Regional Myocardial Function Is Not Affected by Severe Coronary Depressurization Provided Coronary Blood Flow Is Maintained

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It has been suggested that vasodilation distal to a stenosis may cause a profound decrease in perfusion pressure and adversely affect regional left ventricular function. This phenomenon could explain the clinical concept of reversal of regional dysfunction by coronary revascularization. To evaluate the hypothesis that regional myocardial function parallels regional coronary blood pressure in the absence of changes in coronary flow, dogs chronically instrumented with left circumflex coronary artery flow probes, cuff occluders, pressure catheters and segmental function sonomicrometers were studied. By decreasing regional coronary vascular resistance with selective intracoronary dipyridamole and controlling blood flow with a proximal coronary cuff occluder, the mean left circumflex artery pressure was reduced from 83 ± 3 to 38 ± 2 mm Hg while circumflex coronary blood flow was maintained constant. Regional contractile function as measured by circumflex sonomicrometers was unchanged at constant circumflex subendocardial blood flow as measured by radioactive microspheres.

These findings suggest that regional contractile function is dependent on subendocardial blood flow and is independent of coronary perfusion pressure.

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The relative influence of coronary blood pressure and flow on regional and global left ventricular function remains controversial. Several investigators (1,2) described a close relation between coronary perfusion pressure and left ventricular function independent of loading conditions. An extension of this phenomenon was described by Arnold et al. (3), who demonstrated that myocardial function, as measured by developed left ventricular pressure, increased with increases in coronary perfusion pressure. Increasing perfusion pressure at a constant level of coronary flow by the addition of dextran to the perfusate resulted in increases in left ventricular developed pressure and oxygen consumption. Arnold and his coworkers labeled this finding the "garden hose effect." These studies suggested that ventricular function, albeit crudely measured, is proportional to coronary blood pressure at constant coronary flow.

A severe coronary stenosis may result in a significant pressure decrease at normal flow rates. Significant coronary depressurization distal to the stenosis could result in reactive vasodilation of the involved myocardium, which would in turn result in a more profound decrease in pressure distal to the flow-restrictive stenosis. If regional function is critically related to perfusion pressure, severe regional depressurization distal to a stenosis could result in significant dysfunction while maintaining coronary blood flow at levels adequate to ensure tissue viability. The existence of chronic depressurization distal to a coronary stenosis could explain regional dysfunction which is reversible by coronary bypass surgery as reported by Bourassa (4) and Hutchins (5) and their coworkers.

Conversely, Abel and Reis (6) reported that contractility as measured by first derivative of pressure with respect to time (dP/dt) and maximal contractile element velocity (V_max) was related more to coronary blood flow than to coronary perfusion pressure. Downey (7) found that "deep contractile force" was minimally changed at perfusion pressures of 50 to 100 mm Hg, during which time coronary blood flow was relatively constant as a result of autoregulation.

Other investigators (8,9) found that regional contractile function in both the subendocardium and subepicardium was linearly related to subendocardial blood flow. Subepicardial blood flow had little effect on subepicardial function. How-
ever, in these experiments, distal coronary perfusion pressure was reduced as well, thereby providing no evidence as to whether the "garden hose effect" was due to changes in coronary perfusion pressure or coronary blood flow. Many of the previous studies utilized isolated heart preparations or open chest dogs having a profoundly altered cardiovascular hemodynamic state compared with that of intact awake animals.

Accordingly, we measured regional function by sonomicrometers in awake, unsedated, chronically instrumented dogs in the control state and with low coronary pressure at constant coronary flow to test the hypothesis that coronary perfusion pressure regulates regional performance independent of coronary blood flow.

**Methods**

**Experimental preparation.** Ten conditioned mongrel dogs were instrumented aseptically under nitrous oxide/methoxyflurane (Penthrane) anesthesia after sodium pentobarbital injection. A left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. An aortic flow transducer (Zepeda Instruments) was placed on the immediate ascending aorta. Just distal to this flow transducer, an 18 gauge Teflon/Tygon catheter was inserted into the aorta for subsequent pressure measurements and blood withdrawal during microsphere injection. The proximal portion of the left circumflex coronary artery was dissected and an electromagnetic flow transducer (Zepeda Instruments) was placed proximally, followed by a Silastic hydraulic cuff occluder. A 22 gauge Teflon/Tygon coronary cannula was inserted into the distal main circumflex artery for recording perfusion pressure distal to the cuff occluder.

Sonomicrometer crystals for measurement of left ventricular diameter were implanted on the endocardium 3 cm distal to the origin of the left anterior descending and posterior descending coronary arteries. Sonomicrometer crystals for measurement of regional shortening in the circumflex artery distribution were placed mid-wall in the circumferential direction (10–12), perpendicular to the long axis of the ventricle midway between the base and apex. Similar segmental shortening crystal pairs were placed in the left anterior descending artery distribution, mid-wall in the circumferential direction. In addition, an endocardial crystal was placed in the circumflex artery distribution, followed by an epicardial crystal over the minimal transmission distance between the two crystals for measurement of circumflex artery wall thickness. A Konigsburg P22 micromanometer was placed through a stab wound in the left ventricular apex. A Tygon left ventricular pressure catheter was placed adjacent to it for calibration of the micromanometer. A left atrial catheter was inserted through the left atrial appendage for microsphere injection. Teflon-coated stainless steel pacing wires were sutured to the right atrial appendage. The chest was closed, followed by evacuation of air and fluid. The animal was allowed to recover for 7 to 10 days before the experiments were initiated. The catheters were flushed and filled with heparin daily.

**Experimental protocol.** Each dog was studied on 2 consecutive days. The animals were awake, unsedated and lying on their right side during data collection. The heart rate was controlled by atrial pacing at approximately 20% above that of the heart rate at rest. After calibration, baseline recordings were made of aortic, left circumflex coronary artery and left ventricular pressure, as well as wall thickness and segmental shortening in the circumflex artery region, left ventricular diameter, segmental shortening in the left anterior descending artery region and aortic and circumflex coronary artery blood flow using electromagnetic flow transducers. The limits of positive aortic flow were used to define the ejection period. All recordings were made using Ailtek or Konigsburg pressure transducers, Zepeda Instruments dual channel electromagnetic flowmeter, Norland Instruments four channel sonomicrometer and Honeywell VR-16 physiologic recorder.

After control function and pressure measurements were made, 15 μ radioactive microspheres were injected into the left atrium, while aortic blood was continuously sampled for 2½ minutes for measurement of control myocardial blood flow. Dipyridamole was then slowly injected into the catheter implanted in the left circumflex coronary artery in an amount sufficient to double circumflex blood flow at rest without changing systemic blood pressure. Dipyridamole was chosen because of its potent vasodilator properties and absence of positive or negative inotropic effect (13). After circumflex coronary flow was stabilized at an elevated level, it was reduced to control levels by partial inflation of the circumflex coronary cuff occluder (Fig. 1). This maneuver effectively depressurized the distal circumflex artery bed while maintaining baseline circumflex coronary artery blood flow as measured by the electromagnetic flow transducer. Repeat pressure and function measurements were made, followed by repeat microsphere injection with aortic sampling. The protocol was repeated 24 hours later.

**Data analysis.** After measurements on the second day were completed, the dog was killed and the heart removed and fixed in 8% formalin. The heart was then carefully dissected and the sonomicrometer crystal positions were verified. Multiple tissue samples were taken from segments of the myocardium located between branches of the circumflex coronary artery. Each sample was then divided into three equal slices from endocardium to epicardium. Each piece of myocardium was then weighed. The radioactivity in each reference arterial blood sample and each tissue sample was measured with a 1,000 channel pulse height analyzer and sodium iodide crystal (Ultima-2, Norland Corporation
and Tracor Analytic Inc.). Regional blood flow was calculated by a computer program that used least squares analysis (Norland Corporation) (14,15) to separate the activity due to each of the microspheres injected. The physiologic tracings were digitized using a Tektronix digitizing platen and graphics terminal interfaced to a digital equipment VAX 11-780 computer.

**Segmental shortening** was calculated by subtracting the end-ejection length from the length at the onset of ejection and dividing by the length at the onset of ejection. As mentioned previously, the onset and end of the ejection period were determined by phasic aortic flow measured just above the aortic valve plane.

**Circumferential wall stress** \((\sigma)\) (16) was calculated using the formula:

\[
\sigma = 1,333 \frac{[PR]/t}{[1-2(R/L)^2]},
\]

where \(P\) = left ventricular pressure (mm Hg), \(R\) = instantaneous left ventricular radius (cm), \(t\) = instantaneous thickness in the circumflex distribution (cm) and \(L\) = left ventricular length measured at postmortem and assumed constant (cm).

**Mean arterial and mean coronary pressures** were obtained by digital integration of the pressure curves. Mean diastolic coronary pressure was obtained by integration of the coronary pressure curve between the end of the ejection period and the subsequent onset of the ejection period of each sample beat analyzed.

**Statistics.** Data are presented as mean ± standard error. Statistical significance was determined by the paired Student’s \(t\) test.

**Results**

Records obtained from one of the study dogs are shown in Figure 2. Recordings during the control state appear in Figure 2A while tracings during circumflex depressurization appear in Figure 2B. Segmental shortening in the distribution of the left anterior descending and circumflex coronary arteries did not significantly change with coronary depressurization. During the control state, there was no significant difference between aortic and left circumflex coronary artery pressure. With circumflex artery depressurization, a significant gradient developed between mean aortic and mean coronary pressures. Diastolic circumflex coronary artery pressure remained approximately 18 mm Hg greater than left ventricular diastolic pressure.

**Pressure measurement** (Table 1). Systolic and diastolic left ventricular pressures did not change, but mean arterial pressure decreased slightly from 92 ± 2 to 88 ± 1 mm Hg. Average circumflex artery pressure during diastole was 77 mm Hg during the control state and decreased to 29 mm Hg during circumflex depressurization (\(p < 0.001\)).
Coronary blood flow measurements (Table 2). Two methods were used to measure circumflex coronary blood flow. Flow measured with the electromagnetic flow transducer on the circumflex artery did not change significantly from the control state to depressurization. However, transmural flow in the circumflex artery region as measured by 15 μ radioactive microspheres increased significantly from 102 ± 5 to 141 ± 5 cc/100 g. Subendocardial blood flow remained unchanged. The inner/outer ratio (ratio of subendocardial to subepicardial blood flow) was 1.28 ± 0.04 during the control state. This ratio decreased significantly to 0.8 with circumflex artery depressurization. The decrease in inner/outer ratio occurred largely as a result of increased subepicardial blood flow with constant subendocardial blood flow. The increase in transmural blood flow and decrease in inner/outer ratio probably occurred secondary to enhanced epicardial collateral blood flow during circumflex artery depressurization (vasodilation) (17–19).

Regional function measurements. Heart rate was controlled by right atrial pacing and did not change from control to depressurization. Percent shortening in the circumflex artery distribution during the ejection period was unchanged.
Table 2. Circumflex Coronary Blood Flow Measurements*

<table>
<thead>
<tr>
<th>EMF</th>
<th>Control</th>
<th>Depressurization</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(% of control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microsphere blood flow (cc/100 g per min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardial</td>
<td>111 ± 5</td>
<td>121 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Mid-wall</td>
<td>104 ± 4</td>
<td>146 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>Epicardial</td>
<td>90 ± 5</td>
<td>156 ± 6</td>
<td>0.001</td>
</tr>
<tr>
<td>Transmural</td>
<td>102 ± 5</td>
<td>141 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>I/O ratio</td>
<td>1.28 ± 0.04</td>
<td>0.80 ± 0.04</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard error. EMF = electromagnetic flow; I/O ratio = ratio of subendocardial to subepicardial blood flow.

from the control state during depressurization (Fig. 3). Similarly, there was no change in maximal percent shortening or percent wall thickening during the ejection period.

Because approximately 10% of the myocardial mass is due to intravascular blood volume (20), a significant decrease in perfusion pressure in the intramyocardial vessels might result in decreased wall thickness with a consequent increase in instantaneous wall stress. End-diastolic wall thickness did decrease from 1.4 to 1.3 cm, but this change was not significant (Table 3). Similarly, the increase in maximal circumferential wall stress from 2.2 × 10^5 to 2.4 × 10^5 dynes/cm^2 was also insignificant. Thus, no significant change in circumflex artery regional function occurred with severe circumflex artery depressurization at constant heart rate, left ventricular pressure, circumflex artery flow and subendocardial blood flow.

**Discussion**

**Influence of coronary pressure on ventricular function.** The relative importance of coronary perfusion pressure versus coronary blood flow in left ventricular function has been controversial. Opie (21) and Daniell (22) demonstrated that oxygen consumption is related to coronary blood flow in working experimental preparations. Weisfeldt and Shock (23), however, suggested that oxygen consumption was more closely related to perfusion pressure than to coronary blood flow in nonworking hearts. Abel (6) and Arnold (3,24) and their coworkers demonstrated augmented contractile function as measured by developed left ventricular pressure and dP/dt with increased coronary blood flow. Arnold et al. (3) suggested that increased pressure at constant flow caused an increase in left ventricular function as measured by developed pressure and oxygen consumption. Sharf and Bromberber-Barnea (25) demonstrated that either increased coronary blood flow or increased coronary sinus pressure produced a significant increase in left ventricular function as measured by changes in dP/dt, left ventricular pressure and oxygen consumption.

Templeton et al. (26) found that increases in coronary blood flow by either increasing coronary perfusion pressure or administration of nitroglycerin caused increased developed left ventricular pressure and dP/dt in isovolumetrically contracting canine hearts. The changes in function, however, were not accompanied by changes in viscoelastic properties of the heart (diastolic function).

It has been suggested that, for brief periods, pressure alone is sufficient to maintain contractile function in the absence of oxygen. Murao et al. (27) demonstrated in an acute canine preparation that perfusion of a coronary artery by "nonoxygenated" Tyrode's solution for periods of up to 3 minutes produced no significant deterioration in regional contractile function. In a similar preparation, Sugishita et al. (28) showed that there was decreased reactive hyperemia with Tyrode's solution compared with complete coronary occlusion for the same period of time after perfusion. These studies suggested that perfusion pressure supporting wall

Figure 3. Percent segmental shortening during the ejection period in 10 chronically instrumented dogs during the control state and with circumflex artery depressurization. Mean values ± 1 standard deviation appear on either side of individual data.
thickness of the myocardium was sufficient to maintain contractile force. Morgenstern et al. (20) demonstrated that wall thickness correlates with perfusion pressure and myocardial blood volume. Kerber et al. (29) showed that significant wall thinning occurs with acute coronary occlusion, as one would expect with restricted filling of the myocardial vascular bed. This wall thinning occurred essentially instantaneously after occlusion and was accompanied by almost immediate diminution or cessation of contractile function. The changes in contractile function during ischemia occurred before significant depletion of energy stores. Kanaide et al. (30) demonstrated in a rat heart preparation that significant adenosine triphosphate depletion occurred much later than the onset of dysfunction during episodes of temporary ischemia.

Thus, maintenance of an "erectile" state in the myocardial wall may be a critical determinant of local wall stress and local function for brief periods independent of metabolic state. The concept that perfusion pressure provides support of the myocardial wall was also proposed by Stein et al. (31), who found that intramyocardial pressure in the epicardial region exceeded that in the endocardium during diastole during normal cardiac contraction. However, during cardiac arrest, ventricular intracavitary pressure exceeded subendocardial pressure, which in tum exceeded epicardial pressure, as would be predicted by stress calculations.

If chronic depressurization (or flow reduction) distal to a stenosis caused wall thinning and chronic increased wall stress, then one would expect compensatory hypertrophy in myocardial segments distal to a stenosis in an attempt to normalize wall stress. This concept was supported by the work of Chen et al. (32), who demonstrated that patients with multivessel coronary disease had increased wall thickness and myocardial mass index as well as decreased wall stress compared with similar patients without coronary artery disease. Additionally, coronary blood flow per unit mass was decreased in these patients.

Further support of the importance of myocardial depressurization was reported by Vlahakes et al. (33), who found that right ventricular dysfunction secondary to pulmonary stenosis in an acute canine preparation could be reversed by increasing perfusion pressure in the right coronary artery. Obviously, coronary blood flow to the right ventricle was also increased with this maneuver.

Influence of coronary flow on ventricular function. The reports reviewed (3,21–33) suggest that coronary artery pressure plays a significant role in myocardial function that may be somewhat independent of metabolic state. However, in intact awake animals we found that the critical determinant of myocardial function appears to be subendocardial blood flow. Control of circumflex coronary blood flow during the experiments was monitored with an electromagnetic flow probe. Transmural blood flow measured by radioactive microspheres was slightly higher during depressurization (vasodilation) than during the control state.

The disparity of coronary blood flow measurements using the electromagnetic flow probe compared with radioactive microspheres suggests that enhanced epicardial collateral blood flow did occur during regional coronary vasodilation, as described by Becker (17) and supported by the experiments of Bache and Schwartz (19). In the study by Bache and Schwartz, when coronary blood flow, as measured by the electromagnetic blood flow transducer, was reduced to control levels after regional vasodilation, transmural flow measured by microspheres was slightly increased.

If coronary artery pressure was the critical determinant of regional function, we should have observed a significant decrease in segmental shortening and wall thickening in the circumflex artery distribution. Both wall thickening and segmental shortening are very sensitive indexes of regional

### Table 3. Circumflex Segmental Function Measurements*

<table>
<thead>
<tr>
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<th>Control</th>
<th>Depressurization</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 3</td>
<td>115 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (cm)</td>
<td>4.9 ± 0.18</td>
<td>5.0 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Percent shortening during ejection</td>
<td>10.9 ± 0.8</td>
<td>11.1 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal percent shortening</td>
<td>11.8 ± 0.7</td>
<td>12.1 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic wall thickness (cm)</td>
<td>1.4 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Percent wall thickening during ejection</td>
<td>15.5 ± 1.3</td>
<td>14.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal circumferential stress (dyne/cm²)</td>
<td>2.2 ± 0.2 x 10⁵</td>
<td>2.4 ± 0.2 x 10⁵</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard error.
performance (34–36), yet neither changed with depressurization. There was no change in regional function despite the modest increases in transmural blood flow and constant subendocardial blood flow. Our findings agree with the data in anesthetized open chest dogs reported by Downey (7). In his experiments, deep contractile force changed minimally between perfusion pressures of 50 and 100 mm Hg. At pressures of less than 50 mm Hg, coronary blood flow, pressure and contractile force appeared to be linearly related.

Our findings also agree with those of Vogel et al. (37), who studied isolated perfused hearts. During isovolumetric contractions, depressurization at constant flow using adenosine resulted in no changes in wall thickness or diastolic function of the preparation. Their data support the concept that wall thickness or diastolic function is more closely related to coronary blood flow than to perfusion pressure and, hence, tissue engorgement or support is not purely secondary to pressurization.

Conclusion. We have demonstrated that regional depressurization at constant left circumflex coronary blood flow caused no significant change in end-diastolic wall thickness, maximal circumferential wall stress or end-diastolic left ventricular diameter. Similarly, there was no change in circumflex artery contractile function during severe circumflex coronary depressurization. These data demonstrate that coronary blood flow is a critical determinant of contractile function during severe circumflex coronary depressurization. These data demonstrate that coronary blood flow is a critical determinant of contractile function in intact unsedated animals. The “garden hose effect,” as described by Arnold et al. (3), is more likely a coronary blood flow phenomenon and is not due to coronary perfusion pressure.

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