Distribution of the Coronary Blood Flow across the Canine Heart Wall during Systole

By James M. Downey and Edward S. Kirk

ABSTRACT
The transmural distribution of left coronary blood flow during systole was studied by measuring the myocardial uptake of a bolus of $^{86}$Rb introduced into the coronary circulation when the perfusion was limited to the periods of systole. The measurement revealed a transmural gradient of systolic blood flow with a flow rate in the outer fourth of the left ventricle about twice that in the inner fourth. A gradient of flow encompassing all depths of myocardial tissue revealed that intramyocardial pressure during systole was not sufficient to completely collapse the vessels and, therefore, did not exceed intraventricular pressure. The results of this experiment indicate that intramyocardial pressure limits coronary blood flow through a vascular sluice mechanism.

KEY WORDS
vascular sluice model
intramyocardial pressure
subendocardial ischemia
transmural flow gradient
coronary artery
flow in collapsible tubes
$^{86}$Rb uptake

Contraction of the heart inhibits coronary blood flow (1). An earlier study (2) has demonstrated that systole reduces blood flow in the myocardial layers near the endocardium more than it reduces blood flow in the layers near the epicardium. Such a redistribution of myocardial blood flow possibly is the result of a transmural gradient of intramyocardial pressure during systole. Therefore, the increased vulnerability of the subendocardium to ischemic coronary artery disease results from reduced blood flow to this tissue during part of the cardiac cycle (3-5).

To date the redistribution of coronary blood flow during systole has not been adequately described quantitatively. No direct measurements of this redistribution have been reported. Furthermore, it has not been possible to calculate the magnitude of the redistribution during systole, because (1) the physical process whereby intramyocardial pressure influences coronary blood flow has not been postulated and (2) the reported values of intramyocardial pressure disagree considerably (6-10).

In the present study a technique has been developed to determine the transmural distribution of coronary blood flow during systole by measuring the intramyocardial distribution of coronary blood flow with radioactive tracers when the coronary arteries are perfused with left ventricular pressure. Since ventricular pressure falls to near zero during diastole, forward flow and thus the delivery of the tracer was confined to the periods of systole. In light of this technique, a theoretical model that quantitatively describes the relationship between intramyocardial pressure and coronary blood flow is presented in this paper.

Methods
Five mongrel dogs of either sex (13-16.5 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv); additional anesthesia was administered as needed. The hearts were exposed by a left thoracotomy in the fourth intercostal space, and electrocautery was used to promote hemostasis. The dogs were ventilated with a positive-pressure respirator while their chests were open. Heparin (10,000 units, iv) was administered to prevent clotting in the perfusion tubing.

Aortic blood pressure was obtained from a stiff vinyl catheter passed through a femoral artery into the thoracic aorta, and perfusion pressure was recorded from a branch of the perfusion circuit near the coronary cannula. Ventricular pressure was measured by another vinyl catheter passed through the left carotid artery into the left ventricle. Phasic coronary blood flow was measured by a Biotronix extracorporeal electromagnetic flow transducer in the perfusion circuit. A Biotronix sine wave electromagnetic flowmeter was used. A short length of tubing bypassed the flow transducer so that a zero-flow base line could be established without interrupting coronary flow. The bypass was normally pinched closed.
In each surgical preparation the left common coronary artery was exposed by blunt dissection, and a silk thread was passed under it. A metal cannula was introduced through the stump of the left subclavian artery into the left coronary ostium where it was tied in place with the thread.

A simplified diagram of the perfusion circuit appears in Figure 1. Tygon tubing carried arterial blood from a carotid artery to the coronary artery. A branch of this tubing was connected to an 8-mm length of nylon tubing (5 mm, i.d.) passed through an incision in the left atrium into the lumen of the left ventricle. All of the tubing was kept as short as possible and had the largest diameter possible to avoid alteration in the ventricular pressure pulses.

During an experiment the clamp that occluded the ventricular branch of the circuit was removed and immediately placed on the branch from the carotid artery. At the same time 20 \( \mu \text{C} \) of \(^{86}\text{RbCl} \) in 0.1 ml of normal saline was injected into the perfusion line near the coronary cannula. After 60 seconds the perfusion line was clamped, and the heart was removed by cutting the great vessels at the base of the heart. The left ventricular free wall was excised, rinsed under tap water, wrapped in aluminum foil, and frozen. When the tissue was frozen, four 15-cm\(^2\) sections that included the full thickness of the ventricular wall were cut. Sections were taken from the anterior and the posterior apex and the anterior and the posterior base. Each of these four sections was sliced into four equally spaced layers from the outer to the inner wall. Thus, in each heart four myocardial depths were sampled from four locations in the ventricle. Each of the 16 samples was weighed to the nearest milligram and placed in a test tube that contained 3 ml of concentrated nitric acid. When the samples were completely dissolved, thus ensuring a uniform counting geometry, they were counted in a well scintillation counter. The count rate, corrected for background, was divided by the sample weight to yield an activity per gram for each sample. Since no consistent differences were seen between the four different regions sampled all of the data were pooled and analyzed only in terms of myocardial depth. The data were normalized by dividing the activity of each sample by the activity of the entire transmural section from which it was taken. In each heart the four normalized activities for each depth were averaged. Then the means ± se for each depth from all five hearts were calculated.

**Results**

Figure 2 is a phasic record of an experiment during which the left coronary artery was perfused with ventricular pressure (systolic perfusion). The coronary pressure record indicated that little driving pressure persisted during the periods of diastole. The electromagnetic flowmeter revealed that forward flow was confined to systole and that a smaller retrograde flow occurred during diastole. Figure 3 is a record of prolonged systolic perfusion. In all of the experiments, the mean coronary blood flow during systolic perfusion was less than that observed before systolic perfusion was initiated. The gradual increase in mean flow following the onset of systolic perfusion indicated that vasodilation had occurred in the coronary bed. The reactive hyperemia following the return to normal perfusion confirmed this finding. Accompanying the reduced coronary blood flow was a gradual loss of ventricular function during systolic perfusion as evidenced by a slight increase in the diastolic ventricular pressure, a reduction in the positive derivative of the ventricular pressure, and the appearance of alternans.

During one experiment \(^{86}\text{Rb} \) was introduced into the perfusion line coincidently with the onset of systolic perfusion as a blood-flow indicator. In Figure 4 the means ± se of the normalized tissue concentrations of the isotope are plotted against the relative myocardial depth from which each sample was removed. Since the uptake of the isotope by the tissues is primarily limited by the local blood flow, the concentration of the isotope anywhere within the perfusion field is proportional to the local nutritive flow at the time of infusion (11). If the perfusion were uniform across the wall, a horizontal line at a normalized \(^{86}\text{Rb} \) activity of 1.0 would result. However, the perfusion was grossly nonuniform indicating that the outermost samples received over twice the blood flow that the innermost samples received. If the activity of
Phasic record during which ventricular pressure was substituted for aortic pressure for perfusion of the left coronary artery. Forward flow, represented by the area above the base line, was confined to the periods of systole. During diastole a smaller retrograde flow was seen.

Extended period of perfusion with ventricular pressure. The gradual recovery in coronary flow following the transient drop and the reactive hyperemia with the return to systemic pressure indicate that vasodilation occurred. The bottom trace is the derivative of the ventricular pressure.

Plot of the relative uptake of 86Rb across the ventricular wall when the perfusion was confined to the periods of systole. A gradient in the systolic blood flow is indicated. The data are from five dogs.
the innermost sample is divided by that of the outermost sample, the resulting ratio is an index of the flow gradient. The mean ratio and the hemodynamic data for each heart appear in Table 1. The average ratio for all five hearts was 0.52. In addition to these experiments, five other dogs were prepared using similar methods. Since complete hemodynamic data from these five pilot experiments are lacking, they do not contribute to the graph in Figure 4 or the information in Table 1. The average ratio for these experiments was, however, 0.46. In all ten dogs examined a significant transmural gradient was observed.

**Discussion**

In these experiments the coronary arteries were perfused with a pressure that was equal to systemic pressure during systole and near zero during diastole. Since blood was advanced down the coronary arteries only when there was driving pressure during systole, the total coronary flow experienced a myocardial distribution similar to that of blood flowing during systole in the normally beating heart. Several investigators (12,13) have presented evidence that the transmural distribution of myocardial blood flow can be predicted by dividing the area between the coronary perfusion pressure and the left ventricular pressure curves by the area under the left ventricular pressure curve. Subendocardial ischemia occurs at decreasing values of this ratio. The pulsatile perfusion technique used in the present experiments represented the extreme condition—the ratio was zero—and the subendocardium received minimal flow. The ability of this technique to accurately describe the systolic redistribution that is normally present in the heart requires that minimal flow occur in diastole. The presence of retrograde flow during diastole, as seen in Figure 3, indicates that the coronary vessels are compliant. In the face of a falling perfusion pressure their volume was reduced and the blood they contained, therefore, flowed back into the tubing system. The fact that the retrograde flow persisted even in late diastole when perfusion pressure was no longer changing reveals that the pressure in these vessels did not immediately equilibrate with the perfusion pressure. Therefore, a residual forward flow out of these vessels into the capillaries persisted in diastole. This artifact caused the observed gradient to be somewhat less than its actual value.

With this method total coronary blood flow dropped to less than half of its normal value, and an autoregulatory vasodilation of the coronary vessels was evoked. Normally, increased tone in the superficial myocardium causes a compensatory gradient during diastole so that overall perfusion is uniform across the heart wall (5). Profound dilation can remove this gradient so that even a continuous perfusion experiences a nonuniform distribution of flow favoring the epicardium. It is improbable, however, that such a mechanism alone could have caused the blood flow gradient observed in this investigation. Since the isotope was administered coincidently with the transition to pulsatile perfusion, blood flow should have reached the capillaries before appreciable dilation had occurred. About 10 seconds of interrupted flow was required to produce maximal dilation. Because flow was not zero with pulsatile perfusion, the time to maximal dilation should have been still longer. Furthermore, unless the dilation actually reaches a maximal state

<table>
<thead>
<tr>
<th>Dog</th>
<th>Left ventricle weight (g)</th>
<th>Heart rate (beats/min)</th>
<th>Peak ventricular pressure (mm/Hg)</th>
<th>Left ventricular end-diastolic pressure (mm/Hg)</th>
<th>Index of flow gradient*</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>77</td>
<td>180</td>
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<tr>
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<tr>
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<td>66</td>
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<td>110</td>
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<td>58</td>
<td>144</td>
<td>105</td>
<td>0</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean ± sd</td>
<td>69.4 ± 8.0</td>
<td>159.8 ± 23.5</td>
<td>110.4 ± 5.5</td>
<td>102.2 ± 9.4</td>
<td>0.52 ± 0.13</td>
</tr>
</tbody>
</table>

Pressures at 0 seconds are those immediately following the transition to pulsatile pressure. Pressures at 25 seconds are those 25 seconds after the transition to pulsatile pressure. The isotope was injected within a second of the transition.

*The ratio of the activity of the innermost sample to that of the outermost sample is the index of the flow gradient.
before the isotope is in the capillaries, the degree of dilation should be greatest in the regions where flow is least. The effect of such a tone change should decrease flow gradients rather than enhance them.

A loss of contractility should accompany a reduced coronary blood flow. Any resulting elevation in diastolic pressure would obscure the present data, since pressure would be present for forward flow in diastole. Furthermore, elevated diastolic pressure per se seems to be a determinant of subendocardial perfusion (4). Table 1, however, indicates that 25 seconds after the transition to pulsatile perfusion end-diastolic pressures, although elevated over control values, were still quite low.

The actual magnitude of the local blood flow was not calculated. Rather, only its relative distribution across the ventricular wall was sought. Thus, $^{86}$Rb was introduced as a bolus into the coronary artery, and the quantity of isotope each locale retained relative to the others was examined. In this analysis the extraction rate of the tissues was assumed to be constant throughout the myocardium. Actually the extraction rate decreases with increasing flow rates (14). Thus, this technique tended to underestimate the differences in blood flow that actually occurred.

Considering these potential artifacts, it was concluded that any error in the results would tend to underestimate the true blood flow gradient present in the normal heart during systole. The redistribution which was observed in these experiments was substantial compared with the homogeneous distribution of the total coronary flow normally present in the canine heart (12, 13, 15). It is clear that any process which causes the heart to rely on a greater percent of its coronary blood flow being delivered during systole has the potential for causing underperfusion of the subendocardium.

The reduction in coronary blood flow during systole probably resulted from deformation of the coronary vessels by intramyocardial pressure. Several investigators have attempted to measure this intramyocardial pressure and have agreed that the pressure oscillates between a peak value during systole and a near-zero value during diastole. Furthermore, all investigators have reported a gradient of peak pressures across the heart wall with the highest values near the endocardium. There is no agreement, however, on the magnitude of these intramyocardial pressures. Some investigators (6-8) have found pressures reaching values several times ventricular pressure at the endocardium, but other workers (9, 10) have found that intramyocardial pressures do not exceed ventricular pressure anywhere in the ventricle. The discrepancies in these measurements have yet to be resolved.

If the pressure surrounding a coronary vessel actually exceeds the pressure perfusing that vessel, the vessel will collapse, thus precluding any flow through it. However, the intramyocardial pressure need not exceed the perfusion pressure to alter blood flow. We suggest that intramyocardial pressures below perfusion pressure probably limit coronary blood flow by the formation of vascular slues or waterfalls. This concept was developed to describe flow through collapsible vessels (16-18) and is operative in the pulmonary (19) and the renal (20) circulations. In the model shown in Figure 5, partial collapse of the vessel occurs at the point where the pressure inside the vessel falls below tissue pressure when tissue pressure is between arterial and venous pressure. The high resistance of the partially collapsed segment causes the pressure to abruptly drop from tissue pressure to

![Figure 5](http://circres.ahajournals.org/)

**Figure 5**

Waterfall model showing the effect of tissue pressure on flow through a blood vessel. Flow causes pressure inside the vessel to drop from arterial pressure ($P_A$) at one end until the pressure equals the pressure outside the vessel ($P_T$); at this point the vessel collapses. The difference between $P_T$ and venous pressure ($P_V$) is dissipated over the short segment of collapsed vessel at the venous end. The resultant flow is the pressure difference across the patent segment ($P_A - P_T$) divided by its resistance. Flow is independent of $P_V$ when $P_V < P_T$ and thus can be likened to a sluice or a waterfall, where flow is independent of the height of the falls.
venous pressure. Since collapse always occurs at the outflow end, most of the vessel remains patent with its resistance to flow unaffected. Flow adjusts itself to cause a drop in pressure from arterial pressure to tissue pressure across the patent segment. Under these conditions flow is proportional to the difference between arterial pressure and tissue pressure and is independent of venous pressure. It is necessary to determine the site of partial collapse on the coronary vasculature. The coronary anatomy is such that arteries coursing over the surface of the heart send tributaries to the underlying tissue (21). As these vessels drop deep into the myocardium, the surrounding pressure increases. The arteries terminate at their deepest point on the capillaries. Thus, the capillaries are surrounded by the highest tissue pressure. Partial collapse should occur downstream of the capillaries in the veins as they pass back upwards through diminishing tissue pressures. Actually, a continuous partial collapse should occur all along the ascending veins, keeping the luminal pressure in equilibrium with that of the surrounding tissue. Since most of the vascular resistance occurs proximal to the coronary veins this model should be applicable.

During systole the pressure difference (arterial pressure minus tissue pressure) driving flow through the patent segments of the vessels decreases from epicardium to endocardium because of the gradient of intramyocardial pressure across the wall. This decrease creates a transmural gradient in systolic blood flow provided the transmural distribution of vascular resistance of the patent upstream segments is nearly uniform (unpublished observations).

Since the ventricular wall is in equilibrium with the ventricular pressure, a radial compressive stress which falls from ventricular pressure at the endocardium to near zero at the epicardium has been predicted for the myocardium (22). Compressions greater than this obligatory radial stress have been hypothesized (7) and reported from experimental measurements (6-8). Unfortunately, all attempts to measure the intramyocardial pressure have involved the insertion of a measuring device directly into the myocardium. The degree to which this disruptive procedure alters the local stress field is not easily assessed. Brandi and McGregor (9), however, have demonstrated that a foreign body in the myocardium experiences a pressure that is proportional to its volume. If extrapolation to zero volume is performed, intramyocardial pressures are indicated only in the range between zero and luminal pressure. The present experiments advanced this technique one step further. By examining the effect of intramyocardial compression on coronary blood flow, myocardial disruption was completely avoided. If the tissue experienced a stress in excess of perfusion pressure, it would not have been perfused in the pulsatile perfusion experiments because the vessels would have been completely collapsed.

In these experiments perfusion pressure pulses had a value near peak ventricular pressure. The presence of flow in the innermost layers would seem to indicate that these vessels were not completely collapsed during systole. Such an interpretation requires proof that residual flow did not occur during diastole when extravascular compression was low. This proof, of course, cannot be provided. It is significant, however, that a considerable gradient occurred between the innermost two samples. Gradients in tissue pressure can only create a gradient in flow when their values are between perfusion pressure and venous pressure. This finding suggests, then, that most of the ventricle experiences a compression that is below peak ventricular pressure.

References

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_Circ Res._ 1974;34:251-257
doi: 10.1161/01.RES.34.2.251

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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