Uniformity of Transmural Perfusion in Anesthetized Dogs with Maximally Dilated Coronary Circulations

By H. Fred Downey, Fouad A. Bashour, Roger B. Boatwright, Paul E. Parker, and Sarkis J. Kechejian

ABSTRACT

In 14 beating hearts, coronary blood flow was measured electromagnetically in either the left circumflex or the left anterior descending coronary artery, and regional myocardial blood flow was computed from tissue uptake of 7-10 μ radioactive microspheres. Metabolic dilation of the coronary circulation was induced by occluding the coronary artery for 10 or 90 seconds, and pharmacologic dilation was induced by infusing papaverine into the artery. In seven dogs, differently labeled microspheres were administered (1) before coronary artery occlusion, (2) at the peak reactive hyperemic response to a 10-second coronary artery occlusion, and (3) early in the rising phase of the hyperemic response following a 90-second coronary artery occlusion. Myocardial blood flow was distributed uniformly across the left ventricular free wall before occlusion and at peak hyperemia after the 10-second occlusion, but early in the hyperemic response to the 90-second occlusion coronary blood flow preferentially perfused subepicardial tissue. In another group of seven dogs, microspheres were administered (1) before coronary artery occlusion, (2) at the peak hyperemic flow after a 90-second occlusion, and (3) at the peak flow during local intracoronary infusion of papaverine. The left ventricular free wall was uniformly perfused under each condition. However, in 12 vented, fibrillating hearts with coronary circulations dilated maximally by perfusion with venous blood containing either papaverine or adenosine, left ventricular blood flow was preferentially directed to the subendocardium (endocardial-epicardial ratio averaged 1.37 ± 0.08 [SE]). We conclude that the coronary circulation of the normally functioning canine heart can dilate maximally without causing relative subendocardial ischemia because of a gradient of vascularity that favors the subendocardium and compensates for systolic flow limitation in that region.
ing radioactive microspheres, and in the right femoral vein for administering additional anesthetic as required. Blood pressures, the electrocardiogram, and the output from the blood flowmeter (Micron RC1000) were recorded with a Beckman R411 physiological recorder.

Coronary and myocardial blood flows were measured by the electromagnetic flowmeter and by tissue trapping of 7-10μ radioactive microspheres (3M Co.), respectively. By using microspheres labeled with three different isotopes (142Ce, 85Sc, and 89Sr), it was possible to determine myocardial blood flow under three different conditions in each dog. Arterial blood was collected at a constant rate for 3 minutes after each injection of microspheres, and the procedure described by Makowski et al. (6) was used to compute myocardial blood flow in ml/min g⁻¹. Approximately 2 × 10⁶ microspheres were administered for each flow determination. After the final dose of microspheres, the heart was excised and frozen. Samples weighing approximately 8 g were taken from the left ventricular free wall in the region supplied by the left anterior descending coronary artery (control region). Samples were also taken from the central portion of the interventricular septum and from the right ventricular free wall. Except for the right ventricular wall specimens, the samples were divided visually into thirds for transmural measurement of myocardial blood flow; the right ventricular samples were divided in half. The samples were analyzed for radioactivity in a triple-channel gamma counter (Nuclear Chicago 4233), and isotope separation was accomplished by standard techniques of gamma spectroscopy with the aid of a minicomputer (DEC PDP8E).

Dogs with beating hearts were subdivided into two groups of seven dogs each. In group 1, coronary and myocardial blood flows were studied under control conditions and after variable periods of coronary occlusion. Among these dogs, the left anterior descending coronary artery was occluded in four experiments and the left circumflex coronary artery was occluded in three experiments. In this group, the microspheres were injected at peak flow after a 10-second occlusion as indicated by the electromagnetic flowmeter and during the rising phase of the hyperemia after a 90-second occlusion. The time to peak flow averaged 7 seconds after 10-second coronary artery occlusions and 36 seconds after 90-second occlusions. An average of 11 seconds elapsed between release of the 90-second occlusions and administration of the microspheres.

In group 2, flows were measured under (1) control conditions, (2) at peak flow after a 90-second coronary artery occlusion, and (3) during maximal coronary dilation induced by infusion of papaverine directly into the coronary artery. The infusion rate of papaverine (4.5–12 mg/min) was adjusted until further increase caused no additional coronary blood flow as reflected by the electromagnetic flowmeter. During the papaverine infusion, coronary blood flow 15 seconds before, at the time of the microsphere injection, and 15 seconds later averaged 127, 129, and 129 ml/min, respectively. These data are indicative of the stability of coronary blood flow during dilation with papaverine. Papaverine was administered intracoronarily to minimize the systemic effects of the drug. The experimental region of the left ventricular free wall was supplied by the left circumflex coronary artery in five dogs and by the left anterior descending coronary artery in two dogs.

Fibrillating Hearts.—In 12 dogs, studies were conducted in situ fibrillating hearts supported by donor dogs. Ventricular fibrillation was induced electrically and maintained spontaneously. The descending aorta was ligated, and the aortic arch was perfused via the left subclavian artery at constant pressure from a 1-liter blood reservoir. The reservoir was connected to a 20-liter container of compressed air, so that changes in perfusion pressure due to changes in the volume of blood in the reservoir were always less than 5%. A roller pump supplied the reservoir with blood from the donor dog. The temperature of the blood in the reservoir was maintained between 36 and 38°C by placing the reservoir in a heated water bath. This assembly was positioned on a magnetic stirrer that rotated a stirring bar in the reservoir. Coronary perfusion pressure was recorded through a cannula positioned in the aorta via the brachiocephalic artery. Coronary venous blood flow was siphoned from the right ventricle and returned to the donor dog via a femoral vein. The fibrillating left ventricle was vented with a rigid tube (4 mm in diameter) inserted through a stab wound in the apex, and the temperature of the heart was monitored with a telethermometer (Yellow Spring Instruments Co.). This temperature was kept between 36 and 40°C. The thoracotomy was covered with towels moistened with saline, and a heat lamp was positioned over it.

The heart was perfused with arterial blood until all preparations were completed. Then coronary perfusion was stopped, and the reservoir was partially filled with venous blood from the donor. Five minutes later, coronary perfusion was reinstated with venous blood. To further ensure maximal coronary dilation, papaverine (12.4 mg/min, three dogs) or adenosine (1.2 mg/min, nine dogs) was infused into the perfusion line. Venous blood was used because preliminary experiments revealed that coronary blood flow always increased when perfusion was shifted to venous blood irrespective of the rate of adenosine infusion.

While coronary perfusion pressure was stable at 100 mm Hg, approximately 10⁶ radioactive microspheres (7-10μ in diameter) were injected into the perfusion line. The heart was removed, frozen, and later sectioned. Samples were taken from the anterior and posterior wall of the left ventricle, the right ventricular wall, and the interventricular septum. As previously outlined, these myocardial samples were divided transmurally, and their respective radioactivities were measured with a gamma counter.

The experimental design is further clarified in Tables 2 and 3. Tests of statistical significance were made with Dunnett’s procedure (7) when flow distributions and hemodynamics at the time of the second or third administration of microspheres were compared with those observed at the time of the first administration of microspheres. Student’s t-test for paired samples (7) was used when flow distributions delineated by one administration of microspheres were compared or when flows or hemodynamics observed at the time of the second administration of microspheres were compared with those observed at the third administration. Differences with P > 0.05 are described as not statistically significant.

Circulation Research, Vol. 37, July 1975
Representative record of hemodynamic parameters in a dog subjected to 10- and 90-second occlusions of the left circumflex coronary artery. The time constant of the electromagnetic flowmeter used to measure coronary blood flow was 0.02 seconds.

Results

Figure 1 shows representative tracings of aortic and left atrial blood pressures, heart rate, and phasic left circumflex coronary artery blood flow during 10- and 90-second reactive hyperemias in dogs with beating hearts. Occlusion of this artery for 10 or 90 seconds caused only small changes in the monitored pressures and heart rate, but clearly the 90-second occlusion caused a greater peak hyperemic flow. The elevation of phasic coronary blood flow above zero during each beat reflects the increased systolic component of coronary blood flow during reactive hyperemia. Systolic and diastolic coronary blood flows in this dog during subsequent hyperemias were quantified from the phasic flow record. Before occlusion, 14% of the flow in the circumflex coronary artery occurred in systole. This portion increased to 23% at peak flow after a 10-second coronary artery occlusion and to 32% after a 90-second occlusion. The greater delay in reaching peak hyperemic flow after the longer occlusion illustrated in Figure 1 was typical of the responses reported by Coffman and Gregg (8).

Hemodynamic data from the dogs with normally beating hearts are shown in Table 1. Among the dogs of group 1, aortic blood pressure and heart rate remained essentially constant during the experiment. Left atrial blood pressure rose slightly during coronary artery occlusion, but in the case of the 10-second occlusion this pressure had returned to control before microspheres were administered. After the 90-second occlusion in group 1, left atrial blood pressure averaged 8.2 mm Hg at microsphere administration compared with a control pressure of 6.2 mm Hg. After 10-second coronary artery occlusions, peak coronary blood flow measured electromagnetically averaged 310% of control and was further elevated ($P < 0.05$) to 360% of control after the 90-second occlusions (Table 1).

In group 2, aortic pressure was unchanged by the 90-second coronary artery occlusion but decreased 13% during papaverine treatment; heart rate re-

<table>
<thead>
<tr>
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<th>Group 1 ($n = 7$)</th>
<th>Group 2 ($n = 7$)</th>
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<tr>
<td></td>
<td>Control</td>
<td>10-second occlusion</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>121 ± 6</td>
<td>122 ± 6</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>6.2 ± 0.7</td>
<td>6.4 ± 0.8</td>
</tr>
<tr>
<td>Coronary artery flow (ml/min)</td>
<td>23 ± 6</td>
<td>71 ± 22</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>183 ± 6</td>
<td>178 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± se.

Circulation Research, Vol. 37, July 1975
remained constant throughout the experiments. During the 90-second occlusion, left atrial blood pressure increased to 8.4 mm Hg but began to decline soon after the release of the occlusion. By the time microspheres were injected at peak coronary blood flow, left atrial blood pressure had dropped to 6.2 mm Hg, a value not significantly different from the control pressure of 5.9 mm Hg. Among this group, the control coronary blood flow measured electromagnetically averaged 32 ml/min and increased 390% after the 90-second coronary artery occlusion and by a similar amount during papaverine treatment. Since flow in the left circumflex coronary artery of the canine heart exceeds that in the left anterior descending coronary artery (the left anterior descending or the left circumflex) was occluded and were of similar magnitude after either 10- or 90-second occlusions. Flows in the control region of the left ventricle were not significantly changed, but those in the right ventricular free wall increased following interruption of flow into the experimental region (P < 0.05). The uniform transmural distribution of flow in these regions was not altered to any significant degree by the coronary artery occlusions.

After a 10-second occlusion, the endocardial layer of the experimental region tended to receive more flow (P < 0.20) than did the outer layer (Table 2). However, this gradient was reversed (P < 0.02) when the flow tracer was administered at a similar interval after release of a 90-second occlusion. At this time, after the longer occlusion, a 44% increase in epicardial flow was observed, but subendocardial flow was similar to that observed after the 10-second occlusion.

In group 2, the distribution of myocardial blood flow was examined during peak flow after a 90-second coronary artery occlusion and during the maximal dilation elicited by intracoronary infusion by papaverine.
of papaverine. These interventions caused large and essentially identical increases in flow to the experimental region. Compared with the average control flow of 1.02 ml/min g⁻¹, peak flow after a 90-second occlusion was 4.84 ml/min g⁻¹ and 5.00 ml/min g⁻¹ during infusion of papaverine (Table 2). The similarity of the flows observed after a 90-second coronary artery occlusion and during papaverine infusion suggests that these interventions caused maximal dilation of the coronary vasculature. In both of these conditions, the epicardial and endocardial layers were similarly perfused; maximal coronary vasodilation did not result in a transmural gradient of flow. The flow to the midmyocardial region tended to exceed flows to both the inner and the outer region, although the difference was not statistically significant. In this group, after a 90-second occlusion of one major coronary artery branch, flow to regions of the myocardium supplied by other coronary arteries was increased by approximately 25% (P < 0.05). Flows to control myocardium and to the right ventricle and the interventricular septum were elevated (P < 0.05) when papaverine was infused into the experimental region. These flow changes were probably due to direct effects of recirculating papaverine, since these regions showed a similar increase in flow relative to the pretreatment observation. The transmural distribution of flow in the control regions was not altered.

The transmural distribution of myocardial blood flow and the ratio of endocardial to epicardial flows in various sections of the fibrillating hearts are reported in Table 3. In calculating this ratio, data from the inner and outer thirds were used. In the case of the interventricular septum, the flow values of the right and left ventricular sides of the septum are reported individually together with their ratio. The endocardial-epicardial flow ratio of the anterior and the posterior wall of the left ventricle averaged 1.36 ± 0.07 and 1.38 ± 0.08, respectively (different from 1.0 at P < 0.01). These results suggest that the subendocardium of the left ventricle receives more blood flow if the coronary circulation is maximally dilated and the extravascular component of resistance due to systolic compression is removed. However, no transmural gradient of flow was found in the right ventricular free wall or in the interventricular septum. Myocardial flows were greater in the dilated fibrillating hearts (Table 3) than they were in the dilated normally functioning hearts, since the systolic limitation to flow was absent (9).

### Discussion

The most important finding of this investigation is the uniform perfusion of the left ventricular myocardium of the working heart during maximal dilation of the coronary vasculature. The failure of either ischemic or pharmacologic vasodilation to cause a transmural flow gradient suggests that autoregulation is not the only mechanism available to the normal coronary circulation for ensuring adequate perfusion of the subendocardium. The flow gradient observed in the maximally dilated, fibrillating hearts suggests that a gradient of vascularity, which increases toward the endocardium, enables the coronary circulation of normally functioning hearts to maximally dilate without causing subendocardial ischemia.

Phasic recordings of coronary blood flow clearly demonstrate that the beating heart inhibits its own blood supply during systole (1, 2, 10-13). Although, under some circumstances (such as sympathetic

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Left ventricle</th>
<th>Right ventricle</th>
<th>Ventricular septum</th>
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<tbody>
<tr>
<td></td>
<td>Anterior</td>
<td>Posterior</td>
<td>RV</td>
</tr>
<tr>
<td>Endocardial flow</td>
<td>9.99 ± 1.12</td>
<td>9.71 ± 1.36</td>
<td>5.78 ± 0.83</td>
</tr>
<tr>
<td>(ml/min g⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicardial flow</td>
<td>7.37 ± 0.77</td>
<td>7.05 ± 0.76</td>
<td>6.19 ± 1.37</td>
</tr>
<tr>
<td>(ml/min g⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardial-epicardial flow ratio</td>
<td>1.36 ± 0.07</td>
<td>1.38 ± 0.08</td>
<td>0.93 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* This ratio refers to the LV/RV sides of the septum; LV represents one-third of the thickness of the ventricular septum facing the left ventricular cavity and RV refers to that third facing the right ventricular cavity.

*Circulation Research, Vol. 37, July 1975*
are thus in agreement with their observations in the conscious dog, but we cannot account for the transmural gradient that they observed in the anesthetized dog.

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