Effects of atrial pacing on regional myocardial gas tensions with critical coronary stenosis

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O'RIORDAN, JOHN B., JOHN T. FLAHERTY, SHUKRI F. KHURI, ROBERT K. BRAWLEY, BERTRAM PITT, AND VINCENT L. GOTT. Effects of atrial pacing on regional myocardial gas tensions with critical coronary stenosis. Am. J. Physiol. 232(1): H49-H53, 1977 or Am. J. Physiol.: Heart Circ. Physiol. 1(1): H49-H53, 1977.—Changes in myocardial carbon dioxide (PmCO₂) and oxygen tension (PmO₂) measured by mass spectrometry have been shown to provide a useful indicator of the development of regional myocardial ischemia. This study was also designed to define the role of changes of myocardial perfusion in the pathogenesis of the changes in myocardial carbon dioxide tension observed with atrial pacing.

MATERIALS AND METHODS

Ten dogs, weighing 20-25 kg were anesthetized with α-chloralose, 60 mg/kg, after an initial intravenous dose of pentobarbital sodium, 5 mg/kg, endotracheally intubated, and ventilated with room air using a Harvard respirator. Mean aortic pressure was constantly monitored via a cannula placed in the aortic arch and measured with a Statham P23Db transducer. A left anterolateral thoracotomy was performed and the pericardium incised. Retraction of the left atrial appendage gave access to the origin of the circumflex coronary artery (CCA) and a short segment of this vessel was carefully isolated. Sequentially placed on the exposed artery were an electromagnetic flow probe (Biotronex series 6000 flow probe with Biotronex model 610 Pulselogic flowmeter), a variable screw-type constrictor, and a snare to allow temporary occlusion. An atrial pacing lead was inserted into the right atrial wall. Mass spectrometer probes consisting of 22-gauge stainless steel tubing covered with Teflon were inserted in a midposition in the left ventricular wall. One probe was placed in the region of the myocardium supplied by the constricted circumflex coronary artery and a second in the region supplied by the unconstituted left anterior descending coronary artery (LAD). The design, calibration, and technical details of these probes have been previously described (4, 11). Injections of carbonized radioactive microspheres, 7-10 μm, were made via a cannula placed in the left atrium. Left atrial injection of microspheres has been shown to result in their mixing sufficiently with arterial blood to allow accurate measurement of coronary blood flow (15). Blood samples were withdrawn at a constant rate, 7.5 ml/min, from a second cannula placed in the femoral artery. The measurement of the counts in these reference blood samples made possible the calculation of absolute myocardial blood flow, as described below. Thirty
minutes after insertion of the mass spectrometer probes, control measurements of myocardial oxygen tension \((P_{m,\text{O}_2})\) and myocardial carbon dioxide tension \((P_{m,\text{CO}_2})\) were recorded in the regions of the myocardium supplied by both the CCA and LAD. The circumflex coronary artery was then gradually constricted until “critical stenosis” was established. Critical stenosis is defined as that degree of proximal coronary artery stenosis that abolishes the reactive hyperemic response to a 10-s transient occlusion without significantly lowering mean coronary flow (<15% reduction). Fifteen minutes after application of a critical stenosis, \(P_{m,\text{O}_2}\) and \(P_{m,\text{CO}_2}\) were remeasured in the regions supplied by the CCA and LAD. One to two million radioactive microspheres labeled with 141-cerium were then injected into the left atrium and a second reference arterial blood sample was withdrawn from the femoral artery at a constant rate.

The heart rate was then increased by atrial pacing to a rate 50% above the individual animal’s control heart rate. Fifteen minutes after the initiation of atrial pacing, \(P_{m,\text{O}_2}\) and \(P_{m,\text{CO}_2}\) were again recorded in the myocardium supplied by the unstenosed LAD and the constricted CCA. One to two million radioactive microspheres labeled with strontium-85 were then injected into the left atrium and a second reference arterial blood sample was withdrawn. Atrial pacing was then discontinued and the myocardial gas tensions allowed to return to baseline values. Following exsanguination, the heart was excised. After careful dissection, the exact position and depth of the mass spectrometer probes relative to the endo- and epicardial surfaces were measured. Two segments of myocardium, approximately 20 g each, were excised from the regions supplied by the LAD and CCA. These myocardial segments were divided into endocardial and epicardial halves, weighed, and counted for radioactivity in a well-type scintillation counter. The blood samples were also counted by differential spectrometry. The corrected counts per gram of each sample of myocardium were computed and the absolute myocardial blood flow (MBF) was calculated from the formula

\[
\text{MBF} = \frac{C_m \times \text{RBF}}{\text{CR}} 	imes 100
\]

where MBF is the myocardial blood flow per 100 g of left ventricular myocardium, \(C_m\) is the count per gram in a given myocardial sample, RBF is the flow rate at which the reference blood sample was withdrawn in milliliters per minute, and CR is the count in the reference blood sample. Distribution of myocardial blood flow, expressed as a ratio of the counts in the endocardial-to-epicardial layers of myocardium was also calculated.

All data are expressed as means plus/minus 1 standard error of the mean and are analyzed by the paired-Student \(t\) test.

**RESULTS**

**Hemodynamic parameters.** The mean control heart rate prior to atrial pacing for the 10 animals was 146 ± 7 beats/min. During atrial pacing at 50% above each animal’s control heart rate, the mean rate was 227 ± 12 beats/min. Mean aortic pressure was 111 ± 7 and 105 ± 7 mmHg during atrial pacing. This difference was not statistically significant. Application of critical stenosis was associated with a small reduction of 7 ± 1.8% in mean flow in the CCA. The mean remaining reactive hyperemia was 7.8 ± 1.0% of the control hyperemic response. Mean circumflex coronary flow was 38.5 ± 4.2 prior to and 40.1 ± 3.5 ml/min during atrial pacing (P, NS).

**Myocardial gas tensions.** The mean mass spectrometer probe position, expressed as a fraction of the distance from endocardial to epicardial surfaces, was 0.40 ± 0.04 for both probes placed in the region supplied by the LAD and also the probes placed in the region of the CCA. Before the application of critical stenosis, the mean oxygen tension in the region supplied by the LAD was 16 ± 1.9 mmHg, and in the region supplied by the CCA, 46 ± 3.0 mmHg. The myocardial gas tensions before and following application of critical stenosis and subsequently with atrial pacing are presented in Table 1 and Fig. 1. The application of critical stenosis resulted in no significant changes in the gas tensions measured in the region supplied by the LAD. In contrast, in the region supplied by the stenosed CCA, a significant decrease of 6 ± 1.1 mmHg \((P < 0.01)\) in oxygen tension and a significant increase of 17 ± 5.0 mmHg \((P < 0.01)\) in carbon dioxide tension were observed. When atrial pacing was added, there was a small decrease in oxygen tension of 4 ± 1.4 mmHg \((P < 0.01)\) in the region supplied by the LAD, and a small increase in carbon dioxide tension of 7 ± 2.8 mmHg \((P < 0.05)\). In the region supplied by the CCA, a further decrease of 3 ± 0.7 mmHg \((P < .005)\) in oxygen tension and a further increase of 40 ± 12 mmHg \((P < .005)\) in carbon dioxide tension were noted. The magnitude of the increase in carbon dioxide tension with the additional atrial pacing was significantly greater in the region supplied by the CCA.

**TABLE 1. Myocardial blood flow with critical stenosis at rest and with atrial pacing**

<table>
<thead>
<tr>
<th>Group</th>
<th>Control Region Flow, ml/min per 100 g LV</th>
<th>Ischemic Region Flow, ml/min per 100 g LV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Endo</td>
<td>Epi</td>
</tr>
<tr>
<td>1</td>
<td>198</td>
<td>206</td>
</tr>
<tr>
<td>2</td>
<td>199</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
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<td>199</td>
<td>206</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SE</th>
<th>Endo</th>
<th>Epi</th>
<th>Rest</th>
<th>Pace</th>
<th>Rest</th>
<th>Pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF, ml/min per 100 g LV</td>
<td>126 ± 18</td>
<td>118</td>
<td>111</td>
<td>159</td>
<td>128</td>
<td>101</td>
<td>133</td>
</tr>
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<tr>
<th></th>
<th>Mean ± SE</th>
<th>Endo</th>
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<th>Rest</th>
<th>Pace</th>
<th>Rest</th>
<th>Pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF, ml/min per 100 g LV</td>
<td>198 ± 20</td>
<td>224</td>
<td>187</td>
<td>196</td>
<td>200</td>
<td>138</td>
<td>248</td>
</tr>
</tbody>
</table>

Control region, supplied by the unstenosed anterior descending coronary artery. Ischemic region, supplied by the stenosed circumflex coronary artery. Abbreviations: LV, left ventricle; Epi, epicardial half of myocardium; Endo, endocardial half of myocardium; Rest, after application of critical stenosis before atrial pacing; Pace, during atrial pacing; \(P\), calculated by paired-Student \(t\) test.
ATRIAL PACING WITH CRITICAL STENOSIS

CCA than in the region supplied by the LAD (P < 0.01). Although the initial level of oxygen tension prior to atrial pacing was lower in the region supplied by the critically stenosed CCA than in the control region, the magnitude of the decrease in oxygen tension with atrial pacing was not significantly different in the circumflex and LAD regions. After discontinuation of atrial pacing, the myocardial gas tensions returned to their prepacing values.

Myocardial blood flow. Blood flow to the full thickness of myocardium supplied by the critically stenosed CCA was 130 ± 18 ml/min per 100 g of left ventricle (LV); and blood flow to the region supplied by the unconstricted LAD was 119 ± 16 ml/min per 100 g LV (Table 2 and Fig. 2). These two values of MBF were not significantly different. With the addition of atrial pacing, the myocardial blood flow increased to 174 ± 19 ml/min per 100 g LV (P < 0.01) in the region supplied by the LAD. Blood flow to the region supplied by the critically stenosed CCA changed only slightly, 136 ± 17 ml/min per 100 g LV, with the addition of pacing.

The ratios of endocardial-to-epicardial blood flows (endo/epi ratio) are presented in Fig. 3. The endo/epi ratio in the region supplied by the LAD was 1.12 ± 0.05, while in the region supplied by the CCA the ratio was 0.99 ± 0.03. During atrial pacing, there was a small increase to 1.18 (P < 0.05) in the flow ratio in the region supplied by the LAD, while the flow ratio in the region supplied by the CCA decreased to 0.61 ± 0.05 (P < 0.01).

Prior to atrial pacing the absolute myocardial blood flow to the endocardial layer in the region supplied by the LAD was not significantly different from the flow in the same layer in the region supplied by the stenosed CCA (Table 2 and Fig. 4). However, absolute blood flow to the epicardial layer in the circumflex region was slightly but significantly greater than flow in the LAD region (P < 0.05). With atrial pacing, myocardial blood flow increased to the endocardial (P < 0.01) and epicardial (P < 0.05) layers in the region of the myocardium supplied by the LAD. In contrast, in the region supplied by the constricted CCA, while there was a significant (P < 0.05) increase in blood flow to the epicardial layer, there was no increase in flow to the endocardial layer. Myocardial blood flow to the endocardial layer, in fact, showed a small decrease that did not reach statistical significance.

**DISCUSSION**

The data obtained in the present study demonstrate that the addition of atrial pacing results in the development of regional myocardial ischemia as evidenced by an increase in myocardial carbon dioxide tension.
and a decrease in myocardial oxygen tension in the region distal to a critical coronary stenosis. Prior to the initiation of pacing, application of the critical stenosis alone resulted in a substantial fall in oxygen tension from 17 to 11 mmHg in the myocardium distal to the stenosis. The addition of atrial pacing resulted in only a 3 mmHg further decrease. In contrast, myocardial carbon dioxide tension, which increased from 46 to 63 mmHg following application of the critical stenosis, increased 40 mmHg further with the addition of atrial pacing. Thus, it would appear that changes in myocardial gas tensions, especially carbon dioxide tension after the initiation of atrial pacing, provide a useful quantitative index of the development and severity of regional myocardial ischemia.

The myocardium extracts approximately 75% of the oxygen delivered to it under normal conditions, and a low resting oxygen tension, 17-24 mmHg, is observed. Because of the high base-tine rate of oxygen extraction, the myocardium must rely more on increasing coronary flow than on increasing oxygen extraction to meet the increased oxygen demands of higher heart rates. In the presence of a critical coronary stenosis that does not allow the flow to increase, an additional oxygen supply is obtained by utilizing most of the oxygen made available by increased oxygen extraction. Distal to such a stenosis myocardial oxygen tension falls to within 6 mmHg of the oxygen tension measured distal to a more severe degree of stenosis that reduced mean flow 86% (1). In contrast, myocardial carbon dioxide tensions distal to each of these two degrees of stenosis differed by 84 mmHg. Thus, it would appear that myocardial carbon dioxide tension provides a more sensitive indicator of the severity of myocardial ischemia than myocardial oxygen tension.

At oxygen tensions below 10 mmHg oxygen tension, myocardial metabolism must rely predominantly on anaerobic pathways. The resulting increased rate of anaerobic glycolysis would result in the increased production of lactic acid. Buffering of hydrogen ions by the intracellular bicarbonate buffer system would generate carbon dioxide by the equilibrium relationship $\text{H}^+ + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2$. Since myocardial blood flow is decreased under ischemic conditions, the decreased washout of metabolic end products would cause tissue carbon dioxide tension to rise.

Intracoronary pressure has been shown to decrease 30-40 mmHg across a flow-limiting, but not a flow-reducing, coronary stenosis (12). Thus, the pressure perfusing the myocardium distal to such a stenosis would be 30-40 mmHg lower than the pressure in an unstenosed coronary artery. The addition of atrial pacing and its associated decrease in diastolic time per minute would tend to further comprise the perfusion of the deeper myocardial layers that are critically dependent on diastolic coronary flow. The combination, therefore, of a decreased intracoronary perfusion pressure and a decreased time for diastolic coronary flow would put subendocardial layers distal to a critical stenosis at greater risk of developing ischemia during atrial pacing.

Although atrial pacing does not result in an increase
in total flow to the region of myocardium supplied by a critically stenosed artery, a redistribution of flow was observed, with subepicardial layers receiving increased flow and subendocardial layers receiving decreased flow. The increase in flow to subepicardial layers would suggest that further dilation of the resistance vessels in this layer was possible. Moreover, it is possible that resistance vessels in deeper subendocardial layers distal to a critical stenosis are already maximally dilated prior to the initiation of pacing. The decrease in flow observed in the deeper subendocardial layers during pacing might, therefore, be explained by the inability of resistance vessels in deeper layers to dilate further in the face of a fall in vascular resistance in the more superficial vessels. An alternative explanation for this redistribution of blood flow would be a greater increase in vascular resistance in deeper, compared to superficial, myocardial layers during pacing. The mean vascular resistance in subendocardial layers would increase during pacing due to increased systolic time per minute. The rise in resistance could result in an increase in intracoronary pressure distal to the stenosis, which in turn could cause passive dilation of epicardial vessels and thereby increase subepicardial flow.

A similar redistribution of coronary flow has been demonstrated distal to a totally ligated coronary artery (3), and, during atrial pacing distal to a coronary stenosis that reduced coronary flow by 50% (13). The degree of stenosis employed in this latter study was considerably more severe than that employed in the present study. Redistribution of coronary flow distal to a stenosis of severity, more comparable to that used in the present study, has recently been reported during exercise (2) and during reactive hyperemia (1) in awake dogs.

Metabolic studies have confirmed the development of greater degrees of ischemia in deeper, compared to more superficial, myocardial layers. In the distribution of a coronary stenosis that reduced flow by 50%, a gradient in myocardial lactate concentration was found (8). Distal to a coronary constriction more comparable to that employed in the present study, infusion of isoproterenol resulted in a greater increase in the lactate-to-pyruvate ratio and a greater increase in the lactate concentration in subendocardial compared to subepicardial layers (9).

In summary, the results of the present study demonstrate that atrial pacing results in the development of regional myocardial ischemia, evidenced by characteristic changes in myocardial gas tensions when measured by mass spectrometry, in the distribution of a critically stenosed coronary artery. The increase in myocardial carbon dioxide tension is likely the result of decreased washout as well as increased production of the end products of anaerobic metabolism. These data also suggest that myocardial carbon dioxide and oxygen tensions, measured during atrial pacing in regions supplied by coronary arteries with flow-limiting coronary stenoses, provide a useful quantitative indicator of regional myocardial ischemia. The model employed in the present study should prove useful for future work on the pathophysiology of regional myocardial ischemia and the mechanisms by which pharmacologic and hemodynamic therapies relieve the ischemic process.

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