EDITORIAL REVIEW

Why is myocardial ischaemia so commonly subendocardial?

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The vulnerability to ischaemia of subendocardial muscle of the left (and sometimes the right) ventricle is well established [1, 2]. (The terms subendocardial, deep or inner layers are used interchangeably and refer to the innermost one-quarter or one-third of the ventricular wall; similarly, the terms subepicardial, superficial or outer layers refer to the outermost one-quarter or one-third of the ventricular wall.) In coronary heart disease, angina pectoris is associated with electrocardiographic signs of subendocardial ischaemia, some infarcts are subendocardial and transmural infarcts show more necrosis in deep than in superficial muscle. Even when coronary arteries are normal, subendocardial ischaemia or necrosis may occur with severe aortic stenosis or incompetence, pulmonary hypertension, anaemia, shock, hypothermia and cyanotic heart disease. Haemorrhagic subendocardial necrosis is commonly found in patients who die after open heart surgery.

Ischaemia occurs when blood flow and oxygen supply do not match demand. At rest, the left ventricle has a very high oxygen consumption and blood flow per gram and its oxygen extraction is nearly maximal. Increased oxygen demands must, in general, be met by increased blood flow, or else ischaemia results. Some studies suggest that left ventricular subendocardial muscle uses about 20% more oxygen per gram than does the remaining muscle [3], and this could explain some of the subendocardial vulnerability to damage. However, absolute or relative subendocardial underperfusion is usually the major finding whenever there is ischaemia.

Decreased perfusion pressures induce metabolic vasodilatation (autoregulation) and so do increased oxygen demands at constant perfusing pressures; autonomic nerves may modulate this effect. With progressive imbalance between supply and demand, maximal vasodilatation is reached earliest in left ventricular subendocardial muscle [4, 5] and then subendocardial flow becomes pressure dependent. That is, further increases in oxygen demand at constant pressure increase flow in superficial but not in deep muscle; alternatively, further decrease in perfusion pressure decreases deep but not superficial flows. Either way, coronary vascular reserve is lost in deep, but retained in superficial, muscle and there is relative (or absolute) decrease in subendocardial flow; that is, there is a reduced inner/outer flow ratio (the normal inner/outer ratio is about 0.9:1 in anaesthetized animals and about 1.3:1 in conscious animals). A flow ratio decreased below normal is usually associated with biochemical evidence of subendocardial ischaemia [6, 7]. Therefore, subendocardial vulnerability to ischaemia is caused by coronary vascular reserve being lost earlier in subendocardial than in other myocardial vessels, with a resultant fall in the inner/outer flow ratio.

This difference between layers was long attributed to differences in systolic tissue pressures in the left ventricular wall. Many investigators observed that systolic tissue pressures beneath the left ventricular subendocardium equalled or exceeded systolic cavity pressure, but decreased centrifugally to reach low pressures beneath the epicardium. If this is true, then, during systole, superficial but not deep muscle will be perfused, whereas the whole wall will be perfused in diastole. These phasic changes explain the predominance of diastolic flow in the left coronary artery. They also explain why progressive occlusion of a branch of the left coronary artery eventually causes subendocardial underperfusion, since a low pressure cannot effectively perfuse subendocardial vessels open for only part of the cardiac cycle.
Two attempts were made to use this hypothesis to predict and assess subendocardial underperfusion from simple pressure measurements. Griggs & Nakamura [8] devised a coronary/ventricular pressure index and Buckberg et al. [9] developed their DPTI/SPTI pressure index, which was the ratio of the area between the aortic and left ventricular pressures in diastole to the area beneath the left ventricular pressure curve in systole. These pressure ratios were both intended to reflect the myocardial supply/demand ratio. Both indices predicted the left ventricular inner/outer flow ratio in experimental models of coronary occlusion or heart disease, and the prediction was made more accurate by allowing for haemoglobin concentrations [10]. The inner/outer flow ratio decreased when these indices fell below 1.4 or 0.4 respectively. Many problems preventing these indices from being useful in patients have been described [11, 12]. In brief, estimating left ventricular oxygen demand from ventricular pressures is inaccurate, especially in sick hearts, and the critical values of the pressure indices found in normal animals do not apply to hearts with hypertrophy or abnormal coronary vessels. (The indices, however, may be useful in indicating directional change in perfusion in any given patient and also set a limit below which subendocardial ischaemia is likely to occur even in normal hearts.)

In addition to these problems, the underlying hypothesis of differences in flow due to regional differences in systolic intramyocardial tissue pressures is far from secure. Firstly, direct measurements of these pressures may be misleading because devices inserted into the myocardium distort tissues and probably alter local forces [13, 14]. This may explain why the absolute pressures reported vary so much with different techniques; unfortunately, there is no independent standard to use as validation. A second approach, with mathematical models of stress distributions, has not been successful because of oversimplified assumptions [15]. The left ventricle is an irregularly shaped, anisotropic, inhomogeneous structure subject to large strains and its wall is not incompressible because blood can move from one region to another or into the extramural coronary arteries and veins during contraction. No existing model considers all these factors. Furthermore most models equate radial stress to intramyocardial pressure, whereas Baird et al. [16] demonstrated almost normal intramyocardial pressures in the beating empty heart with no radial stresses.

Not only is there uncertainty about what systolic intramyocardial pressures are, but it is no longer certain that a substantial amount of left ventricular muscle is perfused during systole. Douglas & Greenfield [17] estimated the compliance and capacity of the canine extramural coronary arteries and concluded that most of the resting systolic flow recorded by a flowmeter at the origin of the left coronary artery was probably stored extramurally; it would perfuse the muscle in the next diastole. Steinhause et al. [18] observed continuous forward flow throughout the cardiac cycle in arterioles, capillaries and venules in the most superficial intramural left ventricular vessels, but found that flow stopped in systole in arterioles about 0.5-1 mm beneath the epicardium. Their findings support the concept that at rest little of the left ventricle is perfused in systole. If, then, the duration of perfusion of most left ventricular layers is similar, why is subendocardial ischaemia so prevalent? This question becomes even more puzzling because several studies [5, 19, 20] have confirmed the conclusion reached by Moir [1], namely that maximal conductance is greater in subendocardial than in subepicardial vessels. Conductance is the reciprocal of resistance and is calculated as flow through vessels divided by the pressure drop across them. It is a more convenient concept than resistance, since a higher conductance implies more vessels and higher flows at any given driving pressure [21].

One possible explanation for the ischaemia is that during maximal flows there is systolic flow in the outer layers of muscle, so that although the greater maximal subendocardial conductance compensates for shorter subendocardial perfusion time and allows regional flows to remain equal for a time, eventually compensation fails as more and more flow is needed. This explanation though cannot hold when coronary perfusion pressure falls at constant ventricular work because then total and subepicardial flows are not increased.

There is, however, another consideration, namely that there might be much higher diastolic intramyocardial pressures in subendocardial than in subepicardial muscle, a suggestion first made by Rouleau et al. [5]. If these diastolic pressures are above coronary sinus pressure, then they represent waterfall pressures, a concept that goes back to the work of Holt [22], Banister & Torrance [23] and Permutt & Riley [24]. The classical concept of flow through tubes, based on the studies of Poiseuille and Hagen, is that as fluid passes through a tube energy is lost overcoming frictional resistance. This causes pressure to fall from the inlet \((P_i)\) to the outlet \((P_o)\) of the tube. The pressure drop \(P_i - P_o\) is a function of the
flow, the viscosity of the fluid and the geometry of the tube. For a given tube and viscous fluid the flow is a function of \( P_t - P_o \), and induced changes in \( P_t - P_o \) cause proportional changes in flow. When, however, the tube is not a rigid tube, but is a soft-walled collapsible tube that runs through a rigid box in which the pressure surrounding the tube \( (P_c) \) can be raised above the outflow pressure of the tube \( P_o \), then different relationships are observed. If the box pressure \( P_c \) exceeds \( P_o \), then flow through the system is proportional to the pressure difference \( P_t - P_c \). Raising or lowering \( P_c \) has no effect on flow through the tube, as long as \( P_o \) is less than \( P_c \). This is analogous to a waterfall; raising the level of the river below the falls does not influence the flow of water over it. These collapsible tubes have many unusual properties that are well summarized by Brower \& Noordegraaf [25]. For our purposes what is important is that blood vessels passing through tissues have many of the properties of these collapsible tubes and, in particular, the pressure in the box \( (P_c) \) has been regarded as comparable with tissue pressure around the blood vessels. Thus, if arterial pressure \( (P_t) \) is lowered until it equals tissue pressure \( (P_o) \), flow would stop, even though arterial pressure exceeded venous pressure \( (P_v) \). Pressure in the veins beyond the confines of the tissue should not influence tissue flow as long as venous pressure is below tissue pressure, and this has indeed been shown in several organs. Initially, this concept was used to explain differences of flow in different lung zones, but many vascular beds show this phenomenon. If perfusion pressure in a vascular bed is gradually lowered, flow ceases at pressure well above venous pressure; in animal experiments, this is true of the hind limb [26, 27], the brain [28] and the heart [29].

Bellamy [29] reported that during autoregulated flow in a conscious chronically instrumented dog the left coronary arterial pressures and flows declined during a long diastole, that plotting flows against pressures every 0.1 s yielded a straight line relationship and that flow ceased when coronary or aortic diastolic pressure was about 45 mmHg. (This lack of constancy of flow does not negate autoregulation, which takes several seconds to restore flow to control values after a change in pressure.) During peak reactive hyperaemia, the pressure–flow line (the slope of which is conductance) became steeper and could be extrapolated to a pressure at zero flow of about 20 mmHg, well above coronary sinus or left ventricular diastolic pressures. During autoregulation, flow might stop because of critical closure [30, 31], a concept implying that because of tension in the vessel wall the vessel would suddenly close when the transmural pressure fell below some finite value. However, during maximal vasodilatation critical closure in the sense of being due to active wall tension is probably absent [32], so that the zero flow pressure intercept of 20 mmHg has been regarded as being due to a diastolic tissue pressure in the left ventricular wall.

Studies of pressure–flow relations in the canine left coronary artery or its branches are carried out either dynamically, by measuring several pressure–flow values in each diastole, or during steady state by serial partial occlusions that yield one pressure–flow value per occlusion. The values plotted in the dynamic studies are instantaneous diastolic pressures and flows, and in the steady-state studies are usually mean diastolic pressure and mean diastolic flows. These flows, measured in ml/min, are not the same as the total volume of diastolic blood delivered, which is the product of mean flow and the duration of diastole. The pressure–flow lines, as constructed, do not explicitly take heart rate into account and this is often a source of confusion. A long diastolic period may be associated with a large total volume flow in diastole, but does not of itself indicate what type of pressure–flow line is present. Most investigators report linear pressure–flow relations, although recent careful studies show that there is usually minimal curvilinearity at the lower end of the pressure–flow curve. Some investigators suggest that the pressure intercept on the zero flow line is artificially high because coronary vascular capacitance permits flow to continue in the wall after it has reached zero at the flowmeter near the origin of the coronary artery. However, it is doubtful if the low compliance of the coronary arterial system explains shifts of more than a few mmHg.

Three technical complexities need discussion. Firstly, it is in practice difficult to determine low flows and pressures without causing ischaemia and thus altering the system being examined. Secondly, the intramyocardial blood volume, normally about 15% of the volume of the wall, changes as perfusion pressure changes [33]. Since myocardial tissue is dense and of low compliance, decreased intramyocardial blood volume could alter tissue pressures. In fact, increasing this blood volume by obstructing the coronary sinus raises the pressure at zero flow, probably by raising tissue pressures [34]. Therefore, experiments with low perfusing pressures and flows, especially steady-state measurements, may well be causing changes in the tissue pressures that...
they are attempting to measure. Thirdly, it is likely that, as pressures are lowered, flow will be diverted to regions with the lowest diastolic waterfall pressures; in fact, this almost certainly happens during steady-state measurements. As a result, the pressure at which flow actually ceases represents only the lowest diastolic waterfall pressure.

If there are indeed diastolic waterfall pressures in the myocardium, how are they produced? Likely candidates for vessels that act like thin-walled collapsible tubes are the venules and small veins and some evidence supports this contention. In the brain, raising cerebrospinal fluid pressure raises pressure in small cerebral veins by a similar amount and their pressure exceeds the normal low pressure in the sagittal sinus; the transition from low to high pressure occurs in the great vein of Galen [35]. For the heart, too, Tillmanns et al. [36] have measured pressures in subepicardial venules and found these to be about 25/10 mmHg, well above coronary sinus pressure. Even though there will always be a gradient of pressure from small veins to larger veins, the magnitude of the pressure drop found in these studies is greater than can be explained by simple resistive energy loss. The venular pressure may thus reflect local tissue pressures. Why intramyocardial tissue pressures are so high in diastole is uncertain, but they may in part be high owing to distension of a low compliance myocardium with the influx of coronary arterial blood in diastole.

There are many important implications of high diastolic waterfall pressures. The most obvious is that, if diastolic perfusing pressure falls, the pressure head for perfusion is much less than expected. If diastolic waterfall pressures are higher in subendocardial than subepicardial muscle, then the pressure head for perfusion will be lower in deep than superficial muscle; this might well explain the greater vulnerability to ischaemia of subendocardial muscle.

A second important consequence of high pressure intercepts at zero flow concerns evaluating changes in vascular resistance. It has been argued, for example, that vasodilatation obtained by adenosine infusion is not maximal, since, when hypoxaemia is induced, coronary flow increases further. However, there are two interpretations of this observation (Fig. 1). The Figure shows the flow after adenosine (point A) and the increased flow after hypoxaemia is induced (B). Now if the zero-flow (diastolic waterfall) pressure intercept is not altered by hypoxaemia, the new pressure–flow relationship is shown by the broken line (W, B) passing through B. Since this line is steeper than W, A, it is clear that hypoxaemia has increased conductance (or decreased resistance) from that observed during adenosine infusion. However, if hypoxaemia alters the zero flow–pressure intercept from W, to W, the new pressure–flow line W, B has the same slope as W, A and the increased flow after hypoxaemia is not due to an increased conductance. In fact, a series of pressure–flow measurements is needed to make the correct interpretation, much as pharmacologists make dose–response curves rather than single-point responses to evaluate the effects of a drug.

Finally, shifts of zero flow–pressure intercepts may have considerable clinical importance. For example, the coronary vascular effects of two anaesthetic regimens (halothane vs nitrous oxide) were compared recently [37]. One of the major findings was that, during maximal coronary vasodilatation, the pressure–flow line was shifted to the left by halothane; the average zero flow intercept on the pressure axis was 18 mmHg for halothane and 27 mmHg for nitrous oxide. What this means is shown in Fig. 2. At any given coronary perfusing pressure there will be a greater maximal coronary flow with halothane than nitrous oxide. In other words, coronary vascular reserve is increased by a leftward shift of the maximally dilated pressure–flow line. The reason for the shift of the zero flow–pressure intercept has not been determined. It is true that the heart rates were slower and diastolic periods longer for the halothane than the nitrous oxide regimens. However, as mentioned before, maximal myocardial perfusion depends both on the time available for diastolic perfusion and on the position of the slope of the pressure–flow lines.
To summarize, we know now that left ventricular subendocardial vulnerability to ischaemia is due to the fact that with increased oxygen demand or decreased oxygen or blood supply the subendocardial vessels are the first to dilate maximally and become pressure dependent. The long-held views that these subendocardial problems are due to differential perfusion times (subendocardial muscle perfused only in diastole, the remaining muscle perfused throughout the cardiac cycle) need to be modified. Present research is directed to investigating diastolic or waterfall tissue pressures and the possibility that these are higher in the subendocardial than the more superficial muscle. If these findings are substantiated, not only will they affect the interpretation of vascular resistance in different layers but it will be important to find out how these waterfall pressures are controlled and how they may be manipulated to the heart's advantage.

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References