Left Ventricular Function in Diabetes Mellitus

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Since the original description by Rubler et al [1] based on their study from four adult diabetic subjects with non-coronary congestive cardiac failure (CCF) and subsequent observations by the Framingham workers [2] about the most frequent occurrence of CCF among the diabetics than could be explained by hypertension or ischaemic heart disease alone, interest was renewed in the field of cardiac involvement in long-standing diabetic patients. Pathological evidence among the nine diabetic subjects without significant coronary atherosclerosis on post-mortem examination by Regan et al [3] about the presence of Periodic Acid Schiff (PAS) positive material, presumably a glycoprotein in the interstitium of the myocardium, lent further support to the existence of a specific type of heart muscle disease among diabetics.

Impaired left ventricular (LV) function may frequently be detected in asymptomatic diabetic subjects [4J and is related to the extent of diabetes and evidence of microvascular complications. Although systolic and diastolic functions of the heart are impaired in diabetes, many studies have shown that the LV diastolic abnormalities are most common and may infact precede the development,of systolic abnormality [5, 7].

Evaluation of LV function in Diabetic Subjects

Two chief methods of evaluating the LV function utilise the non-invasive technique.

Non-invasive methods include the assessment by

a) Systolic time intervals (STI)
b) Apexcardiography (ACG)
c) Radionucleotide ventriculography
d) Echocardiography and cardiac Doppler

Invasive method is by cardiac catheterisation delineating the coronary artery anatomy and LV angiography. This procedure is usually reserved for symptomatic diabetic subjects with overt or those who manifest CCF and is unnecessary in asymptomatic although long-standing diabetics.

Systolic time intervals (STI's)

Using the technique introduced by Weisler et al [8] in the late 1960's, the STI's can be measured by simultaneous recording of carotid pulse, ECG and phonocardiogram at 100 mm/sec. The three indices viz., the pre-ejection period (PEP), left ventricular ejection time (LVET) and the PEP/LVET ratio are calculated. Most observers have found a significant increase in PEP and shortening of LVET with a resultant reduction in the PEP/LVET ratio among the diabetics [6, 9, 10]. The above parameters which indicate a reduced LV function were correlated to diabetic control, long duration and the presence of microvascular complications like proliferative retinopathy or/and albuminuria. Some workers found a reversibility of these abnormal STI parameters with improvement in the control of diabetes with diet and oral hypoglycaemic agents (OHA) in less than a year in most of the patients [6, 12]. Our own study of STI's in 29 uncontrolled IDDM subjects with a mean age of 20.9 years of varying duration of diabetes showed prolongation of PEP and increase in ratio of PEP/LVET in 24 patients [13]. Besides, the resting heart rate was increased while the LVET and QS_2 interval (Total electromechanical systole) were not altered.

The above observations in the STI's suggest that a definite reduction in the LV systolic function does occur in diabetic subjects. The prolongation of PEP/LVET ratio itself reflects a poor LV contractility and possibly a decreased LV filling consequent to lower LV compliance. These abnormalities are more pronounced in those with long-term complications and may be demonstrably reversed by tight control of diabetes.

Apexcardiographic observations

Apexcardiogram (ACG) which is a displacement record of the movement of the precordium approximately representing the pulsation of the left ventricle has been utilised in knowing the LV systolic as well as diastolic function in diabetic subjects [10]. The 'a' wave of the ACG is abnormally tall, a sign of decreased LV compliance. The method, however, has its own flaws and is not in much use now.

Radionucleotide ventriculography

Most studies using this technique have shown normal LV ejection function (LVEF) among the diabetic patients but a lower EF in response to dynamic exercise compared to non-diabetics [14, 15]. LV diastolic function was abnormal reflecting the reduced ventricular filling in most diabetic patients especially those with autonomic neuropathy [16]. A good correlation has been found between the altered LV function and the long-term diabetic complications utilising the radionucleotide ventriculography [17].

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Echocardiographic evaluation of LV function

Systolic as well as diastolic abnormalities of LV function, more importantly diastolic, have been shown to occur very clearly by using this technique in asymptomatic diabetics [18]. While earlier studies evaluated these LV function abnormalities by M-mode echocardiography, more recent studies have utilised M-mode, 2-D and Doppler techniques in their assessment. Currently, the Doppler echocardiography remains a very useful, sensitive and a reproducible method of evaluating the cardiac function in diabetics with or without symptomatic heart failure.

Detection of LV Systolic dysfunction

Utilising the computer analysis of M-mode and 2-D echocardiography, one can demonstrate the systolic abnormalities by measuring the three indices, viz. LVEF (abnormal, if less than 50%), percentage fractional shortening (%FS, abnormal if less than 36%) and the mitral E-point septal separation (EPSS more than 7 mm) [19]. One study investigated two groups of IDDM subjects, one younger group and another older age group - with echocardiography and radionucleotide ventriculography and found significant systolic abnormalities only in the older age group who had a longer duration of diabetes [18]. All of them had normal coronary angiography. The response to dynamic exercise is decreased while the resting systolic function is normal [20, 21]. The digitised M-mode echocardiography in these diabetics showed a smaller LV diastolic dimension compared to the controls but did not change during exercise in either group. LV end-systolic dimensions decreased in both groups. Fractional shortening, however, increased in quite a few patients surprisingly but it was lower in the diabetic group during peak exercise and remained low even when the adjustment for systolic blood pressure was made [21]. Likewise, another study [22] also demonstrated an increase in the FS in diabetic patients without evidence of cardiac disease or microvascular complications compared with controls. These workers thought that this increase in FS is due to the increase in LV wall thickness and mass compared to healthy controls.

Therefore, conflicting observations regarding the LV systolic abnormalities exist. The net inference is that the decreased LV performance during exercise in diabetic subjects is likely to be due to reduced LV filling which appears to be the basic abnormality. However, an echocardiographic study of LV performance after myocardial infarction showed a greater impairment of LVEF and %FS in diabetics than non-diabetics which could be due to larger size of the infarct and more extensive coronary atheroma among diabetics compared to non-diabetics [23, 24].

LV Diastolic function

It is now clear from the various studies that the primary functional abnormality in a diabetic heart is the impairment of LV diastolic function reflecting the reduced LV filling and that even the systolic functional alteration is the result of reduced LV filling. These abnormalities in diastolic function can be detected by echocardiographic technique in a significant number of diabetics with longer duration of both Type 1 and 2 diabetes with or without overt cardiac disease or other microvascular complications.

M-mode and 2-D Echocardiography

Aerakisnen et al utilising the digitalised M-mode technique studied 36 female IDDM patients with a mean duration of diabetes of 10 years or more and found that the most common abnormality (19 pts) was prolonged rapid filling period while the systolic function was normal in all. Another study [4] recorded simultaneous echo and phonocardiograms in 142 diabetics. The LV relaxation, the rate and duration of cavity dimension increase and wall thinning were determined. Delayed mitral valve opening (MVO) relative to minimal LV cavity dimension and aortic valve closure (AVC) was found in all but 12 subjects, especially in those with microvascular complications. Prolongation of isovolumic relaxation time (IVRT) i.e. measured as period between AVC and MVO (abnormal, if more than 110 m sec), which can be demonstrated using dual M-mode echo preferably at 100 min/sec speed showing simultaneous aortic and mitral valve levels, is an important diastolic abnormality, as found by Sanderson et al [5, 25]. Others using quantitative cross-sectional echocardiography and stress myocardial perfusion scintigraphy found that diabetic subjects had mildly reduced LV end diastolic volumes and impaired diastolic filling as assessed by lower left atrial emptying index compared to controls [26]. The left atrial emptying index is defined on M-mode tracing of the aorta [19].

Doppler techniques

Pulsed Doppler ultrasound interrogation of mitral inflow velocities (Doppler cursor placed at the tips of the mitral leaflets on apical 4-chamber view) gives a simple and reproducible method of determining the LV filling that correlates well with radionucleotide and invasive techniques [27, 28]. Ventricular filling in the normal subjects is characterised by a biphasic pattern with an initial peak velocity of rapid early ven-

tricular filling ('E') and a relatively low peak velocity of late inflow due to atrial contraction (A). Impaired diastolic filling of the left ventricle in both Type 1 and Type 2 asymptomatic diabetics without the evidence of cardiovascular disease and unrelated to microangiopathic complications has been demonstrated using PW Doppler which showed reduction in the early filling velocity (reduced 'E' peak) and compensatory increase in the late flow (increased 'A' peak) and thus increased A/E ratio (i.e. A/E more than 1). Besides, the deceleration of 'E' velocity is prolonged indicating a slow rapid-filling phase ('E' deceleration more than 250 m/sec). Increased atrial contribution to LV filling can be assessed by the area under the late diastolic filling envelope compared to the total diastolic area. Various studies have demonstrated these above Doppler findings in young diabetic subjects without evidence of heart failure [29, 30J. In our own study [31] of 30 NIDDM patients without any clinical or electrocardiographic evidence of cardiovascular disease, abnormalities of LV diastolic function such as reduced 'E' velocity and increased 'A' velocity and increased A/E ratio were seen in as many as 17 subjects. The 'E' deceleration time, however, was prolonged significantly only in 3 subjects.

Whether the subclinical diastolic abnormalities found in diabetics progress to clinically evident heart disease is not clear. A 3-year follow-up study by Charella et al [32] of a group of asymptomatic diabetics with slow filling and wall thinning demonstrable on echocardiography showed 31% developing heart failure and 19% that died. Measurement of LV diastolic function may therefore prove to be a useful indicator of cardiovascular morbidity and mortality in diabetics. Hence, abnormal diastolic function suggestive of reduced LV compliance resulting in a 'Stiff' myocardium appears to be the hall mark of the specific type of diabetic heart muscle disease. The presence or addition of hypertension or coronary artery disease will certainly put a new burden on the already 'non-compliant' myocardium in long-standing diabetics with or without microvascular complications.

Cardiac Catheterisation in the Diabetics

This procedure is usually reserved for the patients with manifestation of clinical heart failure and the main purpose is to confirm or exclude significant occlusive coronary artery disease. Hamby et al [33] in their study of 16 diabetic patients with clinical cardiomyopathy found elevated LV end-diastolic pressure (LVEDP) whereas arterial blood pressure and systemic vascular resistance were normal. Resting cardiac index was low in less than half of the patients and the EF was reduced in most. Coronary angiography revealed normal or minimally obstructed vessels. LV mass also appeared to be uniformly increased in the absence of hypertension. Increase in LVEDP with almost normal LVEDV suggestive of myocardial wall stiffness was thus evident in other studies also [3]. Endomyocardial biopsy done in IDDM subjects with early cardiomyopathic features and normal coronary arteriograms demonstrated arteriolar thickening, interstitial fibrosis and basement membrane thickening [34].

Aetiopathogenesis of LV dysfunction in Diabetes

Although the relationship between the hyperglycaemic state and the abnormalities in myocardial function and metabolism is not totally clear at present, at least one haemodynamic study in juvenile diabetics in whom the stroke volume was diminished while cardiac output remained unchanged, showed reversal of haemodynamic alterations after one year of treatment with diet and insulin [35]. Several factors might contribute to the abnormalities of LV function in diabetics apart from systemic hypertension and atherosclerotic coronary artery disease. Increased levels of growth hormone, increased cardiac sorbitol levels, impairment of Ca^{++} handling and increased 1,2 dihydroglycerol levels with resultant activation of protein kinase - are among the advanced reasons to explain the LV dysfunction in diabetics [36]. Histopathological and histochemical changes in normotensive diabetic patients dying of heart failure with almost normal coronary arteries showed PAS positive staining material in the interstitium, interstitial fibrosis, collagen accumulation in the perivascular loci and increased deposits of triglycerides and cholesterol in the LV musculature [37].

Summary and Conclusions

Abnormalities of LV function occur in long-standing diabetics both Type 1 and Type 2 with or without microvascular complications. LV filling abnormalities (diastolic dysfunction) occur earlier and more commonly than the contractile (systolic) dysfunction in diabetics independent of hypertension or ischaemic heart disease which certainly add a new burden to the existing abnormality.

Echocardiography - M-mode. 2-D and Doppler, remain the most useful, reproducible and sensitive techniques to detect the LV dysfunction and wall motion abnormalities apart from LV mass in these patients.

Hypertension, occlusive epicardial coronary artery disease, the intramural arteriolar disease and myocardial interstitial fibrosis are among the disease processes that are responsible for LV dysfunction.

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