Autoregulation of Coronary Blood Flow: Effect of Interarterial Pressure Gradients

By Thomas E. Driscoll, M.D., Thomas W. Moir, M.D., and Richard W. Eckstein, M.D.

Autoregulation is the term applied to the mechanism(s) which maintain blood flow through an organ relatively constant after changes in perfusion pressure. Results of published experiments on the coronary circulation seem contradictory, not only relative to the presence or absence of autoregulation, but also in regard to the degree to which this process regulates coronary blood flow. Shaw et al. found coronary blood flow completely independent of perfusion pressure over a wide physiological pressure range. Eckel et al. previously described experiments which could be interpreted as autoregulation in the coronary circulation. In these experiments coronary flow was found to return slowly toward control level after an initial rise or fall produced by sudden increases and decreases in perfusion pressure in a single artery. On the other hand, Cross and co-workers emphasized the dependence of flow on coronary driving pressure (aortic pressure minus left ventricular pressure) rather than on vasomotor responses. Steady state coronary resistance values which could be interpreted as evidence of autoregulation were found in 44% of innervated, beating hearts studied by Scott et al. Gregg described a biphasic initial flow response in a single artery when pressure in all major arteries was increased simultaneously by compression of the aorta. These rapid flow changes occurred before the higher coronary perfusion pressure and increase in cardiac work would elevate coronary flow. It was therefore suggested that neural influences on coronary resistance might modify an autoregulatory response to changes in coronary perfusion pressure.

Two different viewpoints prevail currently concerning the presence or absence of autoregulation in a particular vascular bed. One is derived from a study of the steady state flow rate at various perfusion pressures; autoregulation is considered present only if resistance calculated at the steady state increases as perfusion pressure increases. The other, a less rigid definition, is based on the entire pattern of flow from the time perfusion pressure is raised or lowered until a new steady state is achieved. A transient* response consisting of an immediate flow change followed by a return of flow toward control level is viewed as an autoregulatory adjustment.

Either of these interpretations of autoregulation would be subject to error if the collateral circulation between the test artery and surrounding vessels were sufficient to distort either the transient flow response or the final adjusted flow rate. In the normal heart, intercoronary collateral flow is small in volume by retrograde flow measurement. Collateral flow of this magnitude might not be expected to affect significantly the flow pattern in response to changes of perfusion pressure in a single artery. However, Levy et al. have found intercoronary flow in the ischemic heart to be approximately three times as large as that measured by the retrograde flow technique. In

*In this report, transient response refers to both the immediate flow change and the subsequent return of flow to a new steady state.
addition, several workers have found that flow into a superficial coronary artery increases after ligation of an adjacent major coronary artery. Since under these latter conditions a pressure gradient exists between the distal ligated artery and surrounding arteries, the increased inflow may be due to flow through collateral channels into the muscle normally supplied by the occluded artery. If this explanation is correct, an experimental rise in perfusion pressure in a single artery would give an exaggerated initial flow response due to distention of vessels and/or perfusion of more channels. Also, significant flow through collaterals after the adjustment period would result in a falsely high steady state flow. Calculated resistance at this point would be lowered, and autoregulation would be underestimated or masked. Thus, the relationship between the immediate and steady state flow rate as well as the final resistance, upon all of which the concept of autoregulation is based, would be inaccurate. The conflicting reports mentioned above and this possible effect of intercoronary collaterals cast doubt on the accuracy with which autoregulation can be studied in a single coronary artery and whether autoregulation can be recognized from a study of the steady state alone.

Therefore, the following experiments were designed to determine if the flow responses to changes in perfusion pressure in a single coronary artery are modified by variations in collateral flow into or from the experimental coronary artery. Patterns of coronary blood flow subsequent to alterations in perfusion pressure were examined while variations in collateral flow were controlled. This was accomplished by producing identical and simultaneous pressure changes in a test artery and surrounding arteries, thereby maintaining the normal pressure gradients between them. The flow curves were compared with those obtained following pressure changes in the test artery alone, and the concept of autoregulation is examined critically with reference to the overall flow pattern and the steady state resistance values.

**Methods**

Mongrel dogs (18 to 23 kg) were anesthetized with morphine (32 mg per animal) and pentobarbital (20 mg/kg). The chest was opened through the fourth left intercostal space while positive pressure respiration was maintained. After isolating the appropriate vessels, heparin (250 mg) was given intravenously.

A diagram of the apparatus is shown in figure 1. The descending thoracic aorta was ligated and aortic flow diverted into an overhead reservoir from which blood was pumped to a constant pressure chamber. The common left coronary artery was cannulated and received blood from the pressure chamber or directly from the overhead reservoir. The first major branch of the left circumflex artery was cannulated separately and perfused from the pressure chamber. In each determination perfusion pressure was rapidly raised or lowered from 100 mm Hg to a preset level (40, 60, 80, 120, 140, 160, 180 mm Hg) by opening or closing an air inlet to the pressure chamber. The apparatus was arranged so that by turning appropriate stopcocks and clamps, pressure could be changed in the branch artery alone, or branch and common left coronary

* Square wave changes in perfusion pressure were produced; for recording, however, these were electronically damped (figs. 2 to 4).
arteries together. The branch served as the test artery, and its inflow was continuously monitored with a Shipley-Wilson rotameter or an orifice meter. Pressure in the vessels surrounding the branch artery was controlled by regulating common left coronary perfusion pressure. Collateral flow between the test artery and surrounding vessels was estimated from the volume of retrograde flow from the test artery measured while the interarterial pressure gradient was maintained equal to that created by the various experimental alterations of perfusion pressure in the test artery. Pressures in the aortic arch and branch and common left coronary arteries were monitored with Statham P23Gb pressure transducers. Coronary resistance was calculated from steady state pressure-flow relationships and expressed as mm Hg/cc/min.

In a second series of ten experiments, blood was brought from the subclavian artery through a rotameter into either the common left or circumflex coronary artery and coronary flow was recorded while aortic pressure was raised. Central aortic pressure was suddenly increased by (a) clamping the aorta, or (b) raising an overhead reservoir which communicated with the proximal segment of the ligated thoracic aorta. In other experiments total aortic pressure was raised by increasing pressure in a chamber connected to a T-cannula placed in the thoracic aorta.

Results

The pattern of coronary flow in response to sudden change in perfusion pressure was similar in all experiments. Typical flow curves are shown in figures 2 to 4. When branch artery pressure alone was increased (fig. 2A), there was an immediate flow increase (maximal in 1 to 2 sec) followed by a return of flow toward control. Coronary flow temporarily decreased below control when original coronary perfusion pressure was restored. In figure 2B the reverse procedure and effects are shown. The decrease in branch coronary artery pressure caused an initial fall and then a partial return of flow to control. An overshoot of flow above the starting value occurred when pressure was returned to control level. Figure 3 shows the effects of changing branch and common left coronary artery pressure together so that no pressure gradient was created between the two arteries. The flow pattern obtained was almost identical to that observed during a comparable change in branch pressure alone. In figure 3B, coronary flow did not return to the same level as in figure 2B following under perfusion, because in the former instance (fig. 3B) control perfusion pressures were restored before the autoregulatory adjustment resulted in a stable coronary flow rate. These flow patterns were seen in 135 determinations in 20 experiments in which

* For example, the intercoronary flow between the test artery perfused at 180 mm Hg and the common left artery perfused at 100 mm Hg was estimated as follows. Retrograde flows from the test artery were measured while the common left artery was perfused at 180 mm Hg and also while it was perfused at 100 mm Hg. The difference between these two retrograde flows was taken as an estimate of that flowing in either direction between the two arteries at a pressure gradient of 60 mm Hg.

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FIGURE 2

A. Branch mean flow pattern in response to increased branch coronary artery pressure (B) while common left coronary artery pressure (CL) remained constant. B. Branch flow response to decrease in branch coronary artery pressure. AP = aortic pressure. Flow in cc/min, pressures in mm Hg. Perfusion pressures are electronically damped. Time lines one second apart.
perfusion pressure was raised or lowered in steps of 20 to 80 mm Hg. Even after prolonged periods of pressure change (three to five minutes), coronary flow never returned completely to its control value at 100 mm Hg.

Phasic flow curves from the branch coronary artery indicate that during the adjustment period following an elevation in perfusion pressure, end diastolic flow rate declined (fig. 4), and no significant difference in the curves was evident whether a pressure gradient between branch and common left coronary arteries was present or absent.

In each experiment the immediate rise or fall of flow was slightly greater when pressure was raised or lowered in the branch coronary artery alone and common left coronary pressure remained constant. In six experiments in which perfusion pressure was raised suddenly from 100 to 160 mm Hg, the initial increase of flow averaged 1.4 cc/min greater when branch coronary artery pressure alone was raised than when branch and common left coronary pressures were raised together. The collateral flow between the branch and common left coronary arteries in these experiments (at an interarterial pressure gradient of 60 mm Hg) averaged 1.0 cc/min and thus largely accounted for the difference in the initial flow response observed under the two conditions.

When coronary perfusion pressure was increased by raising aortic pressure suddenly, an immediate flow rise and beginning decrease of flow was observed in the circumflex or common left coronary artery (fig. 5). This phase of the flow curve was identical to that seen when perfusion pressure was raised by means of the pressure chamber. In the former instance, a secondary, slow rise of flow occurred. This slow rise of flow was attributed to the in-
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FIGURE 5
Response of left circumflex coronary artery flow to sudden increase in aortic and coronary artery perfusion pressure. Perfusion pressure (PP) is not electronically damped. The secondary, gradual flow rise is attributed to an increase in cardiac work. Remainder of legend as in figure 2.

increased cardiac work at the higher aortic pressure. In four experiments comparisons were made of immediate (peak) flow increases after comparable changes in perfusion pressure produced by (a) raising aortic pressure and (b) raising coronary artery pressure alone (aortic pressure constant). Since steady state flow rates were elevated by the increased cardiac work when aortic pressure was raised, only the immediate coronary flow changes could be compared. There was no significant difference in the per cent flow increase when perfusion pressure was raised by the two methods (table 1).

The steady state resistance values were always compared with the resistance at the control pressures immediately before a change was induced. In 12 experiments (60%), calculated resistance decreased as perfusion pressure was increased in increments ranging from 20 to 80 mm Hg (type I). In three experiments (15%) the opposite occurred: resistance increased at higher perfusion pressures (type II). There were five experiments (25%) in which resistance changes were so variable, or so slight, that no definite directional change was evident. Resistance values and corresponding perfusion pressures representative of a type I and type II response are illustrated in table 2.

Discussion
The pattern of coronary flow in response to changes in coronary perfusion pressure was not significantly affected by sizable pressure gradients between major vessels (figs. 2 to 4). The immediate peak flow and final adjusted flow rates into the branch coronary artery were almost identical regardless of the presence or absence of interarterial pressure gradients between the branch and surrounding coronary arteries. The slight differences in ini-
### TABLE 1

Comparison of the Immediate Coronary Flow Increases Produced by Two Different Means of Raising Perfusion Pressure

<table>
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<tr>
<th>Experiment number</th>
<th>Aortic pressure</th>
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<th>Mean coronary flow</th>
<th>Per cent increase in mean coronary flow</th>
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* C = control readings; E = experimental values.

† (a) = coronary flow increased by raising aortic pressure; (b) = coronary flow increased by means of perfusion pressure chamber.

† Average of two or more determinations.
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TABLE 2

| Type | Perfusion pressure, mm Hg | C | E | C | E | C | E | C | E |
|------|---------------------------|---|---|---|---|---|---|---|---|---|
| I    | Resistance, mm Hg/cc/min | 3.9 | 3.5 | 3.9 | 3.2 | 2.7 | 3.2 | 2.8 | 1.7 |
| II   | Perfusion pressure, mm Hg | 102 | 102 | 80 | 100 | 122 | 100 | 140 | 102 | 158 | 102 | 172 |
|      | Resistance, mm Hg/cc/min | 3.1 | 2.9 | 2.9 | 2.7 | 2.9 | 3.1 | 3.4 | 3.7 | 3.8 | 4.1 | — |

* Resistances are calculated from steady state flows.
† C = control values; E = experimental values.

The changes in coronary resistance observed during the return of flow toward control value may be due to 1) vasomotor activity of resistance vessels, 2) changes in transmural pressure, or 3) viscosity effects. We have previously reported [12] that such flow adjustments in the heart do not result from changes in extravascular pressure. Though viscosity may vary with flow rate, there is no obvious reason to suggest that a primary change in viscosity causes the autoregulatory adjustment which returns flow toward the control rate. Accordingly, autoregulation probably reflects vasoconstriction or vasodilation of arterioles in response to an increase or decrease in perfusion pressure. It was evident from the entire flow pattern that this adjustment occurred whether the final steady state resistance after increasing perfusion pressures was higher or lower than the control resistance value. Even though steady state resistance decreased in 60% of experiments, the immediate flow change and subsequent adjustment were quite similar to those observed in the experiments in which steady state resistance increased. In all experiments return to control pressure from a higher pressure resulted in a decrease in flow below its control value. Similarly an overshoot in flow always occurred when pressure was returned to control after having been lowered. Since collateral flow between vessels is not sufficient to distort the flow curves, these flow rates immediately after a return to control pressure reflect true changes in vascular resistance. The conclusion is that in 60% of experiments (type I) the higher distending pressure kept vascular resistance less than control resistance; in the type II response, autoregulation was sufficient to overcome the distending pressure and raise coronary resistance above control. A variability in steady state coronary resistance was also found by Scott et al. [5] when stepwise increases in flow were produced. However, autoregulation, as indicated by resistance changes prior to reaching the steady state, could have been present in all their experiments. Therefore, a vascular bed may not necessarily be passive (nonautoregulatory) when steady state resistance decreases as perfusion pressure increases.

There is additional reason to suggest that the overall flow pattern rather than steady state resistance values best demonstrates the presence of autoregulation. In every experiment the typical flow pattern described (figs. 2 to 4) was present as long as reactive hyperemia resulted from a brief total occlu-
sion of the test artery. Whenever reactive hyperemia was abolished by drugs, hypoxia, or spontaneous coronary vasodilation secondary to deterioration of the experimental preparation, autoregulatory flow patterns were not present. Under these latter conditions, an increase in perfusion pressure caused sustained increases in coronary flow; there was no return toward control. This situation is analogous to that observed in skeletal muscle where a high flow rate and a high venous \( P_{O_2} \) level are associated with nonautoregulatory vessels. 18

Although Shaw et al. 1 did not report resistance values, increasing resistance at higher perfusion pressures was present in their experiments since coronary flow was unchanged over the pressure range 70 to 145 mm Hg. In contrast, coronary flow did not return completely to control in our experiments even when resistance increased at higher pressures. This has also been the experience of Berne. 14 Fishback and his associates 15 likewise reported that in the isolated, perfused heart although resistance increased at higher perfusion pressure, autoregulation was incomplete in the pressure range 60 to 130 mm Hg.

Gregg 6 found that compression of the aorta resulted in an increase in left coronary artery inflow prior to a significant rise in aortic (and coronary artery) pressure. This was followed by a secondary fall of coronary flow below the control level. The results of the experiments reported here are quite different. Increases in aortic pressure caused prompt increases in coronary flow, but the flow response was proportional to the rise in coronary perfusion pressure (fig. 5), and the initial flow increase was the same regardless of the means by which perfusion pressure was increased (table 1). In addition, the biphasic response described by Gregg 6 was not observed. The results obtained under the conditions of these experiments do not support the concept that increases in aortic pressure initiate reflex alterations in coronary arterial resistance.

Neither do these experiments support the view that coronary blood flow is dependent on a driving pressure. 4 Such conclusions are based on a study of steady state pressure-flow relationships and thus fail to consider the rapid alterations in coronary resistance which follow sudden changes in perfusion pressure. Autoregulatory mechanisms will be overlooked unless both the immediate flow patterns and the steady state pressure-flow relationships are considered.

Summary

In the normal heart, transient and adjusted steady state coronary flow rates in response to changes in perfusion pressure are not significantly affected by collateral flow into and from heart muscle surrounding the area perfused by a test artery. An active autoregulatory adjustment tends to counteract flow changes after perfusion pressure is changed. This adjustment is sometimes sufficient to increase vascular resistance above control values. Usually, however, coronary resistance decreases at higher perfusion pressures even though autoregulation is present. The experiments provide no evidence for reflex control of coronary resistance in response to increases in aortic pressure; the initial flow changes can be accounted for by the corresponding increase in perfusion pressure. It is necessary to examine the entire coronary flow pattern after a sudden change in perfusion pressure in order to formulate concepts which include all the important determinants of coronary blood flow.

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References


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