Brief Reviews

Subendocardial Distribution of Coronary Blood Flow and the Effect of Antianginal Drugs

By Thomas W. Moir

Histological evidence indicates that the subendocardial layers of the left ventricle are vulnerable to ischemia: areas of necrosis in the subendocardium are greater than they are in the epicardium in transmural infarction (1) and in coronary insufficiency (2), suggesting that antegrade coronary blood flow in the subendocardial layers is less than that in the epicardium because of the proximity of the former to intracavitary left ventricular pressure (3). Initial studies showed a gradient in tissue pressure with systolic pressure in the subendocardium exceeding that in the left ventricular cavity and suggested that systolic extravascular compression could be a significant feature in the transmural distribution of coronary blood flow (3).

These findings obtained by indirect methods have been generally confirmed (4-7) by studies using other indirect methods, although the intramyocardial tissue pressure in the inner layers of the left ventricle has not always been found to exceed cavitary pressure (8). Recently, a more direct measurement of myocardial tissue pressure by subminiature pressure transducers (9) has confirmed the presence of a transmural gradient with systolic pressure in the subendocardium of the beating dog heart always greater than that in the ventricular chamber (9). Although indeterminacy regarding the true magnitude of the pressures measured by this method remains because of tissue distortion by the transducers, a transmural gradient in systolic coronary blood paralleling the systolic tissue-pressure gradient has been demonstrated (10). Most likely, the gradient in systolic coronary blood flow is due to the tissue-pressure gradient rather than to left ventricular shear or to traction forces (11). What then is the effect of this gradient in systolic coronary blood flow on total subendocardial coronary blood flow and nutrition?

Experimental evidence can be marshaled to defend either the view that the subendocardium is adequately perfused under circumstances of normal coronary perfusion pressure and left ventricular pressure (12-18) or the view that it is underperfused (19-24) and survives by a hypothetical anaerobic metabolism (19). These opposing conclusions depend on the methods used for estimating endocardial coronary blood flow. Extravascular methods such as clearance of needle deposits of diffusible isotopes and determinations of tissue \( \text{Po}_2 \) with an interstitial \( \text{O}_2 \) electrode indicate endocardial underperfusion, but intravascular techniques such as tissue uptake of intravascularly administered diffusible isotopes and fractional vascular uptake of radioactive microspheres indicate normal or greater-than-normal distribution of flow. Thus, a critique of
the methods is essential for weighing the evidence in support of either view.

The method of externally monitored clearance of diffusible radioisotopes injected into the myocardium, which has shown a slower clearance rate in the subendocardium than in the outer layers of the ventricle (19, 23, 24), has been criticized on the basis of local conditions created by the injection of the isotopes; these include local edema, local hemorrhage, local vasomotion, and leakage of the injectate up the needle track (25, 26). In addition, disparity between coronary blood flow and the rate of isotope removal from the myocardium of the beating dog heart has been shown (26). Sources of error in the interstitial O₂-electrode method, which has demonstrated a lower Po₂ in the endocardium than in the epicardium (19–22), are related to in vitro calibration of the electrode, to movement of the electrode tip in the myocardium, which may cause spuriously high readings in the epicardium if these layers move more than those in the subendocardium (20), and most importantly to electrode size (27). Tissue damage from electrodes with dimensions of 60–330 μ has been demonstrated (20, 27), and either high or low readings can result, depending on the presence of variable degrees of free blood, nonmetabolizing tissue, vascular stasis, and edema (27). All but one (21) of the cited studies employed large electrodes. Moreover, the need for statistical use of the electrode, i.e., repeated determinations in individual animals, would seem to be a prerequisite, since the exact location of the electrode tip is unknown for any single determination. This has been done in two (19, 21) of the studies which showed a decreased Po₂ in the subendocardium; however, in one of these studies (19) a large electrode was used. Consequently only a single study (21) has combined small electrodes with repeated determinations in the same animal. Nonetheless, even with small electrodes a gradient in the amount of injury caused by a degree of tissue compression against the electrode in the subendocardium greater than that in the more superficial layers cannot be excluded.

Tissue uptake methods, which have used intravascular administration of diffusible isotopes, have shown an equal distribution of flow to the endocardium and the epicardium under normal conditions of coronary perfusion pressure and flow but a decrease in endocardial distribution during myocardial ischemia (12–16). These methods can be criticized because cellular transport mechanisms rather than flow may be the factor limiting uptake, particularly in studies in which ⁸⁶Rb is used (28). However, a comparative study of the ⁸⁶Rb method with metered coronary blood flow showed that the method gives an accurate estimate of directional change in coronary flow, although it tends to underestimate metered flow at high flow rates because of decreased extraction (29). The inverse relationship of myocardial extraction to blood flow rate was similar to that reported for both ⁸⁶Rb and ⁴²K in skeletal and cardiac muscle (30–33); this finding suggests that the time the isotope is in the capillary bed and the magnitude of the permeable surface area (32), rather than cellular transport mechanisms, are the major determinants of extraction. This was found to be true under several conditions of myocardial oxygenation and function (29). The fractional uptake of radioactive microspheres has shown an equal or greater flow to the endocardium than to the epicardium (17, 18), but the reliability of the microsphere method as an estimate of flow to small areas of the left ventricular myocardium depends on microsphere size (34, 35). However, recent studies with small spheres (8–10 μ and 15 μ) consistently show that subendocardial flow distribution is equivalent to that in the epicardial layers under normal coronary flow conditions (17, 18).

In the face of this methodological impasse, the issue must finally be whether the subendocardial coronary blood flow to the inner layers of the beating heart is nutritionally adequate. A recent study (36) of metabolic substrates (lactate and pyruvate) in superficial and deep layers of the beating left ventricle found no difference as long as the normal relationship of coronary perfusion pressure and left
intraventricular pressure was maintained. Even during left ventricular systolic hypertension, metabolism in the endocardium, as reflected by these substrates, does not differ from that in the epicardium (37); this is also true during stimulation of left ventricular β receptors (36). However, with reduction in total coronary blood flow produced by coronary constriction, the subendocardial layers of the stressed (36, 37) and nonstressed (38) left ventricle show metabolic signs of ischemia greater than those in the epicardium, as manifested by lactate accumulation and depletion of high-energy phosphate bonds. The high glycogen content of the inner layers of the dog heart due to the subendocardial distribution of Purkinje fibers (39) should not influence the finding of normal ratios of lactate to pyruvate in these layers in hearts with adequate coronary perfusion (36, 37). However, it could accentuate the lactate accumulation found in hypoxic hearts (38). Thus, present evidence indicates that the nutritional needs of the subendocardium are met even under conditions of stress which increase myocardial O₂ consumption, as long as an adequate total coronary blood flow is maintained. To this extent, then, the intravascular uptake methods reflect a more accurate picture of the transmural distribution of flow than do either the extravascular clearance or the interstitial O₂-electrode methods. Adequate nutritional flow is maintained in the endocardium in spite of the gradient in systolic coronary blood flow, but it becomes inadequate when total coronary flow is reduced: the mechanism underlying this phenomenon remains to be examined.

Kirk and Honig (19) suggested that “unless compensated for by a reverse gradient in the vasomotor component of coronary resistance the tissue pressure gradient would produce a non-uniform transmural distribution of coronary blood flow.” They found a transmural gradient in the clearance of tissue deposits of Na¹³¹I and, therefore, did not feel that there was a compensatory transmural gradient in coronary vascular resistance. Rather, they postulated on hypothetical grounds that anaerobic metabolism occurred in the subendocardium (19), and in other studies (40) they suggested that the innermost layers of the left ventricle were perfused directly from the left ventricular cavity via luminal channels. Both of these suggestions have been shown to be unlikely (36, 41), thus making the proposition of a compensatory transmural gradient in coronary vascular resistance a pertinent topic for consideration.

Based on the present evidence of adequacy of nutritional flow to the subendocardium, a mechanism can be proposed for the transmural regulation of coronary flow, which will maintain adequate distribution to the inner layers under conditions of normal coronary flow. As illustrated in Figure 1, ventricular systole produces an intramyocardial tissue-pressure gradient which, through extravascular compression, causes a parallel gradient in.
systolic coronary vascular resistance. Since the intramyocardial tissue pressure in the inner layers is greater than the peak aortic systolic pressure—the coronary driving pressure during systole—coronary flow decreases and may cease in the subendocardium during systole. However, during ventricular diastole—the major coronary flow period—the intramyocardial tissue pressure is not appreciably different across the myocardium, and a gradient in diastolic coronary vascular resistance may exist with the coronary vessels of the subendocardium more widely dilated than those of the epicardium, resulting in a greater diastolic flow in the former than in the latter. This gradient is the result of diastolic autoregulation of the coronary vessels in response to subendocardial underperfusion during left ventricular systole (42) and results in an equality of net distribution of coronary blood flow across the myocardium during each cardiac cycle. Recent studies have confirmed the concept that the subendocardium is dependent on coronary flow during diastole (18). The types of coronary vessels involved in this hypothesis are unknown, but it is reasonable to assume that those capable of vasomotion are important. Although it has been deduced from studies with vasodilator drugs that the large epicardial conductive vessels do not participate in autoregulation (43, 44), the role of the large intramural arteries in this regard is unknown. Arteriolar vessels probably predominate in such a transmural vasomotor gradient, but there is evidence that the coronary capillary bed may be a factor in the maintenance of adequate subendocardial perfusion. An increase in capillarity in the subendocardium has been demonstrated (19), and it could be controlled by precapillary sphincters (45).

A critical feature of the proposed autoregulatory mechanism is a reduction in diastolic coronary vascular resistance that is greater in the subendocardium than in the epicardium, with a resulting decrease in the vasodilatory capacity of the former. Although some investigators have inferred that subendocardial vessels are normally maximally dilated (19, 46), recent studies of coronary blood flow distribution suggest that this is not the case (18). However, generalized myocardial ischemia would be expected to cause vasodilatation to reach its limit more rapidly in the inner than in the outer layers, and the ischemia would be more manifest in the subendocardium because of the now uncompensated underperfusion during ventricular systole. It is of interest to speculate that failure of this coronary autoregulation mechanism occurring independently of generalized myocardial ischemia may play a role in the etiology of the perplexing syndrome of coronary insufficiency with signs of subendocardial ischemia appearing in the absence of coronary artery disease (47–49).

It is unlikely that the greater decrease in coronary blood flow in the subendocardium as compared to that in the epicardium in myocardial ischemia is due to extravascular compression caused by an increase in diastolic intramyocardial tissue pressure which, in turn, might result from an elevation of left ventricular end-diastolic pressure (13). Subendocardial underperfusion has been shown to result from reduction of total coronary blood flow in the absence of elevation of left ventricular end-diastolic pressure; this is compatible with the view that subendocardial ischemia is the result of the loss of the capacity for further diastolic coronary vasodilation in these layers (14). Study of antianginal drugs by the fractional uptake of radioactive microspheres and tissue clearance of $^{85}$Rb has demonstrated that nitroglycerin and propranolol both increase distribution of flow to the subendocardium in the acutely ischemic canine left ventricle (17, 50). The data indicate that this probably occurs through redistribution of flow toward the endocardium rather than through increase in total blood flow. The mechanism causing this redistribution of flow is unknown, but it probably involves either a reduction in systolic extravascular compression or a lessening of myocardial ischemia sufficient to restore the capacity for a difference in diastolic coronary vascular resistance between subendocardium and epicardium (Fig. 1). In the case of
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nitroglycerin these changes could be the result of a decrease in both the afterload and the preload of the ischemic left ventricle (17, 50). The effect of propranolol is undoubtedly more complex, since in addition to its effect on heart rate and myocardial contractility it may secondarily increase coronary vascular resistance by blockade of β-receptor sites (51). Since augmentation of the intramyocardial systolic tissue-pressure gradient has been produced by a variety of interventions affecting β receptors (9), study of the possibility of its reduction by propranolol could provide valuable data in this regard.

A direct action of nitroglycerin on the coronary vessels which results in redistribution of blood flow from the epicardial layers to the subendocardium has been proposed because subendocardial O₂ tension increases after parenteral administration of nitroglycerin in the absence of an increase in coronary blood flow. These studies were done in dogs with normal myocardial oxygenation (22, 46). It is hypothesized that blood is shunted to the inner layers from the epicardium by a selective nitroglycerin-induced vasodilation of the large intramural vessels similar to that demonstrated in the epicardial conductive vessels (43, 44). Since a normal O₂ tension was found in the epicardium in spite of the endocardial shunt and in the absence of an increase in total coronary blood flow, it is difficult to understand these data which are based on single determinations in individual dogs of tissue Po₂ by large-caliber electrodes (177μ). The initially proposed mechanism for maintenance of a normal epicardial Po₂ under these circumstances, namely an increase in capillarity and a reduction in intercapillary distances, has been found not to be the case (M. M. Winbury, personal communication). Of major importance in the further testing of this hypothesis will be studies during preexisting myocardial ischemia, since maximal coronary vasodilation is expected under this condition.

In contrast, in a preliminary report of studies performed in open-chest dogs, intravenous or intracoronary administration of nitroglycerin is alleged to cause a decrease in contractility and distribution of coronary blood flow in the acutely ischemic subendocardium (52). It is postulated that the subendocardial vessels are maximally dilated in the presence of the ischemia and that the epicardial vessels, which presumably are not fully dilated under the experimental conditions of the study, dilate in response to the nitroglycerin and "steal" blood from the inner layers. How this mechanism can be reconciled with the known beneficial effects of nitroglycerin on the signs and symptoms of clinical subendocardial ischemia remains to be explained.

In Summary.—A gradient in systolic coronary blood flow paralleling the intramyocardial tissue-pressure gradient can be demonstrated in experimental animals. Although it is probable that coronary flow decreases or ceases in the subendocardium during ventricular systole, the resultant autoregulatory response causes coronary vessels to dilate more in the subendocardium than in the epicardium during diastole, resulting in a greater diastolic coronary blood flow in the former than in the latter. Thus, a nutritionally adequate coronary blood flow is maintained in the subendocardium each cardiac cycle. However, the endocardium is vulnerable in regard to its coronary blood supply: myocardial ischemia can maximally dilate the subendocardial coronary vessels more easily than it can the epicardial vessels and thus remove the capacity for a greater reduction of diastolic coronary vascular resistance in the subendocardium. The inability to make up the systolic coronary blood flow deficit in the subendocardium under these conditions results in manifestations of ischemia earlier and more severely in the inner layers of the ventricle.

The weight of present evidence indicates that nitroglycerin may increase the distribution of flow to the subendocardium, most likely through its effect on both the preload and the afterload of the ischemic left ventricle. However, direct effects of this drug on the
coronary vasculature have been proposed. β-receptor blockade by propranolol also increases the subendocardial distribution of flow in the ischemic left ventricle, but the mechanism is undoubtedly complex in view of the drug’s effects on myocardial contractility and on the coronary resistance vessels.

References

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