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. Circulation 46:559, 1972.

23. Abenavoli T., Rubler S., Fisher V.J., Axelrod H.I., Zuckerman K.P. Exercise testing with myocardial scintigraphy in asymptomatic diabetic males. Circulation 63:54-63, 1981.

24. Shirley E.K., Proudfit W.L., Hawk W.A. Primary myocardial disease. Correlation with clinical findings, angiographic and biopsy diagnosis. Follow-up of 139 patients. Am. Heart J. 99:198-207, 1980.

25. Regan T.J., Ettinger P.O., Khan M.I., Jesrani M.U., Lyons M.M., Oldewurtel H.A., Weber M. Altered myocardial function function and metabolism in chronic diabetes mellitus without ischemia in dogs. Circulation Research 35:222-237, 1974.

26. Haider B., Yeh C.K., Thomas G., Oldewurtel H.A., Lyons M.M., Regan T.J. Altered myocardial function and collagen in diabetic rheusus monkeys on atherogenic diet. Transactions of the Association of American Physicians. 91:197-203, 1978.

27. Haider B., Ahmed S.S., Moschos C.B., Oldewurtel H.A., Regan T.J. Myocardial function and coronary blood flow response to acute ischemia in chronic canine diabetes. Circulation Research 40:577-583, 1977.

28. Wu, C.F., Haider B., Ahmed S.S., Oldewurtel H.A., Lyons M.M., Regan T.J. The effects of tolbutamide on the myocarddium in experimental diabetes. Circulation 55:200-205, 1977.

———:o:———