The Effect of Coronary Inflow Pressure on Coronary Vascular Resistance in the Isolated Dog Heart

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SUMMARY. The shape of the coronary arterial pressure-flow relationship results from the interaction of a number of poorly understood physiological factors. Experiments in which coronary inflow and outflow pressures were coupled so that driving pressure was held constant showed that changes in inflow or outflow pressures altered coronary blood flow: coronary vascular resistance varied inversely with changes in inflow pressure below 50 mm Hg and with changes in outflow pressure below 80 mm Hg. The magnitude of the influence of inflow pressure on resistance also depended on the fixed level of outflow pressure, the influence being large when the outflow pressure was low, and small when it was high. Inflow and outflow pressures, then, are two physiological factors which are determinants of the shape of the pressure-flow relationship, and their interaction contributes to the degree of curvature found in a particular relationship. These findings suggest that the use of linear regression in the interpretation of pressure-flow relationships results in poor estimation of resistance and zero-flow pressure. Other experiments measuring regional coronary blood flow using radionuclide-labeled microspheres resulted in the same inverse relationship between inflow pressure and resistance, regardless of mural depth, indicating that inflow pressure may influence resistance by distending vessels, rather than by causing sequential cessation of perfusion in successive transmural layers. (Circ Res 54: 760-772, 1984)

THE coronary arterial pressure-flow relationship is used frequently as a tool in developing and testing models of the coronary circulation. A common approach is to characterize this relationship as linear, interpreting the slope of the linear regression of coronary flow on pressure as coronary conductance, and the point where the extrapolation of this line crosses the pressure axis as coronary outflow or back pressure (Bellamy, 1978; Dole and Bishop, 1982b; Eng et al., 1982). However the validity of this approach is not firmly established, and its practice may be misleading, because the true shape and the precise physical meaning of the coronary pressure-flow relationship are still unsettled issues.

Two recent studies indicate that the coronary arterial pressure-flow relationship is often curved (Klocke et al., 1981; Messina et al., 1983), and another study shows that a straight relationship may be obtained even when coronary resistance is known to be changing (Dole and Bishop, 1982a). These studies imply that the shape of the coronary arterial pressure-flow relationship results from a complex interaction of physiological factors. These factors must be identified before the coronary arterial pressure-flow relationship can be appropriately interpreted.

Although curvature has been identified in the pressure-flow relationships of the above-mentioned studies, the causes of this curvature have not been determined. There are many potential mechanisms which could influence curvature, including myocardial ischemia, collateral flow, sequential transmural dropout of vascular beds, myocardial contractility changes, coronary capacitance, anomalous viscosity of blood at low flows, and the effect of intraluminal pressure on resistance vessel diameter. In the present study, we examine this final mechanism. The absolute level of coronary inflow pressure, independent of coronary driving pressure (the pressure drop across the coronary bed), may influence coronary blood flow. This influence could arise because variations of inflow pressure alter the pressure gradient across the vessel wall, thereby changing vessel radius and coronary resistance (Dobrin, 1978). Unfortunately, the true relationship between coronary inflow pressure and flow cannot be easily determined from analysis of the standard coronary arterial pressure-flow relationship. When coronary inflow pressure is varied over a physiological range while coronary outflow pressure is relatively fixed at some low value, the coronary driving pressure will vary directly and closely with inflow pressure. Because driving pressure is a major determinant of flow through vessels, this close coupling of inflow and driving pressures does not allow the individual influences of each of these pressures on flow to be assessed. To characterize the relationship between inflow pressure and flow, inflow pressure must first be uncoupled from driving pressure.
In this study, we have developed a preparation and protocol in which coronary inflow pressure can be uncoupled from coronary driving pressure. This is accomplished by coupling inflow and outflow pressures over a wide range so that driving pressure remains constant. In 10 experiments, we determined the relationship between inflow pressure and total coronary blood flow, and then derived the relationship between inflow pressure and total coronary vascular resistance. We also examined the relationship between coronary outflow pressure and coronary vascular resistance. Since the relationship between inflow pressure and total coronary blood flow could result from either uniform effects of inflow pressure on blood vessels across the heart wall, or from variable effects, depending on the depth of the vessels within the heart wall, radionucleide-labeled microspheres were used in some experiments to measure regional coronary blood flow. This allowed us to determine the most likely physical mechanism underlying the observed relationship between inflow pressure and total coronary resistance.

**Methods**

**Theoretical**

The coronary resistance vessels are imbedded in intramyocardial tissue and are surrounded by larger low resistance conduit vessels. The close proximity of these physical structures may cause complex interactions. Inflow pressure can be directly transmitted to the resistance vessels, causing them to distend. However, inflow pressure can also distend the larger low resistance intramyocardial vessels as well, and this latter effect might increase pressure transmitted to the intramyocardial tissue surrounding the resistance vessels, thereby causing vessel compression. The combined effect of these two competing forces would result in one of three basic relationships between inflow pressure and resistance in the coronary bed, as illustrated in Figure 1A. Here, we assume that inflow and driving pressures are uncoupled such that driving pressure can be kept at a constant level as inflow pressure varies. Panel 1 indicates that there is no relationship between inflow pressure and flow when driving pressure is held constant. Under these conditions, the two competing forces which act on the resistance vessels offset each other, and the relationship is the same as that which occurs in a rigid tube. Panel 2 shows an inverse relationship between inflow pressure and flow, as would occur if the influence of inflow pressure on the surrounding intramyocardial tissue predominated over the direct influence of inflow pressure on the resistance vessels. Panel 3 shows a direct relationship between inflow pressure and flow, as would occur if the direct distending effect of inflow pressure on the resistance vessels predominated. Figure 1B shows these same three relationships displayed with inflow pressure instead of driving pressure plotted on the X axis. The result of this plot is a line with a slope that represents the relationship between inflow pressure and flow. Because driving pressure is held constant for each relationship, the slope also indicates the relationship between inflow pressure and resistance. The slope of the line is zero in panel 1, indicating no relationship between inflow pressure and flow, and therefore no relationship between inflow pressure and resistance; again, this is analogous to flow behavior in a rigid tube. Panel 2 has a negative slope, indicating an inverse relationship between inflow pressure and flow; in this instance, resistance will vary directly with inflow pressure. Panel 3 has a positive slope, indicating a direct relationship between inflow pressure and flow; here resistance will vary inversely with inflow pressure. Due to the complex interaction of forces and the elastic properties of vascular tissue, the true relationship between inflow pressure and flow is probably not described by a straight line. In this study, however, the exact slope of the relationship between inflow pressure and flow is not critical. The important issue is to establish whether a relationship exists, and, if it does, whether it is direct or inverse.

**Experimental Preparation**

To uncouple inflow pressure from driving pressure, it was necessary to use an isolated empty beating dog heart preparation (Fig. 2). Each dog (25-40 kg) was anesthetized with sodium pentothal (10 mg/kg, iv), followed by endotracheal intubation and mechanical ventilation with 1.0-1.5% halothane in 100% oxygen at 2 liters/min (Dupaco Anesthesia Apparatus, Harvard constant-volume respirator). A left 5th-space thoracotomy was performed, and the pericardium was opened along the left phrenic nerve. The superior and inferior venae cavae,azygous vein, pulmonary artery, and ascending aorta were dissected, and umbilical tape was placed around each vessel as close to the heart as possible (Fig. 2). Sodium heparin (10,000 U, iv) was given initially, then hourly (5,000 U). To control perfusion to the left main coronary artery, an extracorporeal perfusion system was constructed. The afferent limb of the perfusion circuit provided oxygenated blood to the coronary bed, and consisted of a large bore cannula in the left femoral artery, an extracorporeal blood oxygenator (Bentley Spruillo BOS-10), a Sarns roller pump, a perfusion chamber, and finally a left main coronary artery cannula, all connected by plastic tubing (Tygon 5/16", s.d.) The cannula was introduced into the left subclavian artery, advanced into the left coronary ostium, and secured by an external silk ligature surrounding the left main coronary artery. An adjustable compressed air source attached to the perfusion chamber to control perfusion pressure of the coronary circulation. The level of blood in the perfusion chamber was kept constant by the Sarns pump under feedback control. An in-line electromagnetic flow transducer (Howell Instruments) measured left main coronary flow. Another perfusion cannula was put into the innominate artery, and its tip was advanced into the ascending aorta between the aortic valve and the aortic ligature to perfuse the right coronary artery when the preparation was completed. This cannula was connected to the perfusion circuit just distal to the perfusion chamber. The arterial port of the oxygenator was connected to the perfusion circuit just before the circuit entered the Sarns pump. This connection remained clamped until the preparation was completed. The efferent limb of the perfusion circuit served as a conduit for return of unoxygenated blood from the isolated heart to the oxygenator, and consisted of a 20F flexible catheter with multiple side holes which was placed in the right ventricle via the right atrial appendage so that several side holes were in both the right atrium and right ventricle as the cannula lay across the tricuspid valve. This catheter was connected to the venous drainage port of the oxygenator. The efferent
limb of the circuit was then clamped until completion of the preparation. A 16F catheter was placed via the left atrial appendage across the mitral valve into the left ventricle to provide a route for left ventricular ejection during isolation of the heart. The external end of this catheter was positioned in the chest cavity, and the catheter was clamped until completion of the preparation. 8F polyvinyl chloride catheters were placed in the left ventricle, right ventricle, and attached to a side port of the left main perfusion cannula, and a small catheter was placed directly into the coronary sinus (Verrier et al., 1981), all for measuring pressure.

Before the heart's circulation was isolated, coronary perfusion consisted of oxygenated blood drawn from the femoral artery, bypassing the oxygenator, and delivered to the left main coronary artery. The heart was isolated by unclamping both the efferent limb of the circuit and the left ventricular ejection catheter, tightening the umbilical tape ligatures around the superior and inferior vena cavae, azygous vein, pulmonary artery, and ascending aorta and, finally, changing the afferent blood source from the femoral artery to the oxygenator. The oxygenator was provided with 100% oxygen at 0.5 liter/min, and blood passing through the oxygenator reservoir was heated by countercurrent exchange with water from a heated bath at 38°C. Once isolation of the heart's circulation was completed, coronary inflow pressure could be controlled by adjusting the compressed air source, and coronary outflow pressure in the right heart could be controlled by adjusting the height of the oxygenator reservoir above the heart. Measurement of coronary flow through the left main coronary artery cannula assured that any flow through an incompetent aortic valve would not be mistaken for coronary flow.

The atrioventricular node was blocked with formalin (Steiner and Kovalik, 1968), and the heart rate was controlled with a rate-programmable external pacemaker (Medtronic) connected to right ventricular pacing wires. All pressure catheters were connected to strain gauges (Statham P23dB) with zero set at mid-chest level, and the electromagnetic flow transducer was connected to a flowmeter (Narromatic RT500). Left main coronary inflow pressure, coronary outflow pressure, and coronary sinus pressures were recorded on a polygraph (Beckman) and on FM magnetic tape (Hewlett-Packard). All data channels were digitized, and further analysis (Florowitz and Glantz,
All data were obtained in the absence of autoregulation by giving chromonar (10 mg/kg) initially, then as needed to prevent a reactive hyperemic response following a 45-second coronary occlusion. Prior to giving chromonar, this length of occlusion resulted in a peak flow increase of 3–4 times the baseline flow; after chromonar, flow also increased similarly above baseline.

Data Analysis

Data were obtained at a heart rate of 100 beats/min and also during prolonged diastoles, obtained by the sudden cessation of pacing. Xylocaine (1%, 0.25–0.50 mg/kg, via the oxygenator) was given as needed to augment the length of diastole. Pressure and flow data during prolonged diastoles were recorded and analyzed beginning about 5 seconds after the onset of diastole and ending just before the first breakthrough beat to ensure a steady state. Data from the beating heart were obtained over a 5-second interval after a steady state of mean pressures and flow had been achieved. In all experiments, resistance was calculated as driving pressure divided by flow (R = ΔP/F). Specific sets of data points, as described below in the protocol, were obtained under both diastolic and beating conditions.

All microsphere data were obtained at a heart rate of 100 beats/min. Microsphere injections consisted of 1.0-ml suspensions of 250–400 X 10^6 15-μm microspheres (3M Company) in normal saline with a small amount of Tween-80 (Heymann et al., 1977). The microspheres for each injection were labeled with one of nine radionuclide markers (153Gd, 113In, 57Co, 51Cr, 67Zn, 55Mn, 99Sr, 111Sn, 58Nb). A different marker was used in each injection during a given experiment. Injections were made into the microsphere injection port of the left main coronary canula (Fig. 2) over 10–15 seconds once mean pressures and flow had been achieved. In all experiments, resistance was calculated as driving pressure divided by flow (R = ΔP/F). Specific sets of data points, as described below in the protocol, were obtained under both diastolic and beating conditions.

At the end of each microsphere experiment, the heart was placed in 4% formalin and stored for 1 week. The left ventricle was then divided into six large pieces, and each piece was subdivided into four transmural layers. Each of these 24 samples was weighed, diced, and placed in a counting vial. The remainder of the heart was divided into 24 equal samples which were similarly treated. All samples were analyzed for γ radioactivity using a 1024 channel well type scintillation γ counter (Tracor Analytic), and radionuclide markers were separated by a least squares technique (Baer et al., 1984). Flow per gram (ml/min) in each of the 24 left ventricular samples was calculated for each injection. The reference flow used in these calculations was the total left main coronary flow determined by the electromagnetic flow transducer. Flow per gram (ml/min) for each left ventricular transmural layer was expressed as mean ± SD of the six large left ventricular pieces.

Protocol

To determine the relationships between coronary inflow pressure and resistance during absolute steady state conditions, we recorded data during prolonged diastoles and in the absence of autoregulation in 10 isolated dog heart preparations. Data were recorded in three separate sets, each set consisting of five separate points (Table 1). Coronary inflow pressure and coronary outflow pressure were controlled for each point so that the coronary driving pressure remained constant for all points within a set, while inflow pressure varied over a physiological range. The three sets of data differed in that each one had a characteristic constant driving pressure—either 10, 20, or 30 mm Hg. For each set of data, then, inflow pressure was uncoupled from driving pressure, allowing us to examine the effect of inflow pressure on flow and resistance at three separate constant driving pressures. The relationship between inflow pressure and flow for each set of data could then be compared to the framework outlined in the theoretical section.

In six of the 10 preparations, the same three sets of data were recorded while the heart was beating, also in the absence of autoregulation, to determine whether the cardiac cycle altered the relationship between inflow pressure and flow noted during the absolute steady state conditions of prolonged diastole.

In eight of the 10 preparations, an additional set of data was obtained. For each point within this set, inflow and outflow pressures were made equal over a range of 20–80 mm Hg, so that there would be no pressure drop and, therefore, no flow across the coronary bed from the artery into the coronary sinus, right atrium, or right ventricle. Any flow measured for these points would indicate flow through the only uncontrolled outflow tract of the left main coronary bed in our preparation, i.e., the Thebesian veins. The pressure drop across this outflow tract would vary for each of these points, equaling inflow pressure (or outflow pressure) minus the left ventricular cavity pressure. This allowed us to assess the influence of uncontrolled Thebesian outflow on our results.

To identify the most likely physical basis for the relationship between inflow pressure and resistance, in four preparations we measured regional left ventricular blood flow in four transmural layers using radionuclide-labeled microspheres. In these experiments, a differently labeled microsphere suspension was injected at each of five different inflow pressures when driving pressure was held constant at 30 mm Hg for each injection. Flow per gram was determined at each of the five inflow pressures in each of the four transmural layers. This allowed us to determine whether the relationship between inflow pressure and resistance is uniform or variable at different depths of the heart wall.

### Table 1

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<th>No.</th>
<th>ΔP = 30</th>
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<td>ΔP</td>
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Each of three sets of data, obtained in all experiments, consisted of five points that varied over a physiological range of inflow pressures. Note that outflow pressure was varied for each point such that driving pressure was held constant for all points within any single set of data. All units are mm Hg.

P<sub>i</sub> = inflow (arterial) pressure in mm Hg; P<sub>v</sub> = outflow (venous) pressure in mm Hg; ΔP = P<sub>i</sub> - P<sub>v</sub>.
Results

At each of the three constant driving pressures (i.e., for each set of data in the protocol), flow varied with the absolute level of inflow pressure. Figure 3A shows the results obtained from a single diastolic experiment. These results correspond to theoretical panel 3 of Figure 1A, indicating that there is a direct relationship between coronary inflow pressure and flow. In Figure 3B, data from the same experiment are presented with inflow pressure instead of driving pressure now plotted on the X axis. At each of the three constant driving pressures, there is a direct relationship between inflow pressure and flow. These results correspond to theoretical panel 3 of Figure 1B, again indicating a direct relationship between coronary inflow pressure and flow, and, by implication, an inverse relationship between coronary inflow pressure and resistance.

Figure 4A shows the results from another experiment in which the points from a single set of data (ΔP = 20 mm Hg) are plotted as in Figure 3B. Again, the positive slope is apparent. In Figure 4B, data from the same experiment are presented with inflow pressure now plotted against resistance instead of flow. This graph illustrates the inverse relationship between coronary inflow pressure and resistance. Because the driving pressure term in the resistance equation (see Methods section) will be a constant for all points in any given set of data, the relationship between inflow pressure and resistance can be easily predicted as the inverse of the relationship between inflow pressure and flow.

Each of the data sets at constant driving pressures of 10, 20, and 30 mm Hg in the 10 preparations were analyzed as in Figures 3 and 4. The results in these figures are representative of all diastolic and beating experiments, i.e., the relationship between inflow pressure and flow for each data set was direct and showed a tendency to plateau at the higher inflow pressures. Each relationship was well fitted to a quadratic equation with correlation coefficients averaging 0.99 (0.02 SD). There was also a strong linear relationship between flow and the logarithm of inflow pressure, with correlation coefficients averaging 0.96 (0.05 SD), and a slightly weaker linear relationship between flow and inflow pressure, with correlation coefficients of 0.94 (0.05 SD). The slope of the linear relationship between flow and the logarithm of pressure was positive and significant when compared to zero in all data sets (P < 0.05 by Student’s paired t-test).

The slope of the linear relationship between flow and the logarithm of pressure for the set of data when driving pressure was held at zero was also significant when compared to zero (P < 0.05, Student’s paired t-test) in all experiments, indicating that thebesian vein outflow changes could be distinguished as inflow pressure was varied. In every preparation, however, this slope was much smaller than each of the slopes of the three sets of data shown in Table 1, as Table 2 indicates (P < 0.05, analysis of covariance, Neuman-Keuls multiple comparisons test). The uncontrolled thebesian vein outflow, therefore, was not accounting for the direct relationship between coronary inflow pressure and flow observed in our experiments. There were six experiments in which both a ΔP = 10 data set and a ΔP = 0 data set were performed. Comparison of absolute flow rates at an inflow pressure of 30 mm Hg for each of those two data sets showed that the ΔP = 0 flow rate averaged 16% of the ΔP = 10 flow rate. Since the ΔP = 20 and ΔP = 30 data sets had absolute flows even higher than the ΔP = 10 data set, comparison of the ΔP = 0 flows to the flows for these two data sets would indicate an even lower percentage value attributable to thebesian flow. This analysis indicates that thebesian flow, although detectable in these experiments, accounts for a small part of the observed flows for the protocol data sets. Thebesian flow averaged 4 ml/min at an inflow pressure of 30 mm Hg. Thebesian flows at higher pressures can be determined using the slope value for the ΔP = 0 data set (Table 2).

The resistance changes noted in our experiments are at least partially due to outflow pressure. Figure 5A indicates the relationship between inflow pres-
FIGURE 4. Part A: the data shown here, obtained during diastole from a single experiment, illustrate the direct relationship between inflow pressure and flow for a single set of data only, i.e., when driving pressure (ΔP) was held constant at 20 mm Hg. Part B: data from the same experiment are presented with calculated coronary vascular resistance replacing coronary blood flow rate on the Y axis. Note the inverse relationship between inflow pressure and resistance. ΔP = driving pressure in mm Hg.

The slopes of the relationship between flow and the logarithm of inflow pressure averaged from all diastolic and beating experiments are categorized by sets of data with different constant driving pressure. The slope of the ΔP = 0 set of data is significantly smaller than the slopes of the other three sets of data, and the slopes of the ΔP = 10, ΔP = 20, and ΔP = 30 sets are also significantly different.

<table>
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<td>sd</td>
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<td>r</td>
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The resistance changes noted in our experiments are also partially due to inflow pressure. Figure 5B illustrates the data from the same four experiments with outflow pressure, instead of inflow pressure, plotted on the X axis. Inflow pressure is now marked next to each point. Again, two patterns can be identified. First, for the three points at any single outflow pressure (i.e., one from each set of data), the inflow pressures are different. There is an inverse relationship between inflow pressure and resistance for any such set of three points, indicating the influence of coronary inflow pressure, independent of coronary outflow pressure, on resistance. Both coronary inflow and outflow pressures, therefore, appear to effect qualitatively similar changes in resistance. In contrast to the parallelism in Figure 5A, however, the second pattern in Figure 5B indicates that the inverse relationship between inflow pressure and resistance shows a tendency to be strong at low constant outflow pressures (10 and 20 mm Hg) and weak or absent at higher constant outflow pressures (30–50 mm Hg). There was some variability in this second pattern among the different experiments, with most showing the relationship clearly; the last two panels in Figure 5B, however, were chosen to illustrate the poorest examples of this pattern. When the results from all preparations were analyzed, comparisons of the resistances from the three points at each constant outflow pressure reflected the pattern shown in the first panel of Figure 5B. The magnitude of the differences among the three resistances was largest when outflow pressure was 10 or 20 mm Hg (P < 0.05, Student’s paired t-test), was less when outflow pressure was...
FIGURE 5. Panel A: the data obtained from four experiments during prolonged diastole show the relationship between inflow pressure and resistance for the three sets of data presented in Table 1. The numbers next to each point indicate outflow pressure in mm Hg. Note that, for any set of three points obtained at a constant inflow pressure (i.e., one point for each set of data), the resistance varies inversely with outflow pressure. This relationship holds over the entire range of outflow pressures from 10 to 60 mm Hg. Panel B: the data obtained during diastole from the same four experiments as in panel A show the relationship between outflow pressure and resistance for the three sets of data presented in Table 1. The numbers next to each point indicate inflow pressure in mm Hg. Note that, for any set of three points obtained at a constant outflow pressure (i.e., one point from each of the three sets of data), resistance varies inversely with inflow pressure. This relationship is most marked at low constant outflow pressures and diminishes as outflow pressure rises. Symbols indicate same constant driving pressures as in panel A.
FIGURE 6. The data from all radionuclide-labeled microsphere experiments are shown. All data were obtained at a constant driving pressure of 30 mm Hg. Each panel represents a single experiment. The lines connect points within a transmural left ventricular layer. Note the positive slope of the relationship between inflow pressure and flow for all layers in all experiments. 1 = subendocardium, 4 = subepicardium.

30 mm Hg (P < 0.10) and was least when outflow pressures were 40, 50, or 60 mm Hg (P > 0.25). Over this range of constant outflow pressures, total variation in inflow pressure was from 20 to 80 mm Hg. Resistance changes due to inflow pressure changes were greatest at low absolute levels of inflow pressure, and diminished as absolute levels of inflow pressure rose. At absolute levels of inflow pressure between 50 and 80 mm Hg, inflow pressure changes had little or no effect on resistance.

The radionuclide-labeled microsphere experiments indicate that the relationship between inflow pressure and flow is uniform across the heart wall (Fig. 6). Flow determinations were made for a single set of data only (ΔP = 30 mm Hg). Each panel represents a different experiment, and each relationship within a panel represents a different transmural layer of left ventricular myocardium. All experiments are qualitatively similar. In each transmural layer, the relationship between inflow pressure and flow has a positive slope, indicating that the pattern of flow in each layer is similar to that of the total coronary bed (electromagnetic flow data). Within each transmural layer, then, coronary resistance varies inversely with coronary inflow pressure. Comparisons of flows at the high and low inflow pressures within each layer consistently showed significant differences (P < 0.01, one-way analysis of variance, Newman-Keuls multiple comparisons test).

Stability of the preparations was determined by monitoring several parameters. Hematocrits varied among the preparations over a range of 30–38%. Septal temperature was continuously measured and maintained between 36 and 38°C. Arterial oxygenation was maintained above 150 torr and arterial pH was adjusted with NaHCO₃, as necessary, to remain between 7.35 and 7.45 units. Arterial carbon dioxide levels were low due to the use of the extracorporeal blood oxygenator; however, they remained stable within and between preparations, averaging 7.1 (2.2 st) torr. Left ventricular mean pressure remained low and essentially constant in each preparation regardless of inflow and outflow pressures, averaging 10.4 (1.8 st) mm Hg in one preparation and 2.3 (0.5 st) mm Hg or less in all others. Simultaneous measurements of coronary sinus pressure and coronary outflow pressure (right atrial pressure) were obtained in over 100 instances over the 10–70 mm Hg range used in the study protocol. These two pressures were essentially identical in each measurement.

Discussion

Critique of Study

It should be emphasized that the findings of the present study pertain to the isolated non-working heart. It would be impossible to obtain our findings in the normal working heart because they would be obscured by the effects of numerous uncontrolled variables such as autoregulation, systole and diastole, changing intracavitary pressure, and changing inflow, outflow, and driving pressures. We believe that the relationships between inflow pressure and resistance that we have found are basic interactions between distending pressure and vascular and peri-vascular tissue. These interactions are almost certainly present in the working heart, as well, although undoubtedly they will be altered or even obscured by the many variables mentioned above. Recognition of the potential effects of the relationships shown in this study will lead to more accurate interpretation of coronary pressure-flow relationships, regardless of the experimental preparations used.

The findings of the present study are limited to pressure-flow relationships derived in the non-working heart in the absence of autoregulation, and are constructed from data obtained either during prolonged diastole, when pressures and flows are in absolute steady states, or during the beating state, when mean pressures and flows are steady. However, with some reasonable assumptions, these findings can be extended to pressure-flow relationships constructed under different conditions. Instantaneous diastolic pressure-flow relationships when autoregulation is absent or when vessels have tone are typically constructed from data obtained over several seconds as inflow pressure declines. Unless the extreme position is taken that the influence of inflow pressure on vessel distension requires longer than several seconds to occur, our findings would apply to pressure-flow relationships constructed under these conditions. When vessel tone is present, however, the autoregulatory changes which may
Thebesian outflow was 16%. This value would have showed that the percentage of flow attributable to drainage both at an inflow pressure of 30 mm Hg flow rates for the AP = 10 data set with Thebesian addition, a different analysis comparing absolute preparation indicated that Thebesian vein outflow were made equal, and therefore any aortic valve the positive slopes obtained in our experiments. In comparison of the slopes of the three sets of data from arterial catheter when inflow and outflow pressures obtained the set of data with driving pressure held at zero to estimate the effect that this portion of coronary outflow not controlled in our preparation would have on our results. Thebesian flow was measured as inflow through the left main coronary artery catheter when inflow and outflow pressures were made equal, and therefore any aortic valve incompetence could not affect our estimates. A comparison of the slopes of the three sets of data from the standard protocol to the slope of the set of data when driving pressure was held at zero in each preparation indicated that Thebesian vein outflow was not sufficient to account for the magnitude of the positive slopes obtained in our experiments. In addition, a different analysis comparing absolute flow rates for the ΔP = 10 data set with Thebesian drainage both at an inflow pressure of 30 mm Hg showed that the percentage of flow attributable to Thebesian outflow was 16%. This value would have been lower for the ΔP = 20 and ΔP = 30 data sets, much closer to the 5.7% reported by others (Hammond and Austen, 1967). The relatively high percentage in our experiments can be explained by the fact that, in our preparation, the driving pressure for our data sets was small (10, 20, or 30 mm Hg) whereas for the Thebesian data set, the pressure drop was much larger, i.e., inflow pressure minus left ventricular cavity pressure (2 mm Hg).

Even though we were able to control inflow and outflow pressures in our experiments, some caution is necessary in concluding that the difference between these two pressures represents true driving pressure. A hidden back pressure, higher than our controlled outflow pressure, would result in a true driving pressure that was smaller than the calculated driving pressure intended by experimental design. Such a back pressure has been suggested by some investigators (Bellamy et al., 1980); however, its existence remains controversial. If a hidden back pressure were to remain at a fixed level above outflow pressure, it would not qualitatively affect the inverse relationship between inflow pressure and resistance that we have observed, although quantitatively resistance would be lower for each point within a data set. The major finding of this study, therefore, would not be changed by the existence of a hidden back pressure that had a fixed magnitude above outflow pressure.

Other hidden back pressures which behave in more complex ways must also be considered. A hidden back pressure with a magnitude above outflow pressure that varies directly with the absolute level of outflow pressure is theoretically possible: at low outflow pressures, the hidden back pressure would be close to outflow pressure, but as outflow pressure rose, as in our data sets, the hidden back pressure would rise higher and higher above outflow pressure. We cannot rule out the possibility of this mechanism from our data; however, resistance calculations using such a hidden back pressure would result in an enhanced inverse relationship between inflow pressure and resistance. The major finding of our study would, therefore, be supported even more strongly using this interpretation.

Finally, a hidden back pressure with a magnitude above outflow pressure that varies inversely with the level of outflow pressure is possible in theory: at low outflow pressures, the hidden back pressure would be much larger than outflow pressure and at higher outflow pressures the difference between the hidden back pressure and outflow pressure would diminish. This situation would occur, for example, if the hidden back pressure remained at a fixed absolute value, being uninfluenced by changes in inflow or outflow pressures. Calculation of resistance using such a back pressure could result in a finding of no influence of inflow pressure on resistance. Using this model, all flow changes that we have observed with changes in inflow pressure...
could be explained by occult changes in driving pressure at constant resistance, negating the major finding of our study. With due concern for the theoretical possibility of such a hidden back pressure, certain observations indicate that a hidden back pressure behaving in this manner cannot explain our findings. We have shown that the flows in our $\Delta P = 10$ data sets are clearly much greater than Thebesian flows, and therefore represent true forward flow. Since we see forward flow at the lowest point in the $\Delta P = 10$ data set, i.e., when inflow pressure is 20 mm Hg and outflow pressure is 10 mm Hg, any alleged hidden back pressure would have to be $<20$ mm Hg in magnitude. One could argue that flow changes noted among any group of points in the data set when outflow pressure is $<20$ mm Hg, i.e., when the hidden back pressure is potentially operative, could be explained by the hidden back pressure. When outflow pressure is above 20 mm Hg, however, the hidden back pressure would not be operating, and the same argument would predict that flow would remain constant for any group of points with outflow pressure $>20$ mm Hg. This is not consistent with our results. As mentioned above, the fact that forward flow is present when inflow pressure is 20 mm Hg limits the magnitude of the hidden back pressure to $<20$ mm Hg. Most of the points in our $\Delta P = 10$ data sets have outflow pressure $>20$ mm Hg, and we observed flow changes for all of these points. The flow changes cannot be explained by a fixed hidden back pressure, and are consistent only with a true change in resistance.

Another concern with our preparation was that the high outflow pressure used to obtain some of the data might induce significant interstitial edema in the heart wall, leading to artifactual changes in coronary resistance in subsequent data collections. To avoid these effects as much as possible, the order of data sets was randomized for each preparation; furthermore, points were obtained within each data set, starting with the one with the lowest outflow pressure and ending with the one with the highest outflow pressure. This procedure assured that any effect edema might have on resistance would be reflected in points obtained at higher absolute pressures, resulting in resistance changes that would be biased against our findings of decreased resistance with higher absolute pressures.

General

The major finding of this study is that the resistance of the coronary vascular bed varies inversely with changes in either inflow pressure or outflow pressure. Therefore, we have identified and characterized two physiological variables that have the potential to cause curvature in coronary arterial pressure-flow relationships.

To uncouple inflow and driving pressures in this study, it became necessary to couple inflow and outflow pressures (Table 2). Initial analysis of the data, as in Figure 4B, indicates that resistance changes occur over the entire range of inflow pressures from 20 to 80 mm Hg. Although these data are plotted with inflow pressure on the X axis, the fact that inflow and outflow pressures were coupled prevented us from determining whether the resistance changes are due to inflow or outflow pressure changes. Because the major focus of the present study was to identify physiological factors which can cause curvature in the standard coronary pressure-flow relationship, we were primarily concerned with determining the influence of inflow pressure alone on resistance; the widely varying inflow pressure has the potential to change resistance and thereby cause curvature in the standard coronary pressure-flow relationship, whereas the relatively fixed outflow pressure, usually found, does not. Further analysis of the data, as in Figure 5, A and B, did allow us to determine the independent influences of inflow and outflow pressures on resistance, allowing us to interpret the data in Figure 4B as follows: The resistance changes at the low inflow pressure end of the relationship are due to the combined influences of both inflow and outflow pressures, but, as we move to the right along the X-axis, the influence on resistance due to inflow pressure diminishes, whereas that due to outflow pressure is stable; finally, at inflow pressures above 50 mm Hg, the resistance changes are essentially all due to the influence of outflow pressure.

The mechanism for the different patterns in Figure 5, A and B, cannot be determined definitively in the present study; however, a plausible explanation involves differential compliance curves for intramyocardial arteries and veins. The compliance of intramyocardial vessels results from the interaction of the vessel wall itself and its surrounding tissue. If the compliance curve determined by the combination of the intramyocardial veins and their surrounding tissue is such that outflow pressures between 10 and 70 mm Hg are on the upward sloping aspect of the curve, the pattern in Figure 5A would be observed. On the other hand, if the compliance curve determined by the combination of the intramyocardial arteries and their surrounding tissue were such that inflow pressures above approximately 50 mm Hg are on the plateau aspect of this curve, the pattern in Figure 5B would be observed. The pressure at which the arterial compliance curve begins to plateau may vary, and this could explain the variability of the relationships in different experiments as indicated by the separate panels in Figure 5B.

Because inflow pressure varies over a wide range in the construction of the standard pressure-flow relationship, inflow pressure will have a prominent influence on producing curvature. Outflow pressure changes little in the standard pressure-flow relationship, so that it cannot influence directly the amount
of curvature present. However, returning to Figure 5B, similar changes in inflow pressure lead to smaller resistance changes at high outflow pressures than at low outflow pressures. The stable level of outflow pressure may limit the amount of influence that inflow pressure changes can exert on resistance; therefore, the level of outflow pressure in a pressurereflow relationship may limit the amount of curvature which inflow pressure can exert in that pressureflow relationship. The variability in the degree of curvature of coronary arterial pressure-flow relationships reported in the literature may result, in part, from the fact that outflow pressures were different in these various studies. This possibility emphasizes the need to measure and report coronary outflow pressure in all studies involving coronary pressure-flow relationships.

Our finding that changes in inflow pressure when inflow pressure is less than 50 mm Hg are most influential in changing resistance is consistent with independent observations noted in standard pressure-flow relationships, in which curvature is most prominent at low pressures (Klocke et al., 1981; Messina et al., 1983). If we were to interpret the effect of inflow pressure on resistance as being a result of vessel distension, the finding is also consistent with the recognized property of limited distensibility of vascular tissue (Dobrin, 1978).

Our measurement of total coronary flow does not identify the physical mechanism underlying the observed inverse relationship between inflow pressure and flow. For resistance to change, the total cross-sectional area of the coronary vascular bed must change, assuming that the other variables in the Poiseuille equation are constant. There are several plausible ways in which this could occur. Inflow pressure may alter the pressure gradient across the vessel wall, thereby effecting changes in vessel radius, inflow pressure may cause random vessel recruitment which is uniform across the heart wall, or inflow pressure may cause the sequential dropout of vascular beds by transmural layers (Downey and Kirk, 1975; Dunn and Gripps, 1983). Our microsphere flow data indicate that flows in all transmural layers vary directly and gradually with changes in inflow pressure. Each transmural layer exhibits the same relationship between inflow pressure and flow as does our total flow (electromagnetic flow data). These observations indicate that the mechanism by which inflow pressure changes resistance is by an effect either on vessel radius, or on vessel recruitment. In either situation, the effect would be uniform across the heart wall. A sequential dropout of vessels by transmural layer beginning in the endocardium cannot explain our microsphere findings. If sequential dropout of vascular beds had been responsible for the observed resistance changes in the present study, the patterns of the relationship between inflow pressure and flow among the different transmural layers would be expected to show measurable flows, with slopes of zero in all layers over the high inflow pressure range, then sudden step changes to flows of zero occurring sequentially—first in the inner layer, and then moving to outer layers, as inflow pressure was decreased (Fig. 7). We would like to emphasize that our microsphere findings are strictly applicable only to our preparation, as a means of clarifying the mechanism of our observed resistance changes. Transmural flow patterns would most likely be markedly altered in a working heart preparation.

The transmural flow patterns revealed by the microsphere experiments, then, support the hypothesis that inflow pressure influences intramyocardial vessel radius. Working within this concept, both the transmural and total flow measurements suggest that increases in inflow pressure cause distension of resistance vessels, and that this distension occurs because the direct intraluminal pressure force exerted by the inflow pressure on the resistance vessels predominates over any opposing force transmitted to the intramyocardial tissue surrounding the resistance vessels. These physical changes are then observed experimentally as an inverse relationship between inflow pressure and resistance.

The standard coronary arterial pressure-flow relationship is commonly constructed by performing linear regression on a set of data obtained by controlling coronary inflow pressure and measuring flow. This statistical procedure yields two pieces of information which are often thought to be of physiological significance—the slope of the regression line, which is taken to represent a constant coronary vascular conductance, and the pressure axis intercept, which is taken to represent the outflow or back pressure. Based on the results of the present study, the validity of this approach can be questioned. We have shown that coronary resistance changes as inflow pressure changes, and, furthermore, that coronary outflow pressure can modify these changes. The interaction of these two factors will tend to produce an amount of curvature that is unique for each coronary pressure-flow relationship. Other unidentified physiological factors may exist which influence the shape of the pressure-flow relationship and completely cancel the curvature that would have been present as a result of the changing resistance, as pointed out in another study (Dole and Bishop, 1982a).

The general implication of these two studies is that a complex interaction of physiological factors (only some of which have been characterized by the present study) is responsible for the ultimate shape of the coronary arterial pressure-flow relationship. As a result, the use of linear regression can cause errors of interpretation. The reliance on the slope of the linear regression line as representative of resistance may be invalid, even when the data fit a straight line perfectly well, due to the particular experimental conditions under which the data were
obtained, as the study previously cited indicates (Dole and Bishop, 1982a). Also, the practice of extrapolation of the linear regression, in failing to reflect the curvature which is often present in the pressure-flow relationship and which is most marked at lower pressures, will result in a pressure axis intercept that overestimates the pressure at which flow stops (Klocke et al., 1981). As a result of these inaccuracies, the changes of slope and pressure axis intercept which occur under controlled experimental conditions may reflect primarily the inappropriate use of linear regression rather than real physiological changes important in understanding the coronary circulation.

In summary, this study shows the following: (1) Coronary inflow pressure influences coronary vascular resistance in an inverse relationship. (2) Coronary outflow pressure also influences coronary vascular resistance in an inverse relationship. (3) The primary physical mechanism by which these pressures influence resistance appears to be by a direct effect of the pressure on resistance vessel distension. There is no indication that sequential dropout of transmural vascular beds is a predominant mechanism. (4) Coronary inflow and outflow pressures are two physiological factors which influence the amount of curvature observed in standard coronary arterial pressure-flow relationships. Other unknown factors probably also contribute to the eventual shape of this relationship. (5) Coronary vascular resistance does not remain constant over the range of inflow pressures used in the construction of standard coronary arterial pressure-flow relationships; therefore, the use of linear regression to determine resistance and zero-flow pressure results in poor estimation of these entities.

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