Regulation of Coronary Blood Flow during Individual Diastoles in the Dog

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SUMMARY. Data derived from instantaneous diastolic coronary artery pressure-flow relationships in the dog have suggested that diastolic coronary vascular resistance may be constant and coronary vasoregulation unimportant during individual diastoles. We tested these hypotheses by using constant pressure perfusion to determine the pattern of coronary blood flow during single diastoles under steady state conditions and when coronary vascular resistance was actively changing. In 20 closed-chest, anesthetized dogs, long diastoles of constant cycle length were obtained by vagal nerve stimulation during simultaneous right ventricular pacing. Cholinergic vasodilation was prevented with intracoronary atropine. There were no differences between early and late diastolic flows (P > 0.8) for cycle lengths of 0.5 to 5 seconds and flows ranging from 40 to 125 ml/min per 100 g. When coronary resistance was actively altered with adenosine, brief coronary inflow occlusions, or abrupt changes in heart rate, diastolic flow varied continuously during each beat (13.0 ± 1.1 (SD) to 33.4 ± 5.4 ml/min per 100 g per sec). In 10 additional animals, instantaneous diastolic coronary artery pressure-flow relations obtained with initial diastolic resistance constant were compared with those obtained when resistance was actively changing. Despite a changing diastolic resistance, the resulting pressure-flow curves remained linear. Values for slope and zero flow pressure were increased during vasoconstriction (P < 0.001) and decreased during vasodilation (P < 0.001). We conclude that, during constant pressure perfusion, coronary vascular resistance is constant during diastole, and when coronary resistance is actively changing, regulation of coronary blood flow occurs continuously during individual diastoles. Furthermore, instantaneous diastolic coronary artery pressure-flow relations may be linear despite changes in coronary vasomotor tone, and thus cannot be used to estimate resistance or back pressure in such cases. (Circ Res 50: 377-385, 1982)

INSTANTANEOUS coronary artery pressure-flow relationships derived from phasic aortic pressure and coronary flow measurements during individual diastoles have been shown to be approximately linear with a positive zero flow pressure intercept (Pfo) that exceeds coronary venous and ventricular diastolic pressures (Bellamy, 1978). Interventions which alter vasomotor tone result in reciprocal changes in both the slope and Pfo of the pressure-flow curve (Bellamy, 1978), whereas changes in ventricular preload influence Pfo without changing the slope (Ellis and Klocke, 1980). These observations have been interpreted as being consistent with the regulation of diastolic coronary flow by a waterfall mechanism (Permutt and Riley, 1963; Downey and Kirk, 1978; Bellamy, 1978) in which the back pressure opposing flow is assumed to be Pfo and is determined by vasomotor tone and extravascular compressive forces. Based on this model, coronary vascular resistance is constant during diastole and can be calculated as the reciprocal of the slope of the pressure-flow regression line (Bellamy, 1978; Bellamy et al., 1980; Ellis and Klocke, 1980). Whereas this may be true during steady state conditions, it is difficult to understand how diastolic resistance could be constant but vary from beat to beat during reactive hyperemia. Yet, the pressure-flow relations during individual diastoles following temporary coronary occlusions have been shown to be linear (Bellamy, 1978; Canty and Klocke, 1979). This would seem to imply that either coronary vascular resistance changes from one beat to the next but not during individual diastoles or that pressure-flow relations may appear linear when resistance is, in fact, changing. Another possibility is that resistance changes occur only during early diastole and were not studied since diastolic pressure and flow points were measured beginning 200 msec after the dicrotic notch of the aortic pressure tracing (Bellamy, 1978). When pressure and flow change in the same direction, inferences about resistance may be subject to misinterpretation (Green et al., 1944). One approach to circumvent this problem is to keep inflow pressure constant, since a change in flow would then be inversely proportional to a change in resistance, provided the potential effects of changes in back pressure are considered.

In the present study, we used constant pressure perfusion and examined the pattern of coronary flow during single long diastoles to address the following questions: (1) Under steady state conditions, is resistance constant during diastole? (2) Does the regulation of coronary blood flow occur on a beat-to-beat basis only or continuously during each diastole? (3) Is the linearity of an instantaneous diastolic pressure-flow
relationship sufficient proof that diastolic coronary resistance is constant?

**Methods**

**General Preparation**

Experiments were performed in 30 healthy adult mongrel dogs weighing 25-30 kg. Animals were premedicated with morphine sulfate (2 mg/kg, sc) and anesthetized with α-chloralose (50 mg/kg, iv) with additional doses of chloralose given as needed throughout the experiment. The dogs were ventilated with oxygen-enriched room air by a positive pressure respirator (Harvard Model 607) to keep arterial oxygen tension between 125 and 150 mm Hg and carbon dioxide tension at 32 ± 2 mm Hg. Metabolic acidosis during chloralose anesthesia was prevented by an intravenous infusion of sodium bicarbonate (150 mm, 5 ml/kg per hour, iv) (Arfors et al., 1971) to maintain arterial pH at 7.40 ± 0.05. Systemic pressure was measured in the aorta with a catheter passed retrograde from the femoral artery and a strain gauge pressure transducer (Statham P23GC). Rectal temperature was held at 37°C with heating pads. Heart rate was measured continuously with a cardiotachometer triggered from the ECG.

**Induction of Long Diastoles**

Prolonged diastoles of varying duration were obtained by vagal nerve stimulation. A midline incision was made in the neck and the right vagus nerve was isolated, cleaned, and coated with mineral oil. A pair of platinum electrodes was attached to the nerve and connected to a Grass stimulator (model SD5), using a stimulus isolation unit. Stimulation parameters were: frequently 30 Hz, duration 5-10 msec, voltage 5-20 V. In some animals, a low stimulus voltage (5-10 V) resulted in prolonged diastoles of relatively constant cycle length (1-1.2 sec). However, in most animals, higher voltage (10-20 V) was used to completely arrest the heart for 10-20 seconds, and ventricular pacing was employed to obtain long (1-5 sec) diastoles of constant length. Lidocaine (1 mg/kg, iv) was given to prevent ventricular escape beats.

Since vagal nerve stimulation has been shown to cause direct parasympathetic coronary vasodilation (Feigl, 1969), preliminary studies were carried out to determine whether low-dose atropine given intracoronary could be used to minimize cholinergic vasodilation without altering vagal chronotropic effects. Heart rate was kept constant by pacing the right ventricle with a catheter inserted through the femoral vein. Coronary pressure was maintained at 125 mm Hg as described below. Diastolic coronary blood flow was averaged for four consecutive beats during the control period and at maximum response following 15 seconds of vagal stimulation (30 Hz, 10 msec, 20 V) before and 5 minutes after administration of atropine. The vasodilatory effects of vagal stimulation were effectively blocked by intracoronary atropine (0.02-0.03 mg) for a period of 20-30 minutes (see Results). During this time with the pacemaker off, vagal stimulation still resulted in prolonged diastoles. In the experiments reported in this study, repeated doses of intracoronary atropine were used to prevent cholinergic vasodilation.

**Coronary Perfusion System**

Pressure in the circumflex artery was controlled by an extracorporeal perfusion circuit which has been described previously in detail (Dole et al., 1981). Briefly, the circumflex artery was perfused from a pressurized arterial reservoir through a specially designed metal cannula advanced through the right carotid artery into the ascending aorta and wedged in the proximal circumflex artery under pressure and flow monitoring. Proximal coronary artery pressure was measured at the cannula tip through an external auxiliary tube opening at the side of the distal end of the perfusion cannula. We have previously shown that heart rate, aortic pressure, coronary blood flow, and left ventricular dp/dtmax were unchanged after insertion or removal of the coronary cannula. In addition, reactive hyperemia and autoregulation were not impaired with the cannula in place (Dole et al., 1981).

Blood was passed from the pressurized reservoir through an electromagnetic flow probe (Zepeda SWF4) before entering the coronary cannula. The reservoir blood was continuously mixed with a magnetic stirrer and heated to 37°C. The reservoir blood volume was held constant by a photoelectric cell fiber optic light system which regulated a pump connected to the reservoir in series. The reservoir pressure was controlled by means of two compressed air tanks connected in parallel, permitting arbitrary alterations in perfusion pressure. Twenty-five liter buffer bottles prevented pressure decay in the reservoir. Pressure changes across the perfusion circuit during reactive hyperemia and adenosine boluses were prevented by manually releasing or adding pressure to the reservoir.

We tested the seal between the cannula tip and circumflex artery for inward leakage of blood from the ascending aorta by observing the response of cannula tip pressure to inflow occlusion. In open chest dogs with the coronary cannula tied in place, a 5-second inflow occlusion caused a fall in coronary pressure to 15-20 mm Hg. At the end of the experiment, we tested the possibility of outward leakage by injecting 2 ml of saturated crystal violet solution into the coronary cannula with the perfusion pressure set to a maximum used during the experiment. Retrograde leakage of blood was identified by staining of the proximal circumflex artery and left coronary ostium by dye at postmortem. Experiments with any evidence of outward or inward leakage were not included. The dye injection also served to delineate the area of myocardium perfused which was removed and weighed. Blood coagulation in the extracorporeal perfusion circuit was prevented by infusion of sodium heparin (initial dose 500 U/kg, iv, then 250 U/kg, iv, every hour). The flowmeter zero was determined by frequent coronary inflow occlusions. The flow probe was calibrated by timed blood volume collections after each experiment with blood from the experimented animal.

**Specific Studies**

**Diastolic Flow during Constant Pressure Perfusion**

In 20 dogs, coronary pressure was maintained constant at a level equal to the mean aortic pressure (80-120 mm Hg). Cycle length then was adjusted by vagal stimulation and ventricular pacing to obtain diastoles of constant duration varying from 0.5 to 5 seconds. Once steady state flow patterns had been reached, early and late diastolic flows were determined by averaging flow measurements from five consecutive beats. For very long diastoles, only two beats were used, inasmuch as prolonged vagal stimulation frequently resulted in escape rhythms and nerve damage. An initial diastolic flow overshoot was characteristically observed. Since flow and pressure were not at steady state during this brief period, early diastolic flow was measured beginning 225 msec after the dicrotic notch of the aortic pressure and flow monitoring. Proximal coronary artery pressure was measured at the cannula tip through an external auxiliary tube opening at the side of the distal end of the perfusion cannula. We have previously shown that heart rate, aortic pressure, coronary blood flow, and left ventricular dp/dtmax were unchanged after insertion or removal of the coronary cannula. In addition, reactive hyperemia and autoregulation were not impaired with the cannula in place (Dole et al., 1981).

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pressure tracing. In seven animals, spontaneous heart rates of 40-60 beats/min allowed observation of relatively long diastoles without vagal stimulation.

Diastolic Flow Patterns during Changes in Vasomotor Tone

In these studies, flow was measured during individual diastoles of 1.0- to 1.5-seconds duration when vascular resistance was changing and coronary pressure was held constant. Coronary resistance was altered by: (1) intracoronary bolus injection of adenosine, 12.5 μg, (2) coronary inflow occlusions 5-10 seconds in duration resulting in reactive hyperemia, and (3) abrupt cessation of rapid pacing at 240 beats/min. In most cases, vagal stimulation and ventricular pacing were used to obtain long diastoles but, in four dogs, intrinsically slow heart rates allowed observations of diastolic flow without vagal stimulation.

Instantaneous Diastolic Coronary Artery Pressure-Flow Relations during Constant and Changing Initial Vascular Resistance

These experiments were designed to determine the effects of relatively rapid and uniform changes in coronary vascular resistance on instantaneous diastolic pressure-flow relations. In 10 dogs, pressure-flow curves were obtained by decreasing coronary pressure at 40 mm Hg/sec from an initial value of 100-120 mm Hg during prolonged diastoles. Simultaneous diastolic pressure and flow points were plotted at 40-msec intervals and the data were fitted by a least squares regression to obtain values for slope, zero flow pressure intercept, and correlation coefficient. The average regression values for three consecutive pressure-flow determinations were used. Coronary resistance was altered by intracoronary bolus injection of adenosine (10-20 μg) to increase diastolic flow by 250-300% above control. Following an adenosine bolus, with coronary pressure constant, the most rapid and uniform changes in flow were observed during the middle third of the rising and falling phases of the flow response. Since we were interested mainly in the effects of relatively uniform changes in vasomotor tone, pressure and flow data were analyzed during this 2- to 2.5-second flow segment. Thus, all pressure-flow relations were obtained when baseline zero changed by less than 3-5 ml/min at the beginning and end of recording runs with full scale being 200 ml/min. All data are expressed as mean ± so. Statistical differences were evaluated by Student’s paired t-test with changes considered significant at the P < 0.05 level.

Data Analysis

Coronary blood flow and pressure, aortic pressure, heart rate, and ECG were recorded on an eight-channel Beckman dynograph (type RM), at a paper speed of 5-50 mm/sec. For experiments in which instantaneous pressure-flow curves were constructed, pressure and flow points were simultaneously digitized on a PDP 11/23 computer (Digital Equipment Corp.) and the data graphed with an X-Y plotter (Tektronix model 4662). Data were analyzed only when baseline zero changed by less than 3-5 ml/min at the beginning and end of recording runs with full scale being 200 ml/min. All data are expressed as mean ± so. Statistical differences were evaluated by Student’s paired t-test with changes considered significant at the P < 0.05 level.

Results

Baseline Hemodynamic Data

In the 20 animals used in these experiments, heart rate averaged 107 ± 42 beats/min, mean aortic pressure 113 ± 10 mm Hg, and diastolic coronary blood flow 81.5 ± 18.5 ml/min per 100 g at a coronary pressure of 106 ± 9 mm Hg. During vagal stimulation, diastolic coronary blood flow increased to a maximum of 25.9 ± 7.3% (range 16.7 to 40.0%) above control (P < 0.001) within 4.7-6.6 seconds. The maximum change in diastolic coronary flow from control during vagal stimulation 5 minutes after intracoronary atropine (0.02-0.03 mg) averaged 2 ± 3.3% (range 4.5 to −6.3%) which was not statistically different from 0 (P > 0.8). Thus, atropine essentially blocked the vasodilatory effects of vagal stimulation on diastolic coronary flow.

Diastolic Flow during Constant Pressure Perfusion

The phasic coronary blood flow pattern during constant pressure perfusion in the 20 animals studied was characterized by an initial diastolic overshoot lasting 160 ± 37 msec (range 100-225 msec) followed by remarkably constant flow throughout the rest of diastole. Figure 1 shows the phasic coronary flow and pressure tracings from two representative dogs. In panel A, constant cycle lengths of 5, 2.5, and 1 seconds were obtained by vagal stimulation and ventricular pacing. In panel B, spontaneous bradycardia permitted observation of relatively long diastoles (cycle length 1.2 sec) without vagal stimulation. For the entire group (200 observations) there were no statistically significant differences (P > 0.8) between early and late diastolic flows for individual beats of constant duration varying from 0.5 to 5 seconds in cycle length and diastolic flow ranging from 40 to 125 ml/min per 100 g. These results indicate that, under the present experimental conditions, coronary vascular resistance is constant during individual diastoles.

Diastolic Coronary Flow during Constant Pressure Perfusion and Changing Vasomotor Tone

In nine dogs, intracoronary bolus injections of adenosine with coronary pressure constant resulted in a pattern of progressively increasing flow during...
single diastoles (cycle length 1–1.5 sec) reaching peak flow within 8–10 seconds. Subsequently, coronary flow progressively decreased during each diastole reaching constant basal values within 8–12 seconds. The maximum rate of change in flow during single diastoles averaged 32.5 ± 4.9 ml/min per 100 g per sec. Figure 2 (panel A) shows tracings from a typical dog.

A similar pattern of gradually changing diastolic flow was observed following temporary coronary inflow occlusions in five dogs with vagal stimulation begun near the end of the occlusion (Fig. 2, panel B) and in three additional dogs with spontaneous bradycardia. The maximum rate of change in flow during single diastoles averaged 22.3 ± 5.4 ml/min per 100 g per sec following 5-second occlusions and 33.4 ± 5.4 ml/min per 100 g per sec following 10-second occlusions. The difference in flow rates for the two occlusion durations was statistically significant (P < 0.01). Thus, during coronary reactive hyperemia, blood flow was regulated during individual diastoles, the magnitude of the diastolic flow response being influenced by the duration of occlusion.

Figure 3 shows the response of diastolic coronary flow following abrupt cessation of rapid ventricular pacing with coronary pressure constant. Coronary flow gradually decreased during each diastole before reaching steady state levels. In six animals, the average rate of change of diastolic flow was 13.0 ± 1.1 ml/min per 100 g per sec. Thus, coronary flow was regulated during individual diastoles following changes in myocardial metabolic demands.

Effects of Changing Coronary Vascular Resistance on Instantaneous Diastolic Pressure-Flow Relations

Figure 4 shows an example of the data analyzed for a single control beat and the instantaneous diastolic pressure-flow curve for that beat. The control pressure-flow relations for the 10 dogs used in this study were linear with an average correlation coefficient of r = 0.985 ± 0.004. The average slope of the regression lines was 1.39 ± 0.45 ml/min per 100 g per mm Hg and the zero flow pressure intercept 46.1 ± 5.7 mm Hg.

Figure 5 shows the effects of increasing coronary vascular resistance (during recovery of flow following an adenosine bolus) on the instantaneous diastolic pressure-flow relation for one dog. Of importance is the fact that the pressure-flow relation obtained during vasoconstriction (closed circles) was approximately linear over the pressure range of 100 to 50 mm Hg (r = 0.996). Although the initial pressure and flow points were similar to that for the curve with initial resistance constant (open circles), the slope of the curve obtained with resistance changing was greater (2.99 vs. 2.25 ml/min per 100 g per mm Hg) and the zero flow pressure intercept higher (49.4 vs. 31.1 mm Hg). A control pressure-flow curve (open triangles) is shown for comparison. Similar data were obtained in five additional dogs and are summarized in Table 1A.

Figure 6 compares the instantaneous pressure-flow relation from one dog when initial resistance was rapidly decreasing (closed circles) to the curve obtained when initial resistance was constant (open circles). As in Figure 5, the pressure-flow curve ob-
Figure 3. Diastolic coronary flow during constant pressure perfusion following abrupt cessation of rapid ventricular pacing. After termination of ventricular pacing at 240 beats/min, flow gradually decreased during each 1.5-second diastole, reaching steady state levels after seven beats (10.5 sec).

Discussion

The importance of this study is that it characterizes the regulation of coronary blood flow during individual diastoles in the dog and also defines certain limitations for using instantaneous coronary artery pressure-flow relations to describe coronary hemodynamics. The experiments employed constant pressure perfusion to examine the pattern of coronary blood flow during long cardiac cycles under steady state conditions and when coronary resistance was actively changing. This approach has the advantage, over previous studies using pulsatile coronary perfusion, of allowing direct inferences to be made regarding the state of vasomotor during the course of a single diastole. The results indicate that: (1) for a given steady state, coronary vascular resistance is constant during diastole, (2) when coronary resistance is changing, regulation of coronary flow occurs continuously during each diastole, and (3) under certain conditions, instantaneous diastolic pressure-flow relationships may be linear when vasomotor tone is actively changing, and cannot be used to estimate coronary vascular resistance or driving pressure in such cases.
FIGURE 5. Instantaneous diastolic coronary artery pressure-flow curves during active vasoconstriction. During control conditions, the diastolic pressure-flow curve (A) was linear (r = 0.987) with a slope of 1.28 ml/min per 100 g per mm Hg and $P_f = 49.4$ mm Hg. During constant adenosine infusion, the pressure-flow relation (O) was characterized by a greater slope (2.24 vs. 1.28 ml/min per 100 per mm Hg) and a lower extrapolated $P_f (31.1$ vs. $49.4$ mm Hg). When coronary resistance was increasing (shortly after peak flow following an adenosine bolus), the resulting pressure-flow curve (•) remained linear (r = 0.995). Compared to the curve obtained with the same initial but constant resistance (O), the curve obtained during vasoconstriction was characterized by a greater slope (2.99 vs. 2.25 ml/min per 100 per mm Hg) and higher $P_f$ (49.4 vs. 31.3 mm Hg).

Diastolic Coronary Blood Flow during Constant Pressure Perfusion

The observation that coronary blood flow is not significantly changed during the course of diastole at a given heart rate when perfusion pressure is constant indicates that resistance is constant during single diastoles under such steady state conditions (Fig. 1). This finding has certain implications regarding possible mechanisms for the maintenance of basal coronary vasomotor tone. According to metabolic models of coronary blood flow control, a certain vasodilator metabolite may regulate flow by influencing coronary resistance (Granger and Shepherd, 1973; Rubio and Berne, 1975). A basic feature of the metabolic theory is the existence of a feedback mechanism which couples coronary flow to the concentration of a vasoactive metabolite. The results of the present study would seem to indicate that if a vasodilator metabolite does contribute to the maintenance of basal diastolic resistance, then, following systole, its concentration must achieve a steady state level quite rapidly, despite continued diastolic flow. Alternatively, a myogenic mechanism could explain why diastolic resistance was unchanged in this study, since vascular transmural pressure was maintained constant throughout diastole.

Although pulsatile perfusion of the coronary bed is clearly more physiological than constant pressure perfusion, the state of vasomotor tone during individual

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Initial coronary pressure (mm Hg)</th>
<th>Initial coronary flow (ml/min per 100 g)</th>
<th>S (ml/min per 100 g per mm Hg)</th>
<th>$P_f$ (mm Hg)</th>
<th>r</th>
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<td>A. Increasing resistance (n = 6)</td>
<td></td>
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<tr>
<td>Control</td>
<td>103.0 ± 10.5</td>
<td>76.6 ± 16.3</td>
<td>1.44 ± 0.53</td>
<td>47.5 ± 7.3</td>
<td>0.986 ± 0.006</td>
</tr>
<tr>
<td>Adenosine infusion</td>
<td>104.2 ± 9.3</td>
<td>176.2 ± 29.4*</td>
<td>2.37 ± 0.50*</td>
<td>29.1 ± 5.2*</td>
<td>0.990 ± 0.004</td>
</tr>
<tr>
<td>Adenosine bolus</td>
<td>103.7 ± 8.0</td>
<td>176.2 ± 28.8</td>
<td>2.97 ± 0.58†</td>
<td>43.5 ± 3.7†</td>
<td>0.990 ± 0.006</td>
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<td>B. Decreasing resistance (n = 5)</td>
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<tr>
<td>Control</td>
<td>105.2 ± 6.4</td>
<td>85.3 ± 11.5</td>
<td>1.47 ± 0.29</td>
<td>45.8 ± 3.1</td>
<td>0.986 ± 0.003</td>
</tr>
<tr>
<td>Adenosine infusion</td>
<td>105.4 ± 5.6</td>
<td>125.6 ± 13.9*</td>
<td>1.97 ± 0.33†</td>
<td>38.2 ± 3.8†</td>
<td>0.985 ± 0.007</td>
</tr>
<tr>
<td>Adenosine bolus</td>
<td>106.8 ± 7.3</td>
<td>125.7 ± 14.0</td>
<td>1.50 ± 0.28†</td>
<td>21.7 ± 9.2†</td>
<td>0.984 ± 0.006</td>
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</table>

All values are mean ± so. $S =$ slope, $P_f =$ zero flow pressure intercept of the instantaneous diastolic coronary artery pressure-flow curve, $r =$ correlation coefficient for the linear regression.

* $P < 0.001$ vs. control; † $P < 0.01$ vs. control; ‡ $P < 0.001$ vs. adenosine infusion; $§ P < 0.01$ vs. adenosine infusion.
Diastoles is not apparent when pressure and flow are decreasing together. It is not likely, however, that coronary vascular resistance changes significantly during diastole with pulsatile perfusion under otherwise steady state conditions. This is supported by the observation that, when coronary pressure was rapidly restored following a gradual decrease in pressure with flow briefly reaching zero (Figure 4), diastolic flow immediately returned to baseline values without an initial period of reactive hyperemia. A similar observation was made by Bellamy (1978), who noted the absence of increased flow following a long diastole in which end-diastolic flow was nearly zero and pressure was similar to that after a brief coronary occlusion. This could be explained by a low level of metabolic activity during prolonged diastoles, since coronary reactive hyperemia has been shown to depend on myocardial oxygen demands during the occlusion period (Bache et al., 1973). Alternatively, a myogenic mechanism for coronary vasodilation could be influenced by the rate of pressure change. Thus, a gradual reduction in pressure similar to the normal decrease in diastolic aortic pressure may not result in reactive hyperemia, in contrast to a rapid decrease in pressure such as that following brief coronary occlusion (Bellamy, 1978).

**Regulation of Coronary Flow during Single Diastoles with Vasomotor Tone Changing**

Figures 2 and 3 demonstrate that when coronary resistance is actively changing, blood flow regulation occurs continuously during individual diastoles. If coronary flow is controlled by a vascular waterfall mechanism, then the regulation of diastolic flow observed in our study could have been due to changes in back pressure as well as in resistance, since only inflow pressure was held constant. However, a simple calculation will show that changes in back pressure alone would not be large enough to account for the changes in diastolic flow observed. Based on data obtained from instantaneous diastolic pressure-flow curves (Bellamy, 1978), the maximum total change in back pressure estimated from the zero flow pressure intercept (Pfo) is about 30 mm Hg. If this change in Pfo is averaged over the five beats observed during adenosine-induced vasodilation in Figure 2A (ΔPfo = 6 mm Hg), then the change in diastolic flow per beat, assuming constant resistance during each diastole, would be 24–50% of the observed flow change. The actual contribution of Pfo to diastolic flow regulation is expected to be somewhat less because the adenosine bolus did not produce maximum vasodilation and capacitance effects were not considered. Thus, a significant change in vascular resistance during each diastole can be inferred.

In the present study, coronary flow progressively decreased with the onset of vagal arrest reaching a steady state level within 3–8 seconds, depending on the initial heart rate and flow (Fig. 3). This can be explained by the expected decrease in myocardial oxygen demands and increase in resistance which follows an abrupt reduction in heart rate (Belloni and Sparks, 1977). An early study by Sabiston and Gregg (1957) demonstrated a 25–50% increase in circumflex coronary flow during vagal arrest or induction of ventricular fibrillation. However, in that study coronary flow was recorded with a rotometer which measured more of a mean flow, whereas the present study used an electromagnetic flowmeter which measured true phasic flow. Thus, mean coronary flow increased with the onset of asystole because the extravascular systolic component of total coronary resistance was removed (Downey and Kirk, 1975).

**Instantaneous Diastolic Coronary Artery Pressure-Flow Relations**

In these experiments, the circumflex artery pressure was reduced, independent of aortic pressure. Thus, intracoronary pressure gradients may have resulted in collateral flow which, potentially, could affect the diastolic pressure-flow curve. Based on retrograde flow measurements (Scheel et al., 1972), the total collateral flow for a 100 mm Hg pressure gradient can be estimated to be 3.2 ml/min per 100 g which is 3.9% of the average basal diastolic flow observed in the present study. It is unlikely that this small amount of collateral flow would have affected our experimental results significantly.

The observation that instantaneous diastolic coronary artery pressure-flow relations are approximately linear, with a positive zero flow pressure intercept (Pfo) exceeding coronary venous pressure, has been interpreted as being consistent with the regulation of coronary blood flow by a vascular waterfall mechanism (Bellamy, 1978; Ellis and Klocke, 1980). The major physiological significance of such a model is that the use of Pfo rather than coronary venous pressure to determine the driving pressure for flow will influence the calculation of coronary vascular resistance, particularly at low perfusion pressures. In addition, since Pfo has been shown to vary from 20 to 50 mm Hg (Bellamy, 1978), coronary flow may be regulated by changes in back pressure as well as in coronary vascular resistance. Although the data derived from analyzing instantaneous coronary pressure-flow curves are consistent with a vascular waterfall mechanism, the validity of the model has not yet been proven. The finding of linear coronary artery pressure-flow curves during single diastoles in the course of reactive hyperemia would seem to imply that coronary vasoregulation occurs only on a beat-to-beat basis, with resistance constant during any single diastole. However, Figure 2B clearly demonstrates continuous diastolic vasoregulation during reactive hyperemia. Thus, it appears that the diastolic coronary pressure-flow curves may be linear when resistance is changing under certain circumstances. The pressure-flow curves obtained following an adenosine bolus in this study (Figs. 5 and 6) support this conclusion. These data indicate that the linearity of an
instantaneous pressure-flow curve does not constitute sufficient proof that coronary vascular resistance is constant.

Based on the above considerations it seems that calculations of resistance and back pressure from linear pressure-flow regressions could result in potentially erroneous inferences about the mechanisms of coronary vasoregulation when changes in vasomotor tone are not recognized. For example, during the initial phase of coronary reactive hyperemia, beat-to-beat analysis of diastolic pressure-flow curves indicates that the zero flow pressure intercept is minimal during the first postocclusion beat, yet the slope of the curves is not maximal for several beats (4 sec). This has been interpreted as suggesting that the zero flow pressure intercept may be a more sensitive indicator of vasomotor tone than the slope of the pressure-flow curve (Bellamy, 1978). In addition, it has also been suggested that diastolic flow patterns during early hyperemia result from directionally opposite changes in back pressure and coronary resistance (Canty and Klocke, 1979). However, the results of the present study suggest that beat-to-beat differences in pressure-flow slopes and intercepts during early hyperemia could be explained by active changes in coronary vascular resistance.

Another case in which the potential for misinterpretation exists is that which occurs when instantaneous diastolic pressure-flow curves are obtained by suddenly turning off the pulse generator in an animal with heart block (Bellamy, 1978). Such curves have been shown to be linear, with the slope but not the pressure intercept dependent on initial heart rate (Ellis and Klocke, 1979). Coronary vascular resistance could be increasing during determination of pressure-flow curves obtained shortly after sudden cessation of ventricular pacing, depending on initial heart rate and other factors influencing baseline myocardial metabolic state.

Recently, Spaan (1979) calculated pressure-flow relations, using data obtained during single diastoles in the course of reactive hyperemia, assuming that the zero flow pressure intercept was constant but that resistance was changing linearly with time. The resulting pressure-flow relations, although slightly curvilinear, were actually quite similar to those observed experimentally. In the present study, linear instantaneous coronary pressure-flow relations were obtained during active vasoconstriction or vasodilation (Figs. 5 and 6; Table 1). This possibility was, in fact, suggested by Bellamy (1979) on theoretical grounds. He pointed out that an instantaneous pressure-flow curve obtained when resistance is rapidly changing may actually be a composite of pressure-flow points from a family of different pressure-flow relations, each characterizing a single steady state resistance. This concept is illustrated in Figure 7. During active vasodilation, the observed pressure-flow curve traverses a series of pressure-flow relations with progressively greater slopes and lower zero flow pressure intercepts. During active vasoconstriction, the observed curve crosses slopes and higher zero flow intercepts. One can show that in order for this to occur, resistance must change as a hyperbolic function of diastolic pressure, as detailed in the Appendix.

In summary, the results of the present investigation indicate that, during steady state conditions, diastolic coronary vascular resistance is constant, and that changes can occur rapidly enough to regulate coronary flow during individual diastoles. In addition, since linear instantaneous diastolic pressure-flow relations may be obtained when coronary vasomotor tone is actively changing, conclusions about resistance and back pressure based on the slopes and zero flow pressure intercepts of pressure-flow curves are not justified in such cases.

Appendix

Linear Diastolic Pressure-Flow Relationships when Coronary Vascular Resistance is Actively Changing

In this section, we calculate how coronary vascular resistance would have to change to explain the linear diastolic pressure-flow relationships observed in the present study when coronary vasomotor tone was actively changing (Table 1). Assuming that the coronary bed can be described by a series of linear instantaneous diastolic pressure-flow relations, each characterizing a given steady state resistance (Fig. 7), then pressure \( P(t) \) and flow \( F(t) \) at time \( t \) are related by:

\[ F(t) = (P(t) - P_{\text{in}})S \quad (1) \]

where \( P_{\text{in}} \) is zero flow pressure intercept and \( S \) = slope of the pressure-flow regression line. If \( P_{\text{in}} \) is the back pressure-opposing flow, then diastolic resistance \( R \) will be given by

\[ R = \frac{P(t) - P_{\text{in}}}{F(t)} \]

FIGURE 7. The dotted lines represent hypothetical instantaneous diastolic pressure-flow relations obtained during various steady state values of coronary resistance. As resistance progressively decreases (1--8), the slopes of the pressure-flow curves become greater and the zero flow pressure intercepts smaller. The solid lines (C and D) represent the observed pressure-flow relations obtained during active changes in coronary resistance. At the onset of diastole, time \( t_1 \), the coronary bed can be characterized by pressure-flow curve 5. During active vasodilation the observed pressure-flow points (line D) traverse a series of instantaneous pressure-flow curves (6, 7, 8) until, finally, at end-diastole, time \( t_e \), the bed is characterized by pressure-flow curve 8. Similarly, just prior to active vasoconstriction, the coronary bed is initially characterized by pressure-flow curve 4. During the course of diastole (\( t_5 \) to \( t_4 \)), the observed pressure-flow curve C traverses pressure-flow relations 3, 2, and 1. Thus, the observed pressure-flow curves
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R = (P - Pfo) - F'' = S'. Assuming now that R changes as some function of time R(t) and that the resulting instantaneous pressure-flow curve remains linear with a zero flow pressure intercept Pfo and slope S', then

F(t) = [P(t) - Pfo]S'.

(2)

Since each pressure-flow point on the curve described by Equation 2 will also be on one of the curves described by Equation 1, R(t) can be determined by equating (1) and (2) and solving for S(t)-1. Thus,

R(t) = S(t)-1

= [1 + (Pfo - Pfo)(P(t) - Pfo)-1]S-1.

That is, R must change as a hyperbolic function of P(t) for the resulting pressure-flow relation to be linear. It should be pointed out that this is an approximation, since Pfo may not be constant during diastole when vasomotor tone is actively changing. Using a similar approach, one can show that if R were constant and Pfo changed with time, then, to obtain a linear pressure-flow curve, Pfo(t) would have to be a linear function of P(t). Finally, if both R and Pfo change with time, it is evident that there are an infinite number of functions which could result in a linear relation between P(t) and F(t).

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