Determinants and Prediction of Transmural Myocardial Perfusion

JULIEN I. E. HOFFMAN, M.D., F.R.C.P.

SUMMARY The vulnerability of subendocardial muscle to ischemic damage is due primarily to the greater risk of underperfusion. Recent studies of coronary autoregulation have shown that as myocardial oxygen needs increase beyond the ability of coronary blood flow to supply oxygen, maximal vasodilatation occurs earliest in subendocardial vessels; any further imbalance then causes subendocardial ischemia, since no further compensatory vasodilatation is possible. In animal experiments relative subendocardial perfusion (the ratio of flow per gram in subendocardial to subepicardial muscle) can be predicted from the DPTI:SPTI ratio of two pressure-time areas, where DPTI = the area between coronary and left ventricular pressures in diastole and SPTI = the area beneath the left ventricular systolic pressure. Early studies demonstrated subendocardial underperfusion when DPTI:SPTI was below 0.7, but more recent studies show that this critical ratio is about 0.4. Applying the results of these animal studies to man must be done very cautiously. Peak ventricular systolic pressure is better than SPTI in predicting myocardial oxygen needs, but neither measure allows for changes in wall tension or contractility.

Second, increased coronary vascular resistance at maximal vasodilatation results in subendocardial underperfusion at DPTI:SPTI ratios above 0.4; these resistances increase with myocardial edema, hypertrophy, coronary vessel disease or increased blood viscosity. Finally, DPTI probably overestimates the actual mean pressure drop across the coronary vascular bed because in diastole intramyocardial tissue pressures may be 20–30 mm Hg.

SUBENDOCARDIAL MUSCLE (the innermost or deepest quarter or one-third of the thickness of the free wall of the left or right ventricle) is exceptionally vulnerable to necrosis and fibrosis, both when coronary arteries are normal and when they are narrowed by atheroma. In patients with normal coronary arteries, left ventricular subendocardial damage has been noted when there is severe aortic stenosis or incompetence,1-5 hemorrhagic shock,6,7 pulmonary embolism,8 prolonged hypothermia,8 after cardiopulmonary bypass,9,10 and in some types of cyanotic heart disease. Similar damage to right ventricular subendocardial muscle has also been found in patients with right ventricular hypertrophy, especially if they also have cyanotic heart disease.1,2,11,12 When coronary arteries are severely narrowed by atheroma, there may be infarction that is either entirely subendocardial or that, even if transmural, shows more intense, more confluent, and longer-lasting damage in the subendocardial than subepicardial muscle.13-18 Animal models of some of these states display similar localized damage.19-21

The lesions are usually thought to be due to ischemia. The fact that ischemic damage preferentially affects subendocardial muscle could come about in one or more of three ways: Subendocardial muscle might use more oxygen, it might be more easily damaged by a decreased oxygen supply, or it might more readily become underperfused. There is evidence that subendocardial oxygen consumption per unit weight is normally about 20% higher than that of subepicardial muscle.22,23 In addition, compared with subepicardial muscle, subendocardial muscle has lower venous oxygen saturations,22,23 tissue oxygen tensions24,25 and NAD+/NADH ratios,26 as well as changes in glycolytic intermediates that suggest a tendency to anaerobiosis.27 These factors might explain why Dunn and Griggs observed that when the ventricles were fibrillated and all coronary inflow was abruptly stopped, a greater accumulation of lactate occurred in subendocardial than subepicardial muscle.28

Despite these metabolic differences, however, most evidence indicates that subendocardial ischemic damage is due to marked underperfusion. The heart is
an organ with an enormous need for oxygen and blood flow (table 1). At rest, the left ventricle uses 20 times more oxygen per 100 g than the whole body, and even with severe exercise the heart still uses five times more than the whole body. To get this vast amount of oxygen the heart needs a high blood flow, and even then extracts most of the oxygen from the blood perfusing it. Although myocardial oxygen extraction can be increased, the margin for increase is small and the resultant fall in oxygen tension makes further extraction an inefficient method of delivering oxygen to tissues. As a result, the increased oxygen delivery needed by the heart when its work increases is obtained mainly by an increased coronary blood flow. This dependence of myocardial oxygen supply on coronary blood flow also implies dependence on coronary vascular resistance since, by the hydraulic equivalent of Ohm's law, flow = pressure drop/resistance, and pressures tend to remain fairly constant.

Changes in coronary vascular resistance are the basis for the phenomenon of autoregulation, a term which indicates that the heart regulates its oxygen supply and blood flow according to its needs. One way of demonstrating this is shown in figure 1, which presents diagrammatically the results of an experiment in which a Gregg cannula is placed in the left main coronary artery of a dog, coronary flow is measured by an electromagnetic flowmeter, left ventricular pressure and cardiac work are kept constant, and coronary perfusion pressure is varied. As coronary perfusing pressure is lowered in steps, the lower horizontal line in the upper panel shows that steady state flow remains constant down to a mean pressure of about 60 mm Hg. Apparently, resistance must have decreased in parallel with the fall in perfusing pressure. Similarly, raising the perfusing pressure does not alter coronary flow until some pressure about 120–140 mm Hg is reached; once again, resistance must have increased in parallel with the increase in pressure for flow to stay constant. The range of pressures over which flow remains constant while perfusing pressure is varied is the autoregulatory range, and it is only when perfusing pressures fall below or above that range that flows decrease or increase, respectively (lower horizontal line, fig. 1A). The fall in flow at low perfusing pressures suggests that vasodilatation can no longer compensate for a

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Exercise

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Date simplified from Ekelund and Holmgren\(^a\) and Kitamura et al.\(^b\)

Abbreviations: LV = left ventricular; \( V_{OE} \) = oxygen consumption.

![Figure 1. Coronary pressure-flow diagrams. A) Upper panel: Two curves with autoregulation. Slanting straight line represents pressure-flow curve when vessels are maximally dilated. B) Lower panel: Solid lines are curves with autoregulation and maximal vasodilatation from upper panel. Dashed lines indicate comparable curves when coronary conductance is decreased.](image-url)
decreased pressure drop, so that at this time at least some vessels are maximally dilated. Whenever vessels are maximally dilated, flow through them depends on the pressure drop so that flow is said to be pressure dependent. In terms of Ohm’s law, when resistance is minimal and can fall no further (maximal vasodilatation), then flow = pressure drop/minimal resistance, and flow is then proportional to the pressure drop, with the value for minimal resistance being the constant of proportionality.

The slanting straight line to the left of the autoregulatory curves in figure 1A is the pressure-flow relation obtained when all the coronary vessels are maximally dilated; for example, by an infusion of adenosine. At any perfusing pressure the vertical distance between the autoregulated and maximally vasodilated curves is a measure of the reserve for further coronary vasodilatation. If, in the autoregulated vascular bed, the coronary artery is occluded for 15 seconds and then released, there will be metabolically-induced reactive hyperemia, and at any given pressure the peak flow during the hyperemia will lie on the equivalent pressure-flow point on the slanting straight line obtained during adenosine infusion. Clearly, as perfusing pressure is reduced the coronary vasodilator reserve decreases; this would be shown by lesser peak reactive hyperemia.

The upper autoregulatory line in figure 1A shows increased coronary flow as a result of an increased myocardial need for oxygen (more cardiac work) or by anemia. Autoregulation vasodilates vessels so that either added oxygen is brought in to meet the increased demands or the reduced oxygen carrying capacity of the blood is compensated for. There is still an autoregulatory range, but the flows are higher at any given perfusing pressure. This means that the coronary resistance is lowered at any perfusing pressure so that the vessels have dilated; it is obvious that the coronary vasodilator reserve has been diminished. As a result, maximal vasodilatation will be reached in some vessels at a higher perfusing pressure than when flows were lower, so that the lower end of the autoregulatory range will be raised.

Another cause of an increased lower limit of the autoregulatory range is illustrated in figure 1B. The solid lines represent the normal autoregulatory and maximally vasodilated curves discussed in figure 1A, and the dashed lines are the equivalent curves obtained when minimal coronary vascular resistance has been increased by thickening of the coronary arteries, increased blood viscosity, myocardial edema or obliteration of some of the coronary arterial branches. At maximal vasodilatation there is less flow at any given pressure, i.e., the maximal conductance has decreased. When there is autoregulation, a normal flow or oxygen supply will be achieved by some vasodilatation of the remaining or narrowed vessels. Once again, coronary vasomotor reserve has been reduced and maximal vasodilatation in certain vessels will be reached at pressures higher than those in the normal state.

A crucial question is whether maximal vasodilatation is reached earlier in subendocardial than subepicardial vessels. Griggs and Nakamura31 studied subendocardial perfusion after reducing the coronary perfusing pressure and realized that maximal dilatation of subendocardial vessels was necessary to their explanation of their findings; they had, however, no direct supportive experimental data. Buckberg et al.39 went one step further and showed that when subendocardial underperfusion occurred, there was much less reactive hyperemia than in the control state; they drew essentially the same conclusions as did Griggs and Nakamura, but still did not prove that maximal vasodilatation took place first in the subendocardial region. Recently, however, studies by Rouleau et al.33 and Winbury (personal communication) leave no doubt that when coronary pressure is lowered progressively, maximal vasodilatation is reached earliest in the subendocardial vessels. In the autoregulatory range, flows per gram are similar in the subendocardial and subepicardial regions. When perfusing pressure is below the lower end of the range subendocardial flow falls, but subepicardial flow is maintained; the subendocardial flow found at that pressure is identical to subendocardial flow found at the same perfusing pressure when all vessels are maximally dilated by an adenosine infusion. At this time there is still some reactive hyperemia, though much less than normal, because there is some vasodilator reserve left in vessels in the midmyocardium and subepicardium.

These experiments indicate that when perfusing pressures change, coronary flow can initially be maintained to each layer of the left ventricle because vasodilatation lowers resistance appropriately. When perfusing pressure drops below a certain level (the lower end of the autoregulatory range) maximal vasodilatation takes place first in the deepest, subendocardial muscle and flow there becomes pressure dependent. Any further fall in perfusing pressure then causes a decreased flow to the subendocardial muscle, but flow remains normal in the rest of the muscle in which the vessels still retain some vasomotor reserve. Further decreases in perfusing pressure will eventually exhaust the autoregulatory ability in successive layers of the free wall of the left ventricle from inside out, but at each low pressure flows will be lowest in the deepest muscle and will increase progressively the more superficial the muscle layer.39

The reasons for the earlier exhaustion of autoregulation in subendocardial vessels are not fully known. If there is a tendency for greater oxygen usage or lower oxygen tensions in subendocardial muscle, one would expect the subendocardial vessels to be more susceptible than subepicardial muscle to reduced blood flows. However, it is likely that physical factors play an even more important part in reducing subendocardial blood flow and exhausting subendocardial vasomotor reserve. Since 1939, when Johnson and Di Palma34 were the first to study left ventricular intramyocardial pressures, it has been known that in
systole, pressures within the myocardium are high and may even exceed intracavitary pressures. However, when anything is placed in the myocardium to measure local pressures, there is a great possibility of artifactually distorting tissues and overestimating the actual pressures that are there. This was shown as early as 1941 by Gregg and Eckstein,35 and to date there is no measuring technique that can be regarded as free from artifact. What does seem clear from several studies is that in systole the pressures in the subendocardial muscle equal or exceed pressure in the left ventricular cavity, and that intramyocardial pressures decrease toward the epicardial surface; most studies suggest that near that surface intramyocardial pressures are very low.36

Although the level of the pressures and the form of their distribution across the wall are not known, there are some indications that intramyocardial systolic pressure is about equal to intracavitary pressure and that it falls off to almost zero at the epicardial surface. Brandi and McGregor37 infused saline into a needle placed in the myocardium, and noted that as the infusion rate was lowered (steady state), the pressure recorded through the needle became lower. They plotted these recorded pressures against infusion rates and extrapolated to the pressure expected at zero infusion rate; in the subendocardium the extrapolated intramyocardial systolic pressure equalled that in the left ventricle and the pressures decreased linearly to almost zero at the epicardial surface. They were careful to state that the extrapolated pressures represented those at an infinitely small point, and that actual pressures around vessels of finite size might be higher. Two studies have given indirect measurements of intramyocardial pressures. Downey and Kirk38 measured flow in a branch of the left coronary artery at different perfusing pressures while left ventricular systolic pressure was kept constant and the vessels were maximally dilated with adenosine. They compared the results with those from a computer simulation of the myocardium as a series of waterfalls with different pressures, and concluded that the intramyocardial systolic (or waterfall) pressure in the deepest subendocardial muscle was equal to cavity pressure. Hess and Bache39 prepared chronically instrumented dogs and measured coronary flows and pressures during continuous coronary flow, while flow was permitted only with each systole, and while flow was permitted only with each diastole. With systolic flow, the coronary flow to subendocardial muscle was about one-fourth to one-sixth that to the subepicardial muscle, implying a gradient of tissue pressure throughout the wall, with the highest pressures in the deep muscle being no greater than cavity pressure.

Given that intramyocardial systolic pressures in deep muscle equal (or at times exceed) those in the left ventricular cavity, it is safe to conclude that there is no flow to subendocardial muscle during systole. There is probably some flow to more superficial muscle layers in which intramyocardial pressures are less than perfusing pressures. This concept corresponds with the fact that only 20%–30% of coronary flow takes place in systole. With these assumptions, it is clear that subendocardial muscle can be perfused only in diastole. Since flows per gram of muscle are about equal across the wall at rest or during exercise, there must be a gradient of resistance across the wall, with the resistance being lowest in the subendocardial muscle and rising toward the surface; in this way subendocardial muscle can get during diastole what more superficial muscle gets over the whole cycle.40 We do not know whether the lower subendocardial resistance is due to more vessels of normal size or else to the same number of vessels that are more dilated than those in the subepicardial muscle.

With the dependence of subendocardial blood flow on diastolic perfusion it is easy to understand why so many studies have shown that reduced coronary perfusing pressures cause profound subendocardial ischemia. It was not until 1968, however, that any attempt was made to predict when subendocardial ischemia would occur. Griggs and Nakamura31 cannulated the left main coronary artery of the dog, reduced coronary perfusing pressures to various degrees, and measured regional myocardial blood flow with a diffusible indicator. They calculated a “coro-

nary-ventricular” pressure ratio as the area under-

neath the coronary arterial pressure curve throughout the cycle divided by the area under the left ven-

tricular pressure curve in systole. When this ratio was below 1.4 there was subendocardial underperfusion, and there was a roughly linear relationship of the coronary-ventricular pressure ratio to the relative subendocardial blood flow measured as the ratio of the subendocardial-to-subepicardial blood flow per gram.

In 197232 we extended that study to a number of animal models of human disease without cannulating the coronary artery. Since subendocardial perfusion occurs only in diastole we chose to measure the area below the coronary arterial pressure in diastole and related it to the area underneath the left ventricular pressure curve in systole. We assumed, on the basis of existing fragmentary evidence, that in diastole the intramyocardial pressure in the wall of the left ventricle was low and similar to the left ventricular diastolic pressure. Therefore we measured the area between aortic and left ventricular pressures in diastole, assuming that aortic and coronary pressures were similar in the absence of coronary occlusive lesions. This area was termed the diastolic pressure time index (DPTI), and when multiplied by heart rate it is an index of the mean pressure product and time available each minute to supply blood to the subendocardium in diastole. The area underneath the left pressure curve in systole was also measured because Sarnoff et al.41 had demonstrated that it was closely related to the left ven-
tricular oxygen needs. They termed it the tension time index (TTI), but since pressure rather than tension is being measured, we subsequently termed it the systolic pressure time index (SPTI).

The reason for taking a ratio of these two areas needs further clarification. From the studies of
autoregulation (fig. 1), it is clear that a reduction of DPTI will not alter subendocardial blood flow as long as the subendocardial vessels retain some vasodilator ability. When DPTI becomes small enough, the subendocardial vessels become maximally dilated and subendocardial flow will be pressure-dependent; the actual subendocardial flow will be the observed mean pressure drop (DPTI) multiplied by the constant of proportionality (1/minimal resistance). It is not possible, however, to determine when maximal subendocardial vasodilatation occurs from DPTI alone, since we also must know what the myocardial demand for oxygen is. This is equivalent to knowing which horizontal line in figure 1A is applicable. If DPTI is low, it might be adequate to supply low oxygen needs, but inadequate to supply greater oxygen needs. One way to assess the oxygen needs is to measure the SPTI. A low DPTI would be adequate to supply oxygen with a low SPTI, but a higher DPTI might be insufficient for oxygen supply if the SPTI (and thus myocardial oxygen needs) were very much increased. The ratio of the two areas would be a better estimator of the balance of myocardial oxygen supply and demand.

We therefore produced changes in DPTI and SPTI by taking open chested, anesthetized dogs and creating arteriovenous fistulae, pacing to high rates, constricting the aorta either just above the valves or near the diaphragm, infusing isoproterenol, and by several other maneuvers. From the hypothesis of the dependence of subendocardial flow on diastolic perfusion pressure and time, we predicted that a reduced DPTI:SPTI ratio would be associated with a decreased proportion of coronary blood flow in diastole and also with a decreased proportion of blood flow to the subendocardial muscle. The latter proportion was judged as the ratio of flow per gram in the subendocardial:subepicardial muscle on the assumption that the subepicardial flow, not restricted by high intramyocardial pressures, would reflect the needs of the myocardium for blood. Both of the predictions were confirmed in the initial studies and in many subsequent ones, so to that extent the original hypothesis was confirmed. It seemed that a practical method of predicting the adequacy of subendocardial flow had been developed, a method that might be applied to the care of patients with cardiovascular problems.

Animal studies showed that as long as the DPTI:SPTI ratio was above 0.7–0.8, flows remained more or less equal across the left ventricular wall; that is, the subendocardial:subepicardial (or inner:outer) ratio was about 1. When the DPTI:SPTI ratio fell below 0.7–0.8, then there was a decreased inner:outer ratio that was linearly related to the DPTI:SPTI ratio (fig. 2). This critical value of the DPTI:SPTI ratio below which relative subendocardial underperfusion occurs has been examined in patients and found to bear some relation to the outcome. However, this critical ratio in normal dogs may actually be closer to 0.4–0.5, and in fact we have obtained this critical value in more recent experiments. The reason for the discrepancy is that in the original studies we did not appreciate the importance of anemia, which not only increases resting coronary flows but at the same time reduces vasomotor reserve and raises the lower limit of the autoregulatory range. This was demonstrated by Brazier et al., who examined dogs with supra-
valvular aortic stenosis (which changes the DPTI:SPTI ratio) and varying degrees of anemia. The dogs with anemia had a critical DPTI:SPTI ratio that was much higher than that in the dogs with normal hemoglobin levels, so that a plot of DPTI:SPTI against the inner:outer ratio for all the dogs showed a poor relationship between the two ratios. They dealt with this problem by the simple method of converting DPTI (which at maximal vasodilatation is a measure of flow) into a measure of oxygen supply by multiplying DPTI by arterial oxygen content; flow times oxygen content is a measure of the total amount of oxygen brought to a tissue. When they did this, the ratio CaO₂ × DPTI:SPTI—known as the myocardial oxygen supply: demand ratio—became very closely related to the inner:outer flow ratio. As long as the myocardial oxygen supply: demand ratio was over 8 to 10, flows remained equal across the wall, but subendocardial underperfusion occurred at lower myocardial oxygen supply: demand ratios. Since a normal arterial oxygen content is about 19 or 20 ml/dl, the critical myocardial oxygen supply: demand ratio can be transformed into the critical DPTI:SPTI ratio at normal hemoglobin levels by dividing by 19 or 20; this yields a critical value for the DPTI:SPTI ratio of about 0.4–0.5, as found by more recent studies done with normal hemoglobin levels.44

Does this mean that we should adopt a critical DPTI:SPTI ratio of about 0.4 or a critical CaO₂ × DPTI:SPTI ratio of about 8 for use in patients? Before doing so we need to consider some of the problems that are likely to interfere with the predictive ability of these ratios, and these problems fall into three areas: the use of SPTI as a measure of myocardial oxygen needs, the value of minimal coronary resistance in various diseases, and the use of DPTI to measure the mean diastolic pressure drop.

The use of SPTI to estimate myocardial oxygen needs requires careful attention. Although it does indeed show a relationship to myocardial oxygen consumption, it is not a close one. Various studies in dogs and man have shown that the best estimator of left ventricular oxygen consumption is peak developed tension times heart rate.45,46 Peak left ventricular systolic pressure times heart rate is not as good, and SPTI times heart rate is an even less good estimator.46,47 (table 2). Jorgensen et al.47 showed that in exercising normal people the myocardial oxygen consumption can be predicted accurately from the product of peak pressure times heart rate both before and after treatment with propranolol, but that SPTI times heart rate is a poor predictor of measured myocardial oxygen consumption after propranolol has been given. If the ratio DPTI: peak pressure is to replace the ratio DPTI:SPTI, normal values for predicting the inner:outer flow ratio from this new pressure ratio are required. Preliminary observations suggest that the critical DPTI: peak pressure ratio is about 0.07, or the critical ratio of DPTI × CaO₂: peak pressure is about 1.4. More complete studies of these ratios are needed to determine if they are better predictors of subendocardial blood flow.

The data show that SPTI is the least efficient predictor of myocardial oxygen need of any index available. They do not show that DPTI:SPTI is an inadequate index of relative subendocardial perfusion, since SPTI may affect subendocardial flow by other means; for example, by altering the time constants for vessels to reopen. When we determine the correlation between the inner:outer flow ratio and either DPTI:SPTI or DPTI: peak systolic left ventricular pressure, we find no differences in predictive value for the two ratios. Further studies of these ratios are needed.

A review of our own and other published studies indicates that the confidence limits with which we can predict myocardial oxygen consumption in man or dog can be narrow in very well-controlled studies, but vary much more widely if pressures, flows and heart rates are allowed to alter over a large range. In part, this variability could be due to changes in contractility which, with wall tension, is the major determinant of myocardial oxygen consumption. Graham et al.48 demonstrated that when contractility was increased at fixed wall tension there was a large increase in left ventricular oxygen consumption, and that at fixed contractility an increased tension also increased oxygen use. However, we have no easy method for incorporating increases or decreases of contractility, even if we could measure them, into formulas for predicting

### Table 2. Correlates of Myocardial Oxygen Consumption

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<th>N</th>
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1 = all measurements in series; 2 = all dogs with 6 or more measurements; 3 = personal unreported data; 4 = includes controls from reference 90; 5 = controls plus propranolol data.

N = number of observations; MVO₂ = mean myocardial oxygen consumption (ml/min/100 g); CV% = % coefficient of variation; PDT = peak developed tension; PP = peak systolic pressure; SPTI = systolic pressure time index; HR = heart rate (beats/min).
myocardial oxygen consumption. In addition, in some instances the two effects tend to cancel out. An increased heart rate itself is inotropic, but because it tends to decrease left ventricular volume the increase in oxygen consumption is less than would occur in isolated muscle strips. This may be why Jorgensen et al. observed equally good prediction of myocardial oxygen consumption during exercise before and after propranolol had been given, and why Krasnow et al. showed that myocardial oxygen consumption per unit of SPTI increased by only 25% during maximal stimulation with isoproterenol. The effect that this would have would be to raise the critical DPTI:SPTI ratio from about 0.4–0.5 to about 0.5–0.6. However, should the inotropic drive increase myocardial oxygen consumption without decreasing ventricular volume, as could occur with very sick hearts, then the critical DPTI:SPTI ratio could be as much as 0.6–0.8; it is unlikely to be much higher from inotropic stimulation alone.

The importance of failure to predict myocardial consumption accurately in individuals should not be overestimated. If the 95% confidence limits for predicting myocardial oxygen consumption from peak left ventricular pressure times heart rate are about 36% of the mean value, as in Jorgensen's study, then for one person in 40 the critical DPTI:SPTI ratio could be as high as 0.54 or as low as 0.26, assuming a mean value of 0.4. On the other hand, in two-thirds of the critical DPTI:SPTI ratio would not vary beyond the range of 0.33 to 0.47, an acceptable range for clinical purposes.

The other two problems relate to the use of DPTI to predict subendocardial blood flow. With maximal vasodilatation in the subendocardium, flow to the subendocardial muscle will be proportional to DPTI. However, there will not be a fixed low value for minimal coronary vascular resistance. Obviously, if there is occlusive coronary arterial disease, the resistance offered to flow by the peripheral resistance vessels and the obstructed vessel will be much higher than normal and subendocardial flow will be less than predicted on the basis of studies of normal dogs. Similarly, the minimal resistance may be elevated if there is myocardial edema, as has been seen in hemorrhagic shock and other diseases. We and others have noted that in dogs with experimental left ventricular hypertrophy there is an increased coronary vascular resistance at maximal vasodilatation, so once again the subendocardial flow expected from a given DPTI would be less than in normal dogs. The effect of the increase in minimal coronary vascular resistance would be to cause earlier pressure dependency than expected, so that the critical DPTI:SPTI ratio (normal hemoglobin) at which underperfusion occurs would be higher than 0.4. This may be why clinical studies seem to show some relationship between clinical outcome after surgery and a critical DPTI:SPTI ratio of 0.7: the higher critical ratio could have been needed because of myocardial edema or other causes of increased coronary vascular resistance. However, until we know to what extent minimal coronary vascular resistance is altered by various diseases, it will be difficult to set a critical pressure ratio that can be used in everyone.

Resistance could be lower than normal if there were more than the normal number of resistance vessels. This is unlikely to occur in acquired heart disease, but could occur in fetal or newborn periods when the capacity to form new vessels might still be present. Archie et al. banded the pulmonary artery in newborn lambs and induced right ventricular hypertrophy. They found that during isoproterenol infusion or volume loading there was a marked increase in right ventricular flow that suggested an above normal vasodilator ability in the right coronary bed.

The last, and potentially most important, difficulty relates to the measurement of the mean pressure drop in any layer of the myocardium. We first became suspicious that there was a problem when in a study done in dogs we produced very low DPTI:SPTI ratios but failed to demonstrate a decreased inner:outer flow ratio. Further examination of the experiments showed that this failure was associated with high aortic and coronary arterial pressures, a point that assumed importance when we realized that in all our earlier studies of this relationship we had always had low diastolic aortic pressures, whether the SPTI had been normal or high. One way of reconciling these two sets of experiments would be to hypothesize that intramyocardial pressure in diastole is normally much higher than the normal diastolic left ventricular pressure. If this were so, then the mean DPTI calculated from aortic and left ventricular diastolic pressures would underestimate the mean pressure drop, and this underestimate would be worse when aortic diastolic pressure was low than when it was high. For example, if the mean aortic pressure in diastole is 40 mm Hg and mean left ventricular diastolic pressure is 10 mm Hg, then the calculated mean pressure drop is 30 mm Hg; if, however, intramyocardial diastolic pressure is 25 mm Hg, then the true mean pressure drop would be 15 mm Hg, and our measured DPTI would be 100% too large. On the other hand, if the mean aortic diastolic pressure is 80 mm Hg, then the estimates of mean pressure drop would be 70 mm Hg using left ventricular diastolic pressure and 55 mm Hg using intramyocardial pressure; the underestimate of DPTI would be only 27%.

The first indication that there might be such high diastolic intramyocardial pressures came in the studies by Rouleau et al. that were referred to earlier in this discussion. In seven dogs with cannulated main left coronary arteries, maximal vasodilatation was achieved by infusing adenosine. Left ventricular systolic pressure was kept at about 100 mm Hg and coronary pressures were reduced below this pressure. In each dog, two or three determinations of regional pressure flow relations were made. By extrapolating the pressure flow curves down to zero flow, it was possible to estimate what the zero flow pressure would be. Since coronary perfusing pressures were usually
well below ventricular systolic pressure, the flows obtained were probably confined to diastole, so the curves represented diastolic pressure flow curves. The zero flow intercept on the pressure axis occurred at pressures of 20-54 mm Hg and were higher in subendocardial (mean 32 mm Hg) than subepicardial (mean 17 mm Hg) muscle. A similar study in two dogs with polycythemia\textsuperscript{54} gave similar results for the intercepts but the slopes of the pressure flow curves — the conductances — were lower in the dogs with polycythemia (fig. 3).

Intramyocardial diastolic pressures of this magnitude were so unexpected that we were concerned that some artifact was responsible for them. However, some data suggest that diastolic intramyocardial pressures can be high. The most convincing is the study by Bellamy\textsuperscript{55} of diastolic pressure flow curves in chronically instrumented dogs with slow heart rates. He demonstrated that these curves were linear and that they intersected the pressure axis to give a zero flow pressure of about 45-55 mm Hg; with a very long diastole there was actually no coronary flow when aortic pressure was about 50 mm Hg. Furthermore, he showed that with maximal vasodilatation the curves become steeper and the intercepts on the pressure axis dropped to about 20 mm Hg. With this confirmation it is possible to review many previous studies of coronary flows and pressures and to note that whenever the coronary artery is occluded there is a residual pressure beyond the obstruction — known as the peripheral capillary pressure — that is often as high as 20 mm Hg. This pressure has frequently been regarded as being related to retrograde flow, but could be related to the diastolic tissue pressure.

To explain how tissue pressures can be so high in diastole, we must invoke a more realistic model of the myocardium than has usually been used. In most models the left ventricle is regarded as becoming thicker-walled during systole, and during this time there are high systolic intramyocardial pressures generated in the wall with the highest pressure on the inside. In diastole the heart relaxes, its wall thins, and tissue pressures drop to very low levels with little difference across the wall (fig. 4A). However, this model does not take into account that the myocardium is a very vascular structure that is attached to a high pressure vascular bed — the aorta. In systole, with high intramyocardial pressures, blood is squeezed out of the heart, so that a jet of blood comes out of the coronary sinus; coronary inflow diminishes, so that evidently the myocardial blood volume decreases in systole. In diastole, as the heart relaxes, coronary sinus outflow decreases and coronary inflow increases, so that myocardial blood volume gets bigger. In diastole the myocardial tissue is in direct continuity with a fluid-filled system — the aorta — with a mean diastolic pressure of 90 mm Hg (fig. 4B). Therefore, there will be distension of myocardial tissue and some transmission of aortic pressure into it, so that diastolic...
TRANSMURAL MYOCARDIAL PERFUSION/Hoffman

SYSTOLE

120

120

DIASTOLE

90

10

A

\[ \text{mm Hg} \]

\begin{align*}
0 & \quad \text{Endo} \\
80 & \quad \text{Epi} \\
160 & \quad \text{Epi}
\end{align*}

\begin{align*}
\text{Endo} & \quad \text{Epi} \\
\text{Endo} & \quad \text{Epi}
\end{align*}

B

\[ \text{mm Hg} \]

\begin{align*}
0 & \quad \text{Endo} \\
80 & \quad \text{Epi} \\
160 & \quad \text{Epi}
\end{align*}

\begin{align*}
\text{Endo} & \quad \text{Epi} \\
\text{Endo} & \quad \text{Epi}
\end{align*}
tissue pressures could be very high and not necessarily related to the diastolic pressures in the ventricular cavity.

If this hypothesis is true, as many experiments suggest, a large field opens up. How do the tissue pressures change as the ventricles dilate or hypertrophy? What is the time course of pressure change during diastole? What effect do edema, fibrosis, vasodilatation and vasoconstriction have? Does an intact pericardium affect these pressures? Since pressures in a coronary artery beyond a severe obstruction are about 30 mm Hg, do intramyocardial diastolic tissue pressures play a part in causing subendocardial ischemia? Does this mechanism play a part in producing infarction when there is atherosomatous narrowing of the coronary artery but no occlusive thrombus? What happens to these tissue pressures during coronary spasm, and could they play a part in producing some of the features of Prinzmetal's (variant) angina? All of these issues must be examined.

To summarize the present state of this field of pathophysiology, much remains to be done to confirm or amend our current concepts of systolic intramyocardial pressures and the effect of these pressures on systolic myocardial blood flow in various parts of the heart, and of concepts of diastolic intramyocardial pressures which may be even more important determinants of regional myocardial blood flow. The importance of metabolic differences in different parts of the ventricles must be defined. Variations in minimal vascular resistance in different disease states must be measured. These remaining tasks should not obscure the real gains that have already been made. The concept of matching oxygen supply to demand is of the greatest importance but is too general to be of specific clinical use. The indices of supply and demand that were originally described have been oversimplified and cannot be used without some changes, many of the details of which still remain to be worked out. However, the myocardial oxygen supply: demand ratio (\(\text{CaO}_2 \times \text{DPTI:SPTI}\)) can at least be used to set limits. A ratio of about 8 is the minimal ratio required for adequate subendocardial perfusion in normal hearts, so that any ratio below 8 is almost certain to jeopardize subendocardial perfusion. Should the heart be abnormal in terms of hypertrophy, possible myocardial edema, excessive inotropic drive or acute ventricular dilatation, a higher critical ratio of at least 16 should be assumed and attempts made to alter pressures to achieve that ratio. The higher the pressure ratio, the more likely is there to be adequate subendocardial perfusion. Greater predictive accuracy that may become available in years to come would certainly be even more useful, but we have enough information now to use estimates of subendocardial perfusion in the management of patients.

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