Endomyocardial Biopsy in Diabetic Cardiomyopathy Procedure, Clinico - Pathological & Structural Functional Correlation

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Endomyocardial Biopsy

The difficulty in getting the myocardial tissue for histopathological examination is apparent. The literature on Endomyocardial Biopsy (EMB) in diabetics is few and far between. However small the tissue may be, biopsy and morphological features have been considered as the final court of appeal.

This report describes our experience in performing EMB in diabetic patients.

The success rate in obtaining EMB specimens in the present series using King's bioptome was 100% whereas the success rate in other centres varied from 80-100%. However, Sakakbara and Konno [1] have achieved a success rate of 100% by using Konno's bioptome.

Side Effects

Barring vague retrosternal discomfort and transient arrhythmias, no other serious complication was encountered. The arrhythmias observed were ventricular premature contractions and supraventricular ectopic beats. Atrial fibrillation occurred in a single case and brief ventricular tachycardia in 4 cases. It is important to stress that all these cardiac arrhythmias occurred only during the procedure and were transient without warranting any therapeutic measures. None of the patients suffered from pericarditis or pericardial effusion or persistent myocardial injury following the biopsy procedure. The post-biopsy ECG was similar to the one taken before it.

Safety of EMB Procedure

This procedure was entirely safe as reported by Mackay et al [2] in their study. All attempts in the present series were made to obtain the specimen from interventricular septum, avoiding the chance of transmural biopsy of the right ventricular free wall. However, Kober et al [3] during their procedure encountered cardiac perforation, haemopericardium and cardiac tamponade in a few cases.

Nevertheless, our experience establishes EMB by King's bioptome as a safe procedure by paying special attention to (i) practising the minimal amount of force needed to open and close the jaw outside prior to putting the bioptome, (ii) making every effort to obtain the specimen from interventricular septum in order that the transmural biopsy of the ventricular free wall is avoided and (iii) a meticulous and close follow-up before, during and after the procedure by ECG and fluoroscopy.

Clinical Profile of EMB Cases

Diabetic heart disease can manifest with wide differences and variations. In order to facilitate a better understanding of the morphological changes, a wide spectrum of patients were included. The case selection was done in such a manner that in these few (16) cases, there was a representation of the entire spectrum of diabetic heart disease. It included patients with symptoms and signs of cardiac decompensation, asymptomatic diabetes mellitus of more than 3 years duration and cases of recent uncontrolled hyperglycaemia (Table 1).

Table 1
Clinical details of diabetics on whom endomyocardial biopsy was done

Group	Mean age (yrs) of DM (yrs)	Mean duration PEP/LVET abnormality	Left ventricular function	Microangiopathic complication
I. Symptomatic (6)	37 (20-49)	7.4	_	3/6
II. Asymptomatic with longer duration of DM (6)	31 (19-47)	6.2	4/6	2/6
III. Asymptomatic with shorter duration of DM (4)	29 (18-42)	0.7	0/4	0/4

Numbers in the parentheses indicate the no. of cases studied.

In group I, there were cases with clinical symptoms and signs of left ventricular failure and congestive cardiac failure or biventricular failure of obscure origin. Few of them had unexplained cardiomegaly and papillary muscle dysfunction. There was no clinical or electrocardiographic evidence of any coronary artery disease.

Group II included cases of DM of moderate severity of 3-5 years duration with preclinical but not overt cardiac decompensation. These can be taken as representative of being asymptomatic but with

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preclinical evidence of diabetic heart disease.

The third group included cases of uncontrolled recent onset hyperglycaemia of a very short duration. The patients in this group had neither overt nor preclinical incipient cardiac decornpensation (indicated by a normal PEP/LVET ratio). Further, none of these cases had any microangiopathic complication. Thus, this group provided the scope for studying the earliest morphological changes in the diabetic myocardium, if any.

The echocardiography was carried out in endomyocardial biopsy cases. Even though echo derived - left ventricular dimensions are criticised owing to the assumption that the left ventricle is ellipsoid, this study indicated that the derangement in left ventricular dysfunction was marked in symptomatic cases. Incipient left ventricular dysfunction could be made out in asymptomatic cases of longer duration.

Histopathological Changes

The histopathological examination of myocardial tissue obtained by EMB has revealed significant and interesting findings (Table 2). DM is a systemic metabolic disorder and the changes it produces are expected to be diffused and widespread. The morphological features observed in the biopsy/tissue may be taken as the representative of the entire myocardium.

The various changes observed can be broadly grouped under two broad headings namely (a) extravascular and (b) vascular.

Extravascular changes
These can be further subdivided into interstitial and myofibrillar changes.

Interstitial changes
The most consistent abnormality noted in the interstitial space of the biopsy specimens consisted of (a) interstitial fibrosis and (b) deposition of Periodic Acid Schiff (PAS) positive material. The interstitial fibrosis was of three types (i) perivascular. (ii) scattered or (iii) mixed.

There was also an increase in quantity of interstitial collagen tissue brought out by special stain like Van Gieson. Accumulation of PAS positive material in the interstitium of the myocardium was the most consistent finding. This implies deposition of glycoprotein material. The Mallory trichrome stain brought out the fibrous tissue in the interstitium.

The above changes were not noted in any of the control myocardial specimen obtained from the non-diabetic subject indicating that the above changes are characterised only in DM.

Ledet [4] had described three major types of fibrosis in diabetic myocardium. The present observation confirms his findings of perivascular and scattered

Table 2
Endomyocardial biopsy details of diabetic cases

Vascular changes	No. of cases			Extravascular changes	No. of cases		
	Symptomatic (6)	Asymptomatic long duration (6)	Asymptomatic short duration (4)		Symptomatic (6)	Asymptomatic long duration (6)	Asymptomatic short duration (4)
Arterial wall thickening	3/6	2/6	1/4	Myofibrillar hypertrophy	4/6	2/6	1/4
Intimal fibroblastic proliferation	3/6	2/6	1/4	Fatty degeneration	2/6	1/6	0/4
				Fibrosis: Periarteriolar	2/6	1/6	0/4
Basement membrane thickening	2/6	1/6	0/4	Scattered	4/6	4/6	2/4
Intimal hyaline deposition	2/6	0/6	0/4	PAS +ve material deposition	6/6	5/6	3/4
				Wavy myocardium	2/6	0/6	0/4

interstitial fibrosis.

Sohar et al [5] and Regan et al[6] had also demonstrated accumulation of PAS positive material in the interstitium of human diabetics. This glycoprotein deposition in the interstitium may be the cause for a reduction in the diastolic compliance in the diabetic heart.

Vascular changes

The changes observed in the intramural coronary arterioles and capillaries in DM were significant and interesting. The changes comprised of

1. Thickening of arteriolar wall and subendothelial fibroblastic proliferation.
2. Intimal thickening.
3. Deposition of PAS positive material staining the mucopolysaccharide material.
4. Subendothelial elastic proliferation.
5. Basement membrane thickening.
6. Formation of mounds and humps.

Zoneraich.et al [7] have studied the myocardial small vessel changes in diabetics. They had observed similar findings of intimal fibroblastic thickening, accompanied by elastic proliferation, humps and mounds and intimal hyalin deposits. However, Zoneraich et al [8] have observed small vessel involvement in 72% of the diabetics.

Their series comprised of autopsied series. The patients included, were cases with documented IHD and of a higher age group. Even so, their data cannot be compared to that of the present study.

Our observations further confirm the findings of Blumenthal et al [9] and Rubler et al [10]:

Comparison of Histopathological Changes in patients with Recent Hyperglycaemia

The most noteworthy observation in the group of hyperglycaemics of 6 months to 1 year duration was the extravascular accumulation of PAS positive material. This small group of 4 patients were specially selected to represent a group of uncontrolled hyperglycaemia of a very short duration without any other microangiopathic complications. They were detected to be diabetic for a duration ranging between 6 months to 1 year and were uncontrolled. The STI was normal in these 4 cases.

The presence of PAS positive material in them indicates accumulation of glycoprotein as the first and foremost metabolic abnormality in such cases. There was mild degree of interstitial fibrosis and collagen deposition. Vascular changes were not observed in any of the diabetic myocardium. Rogan et al (1974), have observed similar findings in their animal models. Deposition of glycoprotein occurred relatively early in their cases (Regan et al, 1 975). The interstitial collagen accumulation, however, was not present in these cases. The normal STI parameters indicate a normal left ventricular performance in these cases.

Possibly, the metabolic changes in the form of glycoprotein accumulation is a very early observation. The uncontrolled hyperglycaemia if allowed to continue might in the long run produce other extravascular changes of a severe degree producing clinical signs and symptoms of cardiac decompensation.

Eventhough extravascular and vascular changes were observed in both asymptomatic and symptomatic groups, the changes observed in the latter were greater and more widespread than the former.

This indicates the significance and relatively important role of those histopathological changes in producing diabetic cardiomyopathy.

Functional-Pathological Correlation in Diabetic Cardiomyopathy (DCM)

Symptomatic group

It is noteworthy that, both the vascular and the extravascular changes were more pronounced. This indicates that these changes are directly responsible for the signs and symptoms of cardiac decompensation.

The asymptomatic group had a raised PEP/LVET ratio implying left ventricular dysfunction. Even though the cardiac decompensation was not overt, this group represents preclinical cardiac dysfunction. This study has shown that morphological changes in these patients were lesser in degree than that in the symptomatic group.

Although the asymptomatic group had a shorter duration of DM, with neither overt nor preclinical cardiac dysfunction, evidences of minimal extravascular changes (mild deposition of glycoprotein etc.) were apparent in these patients. This may be attributed to the uncontrolled hyperglycaemia.

Correlation between Retinal and Renal Microangiopathic Changes and Cardiac Morphology

In the present study, a direct correlation between the presence of other microangiopathic complications in the eye and kidneys and myocardial vascular changes have been observed. The vascular changes in the myocardium was predominantly observed in those diabetics having other microangiopathies. As evidenced here, the small coronary arteries are possibly involved more often than commonly realised and they commonly accompany small vessel disease in other organs.

The term 'diabetic angiopathy' introduced by Lundback (1974) possibly serves as a working hypothesis. Even though there is not yet a complete agreement, the present study has shown that microangiopathy involves the myocardium and goes to some extent hand in hand with other angiopathies. This small vessel disease of the myocardium might be responsible for derangement in microcirculation giving rise to diabetic microangiopathic cardiomyopathy.

The distinct and widespread occurrence of extravascular metabolic changes in all the three groups (though to a varying degree having a direct correlation to functional impairment) unequivocally proves the role of metabolic changes in the genesis of primary myocardial disease in diabetes and may be responsible for the genesis of diabetic metabolic cardiomyopathy.

CONCLUSION

There is unequivocal endomyocardial biopsy obtained histopathological evidences for the existence of a specific myocardial disease in DM and this entity of diabetic cardiomyopathy is borne out of metabolic extravascular alteration and small vessel disease in the intramural coronary arteries. Thus, diabetic cardiac angiopathy possibly goes hand in hand with other microangiopathies.

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