Effects of Inotropic and Chronotropic Stimuli on Acute Myocardial Ischemic Injury

I. Studies with Dobutamine in the Anesthetized Dog

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SUMMARY The effect of i.v. dobutamine on acute myocardial ischemic injury was assessed in 22 anesthetized dogs subjected to serial 10-minute occlusions of the left anterior descending coronary artery. The severity of ischemic injury was determined by mass spectrometric measurement of the increase in intramural carbon dioxide tension (ΔPmCO2) in the ischemic zone. In the nine protocol 1 dogs, dobutamine, 20 μg/kg/min, infused between the control and final occlusion, significantly increased both heart rate (HR) and left ventricular (LV) dp/dt; ΔPmCO2 was significantly higher during the dobutamine infusion than during control occlusion (76 ± 21 vs 56 ± 13 mm Hg, p < 0.01). The nine protocol 2 dogs were atrially paced at a HR of 20–30 beats/min above baseline values during the control occlusion and received dobutamine (12.6 ± 7.8 μg/kg/min) at doses necessary to attain an equal HR (mean 149–154 beats/min) during the last occlusion. Although LV dp/dt was higher after dobutamine, ΔPmCO2 was similar during the two occlusions. Protocol 3 dogs (n = 4) received lower doses of dobutamine (5.6 ± 3.2 μg/kg/min) to produce an increase in LV dp/dt, but not in HR compared with baseline values; ΔPmCO2 was similar during control and dobutamine occlusions. There were no major changes in arterial or venous pressures. Rate-pressure product, an indirect measurement of myocardial oxygen consumption, was increased only by the higher doses of dobutamine in protocol 1.

Thus, inotropic stimulation with dobutamine during coronary occlusion does not cause important augmentation of acute myocardial ischemic injury in the nonfailing heart unless HR is increased simultaneously.

THE SEVERITY of evolving acute myocardial ischemic injury can be influenced by interventions performed before or shortly after experimental coronary artery occlusion.1 Pharmacologic agents and hemodynamic alterations can affect ischemic injury. Although most reports deal with interventions that lessen myocardial ischemic injury, certain interventions can intensify ischemia or increase infarct size.2-4 Even though the role of specific therapy to protect ischemic myocardium in the patient with evolving acute myocardial infarction is not clear, it is widely held that interventions that augment ischemic injury in experimental animals should be avoided in patients with myocardial ischemic syndromes.5, 6

Most deleterious influences on evolving ischemic damage are thought to be mediated by further alterations in the relationship between myocardial oxygen supply and demand in ischemic tissue. An already compromised oxygen supply to the ischemic zone can be further decreased by reduction in myocardial perfusion pressure, preferential shunting of blood to non-ischemic tissue, or a decrease in blood oxygen content. Myocardial oxygen demand can be heightened by increasing heart rate, contractile state, or left ventricular (LV) wall tension.11 Because many studies that showed augmentation of ischemic injury used interventions that simultaneously alter several determinants of myocardial oxygen demand or supply or both, we investigated whether deleterious effects on ischemic damage also result from more selective alterations in these hemodynamic variables.

Methods

Twenty-two mongrel dogs that weighed 17–44 kg were anesthetized with i.v. pentobarbital, 30 mg/kg, intubated with a cuffed endotracheal tube, and ventilated with room air by Harvard respirator. A left thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. The midportion of the left anterior descending coronary artery (LAD) or the proximal portion of its major diagonal branch was dissected free so that temporary coronary artery occlusion could be performed with a silk suture snare. The left jugular vein, left carotid artery and left atrium were cannulated with polyethylene catheters, and a catheter-tip micromanometer (Konigsberg P22) was inserted into the left ventricle through the cardiac apex. A 22-gauge stainless-steel tissue mass spectrometer probe (Chemotron 40-22-1052) with a 1.5-cm Teflon-coated sensing surface at its distal end was inserted into the LV myocardium through a small epicardial incision. The sensing surface was embedded intramurally at a midmyocardial level in the region that showed epicardial cyanosis after a 10–15-second occlusion of the LAD.7, 8 In all instances, the sensing site was at least 4 cm from entry site of the LV apical catheter. The mass spectrometer probes were calibrated before and after each use by exposure to known oxygen and carbon dioxide tensions in a water
tonometer. In nine dogs, bipolar pacing electrodes were sutured onto the right atrium and atrial pacing at a desired rate was performed with a Grass S-88 stimulator.

 Hemodynamic measurements (phasic and mean arterial and left atrial mean pressures, maximal rate of increase in LV intracavitary pressure [LV dP/dt]), and a lead II ECG (for measurement of heart rate) were recorded on a multichannel physiologic recorder (Electronics for Medicine Model VR-12 or DR-8). Reported values for these measurements represent an average from 10 cardiac cycles. The product of heart rate and systolic pressure, an indirect estimate of myocardial oxygen consumption, was calculated and expressed as mm Hg/min × 10\(^3\). Intramyocardial partial pressures of carbon dioxide (PM\(_{\text{CO}_2}\)) and oxygen (PM\(_{\text{O}_2}\)) were measured with a mass spectrometer (Perkin Elmer 1100B) and recorded on an accessory physiologic recorder (Hewlett-Packard model 7754-A) at a paper speed of 0.25 mm/sec.

 Regional myocardial blood flow (RMBF) was determined by the radioactive microsphere technique. Two to 6 million microspheres, 8–10 µm in diameter, were suspended in 0.05% Tween-80 solution and vigorously agitated before injection into the left atrium over 10–15 seconds. Arterial reference samples were obtained from the carotid artery catheter from 15 seconds before through 90 seconds after the start of microsphere injection by constant withdrawal at a rate of 7.75 ml/min with a Harvard pump. Microspheres labeled with \(^{99}\)Sc, \(^{85}\)Sr, \(^{86}\)Nb, \(^{125}\)I (3M Company), \(^{113}\)Sn or \(^{15}\)CO (New England Nuclear) were injected in random order to measure RMBF at four predetermined points in each protocol. Transmural samples of myocardial tissue (average weight 3.77 g) surrounding the mass spectrometer probe and subjacent to the zone of epicardial cyanosis during coronary occlusion were excised after sacrifice of the dog and divided into subendocardial and subepicardial halves. RMBF from these sites, whether measured during control periods or during coronary occlusion, is reported as RMBF\(_{\text{PROBE}}\). Three transmural specimens (average weight 3.12 g) were similarly excised from the nonischemic posterolateral LV wall of each dog, and the average RMBF from both subendocardial and subepicardial halves of these specimens is reported as RMBF\(_{\text{NORMAL}}\) for each dog. Standard, tissue and arterial reference samples were counted in a Packard multichannel gamma scintillation counter with appropriate window settings for each isotope, and after background and energy-crossover corrections, RMBF was calculated by the method of Heymann et al. and expressed in milliliters per gram of myocardial tissue per minute.

 **Experimental Protocol**

 A 10-minute test LAD occlusion was performed to ensure proper function of the in situ mass spectrometer probe and the stability of the preparation. Forty-five minutes after coronary reperfusion, a second 10-minute occlusion was carried out. Heart rate (at either the natural or an atrially paced rate), arterial phasic and mean and left atrial mean pressures, LV dP/dt and RMBF were measured 2 minutes before and 7 minutes after this occlusion; intramyocardial gas tensions were measured continuously. Thirty minutes after abrupt coronary reperfusion, heart rate, pressures and LV dP/dt were again measured, and a continuous infusion of dobutamine was begun and maintained at the same rate during a third 10-minute coronary occlusion performed 15 minutes after the institution of dobutamine. Hemodynamic measurements, including RMBF, were made 2 minutes before and 7 minutes after the beginning of this third coronary occlusion; dobutamine was abruptly discontinued at the time of coronary reperfusion.

 Protocol 1 experiments (n = 9) were designed to assess the effects on acute myocardial ischemic injury of a fixed dose of dobutamine (20 µg/kg/min) known to increase both heart rate and LV contractility. Thus, changes in PM\(_{\text{CO}_2}\) at a baseline chronotropic and inotropic state during the second (control) occlusion were compared with those during the third coronary occlusion while this fixed dose of dobutamine was infused.

 Protocol 2 experiments (n = 9) were designed to compare the effects on acute myocardial ischemic injury of a chronotropically and inotropically effective dose of dobutamine with those of equichronotropic atrial pacing. Accordingly, atrial pacing to a heart rate of 20–30 beats/min above baseline was begun 15 minutes before the second occlusion and was terminated abruptly at the time of coronary reperfusion. Fifteen minutes before the third coronary occlusion, dobutamine was begun at an infusion rate necessary to achieve the heart rate produced by atrial pacing during the prior occlusion. Dobutamine also was discontinued abruptly at the end of the third coronary occlusion.

 Protocol 3 experiments (n = 4) were designed to assess the effect on acute ischemic injury of a dose of dobutamine that produced inotropic stimulation but did not alter heart rate. Accordingly, the second coronary occlusion was performed as in protocol 1 (without chronotropic stimulation). After 30 minutes of recovery, dobutamine was infused at variable rates, such that at the time of the third coronary occlusion, the dog was receiving the highest dose of dobutamine that resulted in a positive inotropic effect (judged by LV dP/dt) without an increase in heart rate. Dobutamine was discontinued abruptly at the end of the third coronary occlusion, and the changes in PM\(_{\text{CO}_2}\) resulting from the second and third coronary occlusions were compared.

 **Assessment of Myocardial Ischemic Injury by PM\(_{\text{CO}_2}\)**

 The severity of acute myocardial ischemic injury for the two experimental coronary occlusions (occlusions 2 and 3) is expressed as the magnitude of the increase in PM\(_{\text{CO}_2}\)=P, i.e., the difference between preocclusion and peak postocclusion values of PM\(_{\text{CO}_2}\). This quantity (\(\Delta\)PM\(_{\text{CO}_2}\)) is reproducible between the second and third of three serial 10-minute coronary occlusions with intervening 45-minute periods of coronary reper-
fused.\textsuperscript{7, 9} Furthermore, $\Delta Pm_{CO_2}$ correlates with increase in intramyocardial hydrogen ion concentration,\textsuperscript{17} with the severity of reduction in RMBF to the ischemic zone, and with ultimate tissue necrosis resulting from more prolonged coronary occlusion.\textsuperscript{18} Interventions that lessen ischemic injury reduce $\Delta Pm_{CO_2}$\textsuperscript{7, 9, 19-21} while pharmacologic agents that worsen ischemic damage increase it.\textsuperscript{7, 9}

Values for $Pm_{O_2}$ from each measurement point are also reported. Occlusion values represent the lowest $Pm_{O_2}$ resulting from that ischemic episode. Changes in $Pm_{O_2}$ are not thought to reflect alterations in ischemic injury.\textsuperscript{7, 21}

Data Analysis

All group data are presented as the mean $\pm$ sd. Data from multiple time periods in protocols 1 and 2 were compared by analysis of variance for repeated measures followed by the Newman-Keuls multiple-range test.\textsuperscript{22} Because of the small number of observations in protocol 3, data from multiple time periods were analyzed nonparametrically by Friedman’s chi-square test followed by the multiple-comparison procedure.\textsuperscript{23} Comparison of $\Delta Pm_{CO_2}$ between the second and third coronary occlusions from all protocols was performed by $t$ test for paired data. A two-tailed $p$ value $< 0.05$ was required from all tests for inference of statistical differences.

Results

Protocol 1

Hemodynamic data from control periods and the two experimental coronary occlusions in protocol 1 dogs are presented in table 1. Heart rate averaged 21-34 beats/min higher after dobutamine infusion than at previous measurement points ($p < 0.001$), and LV $dP/dt$ was similarly increased (average 51-77%, $p < 0.001$) after inotropic stimulation with dobutamine before and during the third coronary occlusion. Systolic arterial pressure was higher ($p < 0.01$) after dobutamine infusion, but decreased during the third occlusion to a level not significantly different from measurement points before dobutamine. Arterial diastolic and mean and left atrial mean pressures were not significantly altered during the experiments, but the calculated rate-pressure product was increased significantly ($p < 0.01$) by dobutamine infusion before the final occlusion.

RMBF$_{PROBE}$ to subendocardial tissue decreased from 0.57 $\pm$ 0.19 to 0.13 $\pm$ 0.13 ml/g/min with the second occlusion ($p < 0.05$); after dobutamine infusion, subendocardial RMBF$_{PROBE}$ with the third occlusion decreased from 1.02 $\pm$ 0.60 to 0.24 $\pm$ 0.25 ml/g/min ($p < 0.01$). Subepicardial flow to ischemic tissue tended to be higher during the third than during the control occlusion (0.43 $\pm$ 0.52 vs 0.23 $\pm$ 0.21 ml/g/min), but these values were not statistically different. Although both subepicardial and subendocardial RMBF$_{NORMAL}$ tended to be higher after dobutamine, there were no statistically significant changes in these measurements in protocol 1 dogs.

Changes in $Pm_{CO_2}$ for the two experimental coronary occlusions in protocol 1 dogs are presented in table 1 and figure 1. During the dobutamine infusion, $\Delta Pm_{CO_2}$ was significantly greater (76 $\pm$ 21 and 56 $\pm$ 13 mm Hg for occlusions 3 and 2, respectively, $p < 0.01$), indicating more intense ischemic damage during the third occlusion. $Pm_{O_2}$ decreased to similar nadir values (2 $\pm$ 2 mm Hg) during the second and third occlusions.

Protocol 2

Hemodynamic data from control periods and the experimental coronary occlusions in protocol 2 dogs are presented in table 2. Equivalent heart rates (mean 149-154 beats/min) were attained by atrial pacing before and during the second occlusion and by variable doses of dobutamine (12.6 $\pm$ 7.8 $\mu$g/kg/min) before and during the third occlusion. LV $dP/dt$ was similar before and after atrial pacing, but was increased by an average of 41-82% after dobutamine infusion ($p < 0.001$ vs values before dobutamine). Arterial systolic, diastolic and mean pressures, left atrial mean pressure and rate-pressure product were not altered significantly during the experiments.

Subendocardial RMBF$_{PROBE}$ decreased to similar levels (0.31 $\pm$ 0.18 and 0.32 $\pm$ 0.15 ml/g/min during the second and third occlusions, respectively), as did subepicardial RMBF$_{PROBE}$ (0.60 $\pm$ 0.26 and 0.53 $\pm$ 0.14 ml/g/min for the two occlusions, respectively). Preocclusion subendocardial and subepicardial RMBF$_{PROBE}$ and RMBF$_{NORMAL}$ tended to be higher after dobutamine infusion than after equichronotropic atrial pacing ($p < 0.05$ for all sites except normal subendocardium).

Changes in $Pm_{CO_2}$ during coronary occlusion in protocol 2 dogs are presented in table 2 and figure 1. There was no significant difference between $\Delta Pm_{CO_2}$ during the control (58 $\pm$ 18 mm Hg) and third occlusions (61 $\pm$ 23 mm Hg). $Pm_{O_2}$ decreased similarly, to 6 $\pm$ 8 and 4 $\pm$ 4 mm Hg during occlusions 2 and 3, respectively.

Protocol 3

Although the small number of experiments in this protocol precludes extensive statistical analysis, the group data (table 3) indicate that heart rate was not increased by variable doses of dobutamine (average 5.6 $\pm$ 3.2 $\mu$g/kg/min) administered before and during the third coronary occlusion, and that there were no major alterations in arterial and left atrial pressures throughout the experiments. LV $dP/dt$ increased in each dog after dobutamine (average 67%, $p < 0.05$), while rate-pressure product did not change importantly. There was no significant difference between $\Delta Pm_{CO_2}$ during the second (55 $\pm$ 9 mm Hg) and third (49 $\pm$ 4 mm Hg) coronary occlusions (fig. 1).

Discussion

These studies show that constant infusion of a relatively high and fixed dose of dobutamine (20 $\mu$g/kg/min, protocol 1) before and during temporary
**Table 1. Hemodynamic Data and Intramyocardial Gas Tensions in Protocol 1 Dogs**

<table>
<thead>
<tr>
<th>Time period</th>
<th>1. Before CAO 2</th>
<th>2. CAO 2</th>
<th>3. Before DOB infusion</th>
<th>4. Before CAO 3 (DOB, 20 µg/kg/min)</th>
<th>5. CAO 3 (DOB, 20 µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>119 ± 19</td>
<td>124 ± 19</td>
<td>121 ± 17</td>
<td>153 ± 19*</td>
<td>145 ± 17*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>114 ± 18</td>
<td>111 ± 13</td>
<td>114 ± 10</td>
<td>133 ± 25†</td>
<td>123 ± 28</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>85 ± 20</td>
<td>84 ± 16</td>
<td>88 ± 17</td>
<td>90 ± 21</td>
<td>88 ± 22</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>98 ± 19</td>
<td>96 ± 15</td>
<td>98 ± 15</td>
<td>104 ± 21</td>
<td>100 ± 20</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>5 ± 2</td>
<td>7 ± 3</td>
<td>8 ± 4</td>
<td>8 ± 4</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2471 ± 1330</td>
<td>2301 ± 1361</td>
<td>2379 ± 1071</td>
<td>4065 ± 1770*</td>
<td>3720 ± 1609*</td>
</tr>
<tr>
<td>RPP (mm Hg/min × 10^4)</td>
<td>13.6 ± 3.0</td>
<td>13.8 ± 2.9</td>
<td>13.7 ± 1.9</td>
<td>20.3 ± 4.5†</td>
<td>17.9 ± 4.9</td>
</tr>
<tr>
<td>RMBF&lt;sub&gt;PROBE&lt;/sub&gt; (ml/g/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>0.84 ± 0.51</td>
<td>0.23 ± 0.21</td>
<td>—</td>
<td>1.65 ± 1.13†</td>
<td>0.43 ± 0.52§</td>
</tr>
<tr>
<td>Endo</td>
<td>0.57 ± 0.19</td>
<td>0.13 ± 0.13¶</td>
<td>—</td>
<td>1.02 ± 0.60‡</td>
<td>0.24 ± 0.25§</td>
</tr>
<tr>
<td>RMBF&lt;sub&gt;NORMAL&lt;/sub&gt; (ml/g/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>0.82 ± 0.44</td>
<td>0.93 ± 0.51</td>
<td>—</td>
<td>1.47 ± 0.77</td>
<td>1.35 ± 0.71</td>
</tr>
<tr>
<td>Endo</td>
<td>0.78 ± 0.30</td>
<td>0.92 ± 0.44</td>
<td>—</td>
<td>1.34 ± 0.65</td>
<td>1.20 ± 0.48</td>
</tr>
<tr>
<td>Ischemic zone Pmco₂ (mm Hg)</td>
<td>11 ± 6</td>
<td>2 ± 2**</td>
<td>11 ± 4</td>
<td>13 ± 4</td>
<td>2 ± 2**</td>
</tr>
<tr>
<td>Ischemic zone Pmco₂ (mm Hg)</td>
<td>29 ± 8</td>
<td>85 ± 17†</td>
<td>28 ± 7</td>
<td>30 ± 8</td>
<td>106 ± 24†</td>
</tr>
</tbody>
</table>

Values are mean ± SD; n = 9 for all measurements except RMBF, where n = 7.

* Time periods 4 and 5 different from 1–3 (p < 0.001).
† Time period 4 different from all others except 5 (p < 0.01).
‡ Time period 4 different from all others (p < 0.01).
§ p < 0.01 vs preoclusion value.
¶ p < 0.05 vs preoclusion value.
** Time periods 2 and 5 different from all others (p < 0.005).
†† Time periods 2 and 5 different from all others and from each other (p < 0.001).

Abbreviations: CAO = coronary artery occlusion; DOB = dobutamine; HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; LAP = left atrial mean pressure; LV dP/dt = maximal rate of rise of left ventricular pressure; RPP = rate-pressure product; Epi = subepicardium; Endo = subendocardium; Pmco₂ = intramyocardial oxygen tension; Pmco₂ = intramyocardial carbon dioxide tension; RMBF = regional myocardial blood flow. See text for explanation of RMBF<sub>PROBE</sub> and RMBF<sub>NORMAL</sub>.

**Figure 1. Magnitude of rise of intramural carbon dioxide tension (ΔPmco₂) after the second (2) and third (3) of serial 10-minute coronary artery occlusions for individual dogs in protocols 1, 2 and 3. Bars represent the mean ± SD. DOB = dobutamine; HR = heart rate. *p < 0.01.**
### Table 2. Hemodynamic Data and Intramyocardial Gas Tensions in Protocol 2 Dogs

<table>
<thead>
<tr>
<th></th>
<th>1. Before CAO 2 (atrial pacing)</th>
<th>2. CAO 2 (atrial pacing)</th>
<th>3. Before DOB infusion</th>
<th>4. Before CAO 3 (DOB, 12.6 ± 7.8 μg/kg/min)</th>
<th>5. CAO 3 (DOB, 12.6 ± 7.8 μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>154 ± 24</td>
<td>154 ± 24</td>
<td>131 ± 22*</td>
<td>149 ± 21</td>
<td>151 ± 19</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>125 ± 26</td>
<td>125 ± 27</td>
<td>121 ± 23</td>
<td>135 ± 31</td>
<td>126 ± 21</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>101 ± 22</td>
<td>101 ± 25</td>
<td>102 ± 26</td>
<td>106 ± 30</td>
<td>100 ± 21</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>111 ± 25</td>
<td>112 ± 26</td>
<td>109 ± 28</td>
<td>121 ± 31</td>
<td>113 ± 23</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>7 ± 4</td>
<td>7 ± 3</td>
<td>6 ± 2</td>
<td>7 ± 3</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>1878 ± 650</td>
<td>1760 ± 624</td>
<td>1569 ± 526</td>
<td>2855 ± 1072†</td>
<td>2651 ± 935†</td>
</tr>
<tr>
<td>RPP (mm Hg/min × 10³)</td>
<td>19.3 ± 5.4</td>
<td>19.1 ± 5.1</td>
<td>15.6 ± 2.8</td>
<td>18.7 ± 4.6</td>
<td>19.0 ± 3.5</td>
</tr>
<tr>
<td>RMBFProbe (ml/g/min)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Epi</td>
<td>1.57 ± 0.87</td>
<td>0.60 ± 0.26†</td>
<td>—</td>
<td>2.39 ± 0.22†</td>
<td>0.53 ± 0.14†</td>
</tr>
<tr>
<td>Endo</td>
<td>0.96 ± 0.60</td>
<td>0.31 ± 0.18</td>
<td>—</td>
<td>1.77 ± 0.75§</td>
<td>0.32 ± 0.15§</td>
</tr>
<tr>
<td>RMBFNormal (ml/g/min)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Epi</td>
<td>1.31 ± 0.68</td>
<td>1.37 ± 0.73</td>
<td>—</td>
<td>2.80 ± 0.74§</td>
<td>1.41 ± 0.66</td>
</tr>
<tr>
<td>Endo</td>
<td>1.39 ± 0.58</td>
<td>1.30 ± 0.56</td>
<td>—</td>
<td>2.21 ± 0.81</td>
<td>1.17 ± 0.48</td>
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<tr>
<td>Ischemic zone PmO₂ (mm Hg)</td>
<td>13 ± 4</td>
<td>6 ± 8¶</td>
<td>18 ± 7</td>
<td>14 ± 5</td>
<td>4 ± 4¶</td>
</tr>
<tr>
<td>Ischemic zone PmCO₂ (mm Hg)</td>
<td>29 ± 8</td>
<td>88 ± 26**</td>
<td>34 ± 10</td>
<td>32 ± 9</td>
<td>93 ± 30**</td>
</tr>
</tbody>
</table>

Values are mean ± SD; n = 9 for all measurements except RMBF, where n = 5.
*Time period 3 different from all others (p < 0.01).
†Time periods 4 and 5 different from 1-3 (p < 0.001).
‡p < 0.01 vs precollision value.
§Time period 3 different from all others (p < 0.05).
¶Time periods 2 and 5 different from all others (p < 0.05).
**Time period 2 and 5 different from all others (p < 0.001).
Abbreviations: See Table 1.

### Table 3. Hemodynamic Data and Intramyocardial Gas Tensions in Protocol 3 Dogs

<table>
<thead>
<tr>
<th></th>
<th>1. Before CAO 2</th>
<th>2. CAO 2</th>
<th>3. Before DOB infusion</th>
<th>4. Before CAO 3 (DOB, 5.6 ± 3.2 μg/kg/min)</th>
<th>5. CAO 3 (DOB, 5.6 ± 3.2 μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>132 ± 7</td>
<td>136 ± 19</td>
<td>129 ± 6</td>
<td>129 ± 6</td>
<td>129 ± 7</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>137 ± 10</td>
<td>127 ± 14</td>
<td>127 ± 14</td>
<td>138 ± 13</td>
<td>128 ± 10</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>106 ± 10</td>
<td>98 ± 15</td>
<td>92 ± 22</td>
<td>111 ± 2</td>
<td>100 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>117 ± 9</td>
<td>113 ± 14</td>
<td>114 ± 5</td>
<td>120 ± 7</td>
<td>115 ± 9</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>10 ± 6</td>
<td>11 ± 4</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>1976 ± 1009</td>
<td>1828 ± 772</td>
<td>1662 ± 765</td>
<td>2783 ± 1669*</td>
<td>2476 ± 1669</td>
</tr>
<tr>
<td>RPP (mm Hg/min × 10³)</td>
<td>17.9 ± 0.5</td>
<td>17.2 ± 0.4</td>
<td>16.2 ± 1.5</td>
<td>17.7 ± 0.9</td>
<td>16.5 ± 0.9</td>
</tr>
<tr>
<td>RMBFProbe (ml/g/min)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Epi</td>
<td>1.25 ± 0.83</td>
<td>0.31 ± 0.19</td>
<td>—</td>
<td>0.94 ± 0.33</td>
<td>0.21 ± 0.14</td>
</tr>
<tr>
<td>Endo</td>
<td>0.96 ± 0.73</td>
<td>0.20 ± 0.12</td>
<td>—</td>
<td>0.58 ± 0.26</td>
<td>0.14 ± 0.08</td>
</tr>
<tr>
<td>RMBFNormal (ml/g/min)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Epi</td>
<td>0.93 ± 0.45</td>
<td>0.90 ± 0.26</td>
<td>—</td>
<td>0.77 ± 0.24</td>
<td>0.70 ± 0.39</td>
</tr>
<tr>
<td>Endo</td>
<td>0.84 ± 0.25</td>
<td>0.87 ± 0.20</td>
<td>—</td>
<td>0.70 ± 0.10</td>
<td>0.61 ± 0.35</td>
</tr>
<tr>
<td>Ischemic zone PmO₂ (mm Hg)</td>
<td>15 ± 1</td>
<td>2 ± 2†</td>
<td>18 ± 3</td>
<td>21 ± 5</td>
<td>7 ± 6†</td>
</tr>
<tr>
<td>Ischemic zone PmCO₂ (mm Hg)</td>
<td>33 ± 5</td>
<td>87 ± 9†</td>
<td>30 ± 7</td>
<td>30 ± 6</td>
<td>79 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SD; n = 4 for all measurements.
*Time period 3 and 4 different (p < 0.05).
†Time periods 2 and 5 different from 4 (p < 0.05).
‡Time period 2 different from 3 and 4 (p < 0.05).
Abbreviations: See Table 1.
coronary occlusion augments acute myocardial ischemic injury in the barbiturate-anesthetized dog (table 1, fig. 1). Both heart rate and LV contractility (LV dP/dt) were significantly higher during coronary occlusion with dobutamine than during the control occlusion. However, the protocol 2 experiments show that when heart rate is similarly elevated during both a control coronary occlusion and one during infusion of dobutamine (12.6 ± 7.8 µg/kg/min), the selective augmentation of inotropic state effected by dobutamine is not necessarily associated with worsening of ischemic damage (table 2, fig. 1). Protocol 3 experiments indicate that lower doses of dobutamine (5.6 ± 3.2 µg/kg/min), which do not increase heart rate, can also augment LV dP/dt without worsening acute ischemic injury.

In early studies of the effects of inotropic stimuli on acute ischemic injury in the barbiturate-anesthetized dog without congestive heart failure, epicardial ST-segment elevation was used as an index of the severity of ischemic damage. Isoproterenol and glucagon, at doses that doubtlessly increased LV contractility, augmented ischemic zone ST-segment elevation during coronary artery occlusion. In these studies, atrial pacing produced less augmentation of ST-segment elevation than equichronotropic doses of isoproterenol, and the deleterious effects of glucagon were also partially mitigated when heart rate was maintained constant by atrial pacing. A study from our laboratory showed that dobutamine (20 µg/kg/min) increased both heart rate and LV dP/dt in the anesthetized dog, and resulted in augmentation of ischemic zone epicardial ST-segment elevation during coronary occlusion; a lower dose of this agent (4 µg/kg/min), which raised heart rate only by 5-10 beats/min, did not augment ischemic damage despite a positive inotropic effect. Ramanathan et al. also showed that the inotropic stimulant dopamine, at doses that do not accelerate heart rate, does not augment ischemic zone ST-segment elevation.

A dissociation of the deleterious effects of increases in heart rate and LV contractility was also noted by Vatner and Baig in conscious dogs subjected to coronary occlusion. Isoproterenol, in doses that increased heart rate and LV contractility, decreased ischemic zone segmental shortening and blood flow, while dobutamine and dopamine, at doses that increased LV dP/dt, did not further reduce ischemic zone contractile function or blood flow when heart rate was not increased. These investigators also found that ouabain given to chronically instrumented conscious dogs with temporary coronary occlusion led to an increase in LV dP/dt without a change in heart rate and improved systolic segment shortening, blood flow and ST-segment deviation in the ischemic zone. Isoproterenol, in equinotropics doses that augmented heart rate, produced opposite effects on these indexes of ischemic severity. In further support of the concept that inotropic stimulation need not worsen ischemic damage, Liang et al. reported an actual decrease in ultimate infarct size in conscious dogs subjected to coronary occlusion and dobutamine infusion (20 µg/kg/min) compared with saline-treated controls; increased LV contractile state and global myocardial oxygen consumption, but only a slight increase in heart rate (< 10 beats/min) were documented in the dobutamine-treated dogs soon after coronary occlusion.

Unlike measurements of myocardial wall motion, which may be affected by changes in loading conditions of the ventricle, or electrocardiographic ST-segment alterations, which depend on electrode position and multiple ionic influences, measurements of changes in intramyocardial gas tensions before and during coronary occlusion offers a direct reflection of the metabolic impact of all components of the ischemic insult. Carbon dioxide is thought to accumulate in ischemic myocardium because of enhanced production (by generation from HCO₃ in the presence of regional acidosis) and decreased clearance by regional blood flow. Indeed, the increase in Pmco₂ with coronary occlusion correlates directly with interstitial hydrogen ion concentration in ischemic tissue, as well as with the magnitude of ST-segment elevation measured by intramyocardial unipolar electrodes and with ultimate morphologic evidence of necrosis after prolonged coronary occlusion.

The absolute magnitude of ΔPmco₂ with coronary occlusion is a reproducible characteristic of the second and third of a series of 10-minute LAD occlusions in the pentobarbital-anesthetized dog. It is not clear why ΔPmco₂ is higher with the first coronary occlusion, although persistent depressions in heart rate and LV contractility after the first occlusion may account for this observation. Interventions (propranolol, hyaluronidase, and nitroglycerin) known to reduce ischemic damage decrease ΔPmco₂ when given before the third coronary occlusion. Isoproterenol, at doses that increase both heart rate and contractility, augments ΔPmco₂ resulting from coronary occlusion in the nonfailing canine heart, and amrinone, a noncatecholamine, nonglycoside stimulant, also increases ischemic damage in this model. The ΔPmco₂ is of value in assessing ischemic injury; Pmco₂ is not a useful index of the severity of the ischemic insult in either the control state or with most interventions.

Although myocardial oxygen consumption was not measured in our studies, rate-pressure product measurements suggest that inotropic and chronotropic stimulation from the higher doses of dobutamine (20 µg/kg/min, protocol 1) resulted in greater myocardial oxygen demand before the third than before the second occlusion. The lack of adverse effect on ischemic damage during the third occlusions with selective augmentation in contractile state (protocols 2 and 3) might be because myocardial oxygen demands were not significantly increased, as reflected by our measurements of similar rate-pressure products throughout these protocols (tables 2 and 3). Alternatively, dobutamine might have increased oxygen delivery to the ischemic zone and compensated for any
increases in oxygen demands associated with inotropic stimulation. Although our measurements of RMBF to ischemic sites immediately surrounding the mass spectrometer probe showed no increase in collateral flow during coronary occlusion after dobutamine, other studies with more sampling sites have shown modest flow increases to ischemic myocardium.4,29 Our studies were not designed to assess possible changes in vessel-to-vessel variability in collateral blood flow at the microvascular level, which might allow greater degrees of oxygen extraction in critical areas of ischemic myocardium.29-33 or to assess changes in myocardial oxygen supply/demand relationships in ischemic myocardium.29

Studies of the effects of inotropic stimulation on acute myocardial ischemic injury would be most relevant for extrapolation to clinical cardiology if they were performed in conscious animals with multivessel coronary artery narrowing and heart failure due to the effects of multiple episodes of ischemia and infarction. Such an experimental model has not yet been developed, although Jentzer et al.24 produced LV failure in anesthetized dogs with successive coronary occlusions and showed that the inotropic stimulant amrinone improves hemodynamic markers of LV failure, but decreases global myocardial oxygen consumption and presumably, oxygen demand in ischemic myocardium. If their results are confirmed with other inotropically active agents, and if direct assessment of ischemic injury or infarct size suggests no change or an amelioration of ischemic damage during drug-induced improvement in hemodynamic abnormalities, our observations and those of Liang et al.28 and Vatner and Baig6,24 take on more relevance, because these studies were performed in nonfailing hearts in which myocardial oxygen requirements tend to be heightened, rather than reduced, by inotropic stimulation.11 Thus, the relative risks and benefits of inotropic stimulants in myocardial ischemic syndromes might need reevaluation. Gillespie et al.38 showed that dobutamine, in doses that do not increase heart rate, can improve hemodynamics considerably without increasing infarct size or exacerbating ventricular arrhythmias.

In conclusion, this study provides evidence that inotropic stimulation of the regionally ischemic canine heart with dobutamine is not associated with further intensification of myocardial ischemic injury, as assessed by measurement of PMco2, unless heart rate also increases. Moderate increases in contractile state without concomitant increases in heart rate may not be associated with important worsening of ischemia; further studies to assess alterations in myocardial ischemic damage, LV contractile state, and regional myocardial oxygen supply and demand are needed to prove this hypothesis.

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