Diabetologia (1997) 40: S130–S133

Diabetologia

Microvascular heart disease in diabetes mellitus

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Epidemiological studies have demonstrated that diabetic patients have an increased risk of developing heart failure independent of serum cholesterol, systolic blood pressure and age [1]. Diabetic patients have a markedly adverse course following myocardial infarction, with high rates of post-infarct failure and death [2, 3], and there is a significant association between dilated cardiomyopathy and a history of diabetes mellitus [4, 5]. Such studies have established the presence of a myocardial disorder in diabetic patients, distinct from macrovascular coronary disease and hypertension, which has led to the concept of diabetic cardiomyopathy. Diabetic cardiomyopathy may be defined as myocardial disease in diabetic patients unrelated to the presence of macrovascular atheromatous coronary artery stenosis. It has non-specific morphological and functional characteristics which include myocyte hypertrophy [6], interstitial fibrosis, arteriolar thickening, capillary microaneurysms and reduced capillary density [7–9], and abnormalities of left ventricular function with alterations in systolic and particularly diastolic function [10, 11]. The development of diabetic cardiomyopathy is likely to be multifactorial; putative mechanisms include stiffening and loss of ventricular compliance due to increased myocardial fibrosis, microvascular dysfunction, structural changes in collagen, alterations in myocardial energy metabolism, and structural changes to the sarcolemmal and contractile protein of the muscle itself. This review will concentrate on the possible relationship between microvascular dysfunction in diabetes and diabetic cardiomyopathy.

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Abbreviations: CBF, Coronary blood flow; EDRF, endothelium-derived relaxing factor; NO, nitric oxide

Coronary microvascular function

Coronary blood flow (CBF) and myocardial oxygen consumption are closely matched in the normal heart through changes in coronary microvascular resistance in response to the metabolic demands of the myocardium [12]. The mechanisms for this matching probably involve metabolic, myogenic, endothelial, and neurohumoral influences on coronary microvascular diameter and hence resistance [13].

The coronary circulation is often studied in vivo by measurement of blood flow changes in a large epicardial coronary artery. CBF is inversely related to total coronary microvascular resistance and hence microvascular dilatation. This technique treats the coronary microcirculation as a single resistance bed with homogeneous behaviour. However, techniques have now been developed to measure microvascular diameter and pressure in vivo in experimental models. Such techniques although limited to animal models, are likely to provide valuable data on the heterogeneous behaviour of the coronary circulation and allow the study of regulatory mechanisms at different levels in the coronary microcirculation.

Myogenic control

The myogenic response comprises vascular smooth muscle contraction in response to an increase in intraluminal pressure and relaxation in response to a decrease in pressure. It is involved in autoregulation in the coronary microcirculation, and responses appear greatest in vessels 30–70 μm in diameter [14].

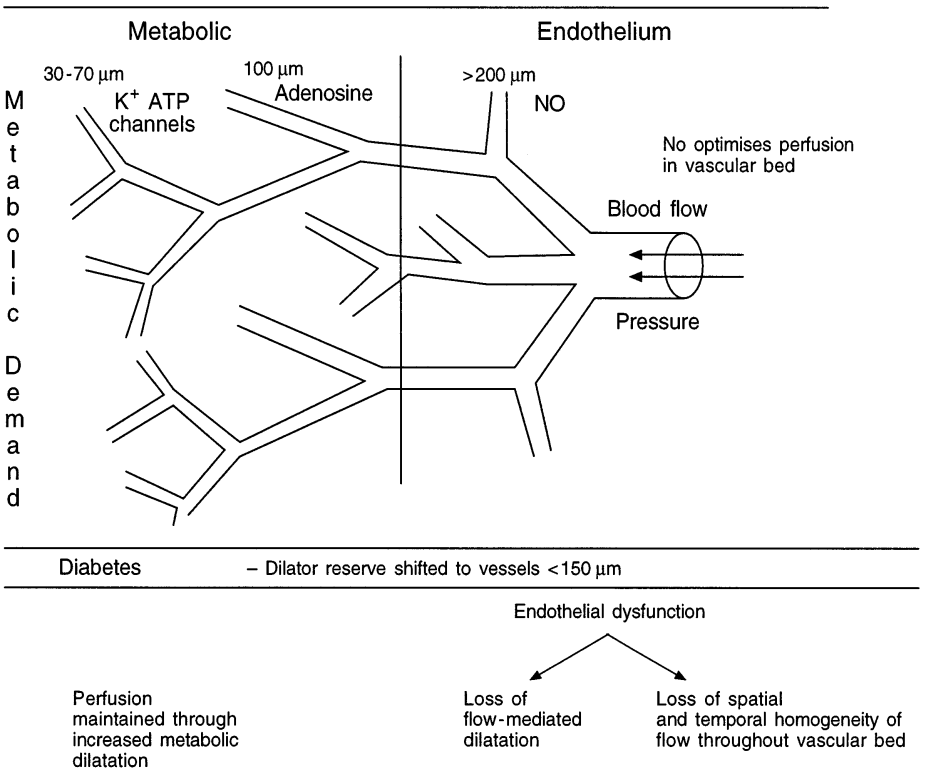

Fig. 1. Schematic representation of coronary microvascular circulation illustrating different sites of action of regulatory mechanisms and pulative effect of diabetes

Metabolic control

Metabolic control is probably the dominant influence on CBF ensuring that flow remains constant for a given level of metabolic demand. Microvascular tone is governed by tissue levels of metabolic substrates or products such as adenosine which primarily dilates vessels less than 150 μm in diameter [15, 17]. Mechanisms other than adenosine may also be involved in vessels less than 100 μm diameter, as demonstrated by the opening of ATP-sensitive K^+ channels during hypoxia [18, 19], and the dilatation over a wide range of vessel sizes caused by increased myocardial oxygen consumption [20].

Endothelial control

Blood flow acting through mechanotransduction of shear stress on the endothelial cell surface results in release of endothelium-derived relaxing factor (EDRF) or nitric oxide (NO) [21]. Increased flow in the coronary bed causes release of NO which integrates and amplifies changes in vessel calibre and resistance throughout the bed [22]. NO has been shown to act on vessels more than 200 μm in diameter, and is necessary for spatial and temporal homogeneity of flow through a vascular bed [22, 23].

Thus, changes in pressure and flow clearly act throughout the coronary bed, where a multiplicity of interacting control mechanisms influence tissue perfusion (Fig. 1).

Diabetes and coronary microvascular function

Experimental diabetes

Stuctural abnormalities. The rat hypertension-diabetes model has provided evidence of microangiopathy. Silicon rubber solution infused in vivo revealed numerous areas of microvascular tortuosity, focal constrictions, and microanuerysm formation. These changes were most prominent in rats with both hypertension and diabetes [24].

Myogenic control. Alloxan-induced diabetic dogs or dogs subjected to hyperglycaemia demonstrated impaired vasodilatation of in vivo coronary arteriolar microvessels in response to a decrease in perfusion pressure [25]. Autoregulation was also impaired following intracoronary infusion of glibenclamide [26].

Metabolic control. Cardiac hyperactivity induced either by pacing or inotropic agents (to increase myocardial oxygen demand) resulted in impaired coronary vasodilatation in spontaneously diabetic rats compared to non-diabetic rats. The diabetic rat heart also had a reduced dilatation to adenosine, but a similar response to sodium nitroprusside [27].

Endothelial control. There is a wealth of evidence from animal models of diabetes of endothelial dysfunction [28, 29] (for reviews of possible mechanisms). The majority of the studies have however been performed using large conduit arteries. Nevertheless

there is evidence of impaired microvascular responses in these models, e. g. reduced endothelium-dependent responses in pial arterioles [30] as well as in the femoral and mesenteric circulations of diabetic rats [31].

Thus it is clear, at least in animal models that diabetes has potential adverse effects on several of the interacting control mechanisms which influence tissue perfusion.

Clinical diabetes

Structural abnormalities. Characteristic morphological features of diabetic microangiopathy include: basement membrane thickening, arteriolar thickening, capillary microaneurysms and reduced capillary density. All of these features have been described in diabetic hearts [32, 33] suggesting a similar disease process in the cardiac microcirculation.

Metabolic control. Pacing-induced increase in CBF was reduced in diabetic compared to nondiabetic subjects. The underlying mechanism for this impairment of metabolic vasodilatation was not clearly established but did not appear to be due to an impaired response to adenosine (in contrast to the rat model) nor due to the use of sulphonylureas which block K^+-sensitive ATPase channels [34].

Endothelial control. Endothelial responses in diabetic (most with hypertension) and non-diabetic subjects were assessed by intracoronary infusion of ACh. Diabetic patients had impaired endothelium-dependent dilatation of the epicardial coronary artery [35]. The diabetic patients also had a reduced coronary flow reserve (maximal pharmacological induced CBF/ basal CBF – an index of vasodilator reserve of the coronary circulation), a finding confirmed in a later study [34, 35].

Discussion

It is clear therefore that both structural and functional abnormalities of the coronary microcirculation are present in experimental and clinical diabetes. The hypothesis that microvascular disease is involved in the development of diabetic cardiomyopathy is attractive.

Control of CBF is complex, involving a vascular scheme where the primary influences of different regulatory elements act at different sites in the coronary circulation. Metabolite- and pressure-induced changes in tone occur in coronary microvessels less than 150 μm in diameter, whereas flow-induced changes in tone occur in larger microvessels. Thus, endothelium-dependent dilatation of the larger microvessels may occur as a result of metabolically induced increases in flow downstream (Fig. 1). A normally functioning endothelium is necessary for homogeneity of flow distribution throughout the vascular bed at different flow rates, with loss of EDRF leading to spatial and temporal heterogeneity of perfusion. However, loss of EDRF activity may not impair the ability of a vascular bed to increase its flow to match an increase in metabolic work, as increased metabolic signals acting on vessels less than 150 μm diameter may override loss of flow-mediated dilatation in larger vessels. Nevertheless loss of EDRF activity reduces the vasodilatory capacity of a vascular bed. This has been demonstrated in both experimental and clinical studies where microvascular responses to adenosine and increased metabolic demand were attenuated by inhibition of NO synthesis [36, 37]. In a recent study however, inhibition of NO synthesis was not associated with attenuation of microvascular responses to metabolic stimuli, the authors concluding that the NO-mediated effect may have been counterbalanced by an increased metabolic signal [38]. In another study in the pig, inhibition of NO synthesis resulted in functional and structural abnormalities of the coronary microcirculation resembling the microangiopathy seen in diabetic cardiomyopathy [39]; however, the animals also became hypertensive.

Endothelial dysfunction by contributing to microvascular abnormalities may explain the reduced coronary flow reserve observed in diabetic patients, the reduced dilator reserve of arterioles due to endothelial dysfunction may lower the threshold for myocardial ischaemia particularly when macrovascular coronary disease is present.

Conclusion

Diabetic cardiomyopathy is thus a real clinical entity. Its pathophysiology is poorly understood, but it is clear that hyperglycaemia and hypertension are important factors. The development of diabetic cardiomyopathy is probably multifactorial, but endothelial dysfunction by contributing to microvascular abnormalities probably plays an important role.

Acknowledgements. I am grateful to Professor M.J. Lewis for his help in the preparation of this paper.

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