Pressure-Flow Relationships in the Coronary Circulation

By Wadie M. Fam, M.D., Ph.D., and Maurice McGregor, M.D.

ABSTRACT

This study was designed to define more accurately the respective influences of perfusion pressure and flow on coronary resistance. Resistance in a coronary branch, perfused at constant flow, was reduced immediately following temporary perfusion arrest. Large epicardial arteries did not appear to take part in this reaction. In the first 10 to 15 seconds after flow was restored, resistance for that flow was uninfluenced by the duration of the preceding perfusion arrest. That mechanism which caused coronary resistance to fall as a result of metabolic factors, such as reduced availability of oxygen, was thus maximally activated. By observing the relationship of coronary resistance to perfusion pressure at this time, it could be shown that resistance vessels and their surrounding structures showed little evidence of distensibility (resistance constant from 20 to 60 mm Hg). The difference between resistance at steady state and resistance at maximal vasodilatation defines the extent of vasomotion attributable at any flow rate to metabolic factors. Perfusion with venous blood caused a fall of resistance which was greater at any flow rate than could be accounted for by the differences in oxygen delivery rate.

ADDITIONAL KEY WORDS reactive hyperemia coronary resistance coronary autoregulation

As in any other vascular bed, coronary flow is determined by the driving pressure and the resistance offered to flow by the coronary blood vessels. The latter in turn depends on the distensibility of these vessels and their surrounding structures, on the one hand, and on the contractile state of the smooth muscle in them, on the other. Although influenced by both neurogenic and blood-borne factors, it appears that a large fraction of the resistance in the coronary bed is determined from moment to moment by some additional factor that varies with the metabolic state of the ventricular muscle and is closely coupled to the availability of oxygen (1-4). So active is this mechanism that it has been impossible to define the influence of perfusion pressure alone on coronary resistance, as the associated changes in flow evoke, through the mechanism referred to, secondary changes of vascular resistance. In the present study an attempt was made to define the respective roles of distending pressure (change of resistance due to passive distension of the vessels as the pressure within them rises) and of the metabolic state of the myocardium (change of resistance due to increased delivery or removal of metabolites such as oxygen) on the observed coronary resistance. Furthermore it is unknown whether all coronary vessels respond in an identical fashion to these two influences. It is unknown, for example, whether the larger arteries on the surface of the heart are sensitive to the metabolic state of the underlying myocardium or whether such reactivity is confined to those vessels which lie deep in the heart muscle in close proximity to the contracting myocardial fibers. The study was so designed as to throw light on this question as well.

Method

Studies were carried out on six mongrel dogs ranging in weight from 21 to 32 kg, anesthetized with an initial dose of chloralose, 30 mg/kg iv,
and urethane, 4 mg/kg iv, repeated as necessary. Artificial ventilation was maintained by a positive-pressure ventilator (Harvard Instrument Company) using an oxygen-enriched gas mixture so that arterial Po₂ was maintained between 150 and 420 mm Hg and arterial PCO₂ between 20 and 42 mm Hg throughout all experiments. All dogs received an initial dose of 75 mg heparin and subsequent doses of 25 mg half hourly.

After exposure of the heart, the circumflex coronary artery was isolated near its origin and cannulated using a short, wide-bore (4 mm i.d.), stainless steel cannula (Fig. 1). The latter was provided with a side-arm 7 mm from its distal orifice for the registration of cannula pressure and was perfused at constant flow rates by a Harvard Instrument "Infusion Withdrawal" pump, with blood withdrawn from the aorta or inferior vena cava through a polyethylene catheter (2 mm i.d. by 30 cm length). An appropriate correction was made in all experiments to allow for the pressure drop from the side-arm to the distal end of the perfusion cannula. Thus, a constant infusion rate could be set at any desired level while the cannula or perfusion pressure, aortic pressure, and left atrial pressure were recorded continuously using appropriate catheters, Sanborn pressure transducers (No. 267A), and a Sanborn polygraph. Mean pressure was obtained by electronic integration of the instantaneous pressure signal.

In addition, in four studies a small distal branch of the circumflex artery was cannulated using a fine (1 mm i.d.) polyethylene cannula, for the measurement of the coronary pressure at a more peripheral site. The pressure difference between the origin of the perfused coronary artery and this distal site could thus be measured using a Sanborn (267B) differential monometer.

In each experiment the flow rate selected at the beginning of the procedure was that which produced a cannula pressure equivalent to or very near the mean aortic pressure after time had been allowed for a steady state to be achieved. Studies were then made during and following brief periods of perfusion arrest, sufficient time being allowed for perfusion pressure to reach the previous value after each intervention. In four experiments comparison was made of the effect of different periods of perfusion arrest. All subsequent studies were made at different perfusion rates, and apart from the four studies mentioned above, the duration of perfusion arrest was held constant (usually 20 seconds) in each experiment. In three dogs after these studies had been performed using arterial blood for coronary perfusion, the procedure was repeated using venous blood withdrawn from the inferior vena cava and again repeated using arterial blood thereafter. Samples of arterial and venous blood were withdrawn at regular intervals for estimation of hematocrit, Po₂ and PCO₂ (Instrumentation Laboratories Model 113), and oxygen saturation by the method of Nahas (5).
Results

Changes in Perfusion Pressure Resulting from Brief Periods of Ischemia

When a perfusion rate had been held constant for some time, perfusion pressure also became constant at what will be referred to as "steady-state" pressure (Fig. 2). The perfusion rate selected at the beginning of each experiment was that which gave a steady-state perfusion pressure comparable to the aortic pressure. If coronary perfusion was then suddenly stopped, perfusion pressure fell to reach a new low and relatively constant pressure, the "stop-flow" pressure referred to in Figure 2. This term is identical to "peripheral capillary pressure" used by many other authors. Values varied in different experiments from 6 to 42 mm Hg.

When perfusion was again started at the previous infusion rate, perfusion pressure rose rapidly to reach, within 5 to 10 seconds, a relatively constant value which was lower than the steady-state pressure, due to postischemic vasodilatation. Thereafter, pressure rose gradually until the previous steady-state value was reached (Fig. 2).

The influence of the duration of the period of arrest of perfusion on the subsequent reactive hyperemia was studied in four experiments by arresting perfusion for periods of 10 to 60 seconds (Fig. 3). It was found that for any given flow rate, the perfusion pressure 10 seconds after flow was restored (i.e., during postischemic dilatation) was identical, irrespective of the duration of the preceding ischemia within this range.

In that the pressure soon after perfusion

Changes in perfusion pressure (full undamped signal) resulting from consecutive intermittent interruptions of coronary perfusion of increasing length (15 to 45 seconds) at two different flow rates. Arrow denotes time lapse of 1 minute. Irrespective of the duration of occlusion, perfusion pressure, for each flow rate, immediately after restoration of flow is identical.
was restored was unrelated to the duration of perfusion arrest, it could be concluded that vasodilatation attributable to myocardial ischemia was maximal at this time (10 seconds after flow was restored). At any given flow rate the difference between the steady-state perfusion pressure and the pressure at the time of postischemic vasodilatation was therefore due solely to that fraction of the coronary resistance which varies with myocardial ischemia. This difference represents the potential for ischemic vasodilatation at any flow rate.

**CHANGES IN PERFUSION PRESSURE AT DIFFERENT PERFUSION RATES**

In each animal on several occasions observations were made during postischemic dilatation (as shown in Fig. 2), at different perfusion rates. The duration of perfusion arrest was held constant. In the example shown in Figure 4 it can be seen that pressure before and after occlusion fell with each reduction of perfusion rate. The steady-state perfusion pressure and the perfusion pressure 10 seconds after restoring perfusion could in this way be compared at different flow rates. An example of such a comparison is shown in Figure 5.

The relationship of pressure to flow during maximal postischemic vasodilatation was close to linear, and extrapolation of the line relating pressure to flow cut the pressure axis at a value close to the stop flow pressure. Thus, over the range of pressure studied (20 to 60 mm Hg) the coronary resistance during maximal postischemic vasodilatation remained nearly constant irrespective of the perfusion pressure or perfusion rate (see Fig. 5).

By contrast, the perfusion pressure or resistance at steady state diminished rapidly with each decrease of flow until maximum vasodilatation was reached (at flow of ± 20 ml/min in the experiment illustrated in Fig. 5). Likewise, when flow was increased, steady-state perfusion pressures rose rapidly. In the example shown in Figure 5, maximum resistance was reached at a flow of approximately 50 ml/min.

The pressure-flow relationships described above were comparable in each preparation and were reasonably repeatable over 30- to 60-minute periods, irrespective of the order in which observations were made, provided that sufficient time was allowed for full recovery to take place between each stop flow observation (1/2 to 2 minutes).

**EFFECT OF PERFUSION OF VENOUS BLOOD**

When, during steady-state conditions, arterial blood was suddenly replaced by venous blood in the perfusion circuit, there was a fall in steady-state perfusion pressure which required from 1 to 3 minutes to reach a new

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1Coronary resistance (mm Hg/ml/min) = [perfusion pressure — stop flow pressure (mm Hg)] infusion rate (ml/min).

*Circulation Research, Vol. XXV, September 1969*
Changes in steady-state values (continuous line) and values observed during maximal vasodilatation 10 seconds after flow was restored (broken line) together with stop-flow pressures and calculated resistances. Observations were made at flow rates of 68, 45, 30, and 15 ml/min.

Changes associated with temporary perfusion arrest when the cannula was perfused with arterial and subsequently with venous blood. A period of 3 minutes elapsed between these two examples. While steady-state pressure falls on commencing perfusion with venous blood, the pressure during maximal vasodilatation is identical.

steady state. By contrast, perfusion pressures during postischemic dilatation were identical whether arterial or venous blood was used (Fig. 6).

Five experiments were designed to determine the relation of pressure to flow during steady state and during postischemic vasodilatation, using both arterial and venous blood.
A comparable experiment to that shown in Figure 5, using arterial blood (solid circles) and venous blood (open circles). Continuous lines represent steady-state values and broken lines the values 10 seconds after restoring perfusion. Observations at different flow rates were made in random order. (Venous blood: $P_O_2$ 48 mm Hg, pH 7.45, $P_CO_2$ 40 mm Hg. Arterial blood: $P_O_2$ 423 mm Hg, pH 7.5, $P_CO_2$ 29.5 mm Hg.)

The perfusion pressure and resistance at steady state during venous perfusion were invariably lower at any given flow rate than equivalent values using arterial blood. Figure 7 illustrates an example of one such experiment. In this example maximum resistance was observed with an arterial flow of approximately 50 ml/min (a rate of oxygen delivery of 10.8 ml/min). Equivalent levels of resistance were not reached during venous perfusion even when the perfusion rate was increased as high as 90 ml/min (oxygen delivery rate of 16.8 ml/min).

Although resistance during postischemic dilatation was generally identical for arterial and venous blood (Fig. 6), it was observed in each experiment that whenever perfusion with venous blood was prolonged for 15 minutes or more the resistance during maximum postischemic dilatation fell slightly (Fig. 7). This fall was irreversible even after prolonged subsequent perfusion with arterial blood.

Changes observed in superficial coronary vessels during reactive hyperemia

The pressure difference between the distal end of the perfusion cannula and the small polyethylene cannula inserted distally into the superficial coronary artery varied from 2 to 9 mm Hg in four dogs. This “gradient” did not vary with the perfusion pressure. As might be expected, when coronary perfusion was arrested, the gradient of pressure in the superficial vessel fell rapidly as shown in Figure 2. On restoration of flow, however, it rose rapidly to reach a value higher than the preceding steady-state value, returning over the subsequent minute to the steady-state level. Thus, in this superficial segment of the vessel, there was no evidence of postischemic vasodilatation, and at the time when the total coronary vascular resistance was at its lowest, during maximal postischemic vasodilatation, resistance in this segment of large artery was actually higher than during steady state.

Discussion

Critique of method

The effect of collateral flow on studies such as these is probably small (1, 2, 6). However, there are several other theoretical objections to the experimental approach employed.

Although the perfusion pump delivered blood at a constant rate into nondistensible tubing, the actual flow rate within the coronary vessels must have fluctuated with the cardiac cycle. The necessity for calculating values for resistance from the perfusion rate set by the pump and the electrically integrated pressure signal constitute an obvious source of error.

Neither pulse nor femoral arterial pressure varied significantly in any of the studies reported. However, perfusion arrest of over 20 seconds sometimes caused detectable elevation of left atrial pressure (Fig. 2), and changes of ventricular contractility following occlusion must have influenced flow during reactive hyperemia (1, 7). Whatever the effect of these changes on the resistances observed, however, they were presumably

Circulation Research, Vol. XXV, September 1969
comparable for equivalent periods of occlusion.

In these experiments, stop-flow pressure always exceeded coronary sinus pressure. Because in the normal dog heart retrograde flow from the perfused branch is negligible in relation to the normal forward flow (8), closure of most vascular channels must have occurred at stop-flow pressure. It is of course arbitrary to select any single value to represent the pressure at which vascular closure takes place as this must vary at different sites within the ventricular wall and must take place earlier in systole than in diastole. However, for purposes of computing coronary vascular resistance, we made the assumption that stop-flow pressure represented the pressure at which closure of most vessels took place.

The resistance in the segment of the superficial coronary vessels studied was computed from the pressure difference between the perfusion cannula tip and the distal polyethylene cannula. As the distal cannula completely occluded the branch into which it was tied, the distal pressure must be considered to be an imperfect index of the "side pressure" existing at the first proximal bifurcation, where the angle of bifurcation was neither 90° nor constant. These defects were, however, common to all observations in each dog and are unlikely to affect the overall pattern of the changes observed.

PRESSURE-FLOW RELATIONSHIP

The relationship between perfusion pressure and resistance in the coronary circulation has been the subject of many previous studies (2, 3), and the plot of steady-state pressure in relation to flow shown in Figure 5 is comparable to those illustrated in the studies of Case and Roven (9, 10). However, in such studies it has been impossible to distinguish between the effect on resistance of changing such factors as oxygen availability due to changing flow, on the one hand, and the influence of changes of distending pressure on the vascular wall and its surrounding structures, on the other. From the present experiments in which flow changes were imposed during maximal postischemic vasodilatation, it can be seen that the resistance of the coronary bed changed relatively little with changes of distending pressure over the range of pressure examined.

METABOLIC REGULATION

The fact that perfusion pressure in the first 5 to 10 seconds after restoration of perfusion was constant for any given perfusion rate and was unrelated to the duration of the preceding arrest of perfusion is not surprising. Olsson and Gregg (1) and Khouri et al. (11) have shown in variable-flow preparations that longer periods of coronary vessel occlusion in the unanesthetized dog do not increase the peak flow in the reactive hyperemia response. In the constant-flow preparation used here it was very clear that resistance at this time was constant whatever the duration of the preceding occlusion (in the range of 10 to 45 seconds), and irrespective of the oxygen content of the blood perfused. It can be concluded therefore, that whatever vasodilatation is attributable to the metabolic state of the myocardium is maximal after 10 seconds of circulatory arrest. Thus, the difference between coronary resistance at maximum vasodilatation and during steady state reflects that fraction of resistance which varies with the metabolic state of the heart muscle. These experiments suggest that the normal operating value of this variable resistance lies towards the upper limit of the flow-resistance curve. Thus, in the example shown in Figure 5 it can be seen that there is increasing vasodilatation as flow falls until a value of approximately 20 ml/min at which point maximum vasodilatation has occurred. Likewise, as flow increases steady-state resistance rises rapidly to reach maximum at a flow of approximately 45 ml/min. Mean aortic pressure at this time was approximately 110 mm Hg, and the level of coronary flow and the resistance which would have pertained if the coronary branch had been perfused from the aorta at this pressure can be derived from the figure. It can thus be seen that at this operating level there was a large vasodilator reserve and a smaller vasoconstrictor reserve available for adjustment of
resistance in response to changes in metabolic needs, in oxygen content of blood, or of perfusion pressure. It should be noted that these conclusions are in contrast to those of Brandfonbrener et al. (12) who found that "in general, as the coronary blood flow was increased the resistance fell," though the reason for this discrepancy is not apparent.

This study does not throw light on the exact mechanism or mechanisms responsible for ischemic vasodilatation. It is known that vasodilatation takes place whenever there is an increase in myocardial energy expenditure (4, 13), or a reduction in the rate of oxygen delivery whether this is brought about by reduction of coronary flow, anemia (14), or hypoxemia (15). Whether the availability of oxygen is the sole factor or whether a vasodilator substance or substances are released from heart muscle in inverse proportion to oxygen availability is not yet known. Because the oxygen content of the venous blood from the perfused area was unknown in our studies, it cannot be assumed that oxygen consumption was equivalent to oxygen delivery rate. However, in no instance could the same level of resistance be achieved during venous perfusion as when arterial blood was employed. This suggests that blood-borne factors other than oxygen availability must play a role in this reaction.

**EPICARDIAL VESSELS**

The large superficial coronary vessels on the surface of the heart did not appear to take part in the postsischemic vasodilatation which follows perfusion arrest (Fig. 2). Resistance within the large vessel was actually higher at the time when the total coronary bed displayed maximum vasodilatation (Fig. 2). This may have been the result of a lower distending pressure or of a temporary reduction in the distensibility characteristics of the vessel, i.e., the opposite of stress relaxation. Thus, the superficial coronary vessels exhibit a higher resistance at lower perfusion pressures and a lower resistance at higher perfusion pressures together with evident stress relaxation. This can best be demonstrated by making step-wise changes in coronary perfusion rate and observing the time course of the changes in pressure (Fig. 8).

The fact that large coronary vessels do not appear to take part in postsischemic dilatation has pharmacologic implications. It is sometimes argued that the nitrites cannot relieve angina through coronary vasodilatation since ischemia alone produces the greatest dilatation possible. However, in most cases of angina pectoris obstruction to flow is in the larger arteries, where, as shown above, ischemia will have no vasodilator effect. The nitrites, however, have a marked effect on these vessels (16). Their administration may thus increase flow to ischemic areas of myocardium either by dilating the narrowed artery itself or its neighbors which are the source of collateral blood flow (8).

**References**


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