Diastolic Coronary Artery Pressure-Flow Relations in the Dog

RONALD F. BELLAMY

SUMMARY  Conscious dogs were used to investigate the relations between aortic (P a) pressure and coronary flow (F) during individual diastoles. When the dogs were in a semibasal state, coronary pressure-flow relations were described by a family of lines, and diastolic flow was a linear function of aortic pressure. For a given perfusion pressure, higher flows were associated with lines of progressively greater slope and lower zero flow pressure intercept (P a-o). Zero flow pressure intercepts were estimated by extrapolation and found to vary between 20 and 50 mm Hg, depending on the magnitude of flow. The zero flow pressure may represent the height of a vascular waterfall caused by vasomotor tone with the resistance-controlling coronary flow being (P a-P a-o)F⁻¹. Interventions that decrease vasomotor tone increase coronary flow by both decreasing vascular resistance and increasing the perfusion pressure gradient. The gradient increases because the effective coronary back pressure is the height of the vascular waterfall and the latter is reduced when vasomotor tone falls. Passive changes in vessel dimensions, arterial recruitment, and autoregulation appear to be of little importance during individual diastoles.

THE RELATIONSHIP between pressure and flow is of fundamental importance in understanding the hemodynamics of a vascular bed. In comparison with other vascular beds, the relationship between pressure and flow in the coronary circulation is modified by two factors: (1) throttling of flow during systole and (2) predominant local control manifested as rapid autoregulation of flow with changing pressure.

Prior reports of coronary pressure-flow relations have not entirely clarified the effects of these factors. Nonphasic pressure flow data were used and thus the effect of systole on the overall relation has not been distinguished. Although the time-dependent nature of autoregulation has been recognized in some studies by differentiating between instantaneous and steady state pressure-flow relations, the point in time following an experimental perturbation at which an instantaneous relation begins to be modified by autoregulation is not known. Previous studies have used data from experiments on dogs with the chest open and thus are subject to the distortion introduced by anesthesia, surgical trauma, and drugs. The conscious instrumented dog, in a semibasal state with a slow resting heart rate, offers a unique opportunity to study diastolic coronary pressure-flow relations in a more physiological state than previously reported. In this study, coronary pressure-flow relations were measured during the diastoles of individual beats in the resting state and when flow was increased by reactive hyperemia and infusion of adenosine.

Methods

The data presented in the paper are from analyses of unpublished records prepared in the course of several
studies done for other purposes. Resting flow and reactive hyperemia pressure flow relations were obtained from dogs which were part of a study on the regression of the coronary collateral circulation.7 The adenosine pressure flow relations were obtained from a study of the coronary vasoactivity of adenosine derivatives.6

All experiments were on chronically instrumented dogs. The instrumentation included aortic and circumflex coronary pressure catheters, an electromagnetic flowmeter proximal to the circumflex catheter, and two occluders just distal to the flowmeter.7 A similar preparation was used to study the vasoactivity of adenosine except that the coronary catheter was used for infusion of a solution of adenosine in saline (0.5 μM/liter). Recordings were made with a Hewlett-Packard 350 system feeding a Honeywell 1912 photo-optic recorder. The flowmeter was made by E. Khouri.

Studies were begun 2-3 weeks postoperatively when the resting heart rate had fallen to the preoperative range of 40-50 beats/min. Circumflex coronary and aortic pressure and circumflex coronary flow were recorded simultaneously at a paper speed of 75 mm/sec. Diastolic pressure and flow were measured at 0.1-second intervals from 0.2 second after the dicrotic notch to the atrial hump in the coronary pressure curve at end diastole. The graphic plot of flow as a function of pressure is referred to as a pressure-flow relation. Frequent baseline zeros were present in the records. Data were analyzed only when the baseline zero changed by less than 2 mm (3-5 ml/min depending on the calibration) during a 15-second occlusion or when short baseline flow zeros at the beginning and end of recording runs agreed within 2 mm.

Records from the collateral regression study were examined for reactive hyperemia tracings in the control period before any arterial stenosis had been induced. Reactive hyperemia always was induced by a 15-second arterial occlusion. Five examples meeting the baseline criteria were found for each of four dogs. Individual reactive hyperemias were analyzed by plotting the pressure-flow relations for beats with diastoles exceeding 1 second. Five resting flow beats and as many reactive hyperemic beats as possible were studied for each dog. Separate analyses were carried out using aortic and circumflex pressure. Data from individual reactive hyperemias were grouped together into convenient time periods following release of the occlusion, i.e., 2-6 seconds, 6-12 seconds, etc.

Because of the frequency of beats with unusually long diastoles in one dog, data from five consecutive reactive hyperemias were combined beat by beat so as to study the change in pressure-flow relations over short periods of time. This was done by combining on one plot individual pressure flow points from the diastoles of beats occurring at approximately the same time (±1 second) during each of the reactive hyperemias. A curve was fitted to this data and forms the pressure-flow relation for a composite beat. Since the heart rates during the individual reactive hyperemias were neither the same nor regular, the number of beats used to generate a composite beat varied and was between two and four. As an example, three of the five tracings had beats beginning approximately 10 seconds following release of the occlusion.

Beats beginning at 9.7, 9.9, and 11.0 seconds were combined to form a composite beat at 10.3 seconds. From 20-50 pressure-flow points from the parent beats were used to generate each composite beat.

Data analysis in the dog with an unusually slow heart rate also involved measuring the pressure-flow relations of 50 consecutive resting flow beats of all lengths, 10 pairs of coupled long (diastole ≥ 1 second) and short (diastole ≤ 0.4 second) beats and 10 randomly chosen beats of intermediate length (diastole > 0.4 to < 1.0 second). Peak reactive hyperemia flow, peripheral coronary pressure at the end of a 15-second occlusion, and aorta coronary pressure gradient also were measured.

A qualitative visual assessment was made on all beats of the degree to which pressure-flow relations departed from linearity both at the beginning and end of diastole. The pattern of increasing concavity toward the flow axis as the beat ended was taken as evidence for autoregulation of flow to falling diastolic perfusion pressure.

Zero flow pressure intercepts were estimated by extrapolation. In some resting flow beats, circumflex coronary flow appeared to have stopped; in most, a short linear extrapolation of the aortic pressure-flow relation was used to estimate the intercept for reactive hyperemia beats.

Coronary pressure-flow relations with adenosine were obtained in one dog by infusing adenosine through the coronary catheter with a Harvard infusion pump. Phasic aortic pressure and coronary flow were recorded when a steady flow state had been reached for a given pump speed. Five beats with diastoles exceeding 1 second were analyzed at each of seven different pump speeds by measuring pressure and flow at 0.1-second intervals. A similar analysis was made on five resting flow beats and one peak flow reactive hyperemia beat following a 15-second occlusion. Adenosine concentration in coronary plasma water was calculated by the following formula

\[
\text{Infusion rate (ml/min)} \times \text{conc (μM/liter)} = \frac{\text{Coronary flow (liter/min)} \times 0.92 \times (1 \text{- hematocrit})}{\text{Coronary pressure (mm Hg)}}
\]

The value 0.92 was selected because 92% of the plasma volume is water.

**Results**

The results section of the paper will be concerned primarily with commenting on the individual figures since most of the information is to be derived from their visual inspection. Figures 1 and 2 show examples of the data analyzed. A control or resting flow beat of unusual length is reproduced in Figure 1. With resting flow beats lasting 2-3 seconds, flow at the end of diastole could not be distinguished from the flow zero. The normal cyclic fall in aortic pressure constitutes the experimental pressure perturbation. The relationship between coronary pressure and flow during the diastole of the long beat is essentially linear with a zero flow pressure intercept, estimated by linear regression, of 45 mm Hg. For resting flow beats, the pressure gradient between aorta and coronary artery is 2-3 mm Hg and the two pressure-flow relations cannot be separated except at peak diastolic flow at the beginning of diastole. The change in resist-
The pressure gradient (ΔP) should actually be calculated per unit length (L), i.e., ΔP/L. For ΔP=Pa–Pv, L would be the length of the vascular bed. Resistance so calculated would be the average hydraulic resistance per unit length across the vascular bed. L would be smaller if the back pressure is in the microcirculation. A rigorous comparison between resistance calculated in different ways would require correction for the difference.
\( P_{f0} = 45 \text{ mm Hg} \)

Resistance calculated as \((P_c - P_{f0}) \cdot F^{-1} = 1.55 \text{ mm Hg/ml per min} \)

Figure 5 shows the diastolic pressure-flow relations for reactive hyperemia following a 15-second occlusion in three different dogs. The same general pattern is apparent; i.e., a linear relation between aortic pressure and flow and higher flows is associated with relations of greater slope and lower zero flow pressure intercept. Data were not pooled among the dogs because (1) there was no certainty that the metabolic state and vascular reactivities were the same and (2) the size of the vascular beds in which flows were measured was not determined. For comparison among animals, flow and resistance must be calculated per unit weight.

Figure 6 shows the aortic pressure-flow relations for reactive hyperemia in the dog with an unusually slow heart rate. To clarify the relations, individual data points have been recorded only for the composite beats beginning at 0.1, 4.3, and 12.4 seconds after release of occlusion. For the same reason only a few of the relations have been plotted after 7 seconds. The same pattern is apparent that was found in Figure 5; however, the more detailed analysis shows that, although the zero flow pressure intercept is minimal at the very beginning of reactive hyperemia, the slopes of the pressure-flow relations of the first several beats are smaller than the slope found for peak flow. This is a manifestation of the well known gradual rise to peak flow that is a characteristic of coronary reactive hyperemia. In this dog the average periph-
eral coronary pressure measured at the end of the 15-second occlusions was 14 mm Hg. The mean peak reactive hyperemia flow exceeded mean resting flow by five times. Reactive hyperemia flow returned to the preocclusion level in 25–30 seconds.

Figure 7 shows the diastolic coronary pressure-flow relations for seven different adenosine concentrations. The relation for each concentration was constructed from five diastoles. Five resting flow beats and one peak flow reactive hyperemia beat are included for comparison. A linear relation appears to exist between coronary flow and aortic pressure when flow is augmented by adenosine infusion. Higher flows are associated with pressure-flow relations of progressively greater slope and lower intercepts. Peak flow reactive hyperemia and vasodilation with adenosine at a concentration of 8.7 μm/liter have identical pressure-flow relations in this dog.

Discussion

In lieu of a general mathematical formulation of the determinants of blood flow, it is convenient to study the relation of flow and pressure graphically in the form of pressure-flow relations. The pressure-flow relations of individual beats have a marked similarity to the instantaneous pressure-flow relations obtained in acute dog preparations with nonpulsatile flow. It would appear that, during diastole, large-vessel coronary perfusion pressure is proportional to the pressure gradient, the nonlinear relation found in larger vessels being absent.

Pressure-flow relations determined in large epicardial arteries are predictive of pressure-flow relations in the microcirculation, where such phenomena as reactive hyperemia and autoregulation occur, only if coronary inflow and outflow are the same at every instance. Although simultaneous comparison of phasic coronary and venous flow has not been reported for conscious animals, inflow and outflow are certainly not the same during systole, but might be so during a long diastole.

Some of the usefulness of this study depends on the pressure-flow relations of beats with long diastoles (>1 second) being representative of beats of all lengths. Figure 3 shows that the assumption is partially justified. Although the zero flow-pressure intercepts for short beats (≤ 0.4 second) is less than in longer beats (> 0.4 second), the short beats were not sampled randomly but only in coupled pairs (Fig. 1). Marked sinus arrhythmia with coupling of very long and very short beats is observed frequently in well trained conscious dogs. The difference in zero flow-pressure intercept may exist because the short beat of a coupled pair represents a slight reactive hyperemia following a period of low flow. There was no statistically discernible difference in the resistance of long and short beats when resistance was calculated as \( (P - P_{\text{sys}}) / F \).

The shape of the pressure-flow relations of individual beats was inspected for departures from linearity. Autoregulation occurring toward the end of diastole could cause the pressure-flow relation to become concave toward the flow axis. This pattern was seen occasionally, but in the great majority of beats, including some with diastoles as long as four seconds, there was no departure from a linear relation. In about a quarter of beats, the beginning of the aortic pressure-flow relation was concave toward the flow axis. This is suggestive of filling of a
vascular bed partially emptied by the preceding systole and/or passive vessel distention. One might expect that turbulence with high flows would cause the pressure flow relation to become convex toward the flow axis. This was not observed. Hofline et al.\textsuperscript{10} have pointed out that a linear pressure-flow relation may be a fortuitous combination of inertial factors and vessel distention. The apparent absence of autoregulation of flow during long diastoles is rather surprising. The coronary pressure at the end of a long diastole approximates the pressure during the short (0.5-second) occlusions used for flow zeros. Although there is a marked reactive hyperemia following the short occlusion, increased flow following the long diastole is barely perceptible. It is only possible to

FIGURE 5 Diastolic circumflex (CIR) coronary pressure-flow relations during reactive hyperemia in three different dogs. Data were obtained from five resting flow beats and from several reactive hyperemia beats for each of several different time periods beginning with the release of a 15-second occlusion. Each symbol is an instantaneous pressure and flow measurement.
speculate as to why this difference exists. If the reactive hyperemia that follows short occlusions is a myogenic response, it may be that the extent of smooth muscle relaxation is dependent on the rate of pressure change. Pressure changes rapidly with the occlusion, but slowly during a long diastole. An alternate explanation is that myocardial oxygen consumption (MVO$_2$) is very low during a long diastole and there is little accumulation of the vasoactive substance(s) that couple(s) MVO$_2$ to coronary resistance. MVO$_2$ during the occlusion (as determined by the number of systoles) has been shown to be an important determinant of the magnitude of the subsequent reactive hyperemia.

The overall appearance of Figures 5-7 suggests that the relationship between coronary diastolic pressure and flow is described by a family of lines, the slopes and intercepts varying inversely. For a given perfusion pressure, higher flows are associated with lines of progressively greater slope and lower zero flow pressure intercept. Although the pressure-flow relations appear discrete, this is only because individual beats are discrete. It is likely that there exists a continuum of many possible relations between the bounds set by peak flow reactive hyperemia and resting flow. There probably exist relations associated with vasoconstriction below and to the right of the relation for resting flow. Whether there are relations above that of peak flow reactive hyperemia depends on whether there are more potent stimuli for coronary flow than a 15-second occlusion. The striking similarity between the relation for reactive hyperemia and vasodilation by aden-
It is likely that the intercept of the pressure-flow relation is determined by vascular smooth muscle tension development and extravascular compression. The slope is a complex function of size of the vascular bed, number of perfused vessels, vessel geometry as determined by smooth muscle tension development, and fluid viscosity. Figure 6 shows that $P_{f=0}$ may be a more sensitive indicator of vasomotor tone than is the slope of the pressure-flow relation. One might expect that whatever process inhibits smooth muscle tension during an arterial occlusion is maximal just before release of the occlusion. Although the minimal $P_{f=0}$ value is found immediately after release of the occlusion, the slope does not become maximal (corresponding to minimal resistance) until 4 seconds have passed. The interpretation of the pressure-flow relation in terms of vascular resistance differs depending on what causes the zero flow pressure.

The existence of a non-zero zero flow pressure intercept is controversial. In a study such as this, done in a relatively normal physiological milieu, the stability of the electromagnetic flow zero during a diastole is crucial to the assertion that flow did, in fact, stop in the presence of a positive pressure gradient across the vascular bed. Unfortunately, stability and accuracy of the flow zero cannot be proven. The zero flow pressure intercepts for high flow beats were obtained by linear extrapolation and thus the absolute values and even whether the pressure intercepts differs from zero are matters for conjecture. That the extrapolated zero flow pressures for individual reactive hyperemia beats may have physical reality is seen in the similarity between the values found in this study and that of Mosher et al. in which flow in the vasodilated coronary bed actually stopped at 20 mm Hg. Although flow appeared to stop in only very long beats, the lack of an inflexion in the terminal portion of the pressure-flow relations for shorter beats is suggestive that they also would have a non-zero zero flow pressure intercept given sufficient duration. Since diastolic flow declines exponentially with time, it may take 5-10 seconds for initially high flow to reach zero. The natural occurrence of diastoles of this length is unlikely, but occasionally is seen following electrical pacing. Figures 8 and 9 are taken from records prepared in the course of a study of coronary hemodynamics and tachycardia. Circumflex coronary blood flow was measured in a group of conscious chronically instrumented dogs with surgically induced complete heart block. The 5-second-long diastole shown in Figure 8 is likely to be the result of an abnormal electrical activity.

**Figure 7** Diastolic pressure-flow relations generated by infusion of adenosine (ADO). Adenosine concentrations are in $\mu$m/liter coronary plasma water. A peak flow reactive hyperemia beat (RH) is included for comparison. Five beats were used to construct all other relations.

**Figure 8** Phasic tracing showing circumflex coronary flow and aortic pressure in a conscious dog with complete heart block paced at a rate of 100 beats/min. The long diastole occurred when the pulse generator was turned off.
8 followed cessation of rapid ventricular pacing. It is likely that, given sufficient time, most diastolic pressure-flow relations would linearly intercept the pressure axis as in Figures 1 and 9.

The zero flow pressure intercept clearly changes with vasodilation and also greatly exceeds coronary venous pressure, peripheral coronary pressure, and diastolic intraventricular pressure. Why resting flow stops for beats in which only half the perfusion pressure has been dissipated is not clear. The conventional explanation for a zero flow pressure is that it represents the critical closing pressure of Burton. Burton postulated that there should exist a transmural pressure below which active tension due to smooth muscle contraction would cause physical closure of arterioles. If $P_{f=0}$ does represent a critical closing pressure, flow stops because resistance becomes infinite. Although increasing viscosity and passive narrowing of the arteries may contribute to the increase in resistance, it is likely that the major cause is closure of precapillary sphincters. The existence of a linear pressure-flow relation requires that closure occur continuously over the entire range of perfusion pressures. If one assumes that the resistance of an individual vessel is constant once it is perfused, it can be shown that the required distribution of closing pressures is approximately log normal. Each pressure-flow relation is characterized by a unique distribution of closing pressures, the distribution becoming narrower and shifting to lower pressure when flow is increased by interventions that decrease vasomotor tone. As flow is augmented by increasing perfusion pressure, there is continuous recruitment of vessels and a consequent fall in total coronary resistance. Once a vessel is recruited, the back pressure by analogy to Poiseuille's law becomes $P_c$. If $P_{f=0}$ represents Burton's critical closing pressure, coronary resistance is calculated as $(P-P_c) F^{-1}$ and is the reciprocal of the slope of a line drawn between $P_c$ and the pressure and flow measurement in question. This is the classical definition of vascular resistance and, as shown in the resistance diagrams of Figures 1 and 2, implies that resistance progressively increases as an individual diastole proceeds.

The existence of a critical closure phenomenon as postulated by Burton has been questioned because (1) it has not been observed experimentally in arterioles, although physical obliteration of the vascular lumen has been described in precapillary sphincters, and (2) it is unlikely on theoretical grounds. The rigorous expression for circumferential wall tension applied to thick-walled vessels predicts that the elastic structures far from being in a state of stretch as predicted by Laplace's law are actually compressed. Even if a critical closure phenomenon exists, the analysis of Permutt and Riley suggests that a major modification in Burton's concept is necessary. Permutt and Riley argued that vascular smooth muscle tension causing a critical closing pressure would create a hydraulic state identical to that found when extramural compressive stress caused a segment of partial collapse in an otherwise distended system of tubes. Hydraulic systems containing a collapsible segment have the same pressure-flow relationship as a waterfall; i.e., flow is proportional to the pressure drop up to the waterfall (segment of partial collapse) and is independent of outflow pressure.

If $P_{f=0}$ is caused by a vascular waterfall, flow stops because there is no pressure gradient between the aorta and the location of the partially collapsed segment presumably in the immediate precapillary portion of the microcirculation. The existence of a linear pressure-flow relation implies little vessel recruitment proximal to the waterfall, and for a given pressure flow relation, a very narrow distribution of zero flow pressures. Vessel recruitment may occur distal to the beginning of the waterfall (in the capillary bed), but it will not affect total flow since this is controlled solely by the pressure-flow relation proximal to the waterfall. Only if the waterfall is altered will changes in outflow resistance change inflow. If a vascular waterfall exists, flow is augmented both by a decrease in the resistance of the prewaterfall segment and by an increase in the pressure gradient caused by a fall in the zero flow pressure. With a vascular waterfall, the back pressure becomes $P_{f=0}$ and the resistance that controls coronary flow is $(P-P_{f=0}) F^{-1}$. It is constant for a given pressure-flow relation because it is the reciprocal of the slope of a straight line. The resistance diagrams of Figures 1 and 2 show that if coronary flow is controlled by a
vascular waterfall mechanism, resistance does not change during a diastole.

There is some evidence that such a mechanism may be operative. Studies on pressure regulation in the microcirculation show that, in some tissues, for a given state of vasomotor tone, the pressure in the immediate precapillary portion of the microcirculation (20-μm arterioles) is fairly constant and is maintained somewhat independent of large-vessel pressure. This is suggestive of one of the characteristics that have been predicted for a vascular waterfall. For a given magnitude of vasomotor tone or extravascular compression, the intraluminal pressure at the site of the waterfall is maintained constant and independent of inflow pressure.

It would seem to be important to determine why coronary flow stops in beats such as are shown in Figures 1 and 8. Without this knowledge it is difficult to make a meaningful calculation of vascular resistance and to understand how the coronary circulation compensates for such stresses as an arterial stenosis and systemic hypotension.

**Acknowledgments**

I am grateful to Dr. Ray A. Olsson for permission to use unpublished data from his studies of the effect of adenosine on the coronary circulation.

**References**

Diastolic coronary artery pressure-flow relations in the dog.
R F Bellamy

doi: 10.1161/01.RES.43.1.92

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/43/1/92

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the *Permissions and Rights Question and Answer* document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/