Coronary sinus occlusion retards necrosis of ischemic myocardium. To test the hypothesis that coronary sinus occlusion induces retrograde venoarterial flow, the coronary arteriovenous pressure gradient and the coronary arterial oxygen saturation were measured distal to a left anterior descending coronary artery ligature in dogs. In parallel, we constructed a mathematical model of known coronary physiology to characterize pressure and flow patterns during coronary sinus occlusion. In dogs, coronary sinus occlusion produced a systolic pressure gradient between the coronary artery and the coronary sinus of -20 ± 9 mm Hg (higher venous pressure, p < 0.0001) and a positive diastolic gradient of 3 ± 5 mm Hg (lower venous pressure p < 0.01). An average reduction in the oxygen saturation in the ligated coronary artery of 20 ± 13% was also observed (p < 0.005) consequent to admixture of venous (desaturated) blood. By graded inflation of the coronary sinus balloon, it was demonstrated that desaturation of arterial blood typically occurs above a coronary sinus systolic pressure of 40–50 mm Hg. The mathematical model indicates the possibility of venoarterial pressure gradients and reversal of flow at the microcirculatory level during coronary sinus occlusion. These studies provide evidence that retrograde flow into the ischemic zone occurs in association with intermittent coronary sinus occlusion. Thus, alternating flow over the ischemic territory may be the mechanism of myocardial salvage during intermittent coronary sinus occlusion. (Circulation Research 1989;65:695–707)

Anti-ischemic effects of coronary sinus occlusion were first described more than 50 years ago.1–4 More recently, using canine models of total occlusion of the anterior descending artery and intermittent balloon occlusion of the coronary sinus, investigators have reported a 44% reduction in infarct size after 6 hours of ischemia,5,6 and 45–74% reduction in infarct size after 3 hours of ischemia.7–9

Despite these impressive results, the mechanism by which intermittent coronary sinus occlusion ameliorates ischemia is uncertain. Microsphere-detectable arterial blood flow to the ischemic zone does not change following coronary sinus occlusion, which indicates no increase in collateral arterial flow, but there is a marked increase in xenon washout.7

The increase in xenon washout from an ischemic region during intermittent coronary sinus occlusion7 suggests increased myocardial perfusion. This perfusion is not detectable by arterial microsphere flow measurements but may account for the preservation of ischemic myocardium following coronary sinus occlusion. This hypothesis is supported by the recent description by Yoshida et al10 of enhanced diffusible tracer washout from ischemic myocardium, which may represent a component of myocardial perfusion that is “hidden” from microsphere detection. Since coronary sinus occlusion markedly increases coronary venous pressure, increased washout of tracers during intermittent coronary sinus occlusion may result from “to and fro” flow into and out of the ischemic bed during coronary artery ligation. Venous blood might enter the microvascular system retrogradely and release some of its residual oxygen to the ischemic myocardium, while toxic metabolites and diffusible tracers might be removed. If this hypothesis is correct,
two predictions can be made with regard to coronary physiology during coronary sinus occlusion: 1) There must be an alternating pressure gradient between the arterial and venous sides of the ischemic bed. 2) The arterial blood distal to the ligation must desaturate during coronary sinus occlusion as venous blood enters the arterial system.

We conducted experimental studies in dogs in which simultaneous coronary arterial and venous pressures were measured. In a separate group of dogs, we measured oxygen saturation in the artery distal to ligation before and after coronary sinus occlusion. To integrate these and other observations, we formulated a mathematical model of the coronary circulation that combines the interchange between venous and arterial epicardial and intramyocardial capacitances, resistances, and the intramyocardial pressure. These theoretical results together with the experimental results support the hypothesis that bidirectional flow over the microcirculation exists during coronary sinus occlusion and may be responsible for increased “effective” perfusion in the ischemic area.

Materials and Methods

Experimental Studies

Experiments were conducted in 13 large mongrel dogs. In seven dogs, the coronary hemodynamic response to intermittent coronary sinus occlusion was studied. In eight dogs, we examined the effect of intermittent coronary sinus occlusion on the arterial blood saturation in the ischemic zone (two of the dogs underwent both studies). The dogs were anesthetized by intravenous injection of 5 mg/kg pentobarbital, intubated, and ventilated by a ventilator (model 710A, Harvard Apparatus, South Natick, Massachusetts). Anesthesia was maintained throughout the experiment by additional pentobarbital as needed. Left ventricular, aortic, and right atrial pressures were measured by micromanometers (Millar Instruments, Houston, Texas) that were positioned via femoral cutdown. A left thoracotomy was done in the fifth intercostal space, and the pericardium was opened. A snare was placed around the left anterior descending coronary artery (LAD) distal to the snare or the distal LAD itself. Aortic and coronary sinus pressures were measured as described above. In three dogs, we also measured oxygen saturation during coronary sinus occlusion with varying balloon volumes and inflation times. This was done to investigate the relation of oxygen desaturation in the ligated coronary artery to the coronary sinus systolic coronary pressure.

Mathematical Model

A schematic representation of the model of the coronary vasculature is shown in Figure 1. The left ventricle is divided into two zones: a normal and a potentially ischemic zone. The arterial and venous systems are lumped into epicardial (subjected to pericardial pressure which is assumed here as zero) and intramyocardial vessels (which are exposed to the intramyocardial pressure). Each of the above compartments is characterized by a specific capacitance, that is, the arterial intramyocardial and epicardial \( C_{\text{sin}} \) and \( C_{\text{ep}} \) and venous \( C_{\text{sin}} \) and \( C_{\text{ep}} \) capacitances, respectively. The resistance of the coronary circulation is lumped into arterial epicardial resistance \( R_{\text{ep}} \), venous epicardial resistance \( R_{\text{ep}} \), and microcirculatory resistance \( R_{\text{m}} \). The latter comprises resistance at the level of arterioles, capillaries, and venules. Both \( R_{\text{ep}} \) and \( R_{\text{ep}} \) represent lumped resistance values for epicardial as well as the larger intramyocardial vessels.

For flow over the microcirculatory resistance, the model assumed vascular waterfall behavior. For the segment shown in Figure 2, \( C_{\text{sin}}, C_{\text{ep}}, C_{\text{sin}}, \) and
NORMAL ZONE | ISCHEMIC ZONE

CORONARY SINUS

**Fig. 1.** A schematic description of the coronary circulatory model. A normal and ischemic zones are shown each represented by arterial and venous sections further divided into epicardial and intramyocardial vessels. \( C_{ep} \) and \( R_{ep} \), arterial epicardial capacitance and resistance; \( C_{im} \) and \( C_{vim} \), intramyocardial arterial and venous capacitance; \( C_{vcp} \) and \( R_{vcp} \), venous epicardial capacitance and resistance; \( R_{i} \), microcirculatory resistance; \( R_{ac}, R_{ve}, \) and \( R_{lb} \), resistance of the arterial and venous collaterals and of the thebesian vessels; \( P_{im} \), intramyocardial pressure.

\( C_{vcp} \) and the intramyocardial pressure \( (P_{im}) \) external to the vessel are shown. As a first order approximation it is assumed that the pressure flow relation is linear with a zero flow intercept. Assuming that the gradient over the microcirculatory segment shown is antegrade arterial intramyocardial pressure \( (P_{im}) \) venous intramyocardial pressure \( (P_{vim}) \) if \( P_{im} \) is greater than \( P_{vim} \), then total collapse of the segment occurs and flow is abolished.

\( P_{im} \) is defined here as the critical no-flow pressure of the segment under zero external pressure (i.e., the minimum arterial to venous pressure gradient that will cause flow). For the totally relaxed case in which venous pressure \( (P_{vim}) \) and \( P_{im} \) are zero, line 1 in Figure 3 indicates the pressure flow relation. If \( P_{im} \) is not zero, but less than \( P_{vim} \), then flow over the segment follows line 2 in Figure 3; that is, it is proportional to the pressure gradient over the microcirculation minus the critical pressure \( (P_{im}-P_{vim}-P_{ct}) \). If \( P_{im} \) is midway between \( P_{im} \) and \( P_{vim} \), then, in accordance with the concept of flow limitation and critical pressure, flow is proportional to \( P_{im}-P_{im}-P_{ct} \) (line 3).

The above relations, which were developed for conditions where antegrade flow over the microcirculation occurs, apply in reverse order for conditions where the pressure on the venous side of the circulation is higher than the pressure on the arterial side. Under these conditions, retrograde flow across the microcirculation may occur.

On the basis of an approach taken previously, it is assumed that both \( R_{i} \) and \( P_{im} \) are subjected to autoregulation, which is described by an autoregulatory weigh function \( (T_{w}) \). \( T_{w}=0 \) describes maximum vasodilation or minimum resistance, and \( T_{w}=1 \) means maximum vasoconstriction or maximum resistance. The value of \( R_{i} \) during maximum vasoconstriction is assumed to be five times larger than the corresponding value during maximum vasodilation. \( T_{w} \) for any vascular territory is assumed to vary so that the total flow demand of that territory is met.

Based on data from the literature arterial and venous collaterals are described by simple resistances \( (R_{ac} \) and \( R_{ve} \), respectively). The venous blood from ischemic and nonischemic zones is drained by the coronary sinus. An alternative resistance for venous drainage into a low pressure chamber \( (R_{lb}) \) is also assumed. This term includes both venous drainage into the atria by channels other than the coronary sinus as well as the thebesian flow. It is assumed that the contraction of the left ventricle obstructs the thebesian vessels during systole, thus preventing this shunting flow from the left ventricle to the right atrium.

While the existence of the arterial collateral circulation is well characterized, venous collaterals have received less attention over the years. A recent study by Nakazawa et al reemphasized the importance of the venous interconnections, which may allow extensive movement of venous blood when the coronary sinus is occluded.

Finally, \( P_{im} \) is assumed to follow a half sinusoidal pattern and its magnitude represented by a certain fraction of the left ventricular pressure. A detailed description of the equations representing the model, the mathematical analysis, and the selection of the parameters are given in the "Appendix."

**Results**

**Hemodynamic Studies**

An example of the aortic, left ventricular, coronary artery, and coronary sinus pressures under normal conditions is shown in Figure 4 (top). Only minor pressure gradients exist between the aortic...
and coronary arterial pressures. Coronary sinus pressure is low but shows typical systolic peaks. During coronary sinus occlusion (Figure 4, bottom), high coronary venous pressures are observed. A time delay of 20–30 msec is present in the coronary sinus pressure tracing relative to the aortic and coronary artery pressures. This delay represents the time required for transmission of the pressure wave through the fluid-filled coronary sinus catheter.

Data for coronary artery ligation are shown in Figure 5 (top). As expected, there is a marked decrease in the coronary artery pressure but no significant change in the coronary venous pressure. The arteriovenous pressure gradient was positive throughout the cardiac cycle.

When, in addition to coronary artery ligation, the coronary sinus was occluded (Figure 5, bottom), both the arterial and venous coronary pressures increased substantially. The arteriovenous pressure gradient was calculated, a biphasic pattern was noted in the ischemic zone with positive gradients (i.e., arterial pressure greater than venous pressure) during diastole and negative gradients (venous pressure higher than arterial pressure) during systole. The left ventricular and aortic pressures did not change significantly during coronary sinus occlusion.

A summary of the results obtained in the dogs is displayed in Table 1. In general, coronary sinus occlusion caused a large increase in the systolic coronary sinus pressure and a small increase in the coronary diastolic venous pressure. Coronary artery pressure distal to the ligation also increased during coronary sinus occlusion. The overall effect of coronary sinus occlusion was to produce a negative pressure gradient from distal coronary artery to coronary sinus during systole (p<0.0001) and positive pressure gradient during diastole. Coronary sinus occlusion was also associated with small and insignificant decreases in aortic and left ventricular pressures, with or without LAD ligation.

**Oxygen saturation.** A tracing from one of the experiments showing the effect of coronary sinus occlusion on the coronary sinus pressure and coronary arterial oxygen saturation is shown in Figure 6. Approximately 10 seconds after inflation of the coronary sinus balloon, oxygen saturation in the distal coronary artery begins to decline. Fluctuations in the coronary arterial oxygen saturation occur in phase with the cardiac cycle, suggesting that venous and arterial blood were in contact with the electrode in alternating sequence. Table 2 summarizes the results of the saturation study in eight dogs. Note that in the first dog the coronary sinus pressure following coronary sinus occlusion was relatively low. No change in the coronary arterial oxygen saturation was measured for that dog. The other seven dogs show a response characterized by a significant decline in arterial oxygen saturations in the ischemic arterial bed during coronary sinus occlusion (p<0.005).

In the above group of eight dogs, we sought to determine the relation between arterial oxygen desaturation in the ischemic bed and the systolic coronary sinus pressure achieved. A correlation plot of arterial desaturation versus systolic coronary sinus pressure is presented in Figure 7. There is a strong correlation (r=0.91, p<0.01) between these two parameters, indicating that the higher the coronary sinus pressure the greater the desaturation.

**Mathematical Model: Conditions and Predictions**

Normal conditions were simulated by assuming an arterial input pressure of 80 mm Hg into the two zones. The numeric results are listed in Table 3.
With an autoregulatory function of $T_w=0.6$, normal coronary perfusion is achieved. Simulated perfusion through the myocardium under normal conditions is presented in Figure 8 (left). Most coronary perfusion occurs during diastole. This is consistent with the increased $P_{in}$ during systole, which is assumed here to impede coronary flow via the vascular waterfall mechanism.

Ischemic zone perfusion following coronary artery ligation is shown in Table 3 and Figure 8 (middle). In this simulation it is predicted that maximum vasodilatation occurs as represented by $T_w=0$, since the metabolic demand of the tissue exceeds supply. The flow to the ischemic zone is entirely due to flow through the arterial collaterals and occurs during diastole.

Intermittent coronary venous occlusion after coronary ligation induces bidirectional flow over the microcirculation (Figure 8, right). The magnitude of the venoarterial flow component is strongly dependent on the coronary $C_{vp}$. Only with relatively high capacitance value does substantial retrograde flow occur over the microcirculatory bed.

To determine the driving force for the bidirectional flow, we calculated the pressures in the epicardial artery and vein during normal conditions and during coronary artery ligation both before and after coronary sinus occlusion (Figure 9). For this analysis, it was assumed that the aortic and coronary arterial pressures are equal to left ventricular pressure during ejection and thus are described by a sinusoidal function at that time. As seen by the
 experimental data (Figure 5), this is not unrealistic because the difference between left ventricular and aortic pressure is less than 4 mm Hg during ejection. While the aortic valve is closed, arterial pressure is assumed to follow an exponential decay function. Note that in the normal case the coronary epicardial arterial pressure resembles typical experimental data. Note also that both predicted and experimental coronary venous pressure shows low amplitude systolic waves (Figures 4, top, and 9A). Coronary sinus occlusion (Figure 9B) causes a marked increase in coronary venous pressure as observed experimentally. When coronary artery ligation was simulated (Figure 9C), systolic and diastolic coronary artery pressure fell to low levels, and the arteriovenous pressure gradient remained positive throughout the cycle. A simulation of occlusion of the LAD and coronary sinus is presented in Figure 9D. During systole, coronary venous pressure rises to levels substantially in excess of the increase in coronary arterial pressure. As a result, a retrograde pressure gradient over the microcirculation is generated. In diastole, both the arterial and venous pressures are increased over the corresponding values of the pressures in the normal case and the arteriovenous pressure gradient is positive, favoring antegrade flow. Thus, "to and fro" gradients predicted by the simulation are similar to the experimental findings.

Discussion

In the present study, we sought to examine the possibility that the origin of the "hidden" flow during coronary sinus occlusion is venous, and the mechanism by which this flow reaches the microcirculation of an ischemic territory is bidirectional.
TABLE I.A. Pressure Measurements Before and During Coronary Sinus Occlusion in the Normal Bed

<table>
<thead>
<tr>
<th>Dog</th>
<th>CA</th>
<th>CS</th>
<th>LV</th>
<th>Ao</th>
<th>RA</th>
<th>DIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>1</td>
<td>106/69</td>
<td>14/4</td>
<td>110/5</td>
<td>110/76</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>115/101</td>
<td>17/6</td>
<td>120/8</td>
<td>119/98</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>103/76</td>
<td>22/4</td>
<td>103/8</td>
<td>102/75</td>
<td>8</td>
</tr>
<tr>
<td>Average±SD</td>
<td></td>
<td>108±5/</td>
<td>18±3/</td>
<td>111±7/</td>
<td>110±7/</td>
<td>9±2</td>
</tr>
<tr>
<td>During</td>
<td></td>
<td>82±14</td>
<td>5±1</td>
<td>7±1</td>
<td>83±11</td>
<td>7±1</td>
</tr>
<tr>
<td>1</td>
<td>102/64</td>
<td>66/6</td>
<td>107/6</td>
<td>107/6</td>
<td>12</td>
<td>36/58</td>
</tr>
<tr>
<td>2</td>
<td>106/92</td>
<td>79/18</td>
<td>112/8</td>
<td>110/90</td>
<td>8</td>
<td>28/85</td>
</tr>
<tr>
<td>3</td>
<td>89/64</td>
<td>44/13</td>
<td>95/5</td>
<td>89/64</td>
<td>8</td>
<td>33/53</td>
</tr>
<tr>
<td>Average±SD</td>
<td>99±7/</td>
<td>63±14/</td>
<td>104±8/</td>
<td>102±9/</td>
<td>9±2</td>
<td>32±3/</td>
</tr>
</tbody>
</table>

Measurements are in milliliters of mercury. CA, coronary artery; CS, coronary sinus; LV, left ventricle; Ao, aortic; RA, right atrial; DIF, peak systolic arterial to coronary sinus gradient (systolic/diastolic).

Since it is not yet possible to measure dynamic tissue perfusion at the microcirculatory level, we chose to examine the possibility that venous blood penetrates the ischemic region during coronary sinus occlusion. When a certain level of coronary sinus pressure was achieved during sinus occlusion, arterial oxygen saturation in the ischemic bed decreased. In one dog, the coronary sinus pressure during coronary sinus occlusion was relatively low, possibly due to aberrant venous anatomy, and no evidence for retrograde flow, as measured by oxygen saturations, was noted. In three dogs, the desaturation phenomenon was a threshold function of the coronary sinus pressure, with desaturation occurring above coronary sinus pressures of 35–75 mm Hg. Thus, with a demonstration that venous blood flows retrogradely (as shown by the oxygen saturation study), and arterial blood flows antegrade (as shown by microspheres measurements) during coronary sinus occlusion, the most fitting conclusion is that alternating "to and fro" perfusion is present. The experimental data suggest that oxy-

TABLE IB. Pressure Measurements [mm Hg] Before and During Coronary Sinus Occlusion (CSO) During Coronary Artery Ligation (CAL). Abbreviations as in Table IA

<table>
<thead>
<tr>
<th>Dog</th>
<th>CA</th>
<th>CS</th>
<th>LV</th>
<th>Ao</th>
<th>RA</th>
<th>DIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>During</td>
<td>1</td>
<td>41/12</td>
<td>6/0</td>
<td>109/5</td>
<td>109/82</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>38/13</td>
<td>12/7</td>
<td>117/8</td>
<td>116/94</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>27/12</td>
<td>21/6</td>
<td>105/7</td>
<td>104/79</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>28/7</td>
<td>8/2</td>
<td>100/79</td>
<td>100/79</td>
<td>8</td>
</tr>
<tr>
<td>Average±SD</td>
<td></td>
<td>34±5/</td>
<td>12±6/</td>
<td>110±5/</td>
<td>107±6/</td>
<td>9±2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11±2</td>
<td>4±3</td>
<td>7±1</td>
<td>8±6</td>
<td>6±3</td>
</tr>
<tr>
<td>CAL</td>
<td>1</td>
<td>46/13</td>
<td>57/4</td>
<td>103/6</td>
<td>103/75</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>65/19</td>
<td>75/13</td>
<td>111/8</td>
<td>109/88</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>39/15</td>
<td>50/13</td>
<td>98/7</td>
<td>96/73</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21/8</td>
<td>61/6</td>
<td>100/78</td>
<td>100/78</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>46/36</td>
<td>64/20</td>
<td>100/79</td>
<td>100/79</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>50/38</td>
<td>74/44</td>
<td>115/100</td>
<td>115/100</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>54/35</td>
<td>86/40</td>
<td>126/106</td>
<td>126/106</td>
<td>8</td>
</tr>
<tr>
<td>Average±SD</td>
<td>47±10/</td>
<td>68±11/</td>
<td>104±5/</td>
<td>108±10/</td>
<td>9±2</td>
<td>-20±8/</td>
</tr>
</tbody>
</table>

Measurements are in milliliters of mercury. CA, coronary artery; CS, coronary sinus; LV, left ventricle; Ao, aortic; RA, right atrial; DIF, peak systolic arterial to coronary sinus gradient (systolic/diastolic). CSO, coronary sinus occlusion; CAL, coronary artery ligation.
Figure 6. An example of the coronary artery oxygen saturation tracings (top), coronary sinus (CS) pressure (middle), and aortic (Ao) (bottom) pressures. Note that during coronary sinus occlusion the coronary pressure increases considerably followed by a decrease in the oxygen saturation of the blood in the ligated coronary artery. This picture reverses promptly on cessation of coronary sinus occlusion (CSO).

Gen desaturation in the distal occluded coronary artery is a function of the arterial collateral flow in addition to the coronary sinus pressure. When the collateral resistance is low and the collateral flow is great, as suggested by high pressure in the distal portion of the ligated LAD before coronary sinus occlusion, the desaturation is minimized.

The possibility that the desaturation of arterial blood could be caused by factors other than venous backflow was also carefully examined. Steinke and Shepherd have shown that oxygen saturation measurement by reflectance techniques are sensitive to the hematocrit. The hematocrit of distal LAD blood was measured before, during, and after coronary sinus occlusion in four dogs and did not change.

On the basis of simulation study and the experimental measurements, it is likely that the following events occur during coronary artery ligation and coronary sinus occlusion. Isolated coronary artery ligation permits an increase in the collateral flow to the ischemic zone. This, together with near maximal vasodilation, results in a small but measurable (by microspheres) perfusion to the ischemic zone. The phasic changes of the coronary arterial pressure in the ischemic bed probably results from systolic squeezing of intramyocardial blood into the arterial epicardial system. Smaller phasic changes in venous pressure were also observed and can also be attributed to the cyclic effect of $P_{cm}$. The magnitude of these pressure waves is low relative to those on the arterial side due to the low resistance of the epicardial veins allowing quick drainage of venous blood to the right atrium during systole. The arterial to venous gradient is always positive under these conditions, and thus, as predicted by the simulation, the flow in the microcirculation will be antegrade or zero throughout the cardiac cycle. However, local reversal of gradients may occur even without venous occlusion leading to translocation of blood from subendocardium to subepicardium, thus explaining the "hidden component" of perfusion which was detected in an ischemic bed not subjected to increased venous pressure.

| Table 2. Oxygen Saturation and Coronary Sinus Pressures Before and During Coronary Sinus Occlusion in the Ligated Coronary Artery |
|---|---|---|---|---|
| Dog No. | Baseline $O_2$ saturation (%) | $O_2$ saturation decline (%) | CS pressure during CSO (mm Hg) | Ao pressure during CSO (mm Hg) |
| 1 | 76 | 0 | 42/12 | 105/87 |
| 2 | 60 | 36 | 78/30 | 120/74 |
| 3 | 72 | 40 | 100/20 | 130/90 |
| 4 | 68 | 13 | 64/6 | 100/78 |
| 5 | 80 | 20 | 81/44 | 115/100 |
| 6 | 90 | 13 | 54/36 | 108/75 |
| 7 | 62 | 8 | 62/30 | 115/90 |
| 8 | 70 | 28 | 86/38 | 135/84 |
| Average±SD | 72±9 | 20±13 | 71±16/27±12 | 116±11/85±8 |

CS, coronary sinus; CSO, coronary sinus occlusion; Ao, aorta.
When the coronary sinus is occluded, blood that is squeezed into the epicardial venous system during systole is trapped there creating a high systolic venous pressure. Although anatomical data about the venous drainage of the heart through the principal (coronary sinus) and alternate (thebesian system, accessory veins) exist,\(^6\) it is very difficult to estimate the efficiency of alternate pathways for coronary venous drainage during systole. Despite these limitations, the values that we selected to represent the thebesian resistance, which includes all other possible alternate pathways, for use in pressure simulations produced results similar to the experimental data. It is important to realize that we assumed that the thebesian system drains into a low pressure system. We included within that assumption a hypothesis that the thebesian vessels that drain into the left ventricle are closed during myocardial contraction. Without this assumption, an open venous pathway would connect the high pressure in the left ventricle to the low pressure atria during systole.

The computer simulation indicated that coronary sinus occlusion results in decreased forward perfusion over the ischemic bed (Table 2). Although coronary sinus occlusion is known to decrease perfusion in the nonischemic bed,\(^1\) we did not detect any change in flow to the ischemic bed associated with coronary sinus occlusion by the microsphere technique.\(^1\) The reason for the decrease in forward flow predicted by the simulation is the decrease in the coronary arteriovenous pressure gradient under the consideration of an already maximally dilated ischemic vascular bed with fixed microvascular resistance. There are three possible explanations for this discrepancy between predicted and experimental results. Elevated microvascular pressures during coronary sinus occlusion may cause regional vasodilatation and further reduction in coronary resistance. Alternatively, collateral resistance may fail with the same effect. Finally, although microspheres were injected into the left atrium during coronary sinus occlusion, their transit from the left atrium to ostia of the coronary arteries is dispersed over a broader period of time. Thus, many microspheres undoubtedly entered the coronary circulation when the coronary sinus was not occluded.

As shown by the simulation and the experimental data the pressure in the coronary artery distal to the occlusion increases during coronary sinus occlusion. This is due to increased venous pressure in systole leading to venous retrograde flow and to increased venous pressure in diastole, which impedes drainage of collateral arterial flow. The theoretical model predicts that the venous backflow is sensitive to epicardial arterial and venous capacitance. Retrograde flow over the microcirculation causes pressure to rise on the arterial side that opposes the gradient for flow. This pressure rise must be damped by sufficiently large arterial capacitance for substantial retrograde flow to occur. In this study, arterial epicardial capacitance larger than reported values (0.002 to 0.003 ml/mm Hg\(^{17-18}\)) was required to allow retrograde flow. This use of high capacitance may be valid because of the nonlinearity of the arterial system (larger compliance at lower pressures\(^1\)). Alternatively, some of the intramyocardial vessels in the subepicardium that are exposed to low \(P_{ atm}\) changes may behave as epicardial capacitance vessels, which are not subjected to significant external pressure changes. In other words, the intramyocardial capacitance of the external layers subjected to low \(P_{ atm}\) accepts retrograde blood from the deeper layers during systole and in this sense behaves like a \(C_{ sep}\). The sensitivity of the venous backflow to the coronary capacitance is supported by the experiments as discussed above.

The overall results of all of these effects is bidirectional flow over the microcirculatory ischemic bed during intermittent coronary sinus occlusion. Perfusion of the ischemic region with venous blood originating from normal regions would account for the increased washout of tracers and possibly other waste products from the ischemic region. Furthermore, oxygen in venous blood from nonischemic myocardium would be extracted by the ischemic tissue.

With several rough assumptions the amount of coronary backflow can be quantified from the degree of desaturation. The assumptions are 1) arterial}

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**Figure 7.** The correlation between the oxygen desaturation and the peak systolic coronary sinus pressure in the group of dogs studied (\(r=0.91\)).

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**Table 3. Global Results of the Computer Simulation for Coronary Sinus Occlusion and Coronary Artery Ligation**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CAL</th>
<th>CAL+CSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow in the normal zone (ml/min/100 g)</td>
<td>76</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Flow in the CAL zone (ml/min/100 g)</td>
<td>76</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Arterial collaterals flow (ml/min/100 g)</td>
<td>0</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>(T_{ ref}) in the normal zone</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>(T_{ ref}) in the CAL zone</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CAL, coronary artery ligation; CSO, coronary sinus occlusion.
collateral flow is 10% of normal flow (10 ml/min/100 g), 2) there is complete mixing of the retrograde venous blood and the arterial blood distal to the occlusion, and 3) venous blood further desaturates from 40% to 20% when flowing retrogradely over the microcirculation of an ischemic region.

Based on these assumptions, and the average desaturation given in Table 2:

\[ F_{cv} \times 20\% + F_{ac} \times 72\% = (F_{cv} + F_{ac}) \times 52\% \]

where \( F_{cv} \) is venous backflow and \( F_{ac} \) is arterial collateral forward flow. For the above value of collateral flow, the venous backflow is 6 ml/min/100 g.

This estimate is probably low, as it is based on desaturation across the microcirculation (i.e., the distal coronary artery) not within the microcirculation.

The degree of backflow was also estimated from the mathematical model. A value of 35 ml/min/100 g was found for the larger capacitance by integrating the retrograde flow component. This value contrasts with the estimate of 6 ml/min/100 g based on oxygen desaturation. The available data do not offer reconciliation of these discrepant estimates. The difference may be due to overestimation of backflow by the model due to overestimation of the arterial capacitance. Alternatively, incomplete mixing could lead to underestimation of backflow from desaturation data.

Based on the above estimates, the degree of oxygen delivery to the ischemic myocardium may also be calculated. For retrograde venous flow and desaturation from 40% to 20%, an oxygen delivery of 1.4 ml/O2/100 g will occur for the high flow case (35 ml/min/100 g). While this contribution of oxygen by retrograde flow is relatively small, the retrograde perfusion may have other beneficial effects due to washout of toxic metabolites.

The model presented here, which is partially supported by experimental data, uses a simplified approach to explain the coronary circulation hemodynamics during coronary sinus occlusion. Some of the assumptions that were used require special attention:

*The transmyocardial distribution.* It is established that parameters such as capacitance, resistance, intramyocardial pressure, and vascular tone are distributed across the wall of the left ventricle. In the model they are lumped into representative values which describe the average of the different myocardial layers. A distributed model might better explain phenomena under these conditions. For example, higher \( P_{in} \) in the subendocardial than the subepicardial layers could lead to retrograde arte-
rial systolic flow from the deeper to the outer layers, higher retroperfusion levels at the subendocardium, and a different anti-ischemic effect for the subendocardium and subepicardium, which cannot be explained by the current model.

Distribution along the vessels. The coronary parameters of capacitance and resistance are assigned here to epicardial and intramyocardial large vessels on one hand and to smaller resistance vessels on the other hand. Obviously, in reality there is no clear segmentation between vessels. The significant capacitance assigned to the microvessels which, lumped in this analysis distal and proximal to the resistance, may have a large effect on the model predictions. Despite these limitations the present form of the model can account for the major results in the compartments which are accessible to measurement.

The waterfall concept. The waterfall concept that was applied here to describe the effect of tissue pressure on flow through the coronary circulation is controversial.21,22 While the waterfall concept may be criticized on the grounds that no direct evidence of vessel collapse has been presented, the shift of the pressure flow relation in the general microcirculation by external pressure has been shown to occur.23 Whether this shift occurs due to collapse of segments or due to other rheological factors would not change the equations used here. On the other hand, the model used here cannot account for the locations of collapse. With regard to these limitations, it should be noted that extensive sensitivity analysis of the model assumptions has determined that alternating flow would also result from non-waterfall behavior in the microcirculation. Thus, the use of a waterfall model is not a prerequisite for the major conclusions of this study.

Other possibilities may account for the increased washout of tracers and the protective effect of coronary sinus occlusion on ischemic myocardium. Intermittent coronary sinus occlusion may cause increased filtration of fluids and solutes into the lymphatic system.24 However, this mechanism, which could wash tracers and toxic substances out of the ischemic region, cannot explain the decrease in oxygen tension in the coronary artery in the ischemic zone. Thus, we conclude that enhanced lymphatic drainage may occur in addition to the bidirectional flow mechanism but is not the only mechanism. Another possible mechanism is perfusion of the ischemic tissue by arterial collaterals, which do not allow for passage of spheres. This mechanism is not supported by recent observations in several different species.25 While such a mechanism may explain tissue salvage close to the border zone, it is very unlikely that blood would travel long distances into the center of the ischemic zone in such small diameter collaterals. Direct perfusion of subendocardial layers by blood reaching retrogradely from the ventricular cavity via the thebesian vessels is also possible. Subendocardial to subepicardial excitation may provide a mechanism by which ventricular blood is "trapped" and squeezed retrogradely in small subendocardial venules.

In summary, experimental data in dogs together with a mathematical model of the coronary circulation demonstrate that an alternating arteriovenous pressure gradient exists in the ischemic region during coronary sinus occlusion. Arterial oxygen tension in the ischemic zone decreases during coronary sinus occlusion, consistent with the passage of blood from the venous to arterial side. Together, these data indicate that bidirectional flow over the microcirculation is the mechanism by which coronary sinus occlusion enhances perfusion to the ischemic bed.

Appendix

A schematic representation of the model of the coronary circulation divided into normal and ischemic zones is shown in Figure 1. As shown, the coronary circulation is lumped into capacitive and resistive elements. The model is represented by the following equations with the corresponding symbols explained in Table A1:

1. Normal zone:

\[\frac{dP_1}{dt} = \frac{dP_{in}}{dt} \quad (A1)\]

\[\frac{dP_2}{dt} = \frac{[(P_1 - P_2)/R_{sep} - (P_2 - P_6)/R_w] - DP/R_c/C_{sum}}{(P_2 - P_6)/R_K} \quad (A2)\]

where \(DP\) is the net driving pressure over the microcirculatory bed and is defined below (Equation A9–A11).

\[\frac{dP_3}{dt} = \frac{[(P_3 - P_4)/R_{sep} - (P_3 - P_6)/R_{sep} - (P_3 - P_7)/R_{vc}]/C_{vim}}{(P_3 - P_4)/R_{sep}} \quad (A3)\]

for an unobstructed coronary sinus:

\[\frac{dP_4}{dt} = \frac{[(P_3 - P_4)/R_{sep} - (P_4 - P_8)/2R_c]/C_{sep}}{(P_3 - P_4)/R_{sep}} \quad (A4a)\]

while for an occluded coronary sinus:

\[\frac{dP_4}{dt} = \frac{[(P_3 - P_4)/R_{sep} - (P_4 - P_8)/2R_c]/C_{sep}}{(P_3 - P_4)/R_{sep}} \quad (A4b)\]

2. Ischemic zone:

For a nonoccluded artery, the pressure is equal to the normal zone, that is,

\[\frac{dP_5}{dt} = \frac{dP_{in}}{dt} \quad (A5a)\]

while pressure for an occluded coronary artery is given by:

\[\frac{dP_5}{dt} = -(P_5 - P_6)/(R_{sep} \cdot C_{sep}) \quad (A5b)\]

The rest of the equations are similar to the above except for the different direction of the collateral flow:

\[\frac{dP_6}{dt} = [(P_5 - P_6)/R_{sep} + (P_2 - P_6)/R_w - DP/R_c]/C_{aim} \quad (A6)\]
TABLE A1. List of Pressure Variables Used in Differential Equations A1-A8, Corresponding to Figure 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal bed</th>
<th>Ischemic bed</th>
<th>Description</th>
<th>Corresponding compartment symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>P5</td>
<td>Arterial epicardial</td>
<td>aep</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>P6</td>
<td>Arterial intramyocardial</td>
<td>aim</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>P7</td>
<td>Venous intramyocardial</td>
<td>vim</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>P8</td>
<td>Venous epicardial</td>
<td>vep</td>
<td></td>
</tr>
</tbody>
</table>

\[
dP7/dt = \left[ \frac{DP}{R_t} - \frac{(P7 - P8)}{R_{wep}} - \frac{(P7 - P_v)}{R_{tb}} + \frac{(P3 - P7)}{R_{vc}} \right] / C_{vim} \quad (A7)\]

For the case of an unobstructed coronary sinus:

\[
dP8/dt = \left[ \frac{(P7 - P8)}{R_{wep}} - \frac{(P8 - P_a)}{R_c} / C_{wep} \right] \quad (A8a)\]

while for an occluded coronary sinus:

\[
dP8/dt = \left[ \frac{(P7 - P8)}{R_{wep}} + \frac{(P4 - P8)}{2R_c} / C_{wep} \right] \quad (A8b)\]

Flow Over the Microcirculation

It is assumed that the driving force over the microcirculation, DP, is a function of the upstream pressure, the downstream pressure, the external (intramyocardial) pressure and the critical pressure. It is furthermore assumed that \( P_{in} \), is higher than \( P_{vin} \), as shown in Figure 3. Note that \( P_{in} \), and \( P_{vin} \), which are used here to describe the general upstream and downstream pressure over the microcirculation, correspond to \( P2 \) and \( P3 \) for the normal zone and to \( P6 \) and \( P7 \) for the ischemic zone, respectively. Three possible conditions can be postulated:

1. If \( P_{in} \), is higher than both upstream and downstream pressures, total collapse and zero flow ensue. This is expressed as:

\[
DP = 0 \quad (A9)\]

2. If both upstream and downstream pressure are greater than \( P_{in} \), then for gradients \( (P_{in} - P_{vin}) \), greater than \( P_{ct} \),

\[
DP = P_{in} - P_{vin} - P_{ct} \quad (A10)\]

and otherwise \( DP = 0 \), as the critical pressure was not exceeded.

3. If \( P_{in} > P_{vin} > P_{vin} \), then, according to the waterfall concept, the flow is proportional to the upstream pressure \( P_{in} \), minus the external pressure \( (P_{vin}) \), with correction for the effect of the critical pressure. This corresponds to line 3 in figure 3 and is expressed by:

\[
DP = P_{vin} - P_{vin} - P_{ct} \quad (A11)\]

Similar relations are applicable for conditions associated with venous pressures which are higher than arterial pressures. The above equations (A9–A11) regarding microcirculatory flow are incorporated into the appropriate equations (i.e., Equations A2, A3, A6, and A7).

Autoregulation

It is assumed that autoregulation affects primarily the resistance vessels which are represented by the parameter \( R_c \). In keeping with the previous approach\(^{11}\) we assume that autoregulation is represented by \( T_{wr} \), which will yield a maximum resistance for \( T_{wr} = 1 \), which is five times the minimum resistance for maximal vasodilatation (\( T_{wr} = 0 \)). An important feature of autoregulation is its effect on \( P_{in} \), which is higher for vasoconstricted vascular bed than for vasodilated bed.

Parameter Estimation

The set of parameters used in the model is given in Table A2. Estimation of the parameters in the model was based on data from the literature summarized by Klocke et al\(^{21}\) and Beyar and Sideman,\(^{11}\) and on logical assumptions where experimental data are absent or inconsistent. The values of the arterial capacitances used in our model are consistent with previous studies, as summarized by Klocke et al\(^{22}\) and Spaan,\(^{21}\) which represent the sum of both epicardial and intramyocardial capacitances. Epicardial capacitances are assumed to be smaller than intramyocardial capacitance. Venous capacitance is assumed to be larger than arterial capacitance. In Spaan's review\(^{21}\) total capacitance values are 0.138 ml/mm Hg/100 g, a value close to our model value of 0.075 ml/mm Hg/100 g. Inflow capacitance measured by others is typically smaller since they only partially represent the arterial side. These values range between 0.0016 and 0.014 ml/mm Hg/100 g, similar to our selected value of 0.015 ml/mm Hg/100 g. Even larger values have been proposed by Downey et al\(^{26}\) for the inflow capacitance (0.017–0.059 ml/mm Hg/100 g), which may justify the need to use higher \( C_{wep} \) to generate venous retroperfusion. Based on the sum of all the capacitances

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardial capacitance</td>
<td>Arterial</td>
<td>( C_{wep} )</td>
</tr>
<tr>
<td>Intramyocardial capacitance</td>
<td>Arterial</td>
<td>( C_{wep} )</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>( C_{wep} )</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>( C_{wep} )</td>
</tr>
<tr>
<td>Epacardial (proximal) resistance</td>
<td>[mm Hg g s/ml]</td>
<td>( R_{wep} )</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>( R_{wep} )</td>
</tr>
<tr>
<td>Microcircularty resistance</td>
<td>[mm Hg g s/ml]</td>
<td>( T_{wr} = 0 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( T_{wr} = 1 )</td>
</tr>
<tr>
<td>Collateral resistance</td>
<td>[mm Hg g s/ml]</td>
<td>( R_c )</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>( R_c )</td>
</tr>
<tr>
<td>Thebesian resistance</td>
<td>[mm Hg g s/ml]</td>
<td>( R_{wep} )</td>
</tr>
<tr>
<td>Intramyocardial pressure</td>
<td>[mm Hg]</td>
<td>( P_{vin} )</td>
</tr>
</tbody>
</table>
the intramyocardial blood volume is approximately 6 ml/100 g at 100 mm Hg arterial pressure. This value is within the range of the published data and may be even larger if we account for the nonlinearities of the capacitance.

The resistances in the system are distributed between the microcirculation and the larger arterial and venous vessels. This distinction is of course arbitrary but is an inherent feature of all lumped parameter models. In this model, a proximal resistance which is approximately 10% of the total resistance for an autoregulated bed and higher for the vasodilated bed is logical. The collateral resistance could be estimated from the magnitude of the residual flow after coronary artery ligation which in the dog is known to be a small fraction of the baseline flow. An estimate for thebesian resistance is derived from increase in the systolic and diastolic coronary sinus pressures after coronary sinus occlusion. Finally, intramyocardial pressure was assumed as half the cavity pressure assuming a distribution between the microcirculation and the larger arterial layers and zero pressure at the epicardial layers.

Solution of the Model

The model is represented by the basic set of eight differential equations (A1-A8), which are solved by the Runge-Kutta-Verner method in steps of 0.01 seconds. The cycle is repeated adjusting autoregulatory function until steady state conditions are obtained. The solution of the set of equations yields the pressure functions in each of the compartments from which the flows are calculated given the resistance values of the different elements. The output is then obtained both graphically and numerically.

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Intermittent coronary sinus occlusion after coronary arterial ligation results in venous retroperfusion.

R Beyar, A D Guerci, H R Halperin, J E Tsitlik and M L Weisfeldt

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