Diabetic Cardiomyophathy: An Intrinsic Problem of Cardiac Membranes

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Cardiovascular disease is the major cause of death in diabetic patients and is far more prevalent than in the non-diabetic population. Although accelerated atherosclerosis and coronary artery disease remain the most important contributing factor for cardiac dysfunction in diabetes, a syndrome of diabetic cardiomyopathy has been recognized in the recent past and is characterized often by congestive heart failure in the absence of coronary artery disease. In spite of the fact that several reports indicate intrinsic defects in cardiac sarcolemma, sarcoplasmic reticulum and mitochondria (which normally play crucial role in the excitation-contraction coupling of heart and maintaining intracellular ion hemostasis), the pathogenesis of membrane abnormalities leading to cardiac dysfunction remains obscure in diabetic cardiomyopathy. It is felt that the next millennium will certainly continue to be expended in developing newer therapeutic strategies since insulin administration alone often fails to prevent or reverse cardiac abnormalities associated with this disease.

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Although it has been generally considered that ischemia due to atherosclerosis and microangiopathy is implicated in diabetic cardiomyopathy, a growing number of recent studies have demonstrated diabetes-induced cardiac dysfunction without any conclusive evidence of ongoing small or large vessel disease[1]. In addition, it has become clear that the eventual manifestation in diabetes with or without myocardial ischemia is decreased cardiac performance but its pathophysiological mechanisms are poorly understood. How is heart function altered in diabetes? The purpose of this article is to discuss briefly our present knowledge on diabetic cardiomyopathy. The treatise has been restricted to the cellular mechanisms involved in cardiac dysfunction due to this disease process. It may be pointed out that most of the clinical evidence for diabetic heart disease was concerned earlier with the vascular changes and autonomic neuropathy. The clinical/pathological work and the epidemiologic data from the Framingham study[2] have provided evidence that the chronic diabetes mellitus is often associated with a specific type of cardiomyopathy. Furthermore, the majority of experiments indicate that the cardiac function is altered as a result of deranged intrinsic cardiac metabolism in diabetes. In order to focus on this entity, it is my intention to examine the hypothesis that various metabolic factors are involved in the pathogenesis of cardiac membrane defects and these are then affecting the cardiac contractile machinery and heart pump function. At the outset, the constraints of such an approach must be clearly understood. Cardiac function at a cellular level is mostly determined by the integrated activities of the contractile proteins and several subcellular membrane systems such as sarcolemma, sarcoplasmic reticulum and mitochondria[3]. Since membrane systems play critical roles in regulating the ionic hemostasis in the cell, it has been suggested earlier[4] that irrespective of the nature of a pathophysiological condition, depression in myocardial contractility is associated with defects in the ability of one or more of these subcellular organelles to control ion fluxes in the cell[5]. Accordingly, it seems reasonable to believe that membrane dysfunction may be implicated in the overall diabetic-induced changes in cardiac performance. Secondly, extracardiovascular tissue (such as renal parenchyma) may have an indirect role in the development of diabetic cardiomyopathy. Thus attempts to delineate the factors derived from intra and extra cardiac tissues are needed, and it is with such a physiologically based approach to the investigation of the basic understanding of diabetic cardiomyopathy that this article will be concerned.

Diabetes and Intrinsic Problems in Cardiac Tissues

The sarcolemmal membrane is considered to be of crucial

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importance in controlling cation fluxes and maintaining cellular integrity during the excitation-contraction coupling process in the heart. Several studies have shown defects in the heart sarcolemmal enzymatic activities and composition in diabetes[6] . These include a depression in Na+, K+ - ATPase, Ca2+ - pump ATPase and altered membrane architecture. Such changes are responsible for an increase in the intracellular Ca2+ concentration (Ca2+ overload) which is known to produce abnormalities in cellular structure, function and metabolism[7].

Mitochondrial function is disturbed in diabetes as varying degrees of depression in the oxidative phosphorylation were observed in diabetic hearts. It is reasonable to believe that such changes in mitochondrial function will lead to lower levels of ATP in diabetic hearts.[8] Accumulation of long chain acyl carnitine due to mitochondrial defect is also noted in diabetes[9]. In addition, mechanical studies on isolated papillary muscle from diabetic hearts have revealed abnormalities in both contraction and relaxation process.[10] The onset of relaxation was delayed, the rate of relaxation was slower and there was a delay in reaching the peak relaxation in diabetic cardiac muscle. Since sarcoplasmic reticular Ca2+ transport has been intimately related to cardiac relaxation process, several investigators have also shown defects in Ca2+ transport activity of sarcoplasmic reticulum isolated from diabetic myocardium[11]. There are also studies which show a diabetic-induced shift of myosin isozyme from the normally predominant V form to the less active V3 form.

Cardiac Membrane Dysfunction in Diabetes: Is it due to coronary artery disease?

Since cardiac disease is often attributed to coronary arterial disease with consequent obstruction of blood flow due to atherosclerosis, the possibility remains that cardiac membrane dysfunction may result from ischemia associated with this disease. Is atherosclerosis or small vessel disease the fundamental alteration in diabetes-induced cardiomyopathy? Several lines of evidence now indicate that arterial disease sufficient to produce acute or chronic myocardial tissue alterations does not always exist in diabetes and vessel pathology may have little or no relation to the cardiac lesion in diabetes[12]. Experimental evidence also suggests that cardiac metabolic defects in diabetes differ from those of ischemic condition. For example, the uptake of free fatty acid by cardiac muscle is decreased following the induction of myocardial ischemia, the rate of glycogen breakdown is augmented and the tissue lactate content is raised significantly[13]. On the other hand, in diabetes the reduction in substrate flow through the glycolytic pathway results in an increase in heart glycogen content, reduction in the lactate: pyruvate ratio while lipid metabolism predominates in heart. Most importantly, vascular changes occur after structural derangement in the myocardial muscle cells exposed to diabetic condition is clearly evident. However, there is no doubt that one cannot exclude at present the potential for an occlusive process that is simultaneously present and rapidly developing. Accordingly, in such cases the contribution of microangiopathy and atherosclerosis in further deteriorating cardiac function could be significant at any given stage of diabetes.

What Are The Factors Initiating Membrane Defects In Diabetes?

A number of studies indicate that emotional factors may aggravate the metabolic state in diabetes[14]. For example, stress and myocardial infarction, where circulating levels of catecholamine increase markedly, are known to induce diabetic like changes in metabolism[15]. Interestingly, it has been shown earlier by us that plasma catecholamines begin to rise as soon as plasma levels of insulin begin to decline in-experimentally-induced diabetes mellitus[16]. High levels of plasma catecholamines can directly produce cell damage. High levels of plasma catecholamines may also become available for oxidation to form adrenochrome and free radicals[17]. Since both free radicals and adrenochrome have been reported to exert toxic effects on the myocardium[18], it is very likely that catecholamines or their oxidation products are involved in diabetes-induced membrane damage. It may be pointed out that the role of insulin deficiency in inducing pathological changes in the myocardium can not be overlooked because of the profound metabolic effects of insulin in various tissues including heart.

Insulin deficiency has been shown to elevate plasma lipid concentrations and increase accumulation of fats as well as their metabolites, long chain acyl carnitine in the diabetic myocardium. Therefore, insulin deficiency may have a pivotal influence in initiating membrane defects in diabetes. Nevertheless, the fact remains that the myocardial abnormalities seen in various clinical studies exist despite insulin treatment. Does the reversal of diabetes-induced myocardial abnormalities depend fully on glucose lowering therapy? It is, indeed, an interesting question and a definitive answer must await extensive work in this direction.

Role of Atrial Natriuretic Peptide in the Development of Diabetic Cardiomyopathy and Congestive Heart Failure

Hypertension which is present in a vast population of longstanding diabetes, has been implicated in many diabetic complications. It is well known that lowering blood pressure in these subjects may prevent diabetic nephropathy[19]. Paralleling these observations on the pathogenesis and prevention of the more common diabetic complications, there is a growing awareness of another consequence of diabetes mellitus: cardiomyopathy. In addition, it is now believed that diabetes is likely to sensitize the myocardium so that superimposed hypertension with its attendant vascular changes results in progressive myocyte damage leading ultimately to congestive heart failure. It may be pointed out that the heart has been shown to secrete a hormone called atrial natriuretic peptide (ANP). The hormone has a natriuretic action and is known to influence blood pressure and blood volume. One can speculate that decreased ANP binding sites in the kidney or in the vascular tissue may be

responsible in part for the development of congestive heart failure in diabetes. We have shown also that congestive heart failure in diabetes with hypertension may be due to uncoupling of the ANP receptor-effector system in the kidney basolateral membranes[20]. Therefore, extracardiac tissue plays also a major role in understanding the complex biochemical mechanism in the development of diabetic cardiomyopathy.

CONCLUSION

The above discussion clearly indicates that there is a growing need to understand the structural and functional events which occur after the onset of diabetes so that better therapeutic strategies may emerge to protect the myocardial membrane as well as extracardiovascular tissues and the development of diabetic cardiomyopathy.

In view of various factors contributing to cardiac dysfunction in diabetes, it may be that no single therapeutic approach will exist as a panacea of this disease. Newer therapeutic agents in combination with insulin are warranted in the future to deal with the problems associated with diabetic cardiomyopathy (Table-1).

Table 1. Newer Therapeutic Agents in Diabetic Cardiomyopathy

Agents	Effects
Vanadate	decreases plasma glucose
Methyl palmoxirate	inhibits carnitine transferase
Methionine	enhances cardiac contractility by phospholipal-N-methylation
Verapamil	inhibits Ca2+ overload
Vitamin E	works as antioxidants
Atrial natriureticpeptide	regulates blood volume and cardiac load
Future?	membrance stabilization and prevention of diabetic cardiomyopathy

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