Mechanism for Flow Distribution in Normal and Ischemic Myocardium during Increased Ventricular Preload in the Dog
By John K. Kjekshus

ABSTRACT
The effects of increased ventricular preload on the distribution of regional blood flow in normal and ischemic myocardium were determined in deep and superficial regions of the left ventricle by using labeled microspheres. The ratio of flow in deep regions to flow in superficial regions in nonischemic tissue was 1.06 ± 0.06 and increased to 1.14 ± 0.06 when left ventricular end-diastolic pressure was raised from 4.8 ± 1 mm Hg to 18 ± 2 mm Hg by intravenous infusion of blood. In ischemic areas the ratio of flow in deep regions to flow in superficial regions fell simultaneously from 0.71 ± 0.12 to 0.45 ± 0.07 (P< 0.001). Control of coronary flow during increased preload was studied in a separate preparation in which coronary flow was decreased in steps by reducing coronary perfusion pressure during periods of constant cardiac performance. The increased preload was associated with loss of autoregulation of coronary flow. It is suggested that, in myocardium with unrestricted coronary supply, regional distribution of flow is independent of gradients in tissue pressure during the described changes in preload due to an autoregulatory mechanism. However, when autoregulation of coronary flow is abolished by coronary artery occlusion, the coronary bed is fully dilated, and distribution of flow is directly dependent on gradients in myocardial tissue pressure. Increased ventricular preload consequently augments the underperfusion of the subendocardial regions of an ischemic area.

KEY WORDS coronary flow autoregulation S-T segment elevation myocardial tissue pressure gradient epicardial-endocardial flow coronary artery occlusion microspheres left ventricular diastolic pressure

Previous studies have suggested that the subendocardium of the left ventricle is more susceptible to ischemia than is the subepicardium (1, 2). Some authors (3-6) have found that deep regions are relatively underperfused in experimental animals even under unstressed conditions; however, this finding has been denied by others (7-10). The allegedly nonuniform distribution of blood flow and glycolytic metabolism has been attributed to extravascular resistance in the deep layers higher than that in the superficial layers due to transmural gradients in myocardial tissue pressure during systole (11-14). Although the myocardium of the left ventricle is perfused mainly during diastole, the effect of increased diastolic ventricular pressure, and presumably myocardial tissue pressure, on the regulation and the distribution of myocardial flow is as yet undefined. Distention of the left ventricle results in increased tissue pressure almost exclusively in the innermost regions of the wall (15, 16). Increased tissue pressure in diastole therefore might interfere with distribution of flow to the various regions of the wall and impair blood supply to deep layers of the myocardium.

Diastolic ventricular pressure very often increases following extensive myocardial infarction (17), which might by itself interfere with flow distribution to the infarcted area and its surrounding regions. On the other hand, elevation of ventricular preload has been suggested as a means of improving cardiac output during acute ischemic heart failure (18). In morphological studies, the ischemic changes in the inner wall of the left ventricle are accentuated by ventricular preloading (1). Accordingly, the present experiments were designed to examine the effects of increased ventricular preload on coronary regulation and...
transmural distribution of blood flow in nonischemic and ischemic regions of the left ventricle.

Methods

Regional Coronary Blood Flow.—Eleven mongrel dogs weighing 18–22 kg were anesthetized with sodium pentobarbital (25 mg/kg, iv), and positive-pressure breathing was established through an occlusive intratracheal tube. The left ventricle was exposed through a left thoracotomy. A silk thread (3-0) was placed loosely around a branch of the left descending coronary artery. A short polyethylene catheter inserted through the left ventricular apex was used for left ventricular pressure measurements (Statham P23Gb). Catheters tied into the left atrial appendage and a femoral artery served as routes for injecting radioactive-labeled microspheres and sampling arterial blood, respectively. A femoral vein was cannulated for blood infusion. In six dogs a catheter in the right atrium or in the coronary sinus was used for pressure determinations.

Distribution of myocardial flow was determined as previously described (6). 

\[ {^{141}C}e- \text{or } {^{85}Sr}-\text{labeled microspheres (Minnesota Mining & Manufacturing Company) suspended in saline were injected into the left atrium as a bolus. The mean diameter of the microspheres was } 14.0 \pm 3 \mu \text{ (so). Approximately } 1.2 \times 10^8 \text{ carbonized microspheres containing } 20 \mu \text{c were used for each injection. Aggregation of the microspheres prior to injection was prevented by vigorous stirring with a Teflon-covered magnet. A catheter in the femoral artery permitted blood to be drawn at a constant rate using a calibrated suction pump. A few seconds before each microsphere injection, a timed collection of reference flow was begun and maintained at a constant rate of } 4-8 \text{ ml/min for 5 minutes.}

The experiments were performed after ligation, and 30 minutes were allowed for steady hemodynamic conditions to be reached. The first bolus of radioactive microspheres was then injected into the left atrium after starting flow collection. Subsequently, homologous blood without hemolysis was infused into the femoral vein at a rate of 50 ml/min. The blood was taken from a donor dog on the day before the experiment and heated to body temperature before use. Left ventricular end-diastolic pressure rose, and when a steady level was attained, usually after 10 minutes, a second bolus of microspheres labeled with a second nuclide was injected into the left atrium after initiating reference flow collection. The dogs were then killed with a massive dose of sodium pentobarbital, and their hearts were excised and washed. Tissue samples of the full wall thickness were obtained from 10–12 sites in and outside the infarcted area. Each sample, about 1 cm in diameter, was divided into two equal portions (0.5 g), one epicardial and one endocardial. The weighed tissue samples and samples of the collected blood were placed in plastic vials and counted in a well counter at each of two different energy windows. The counts for each nuclide were corrected, and the counts per gram of tissue for each isotope in the tissue were calculated. Assuming uniform distribution of microspheres in the blood, local myocardial flow \((MF)\) was calculated using the formula

\[ MF = \frac{RF \times TC \times 100}{RC} \]

where \(RF\) is the reference flow, \(RC\) is the total amount of radioactivity in the timed blood sample collected from the femoral artery, and \(TC\) is the counts/min g\(^{-1}\) myocardium. Radioactivity accumulated in venous blood indicated that less than 2% of the microspheres traversed the peripheral vasculature. Additional experiments in two dogs were performed in which the second bolus of microspheres was injected at the usual time but in the absence of preloading.

In four dogs, infarct size was estimated by epicardial mapping of electrocardiographic changes before and during increased ventricular preload. Changes in S-T segment elevations at 10–14 sites in the vicinity of the occluded coronary artery were recorded with a cotton-wick electrode as previously described (19). Myocardial flow was estimated in tissue samples from the same sites. The electrocardiogram was obtained before and after each bolus injection of microspheres and recorded on an electrocardiographic recorder (Elema-Schönander, Sweden).

Validation of the Microsphere Technique.—Local myocardial blood flow was estimated from hydrogen washout curves recorded simultaneously with microspheres injected into five dogs. Hydrogen tension was recorded polarographically with platinum electrodes inserted into the outer and inner halves of the myocardial wall as described previously (20). Hydrogen gas was administered via the tracheal tube until myocardial hydrogen tension became stable. It was then stopped, and mean flow in ml/min 100 g\(^{-1}\) tissue was calculated from the half-time of the monoeponential slope of the curve. Hydrogen desaturation curves were obtained before and after injection of microspheres. After the last hydrogen desaturation, the dogs were killed, and the tissue around the electrodes (0.8 g) was excised and counted in the manner previously described. In three dogs, coronary flow was obtained using an electromagnetic flowmeter on the left coronary artery during microsphere injection. Prussian blue dye was ultimately injected into the coronary artery which was clamped 3 seconds later. The dog was then killed, and the colored region was cut out and weighed. The microspheres in the whole sample were counted as described above.

In 18 tissue samples from three dogs the microspheres in deep and superficial halves of normal and ischemic areas were recovered by digesting the tissue with 70% nitric acid. The size of the microspheres was determined by a calibrated eyepiece.

Total Coronary Flow.—Experiments were performed in 12 thoracotomized dogs weighing 18–28 kg. A catheter inserted through the left ventricular apex was used for left ventricular pressure measurements (Statham P23Gb); another catheter was advanced to the right atrium or the coronary sinus for pressure measurements (Statham P23Gb). The left common carotid artery was cannulated and perfused from the left carotid artery. Coronary flow was measured with an

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electromagnetic flowmeter on the perfusion line, and coronary pressure was measured distal to an adjustable clamp. In 6 dogs the coronary pressure-flow relationship was studied by stepwise constriction of the coronary shunt before and during elevation of left ventricular end-diastolic pressure produced by infusion of homologous blood (50 ml/min). In the remaining 6 dogs the coronary pressure-flow relationship was studied during a selective increase in pressure in the coronary sinus by partial constriction of the pulmonary artery or during inflation of a balloon in the coronary sinus.

In an additional study using five thoracotomized dogs, the coronary sinus was catheterized, and coronary flow was determined with the hydrogen-desaturation technique. Hydrogen was measured polarographically with a platinum electrode in the coronary sinus as previously described (16). Left ventricular pressures were measured as described above. Cardiac output was determined with an electromagnetic flowmeter on the root of the ascending aorta. Arterial and coronary venous blood samples were obtained simultaneously and analyzed for oxygen saturation by the method of Aukland (21). Oxygen content was calculated using a conversion factor of 1.34 ml oxygen/g hemoglobin. After control observations, left ventricular preload was increased as in previous experiments. All determinations were then repeated during a period of constant cardiac performance.

Statistics.—Paired observations were analyzed statistically by Student’s t-test.

Results

Distribution of Regional Flow.—Figure 1 demonstrates the correlation between coronary flow calculated from local hydrogen desaturation curves obtained with platinum electrodes and values for local coronary blood flow calculated from the microspheres in the tissue surrounding the electrodes. In eight measurements in five dogs, the flow of microspheres was within 20% of that obtained with hydrogen desaturation. A similar relationship was shown in three dogs between coronary flow obtained using an electromagnetic flowmeter and the weight of the perfused myocardium and flow calculated from the microspheres in the perfused myocardium.

Table 1 shows flow distribution to superficial and deep regions of the myocardium in nonischemic and ischemic hearts.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td><strong>Distribution of Flow during Increased Left Ventricular Preload in Infarcted Heart in Six Dogs</strong></td>
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<tr>
<td></td>
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<tr>
<td>Left ventricular peak systolic pressure (mm Hg)</td>
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<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
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<tr>
<td>Heart rate (min⁻¹)</td>
</tr>
<tr>
<td>Flow (ml/min 100 g⁻¹)</td>
</tr>
<tr>
<td>Nonischemic (26)</td>
</tr>
<tr>
<td>Superficial (S)</td>
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<tr>
<td>Deep (D)</td>
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<tr>
<td>Flow ratio (D/S)</td>
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<tr>
<td>Ischemic (30)</td>
</tr>
<tr>
<td>Superficial (S)</td>
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<tr>
<td>Deep (D)</td>
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<td>Flow ratio (D/S)</td>
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</table>

All values are means ± SE. Number of samples tested is given in parentheses. Probability values for differences between paired data were obtained by Student’s t-test.
and ischemic areas. Under control conditions, myocardial flow in endocardial (D) and epicardial (S) halves of the left free wall of the ventricle averaged $145 \pm 12 \text{ ml/min 100 g}^{-1}$ and $138 \pm 9 \text{ ml/min 100 g}^{-1}$, respectively. The D-S ratio in corresponding samples averaged $1.06 \pm 0.06$ and was not different from unity (Table 1). Repeated microsphere injection during a steady hemodynamic state showed no consistent differences in flow values. Outside the grossly identifiable ischemic area epicardial flow averaged $120 \pm 4$ and $118 \pm 9 \text{ ml/min 100 g}^{-1}$ 30 minutes later ($P > 0.1$, $N = 6$). Endocardial flow in corresponding sites averaged $111 \pm 9$ and $130 \pm 5 \text{ ml/min 100 g}^{-1}$, respectively ($P > 0.1$, $N = 6$). In the ischemic area, epicardial flow amounted to $45 \pm 8$ and $49 \pm 10 \text{ ml/min 100 g}^{-1}$ during the first and the second injection, respectively ($P > 0.1$, $N = 6$). Endocardial flow in corresponding samples averaged $32 \pm 7$ and $33 \pm 10 \text{ ml/min 100 g}^{-1}$, respectively ($P > 0.1$, $N = 6$).

In three dogs the deep and superficial layers of the left ventricle were digested so as to measure the diameters of the microspheres. The distribution in size of the microspheres was similar in inner and outer halves of the wall, $14.5 \pm 3.8 \mu \text{m}$ (sn) and $15.0 \pm 3.6 \mu \text{m}$ ($N = 9$), respectively, in nonischemic tissue and $15.1 \pm 2.6 \mu \text{m}$ and $15.1 \pm 1.9 \mu \text{m}$ ($N = 9$), respectively, in ischemic tissue.

Figure 2 illustrates D-S ratios in nonischemic tissue over a wide range of flow rates induced by infusing low molecular weight dextran or by bleeding (40 samples from five dogs). The D-S ratios were slightly larger than unity and essentially unchanged in the low flow range, but they tended to increase at flow rates above $175 \text{ ml/min 100 g}^{-1}$. In contrast, during the control period in ischemic areas the D-S ratio was $0.71 \pm 0.12$, which is significantly lower than that in nonischemic areas ($P < 0.001$) (Table 1), reflecting a marked decrease in flow to the endocardium. On the average, flow to deep regions was reduced $77\%$ and flow to corresponding superficial regions was reduced $53\%$ compared with average flow in nonischemic myocardium.

**Effect of Diastolic Ventricular Pressure Augmentation on Regional Flow Distribution in Nonischemic Regions.**—Hemodynamic data are given in Table 1. Peak left ventricular systolic and end-diastolic pressures were essentially unaffected by coronary artery occlusion 30 minutes after the occlusion. Blood infusion increased peak left ventricular systolic pressure from $105 \pm 6$ to $125 \pm 9 \text{ mm Hg}$ and left ventricular end-diastolic pressure from $5 \pm 1$ to $18 \pm 2 \text{ mm Hg}$. Heart rate remained essentially unchanged. Right atrial or coronary sinus mean pressure as recorded in six separate dogs amounted to $6 \pm 0.5 \text{ mm Hg}$, and corresponding left ventricular end-diastolic pressure was $5 \pm 2 \text{ mm Hg}$. Blood infusion increased right atrial and left end-diastolic pressure in all dogs examined. When steady hemodynamic conditions were attained, mean right atrial pressure amounted to $13 \pm 3 \text{ mm Hg}$, but end-diastolic pressure in the left ventricle was significantly higher, $20 \pm 2 \text{ mm Hg}$ ($P < 0.05$).

Microspheres injected during increased left ventricular end-diastolic pressure indicated a different effect on flow distribution in nonischemic and ischemic areas. In deep regions of the nonischemic part of the left ventricle, flow was significantly increased by an average of $25\%$ ($P < 0.05$). The increase in superficial regions was less consistent ($P > 0.05$). The D-S flow ratio during raised preload increased to $1.14 \pm 0.06$ (ns). In contrast, during increased preload, flow to deep regions in the ischemic area was further decreased by an average of $30\%$ ($P < 0.005$), but flow to superficial regions remained virtually unchanged. The average D-S flow ratio in ischemic tissue was accordingly reduced from $0.71 \pm 0.12$ to $0.45 \pm 0.07$ ($P < 0.001$). This reduction might indicate that increased left ventricular end-diastolic pressure increased the ischemia in deep regions; however, in nonischemic tissue any change in the gradient in tissue pressure...
Correlation between epicardial S-T segment elevation and reduction in myocardial flow in corresponding samples from a dog subjected to coronary artery occlusion. Epicardial S-T segment elevation was measured before (open circles) (left ventricular end-diastolic pressure = 8 mm Hg) and during (solid triangles) increased ventricular preload with infusion of blood (left ventricular end-diastolic pressure = 20 mm Hg). Circled numbers at the top of the figure indicate myocardial tissue flow in tissue samples of the full wall thickness as percent of average flow in nonischemic regions; top and bottom numbers show flow before and during the preloaded condition, respectively. The sample sites represented on the abscissa appear on the diagram of the heart at the top of the figure. LV = left ventricle, LA = left atrium and LAD = left anterior descending coronary artery.

TABLE 2

Coronary Blood Flow at Control and Lowest Autoregulating Perfusion Pressure before and during Increased Ventricular Preload in Six Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>A</th>
<th>B</th>
<th>Preload</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left coronary perfusion pressure (mm Hg)</td>
<td>94 ± 4</td>
<td>64 ± 3</td>
<td>111 ± 5*</td>
<td>93 ± 3*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left coronary blood flow (ml/min)</td>
<td>61 ± 5</td>
<td>58 ± 5</td>
<td>84 ± 12*</td>
<td>74 ± 10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular peak systolic pressure (mm Hg)</td>
<td>105 ± 4</td>
<td>124 ± 5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>2.5 ± 1.0</td>
<td>19.3 ± 2.7*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>147 ± 6</td>
<td>146 ± 6*</td>
<td></td>
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</tr>
</tbody>
</table>

All values are means ± se. A = coronary hemodynamics during free flow. B = lowest perfusion pressure at which autoregulation was observed.

*P > 0.05 (Student's t-test for paired data).
†P < 0.01 (Student's t-test for paired data).

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Coronary pressure-flow relationship from one dog before and during increased preload (left ventricular end-diastolic pressure = 18 mm Hg) induced by intravenous infusion of blood.
coronary flow to decreased coronary perfusion pressure was similar in all six dogs (Table 2). A typical curve illustrated in Figure 4 exhibits a range of perfusion pressures from 65 to 110 mm Hg in which coronary flow was maintained independent of perfusion pressure. At pressures lower than 60 mm Hg coronary flow was directly dependent on perfusion pressure. By extrapolating to zero flow, a mean critical perfusion pressure of 25 mm Hg was obtained. When diastolic ventricular pressure was increased by rapid intravenous infusion of homologous blood, diastolic ventricular pressure increased to 19 mm Hg, coronary blood flow rose by 6%, and heart rate was unchanged. Reduction of coronary perfusion pressure in this condition was followed by an almost immediate reduction in flow, which was proportional to the decrements in pressure. Flow extrapolated to zero at a coronary perfusion pressure of 33 mm Hg, suggesting an increased extravascular resistance in this setting. At any given reduction of coronary perfusion pressure, coronary flow was considerably lower than that observed during low diastolic ventricular pressure. When myocardial flow and oxygen demand were increased by isoproterenol administration (2.0 μg/min, iv) over and above the increase during hypervolemia, the autoregulatory range was not different from that in control experiments (Fig. 5). However, in these experiments left ventricular end-diastolic pressure was reduced. Maintained autoregulation in this setting, therefore, suggests that diastolic ventricular pressure rather than the increase in myocardial oxygen consumption contributes to the exhaustion of the autoregulatory mechanism.

In six dogs coronary sinus pressure was increased by partially constricting the pulmonary artery or by inflating a balloon inserted into the coronary sinus. The influence of an increase in coronary sinus pressure exclusive of changes in left ventricular pressures could thereby be tested (Table 3). Results of one experiment (Fig. 6) in the present study demonstrated unchanged coronary autoregulation when a balloon was inflated in the coronary sinus, which increased coronary sinus pressure but did not change left ventricular pressures. However, loss of autoregulation was observed during hypervolemia and increased left ventricular end-diastolic pressure. The increase in coronary sinus pressure

**TABLE 3**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Increased coronary sinus pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Left coronary pressure (mm Hg)</td>
<td>88 ± 5</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>Left coronary blood flow (ml/min)</td>
<td>71 ± 9</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>Left ventricular peak systolic pressure (mm Hg)</td>
<td>105 ± 4</td>
<td>105 ± 4*</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>2.2 ± 1</td>
<td>1.7 ± 0.8*</td>
</tr>
<tr>
<td>Mean coronary sinus pressure (mm Hg)</td>
<td>4.7 ± 0.8</td>
<td>18.3 ± 3.6*</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>138 ± 7</td>
<td>135 ± 8*</td>
</tr>
</tbody>
</table>

All values are means ± se.

*P > 0.05.

†P < 0.01.
MYOCARDIAL FLOW DISTRIBUTION

LVP mmHg
EDP mmHg
dP/dt mmHg sec⁻¹
LCF ml • min⁻¹
LCP mmHg
CSP mmHg

**FIGURE 6**

Left ventricular pressures and coronary flow during stepwise coronary artery constriction under control conditions (left), during increased coronary venous pressure obtained by inflating a balloon in the coronary sinus (center), and during hypervolemia (right). LVP = left ventricular pressure, EDP = left ventricular end-diastolic pressure, dP/dt = first derivative of left ventricular pressure, LCF = left coronary flow, LCP = left coronary artery pressure, and CSP = coronary sinus pressure.

following hypervolemia was much less than the increase during balloon inflation and is therefore probably not responsible for the reduction in the autoregulatory capacity of the coronary arteries.

Additional experiments were performed in five dogs to study the effect of increased preload on myocardial oxygen extraction (Table 4). Although coronary flow and myocardial oxygen consumption increased, coronary arteriovenous oxygen extraction decreased, suggesting that the increase in coronary flow was in excess of that necessary to meet the increased oxygen requirement.

**Discussion**

Several investigators (12–14) have found a heterogeneous distribution of myocardial tissue pressure during systole: in deep layers of the myocardial wall tissue pressure exceeds arterial blood pressure for a major portion of the cardiac cycle. Also, ventricular diastolic pressure is transmitted to the innermost layers of the wall where a high tissue pressure becomes established; however, the outer layers of the wall are less affected during ventricular distention (14). A gradient in the extravascular component of the coronary resistance across the ventricular wall is thus probably encountered in systole as well as in diastole. The present finding, as well as those of previous investigators (7–10, 22), of an almost homogeneous distribution of flow across the free wall of the nonischemic left ventricle, with a relatively larger increase to the inner half of the wall during increased ventricular preload, therefore implies active regulation of the vascular tone of the coronary arteries which fully compensates for the gradient in the extravascular component of coronary resistance.

Although myocardial oxygen consumption is generally regarded as the major determinant of coronary flow regulation (23), experiments performed during free coronary flow showed that an increase in diastolic ventricular pressure, and presumably myocardial tissue pressure, was associated with a reduction in coronary arteriovenous oxygen extraction. This finding suggests that

| Table 4 |
|---|---|---|
| **Myocardial Hemodynamics and Oxygen Metabolism before and during Increased Left Ventricular Preload in Five Dogs** | **Control** | **Preload** |
| Left ventricular peak systolic pressure (mm Hg) | 131 ± 12 | 143 ± 15 |
| Left ventricular end-diastolic pressure (mm Hg) | 4.0 ± 0.9 | 15.4 ± 1.7 |
| Heart rate (min⁻¹) | 158 ± 19 | 143 ± 17 |
| Cardiac output (liters/min) | 2.1 ± 0.4 | 3.0 ± 1.0 |
| Coronary blood flow (ml/min 100 g⁻¹) | 107 ± 18 | 145 ± 30 |
| Hemoglobin (g/100 ml) | 12.4 ± 0.9 | 12.0 ± 1.1 |
| Arterial oxygen content (ml/100 ml blood) | 15.3 ± 1.2 | 14.7 ± 1.0 |
| Coronary arteriovenous oxygen extraction ratio (%) | 74 ± 3 | 65 ± 4 |
| Myocardial oxygen consumption (ml/min 100 g⁻¹) | 11.6 ± 1.6 | 12.9 ± 1.9 |

All values are means ± se. Probability values for differences between paired data were obtained by Student's t-test.

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coronary blood flow increased over and above that required to satisfy the increased oxygen consumption. Since the coronary arteriovenous oxygen difference is increased by any compromise in coronary circulation, the finding of decreased oxygen extraction when ventricular preload was augmented supports the notion that the rise in tissue pressure is effectively compensated for by changes in vascular tone. Accordingly, autoregulation of coronary flow in nonischemic hearts was almost abolished when ventricular end-diastolic pressure exceeded 20 mm Hg. In contrast, when a marked increase in coronary flow and oxygen consumption was imposed by pressure loading (24) or by isoproterenol infusion without increasing left ventricular diastolic pressure, autoregulation was not abolished. Different hemodynamic mechanisms therefore appear to be activated; the autoregulatory mechanism was independent of changes in vascular tone regulated by increased oxygen demand. Bayliss (25) was the first to suggest that the transmural pressure difference of the vessels was a determinant of vascular tone. This hypothesis implies dilatation of the vessels following either a reduction in arterial pressure or an increase in extravascular pressure, culminating in abolished autoregulation. Consequently, when autoregulation is abolished by increasing myocardial tissue pressure, lowering of coronary pressure results in reduced coronary flow. Conversely, when autoregulation is abolished by reducing coronary artery pressure, myocardial tissue pressure will determine local flow rates, thus explaining the gradient in flow distribution in ischemic tissue. Since coronary sinus pressure was increased during hypervolemia, although to a lesser degree than was left ventricular diastolic pressure, a rise in coronary venous pressure may reduce coronary driving pressure and thereby impede coronary flow. However, when coronary sinus pressure was increased without changing left ventricular pressure by inflating a balloon in the coronary sinus or by constricting the pulmonary artery, coronary flow to the left ventricle was unaffected, as shown previously (26) and in this experiment. Furthermore, a rise in coronary sinus pressure alone without any pressure change in the left ventricle did not abolish coronary autoregulation until pressures were attained that were much higher than those obtained during volume loading. This finding might indicate that the effective driving pressure for coronary flow is more dependent on the difference between arterial and myocardial tissue pressure than on the difference between arterial and venous pressure. Coronary sinus pressure is probably of small importance in determining myocardial tissue pressure during diastole compared with the importance of left ventricular pressures.

The finding of abolished coronary autoregulation in conditions with increased myocardial tissue pressure suggests that the precapillary arterioles are dilated as much as they can be by the effect of autoregulation. Unchanged or increased coronary flow is thereby provided for despite the increase in extravascular resistance.

The present results suggest that the compressive effect of increased tissue pressure associated with augmentation of ventricular preload is effectively counteracted by changes in active vascular tone in nonischemic tissue. The autoregulatory mechanism thus serves to prevent passive redistribution of flow due to changes in tissue pressure. Confirmatory evidence of such a mechanism has been obtained in the kidney (27). A reduction in transmural pressure difference of renal vessels due to increased intrarenal pressure, renal artery pressure being constant, resulted in a vasodilatation with increased flow through the kidneys. This increase in renal blood flow was dependent on an active autoregulatory mechanism.

In contrast to the distribution pattern observed in nonischemic tissue with intact autoregulation, flow was reduced proportionately more in the deep layers of the myocardial wall than it was in the superficial layers following acute coronary occlusion; this finding confirms previous studies (2, 7–10). Flow to the ischemic area is delivered by collaterals not capable of providing a normal perfusion pressure; the autoregulatory capacity is thus exceeded in the ischemic area. Since active regulation of vascular tone is abolished, delivery of flow to different areas therefore reflects regional differences in tissue pressure. The present investigation demonstrated that the effect of increasing ventricular preload was associated with a further reduction in flow to deep layers of the ischemic region; this finding is compatible with a rise in extravascular resistance in subendocardial layers larger than that in subepicardial layers, which implies an unfavorable effect on the ischemia in the subendocardial regions. In the outer half of the wall, flow was unchanged. However, considering the increase in arterial pressure and subepicardial flow in nonischemic areas, a relative increase in the hypoxia might also be anticipated in this region. Mapping of epicardial electrocardiographic changes showed...
that the extent and the magnitude of the S-T segment elevation was increased by augmenting the ventricular preload. S-T segments are a reliable index of acute ischemic injury and effectively predict the ultimate extent of cell necrosis (19).

Previous studies (19) have shown that a rise in aortic pressure decreases the size of an infarction, implying increased blood supply to the ischemic area. This finding is clearly the reverse of the present observation of an increase in the ischemic injury during increased preload. The increase in arterial blood pressure (Table 1) indicated by the rise in left ventricular systolic pressure was not, therefore, effective in compensating for the increase in extravascular resistance imposed by the ventricular preload.

Although increased preload has been shown to increase ventricular performance in ischemic heart failure in man (28) or in the experimental animal (29), the present experiments suggest that this increase is achieved at the expense of an increase in the ischemic area, particularly in the deep regions of the heart. It has recently been observed (30) that acutely increased left ventricular preload with low molecular weight dextran reduces the anginal threshold in patients with ischemic heart disease. It is conceivable that in these patients the autoregulation of coronary flow is abolished in areas with coronary stenosis. The increased ventricular filling pressure might, in that event, impede coronary flow during diastole, especially to subendocardial regions, and might explain the reduced anginal threshold. Since nitroglycerin reduces the left ventricular preload (31), the subsequent reduction in myocardial tissue pressure might contribute to the antianginal effect of nitroglycerin on a purely mechanical basis. Confirmatory evidence has been provided by the fractional uptake of radioactive microspheres and the tissue clearance of $^{86}$Rb, demonstrating that nitroglycerin increases distribution of flow to the subendocardium in the acutely ischemic canine left ventricle (10, 32).

Compared with other methods for measuring local myocardial blood flow, the use of microspheres has the advantage of facilitating multiple determinations in the same animal thus allowing it to serve as its own control. However, the validity of the method has been questioned. Measurements of local myocardial flow with $14 \mu$m microspheres in nonischemic myocardium at low diastolic ventricular pressure agree with previous studies performed with microspheres of a similar size (10) and with studies using uptake of $^{86}$Rb (8) or $^{111}$-iodoantipyrine (9). A proportionately larger flow to subendocardial regions has been observed with $50 \mu$m microspheres (31). A preferential streaming of microspheres to deep layers due to the momentum of the spheres and to their inability to execute sharp turns has therefore been suggested. By using smaller microspheres in the present study, D-S flow ratios were kept essentially constant and only slightly larger than unity in the flow range studied. The D-S flow ratio only began to increase at flow rates above 175-200 ml/min 100 g$^{-1}$. Therefore, it seems likely that distribution was not affected by inertia of the small microspheres in the flow range examined.

However, studies on myocardial flow distribution using washout of locally injected deposits of a radioactive tracer have consistently shown a smaller flow rate in deep regions, averaging 70% of flow to superficial regions in the unstressed heart (3, 4). This observation is at variance with the present and previous findings (7-10). In addition, myocardial flow determined from locally injected deposits has shown a smaller flow rate compared with flow rates determined from intracoronary injections (4). It is conceivable that the volume of the intramyocardial injectate increases local tissue pressure in excess of that effectively counteracted by the autoregulatory mechanism. The induced extravascular resistance will consequently impair flow in that particular area, an explanation supported by previous observations of a reduction in washout rates when injection volumes exceed 0.005 ml (34). Accordingly, washout rates from local depots should be most depressed in regions with the highest tissue pressure.

As the amount of radioactivity in the microspheres increases by the third power of the radius and as the microspheres vary in diameter within the range of $6 \mu$m to $25 \mu$m, a preferential accumulation of larger microspheres in deep regions might have spuriously affected the calculated local flow rates. However, the equal distribution of diameters in different layers of the myocardium, as shown previously (31) and in this study, makes this supposition unlikely.

Failure to trap microspheres in the peripheral vasculature might have affected the flow calculation. In the present experiment, however, less than 2% of the arterial activity escaped to the venous side. The good correlation between independent measurements of regional blood flow to different layers of the left ventricular myocardium further
supports the usefulness of microspheres for assessing regional blood flow.

From the present data it seems probable that gradients in the extravascular component of coronary resistance are effectively compensated for by the autoregulatory mechanism of the coronary vessels. With abolition of coronary autoregulation, a nonuniform distribution of blood flow across the ventricular wall is produced. Factors which increase the ventricular tissue pressure in this setting will contribute to the development of subendocardial ischemia. This finding may have pathogenic importance in patients suffering attacks of anginal pain and in the development of myocardial necrosis in patients with extensive myocardial infarction.

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References


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