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Sympathetic Influences on Coronary Perfusion and Evolving Concepts of Driving Pressure, Resistance, and Transmural Flow Regulation

SINCE THE HEART is basically an aerobic organ, maintenance of O_2 delivery adequate to meet myocardial metabolic requirements is of paramount importance. An understanding of mechanisms controlling myocardial O_2 delivery is essential for developing and evaluating therapeutic interventions for situations in which O_2 delivery falls short of O_2 demand, *e.g.*, myocardial infarction. The article by Klassen and colleagues[1] in this issue of ANESTHESIOLOGY examines effects of acute sympathectomy produced by epidural anesthesia on transmural myocardial perfusion, and thus O_2 delivery, in circumstances of normal as well as decreased flow.

There is no question that interest in—and appreciation of—autonomic neural mechanisms for regulating coronary blood flow have increased appreciably during the past few years. The preponderance of earlier work was performed in anesthetized animals, where neural effects were undoubtedly blunted and quantitative observations difficult to extrapolate. Nevertheless, it was possible to demonstrate that activation of the alpha-adrenergic portion of the sympathetic nervous system could exert a vasoconstrictor effect on the coronary vasculature, with a decrease in coronary inflow.[2,3] As experiments in conscious animals became more common, the potential importance of this mechanism became clearer.[4,5] More recently, several groups[6,7] have suggested that tonic alpha-adrenergic tone may limit the ability of the coronary vasculature to autoregulate in response to an ischemic stimulus, and may participate importantly in the control of myocardial O_2 delivery and the transmural distribution of myocardial blood flow.[6–8]

Although evidence in man supporting this concept is limited, a recent study comparing normal subjects and cardiac allograft recipients[9] has suggested that significant vasoconstrictor tone is present in the normal coronary vasculature under basal conditions. This vasoconstrictor tone may be augmented to the point of angina production in some patients with coronary-artery disease.[10] Coronary-artery vasospasm, a common pathophysiologic mechanism in the variant angina syndrome, may also be related to abnormalities in the sympathetic nervous system.[11] Maseri *et al.*[12] have suggested that coronary-artery spasm is even responsible for the production of myocardial infarction in selected patients with coronary-artery disease.

Thus, a substantial body of evidence now supports the notion that the sympathetic nervous system plays an important role in myocardial flow regulation under normal circumstances and in disease states. Advantages of epidural anesthesia as an investigative tool for producing sympathetic blockade include ready reversibility, the ability to test segmental distribution, the avoidance of trauma to sympathetic nerves traveling with the coronary arteries, and the lack of interference with parasympathetic innervation. However, in attempting to place any individual study of autonomic effects into perspective, the work must be evaluated in light of changing concepts of flow regulation within the coronary vasculature. This area has evolved importantly during the past two to three years, particu-

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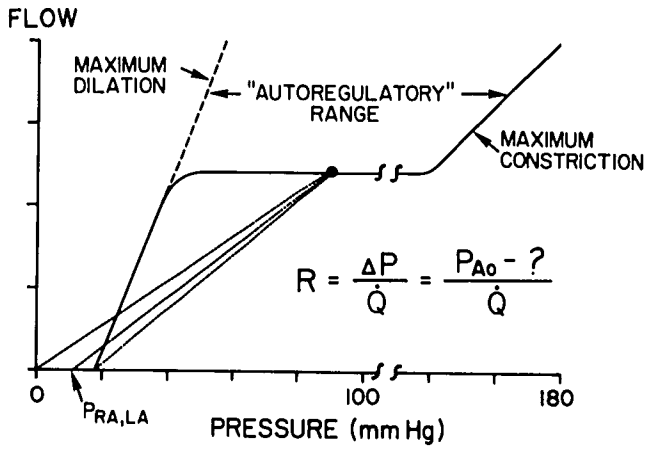

FIG. 1. Pressure–flow relationships in the coronary vasculature. Dotted lines illustrate different calculations of resistance, depending on the choice of "back pressure." See text for details. R = resistance, ΔP = driving pressure, $\dot{Q}$ = flow, P_{Ao} = aortic (inflow) pressure, $P_{RA,LA}$ = right and left atrial pressures.

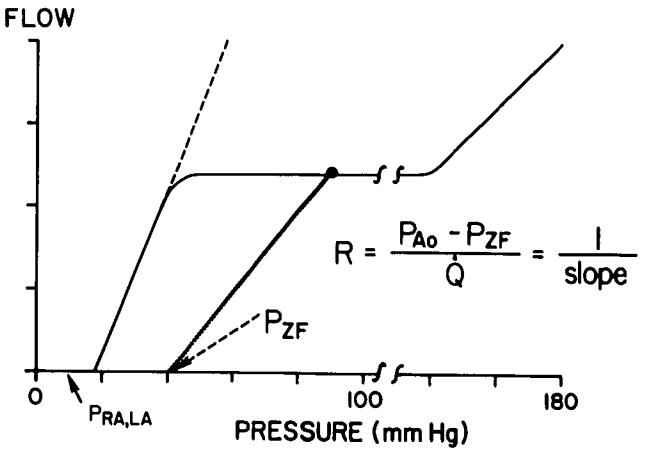

FIG. 2. Pressure–flow relationship during a single diastole. The thick dotted line illustrates that the relationship is linear, with a pressure-axis intercept that is higher than any of the values for "back pressure" suggested in figure 1. P_{ZF} = zero-flow pressure; other abbreviations as in figure 1.

larly in regard to concepts of driving pressure and vascular resistance.

Relationships among flow ($\dot{Q}$), pressure and resistance in the vasculature of the left ventricle have most frequently been expressed in a formulation similar to Ohm's law, $\dot{Q} = \Delta P/R$, where ΔP = driving pressure and R = vascular resistance. ΔP is more complex than previously appreciated, and approaches employing Ohm's law need to be re-examined. Figure 1 schematically represents traditional concepts of pressure–flow relations within the coronary vasculature. The solid black line depicts the relationship between flow and pressure over a wide range of these values. The range of pressure over which flow remains relatively constant—the so-called "autoregulatory" range[13]—lies between the bounds of maximum vasodilation on the left and maximum vasoconstriction on the right. The black dot represents a typical operating point within this range. Vascular resistance calculated for the point usually employs the Ohm's law formulation and places the point on one of the three dotted pressure–flow lines, depending on the value chosen for ΔP. ΔP has most often been taken as the difference between inflow and right atrial pressures, or as inflow pressure alone. Some investigators have used mean pressure for the entire cardiac cycle, while others have chosen mean diastolic values because of the preponderance of coronary blood flow during diastole. During the past few years attention has focused increasingly on the difference between inflow and left ventricular (or left atrial) diastolic pressures, since local tissue pressure limit may flow even during diastole.[14] Previous studies of autoregulation[15] suggest that the minimum pressure required for any flow during maximum vasodilation (the intersection of the pressure–flow curve with the pressure axis) is actually higher than either right or left atrial pressures. Thus, the proper choice of driving pressure is importantly at issue. Overestimates of ΔP lead to overestimates of coronary vascular resistance.

Figure 2 schematically represents recently obtained data that indicate that the magnitude of this problem is greater than previously suspected. When instantaneous pressure–flow relationships are quantified during single long diastoles, flow appears consistently to be a linear function of inflow pressure.[14,16] The reciprocal of the pressure–flow line provides a direct measure of coronary vascular resistance, and the pressure axis intercept, an estimate of the minimum inflow pressure required for any diastolic perfusion. The latter, termed zero-flow pressure (P_{ZF}), has been reported by Bellamy to be ~40 torr in conscious dogs under basal conditions,[14] and has recently been verified in our laboratory to be three to five times greater than mean left or right atrial pressure in open-chest dogs. Thus, forces opposing diastolic flow in the immediate vicinity of intramyocardial vascular channels are appreciably higher than previously considered. In addition—as will be discussed momentarily—this quantitatively important "back pressure" to flow can change in conjunction with physiologic interventions, and probably plays a dynamic rather than static role in the regulation of coronary blood flow.

It has long been appreciated that coronary blood flow can increase severalfold without a change in inflow (aortic) pressure. Commonly referred to as coronary "reserve," this capacity has been related to an inherent ability to decrease coronary vascular

resistance severalfold. In figure 2, this would correspond to increasing the slope of the thick dotted pressure–flow line. The maximum possible increase would correspond to the slope of the line at the left representing maximum vasodilation. While changes in coronary vascular resistance are the major mechanism involved in coronary reserve, changes in P_{ZF} may also play a role—*i.e.*, options for adjusting flow may include changes in position as well as slope of the diastolic pressure–flow relationship. Bellamy reported substantial decreases in P_{ZF} following total inflow occlusion or maximum pharmacologic vasodilation.[14] Our laboratory has recently observed that P_{ZF} appears to vary during modest changes in coronary vascular pressure and blood flow that would traditionally be attributed entirely to changes in coronary vascular resistance. Decreases in P_{ZF} occur as part of the compensation for effects of arterial stenosis. With mild stenoses, these decreases sometimes allow driving pressure to be maintained at near-normal levels, with preservation of basal perfusion without an appreciable change in resistance. We have also found that P_{ZF} and coronary vascular resistance change in directionally opposite fashion during the early phase of reactive hyperemia following total inflow occlusion. This observation further suggests that P_{ZF} and resistance are controlled by independent mechanisms. When coronary reserve has been exhausted, the coronary vasculature is presumed to be maximally dilated and the circulation to be operating on the "maximum vasodilation" line illustrated in figures 1 and 2. The position of this line is determined by P_{ZF}, which is presumably at or near a minimum value in situations in which maximum vasodilation has occurred. The demonstration that the diastolic pressure–flow curve can be shifted to the right by increased preload in the face of maximum vasodilation[16] reminds us that local tissue forces can alter flow independently of changes in vascular resistance, inflow pressure, or both. Additional studies during changes in autonomic neural activity are desirable to clarify any role of changes in P_{ZF} in flow responses to epidural anesthesia or other forms of sympathetic blockade.

In considering figures 1 and 2 from the viewpoint of the anesthesiologist, the situations of anemia and left ventricular hypertrophy are also of interest. The anemic patient requires a higher coronary blood flow to achieve normal O_2 delivery at any given level of myocardial metabolic demand. As outlined by Hoffman,[13] the horizontal portion of the overall pressure–flow relationship—*i.e.*, the portion within the autoregulatory range—is therefore elevated. Since the elevated portion intersects the maximum vasodilation line at a higher-than-usual pressure, maximum vasodilation occurs at a higher-than-usual inflow (aortic) pressure. In the case of hypertrophy, proliferation of vascular channels may not always keep pace with the increase in myocardial mass. If perfusion were expressed on the basis of flow per unit mass, the slope of the maximum vasodilation line in figures 1 and 2—representing maximum possible coronary conductance—would be decreased. This again causes maximum vasodilation to occur at a higher-than-usual inflow pressure. Thus, patients with these two conditions are particularly vulnerable to myocardial ischemia during periods of hypotension.

One additional implication of figures 1 and 2 relates to investigations, such as the one described in this issue, in which coronary flow is supplied through a constant-flow pump. The normal autoregulatory circumstance is characterized by a constant flow in the face of changing inflow pressure at a constant level of O_2 demand. Recent data from Rouleau and colleagues[17] confirm that constant-flow preparations "force" marked changes in pressure when flow is varied by a small amount in the autoregulatory range. In addition, if the naturally occurring "autoregulated" value of flow happens not to be chosen for the pump setting, the animal is largely precluded from having coronary perfusion pressures in the autoregulatory range.

During recent years it has become clear that the principles outlined for overall left ventricular perfusion require important refinement when considering perfusion in different tissue layers. Since mechanical effects of ventricular contraction impede systolic perfusion to a greater extent in the inner layers of the heart than the outer, the inner layers must receive a proportionately greater portion of their perfusion during diastole. Myocardial O_2 requirements are at least as great in the subendocardium as the subepicardium[18,19]; possible transmural differences in local O_2 extraction[20–23] do not negate the need for the full-cycle level of subendocardial flow to at least equal that in the subepicardium. Diastolic flow to the inner layers of the heart therefore exceeds that to the outer, and mechanisms for achieving this augmentation in diastolic endocardial perfusion continue to be studied intensively. Potential options relate to transmural differences in resistance and driving pressure.

Subendocardial resistance relates to both capillarity and extent of vasodilation. Studies several years ago indicated a greater number of open capillaries in the subendocardium during normal perfusion,[24,25] and it was reasonably suggested[19] that the subendocardium normally uses a portion of its vasodilatory reserve to compensate for the "throttling" effect of systole on coronary inflow. More recent work indicates that minimum possible resistance (during maximum vaso-

dilation) is less in the subendocardium than in the subepicardium,[17,26,27] *i.e.*, that total vasodilatory reserve in inherently greater in this area. Potential transmural differences in driving pressure also require further investigation. Diastolic driving pressure is pivotal for the subendocardium; a smaller value than that in the subepicardium has been presumed on the basis of the normal difference between intraventricular and pericardial diastolic pressures. The recognition that P_{ZF} ordinarily exceeds intraventricular diastolic pressure implies that driving pressures in all transmural layers have been overestimated frequently—particularly at low aortic pressures—and that attention must be focused on the absolute magnitude of P_{ZF}, as well as possible transmural differences. Recent studies by Rouleau and colleagues,[17] using pressure–flow data derived from microsphere measurements during full-cycle perfusion and maximum vasodilation, conclude that transmural differences in P_{ZF} play an important role in transmural flow regulation (with subendocardial P_{ZF} normally exceeding that in the subepicardium). Data from our own laboratory,[16] obtained by use of microsphere measurements during selective diastolic perfusion and maximum vasodilation, suggest that a directionally similar transmural gradient in P_{ZF} at normal preload is accentuated at increased preload.

What is the impact of these various factors on transmural perfusion? One important concept is the restraint with which changes in endocardial/epicardial flow ratios must be interpreted in any detailed mechanistic sense. Such interpretations require consideration of several factors that are operative simultaneously. In addition to local driving pressures and resistances, these include the absolute levels of endocardial and epicardial flow and diastolic aortic pressure. Decreasing values of the latter assume increasing importance, since they accentuate transmural differences in driving pressure related to transmural differences in P_{ZF}. In the presence of coronary-artery disease, the situation is even more complex, since diastolic aortic pressure does not reflect coronary arterial pressure downstream to an obstructive lesion. The caution with which Klassen *et al.*[1] have discussed the changes in endocardial/epicardial flow ratios observed during epidural anesthesia is typical of a laboratory widely respected for its contributions to our understanding of coronary circulatory physiology.

Also to be emphasized is the convincing body of evidence, recently summarized by Hoffman,[13] indicating that ischemia is ordinarily evident earlier—and to a greater extent—in the subendocardium than the subepicardium. Although local perfusion depends on the complex interplay between local resistance and driving pressure (as modulated by autoregulation), coronary reserve is exhausted earlier in the inner layers of the heart under most conditions.[17,28] Once reserve has been exhausted, flow at any given inflow pressure becomes critically dependent upon local resistance and the local forces governing "back pressure" to flow. Subendocardial ischemia reflects an inadequacy of flow for local O_2 demand despite full utilization of coronary reserve mechanisms. Attempts to define hemodynamic indices reflecting such an imbalance began with the coronary–left ventricular pressure ratio of Griggs and Nakamura.[29] In a widely admired series of studies spanning the past several years, Hoffman, Buckberg and colleagues have carefully defined advantages and limitations of the so-called DPTI:SPTI ratio.[18] DPTI, the diastolic pressure–time index, is the area between the coronary arterial and left ventricular pressure curves during diastole, and is considered to reflect O_2 supply. SPTI, the systolic pressure–time index, is the area under the left ventricular pressure curve during systole and is taken to reflect O_2 demand. When the DPTI:SPTI ratio decreases to less than 0.4, coronary reserve is ordinarily exhausted, with local perfusion falling short of O_2 requirements. Despite the conceptual attractiveness and pratical utility of the ratio, specific applications must be made in the context of important limitations. As recently summarized by Hoffman,[13] these limitations relate both to SPTI as an index of local O_2 demand and to DPTI as an index of local O_2 supply. While effects of anemia can be corrected for reasonably easily, effects of the other factors influencing endocardial/epicardial flow ratios are more troublesome.

In view of the complexities of coronary circulatory control, findings in many experimental circumstances remain difficult to extrapolate to other experimental circumstances, much less to man. Important additional insights into the autonomic control of coronary flow are expected in the near future. For the moment, the clinical anesthesiologist—like his counterparts in other clinical disciplines dealing with cardiac patients—must continue to extrapolate findings from complex experimental preparations with caution.

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