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 (Pm\(_{\text{CO}_2}\)) and oxygen tension (Pm\(_{\text{O}_2}\)) measured by mass spectrometry have been shown to provide a useful indicator of the severity of regional myocardial ischemia (10). The present study utilized mass spectrometry to assess the severity of regional myocardial ischemia developing during atrial pacing in the presence of a flow-limiting proximal critical coronary artery stenosis. Myocardial blood flow (MBF) to subepicardial and subendocardial layers was measured by the radioisotope microsphere technique. Application of a "critical stenosis" resulted in a 6-mmHg decrease in Pm\(_{\text{O}_2}\), and a 17-mmHg increase in Pm\(_{\text{CO}_2}\), in the region of the myocardium supplied by the stenosed vessel. The addition of atrial pacing resulted in a 3-mmHg further decrease in Pm\(_{\text{O}_2}\), and a 40-mmHg further increase in Pm\(_{\text{CO}_2}\). In the region of myocardium supplied by the critically stenosed vessel MBF increased in the subepicardial layer, but decreased or remained unchanged in the subendocardial layer. The failure of myocardial blood flow to increase in deeper myocardial layers in response to the increased myocardial oxygen demand of atrial pacing provided a mechanism for the development of subendocardial ischemia in the presence of a critical coronary stenosis.

MATERIALS AND METHODS

Ten dogs, weighing 20–25 kg were anesthetized with \(\alpha\)-choloralose, 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 coronary blood flow; myocardial oxygen tension; regional myocardial ischemia; myocardial carbon dioxide tension; mass spectrometry; radioactive microspheres

Myocardial carbon dioxide tension as measured by mass spectrometry has been shown to provide a useful indicator of the severity of regional ischemia induced by progressive reduction of coronary blood flow (10). Regional ischemia can also be induced distal to a hemodynamically significant coronary artery stenosis by increasing myocardial oxygen demands with atrial pacing. A coronary stenosis that prevents coronary flow from increasing after a hyperemic stimulus and yet results in little or no reduction in mean flow has been defined as a critical stenosis. This degree of stenosis has been shown to correspond angiographically to a 65–75% lumen

The present study was designed to test the hypothesis that during atrial pacing myocardial carbon dioxide tension in a region supplied by a coronary artery with a critical stenosis will 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.
minutes after insertion of the mass spectrometer probes, control measurements of myocardial oxygen tension (Pm_o2) and myocardial carbon dioxide tension (Pm_co2) 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, Pm_o2 and Pm_co2 were remeasured in the regions supplied by the CCA and LAD. One to two million radioactive microspheres labeled with 141-cerium were then injected by 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, Pm_o2 and Pm_co2 were again recorded in the myocardium supplied by the unconstricted LAD and the constricted CCA. One to two million radioactive microspheres labeled with strontium-85 were then injected 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, Pm_o2 and Pm_co2 were again recorded in the myocardium supplied by the unconstricted LAD and the constricted CCA. One to two million radioactive microspheres labeled with stron- tum-85 were then injected and also the probes placed in the region of the CCA.

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 mmHg 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>Eqtn No.</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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<tbody>
<tr>
<td></td>
<td>Endo</td>
<td>Epi</td>
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<td>97</td>
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</tr>
</tbody>
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Mean 126 ± 118 111 ± 59 128 ± 103 133 ± 171 123 ± 29 217 ± 22 NS < .05

Control region, supplied by the nonstenosed anterior descending coronary artery. Ischemic region, supplied by the stenosed circumflex coronary artery. Abbreviations: LV, left ventricle. Endo, endocardial half of myocardium. Epi, epicardial 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 un

![FIG. 1. Regional myocardial carbon dioxide (PmCO₂) tensions with critical stenosis at resting heart rates and with atrial pacing.](http://ajpheart.physiology.org/)

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-line 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, oxygen 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 \( H^+ + HCO_3^- \rightarrow H_2O + CO_2 \). 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 compromise 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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REFERENCES


