Development of Short-term Myocardial Hibernation
Its Limitation by the Severity of Ischemia and Inotropic Stimulation

Rainer Schulz, MD; Jochen Rose; Claus Martin, PhD; Otto-Erich Brodde, PhD; Gerd Heusch, MD, FESC

Background. Short-term hibernating myocardium is characterized by a decrease in contractile function in proportion to the reduced myocardial blood flow. Myocardial creatine phosphate content, initially decreased during the first minutes of ischemia, returns to near-control values, the ischemia-induced net lactate production is attenuated, and the myocardium remains viable despite ongoing hypoperfusion and contractile dysfunction. Hibernating myocardium after 85 minutes of ischemia maintains an inotropic reserve and responds to short-term intracoronary dobutamine infusion with increased work; however, this inotropic response is at the expense of metabolic recovery. Therefore we hypothesized that the development of myocardial hibernation is a delicate process that is easily disturbed by unfavorable alterations in the oxygen-supply demand balance.

Methods and Results. To study the impact of prolonged inotropic stimulation on the development of myocardial hibernation, the left anterior descending coronary artery was cannulated and hypoperfused at constant flow in 12 enflurane-anesthetized swine. The reduction of coronary inflow was followed by a reduction of regional myocardial work (sonomicrometry) from 248±59 mm Hg·mm to 73±35 mm Hg·mm (P<.05) at 5 minutes of ischemia. Dobutamine (2.5±1 μg/min) was then infused for an additional 85 minutes. Work was increased at 5 minutes of dobutamine to 139±34 mm Hg·mm (P<.05 versus 5 minutes of ischemia). However, this increase was only transient, and after 85 minutes of dobutamine, work was decreased below the initial ischemic value (42±34 mm Hg·mm). At 5 minutes of ischemia, creatine phosphate content was reduced from 8.80±1.97 to 6.21±3.87 μmol/g wet wt, and myocardial ATP content was decreased slightly from 4.75±0.92 to 4.12±1.29 μmol/g wet wt (both, P=NS). After 5 minutes of dobutamine, further reductions in creatine phosphate content to 3.11±0.76 μmol/g wet wt and in ATP to 3.14±0.81 μmol/g wet wt were observed (both, P<.05 versus control). During the remainder of the continuous dobutamine infusion, creatine phosphate content remained unchanged, whereas ATP further decreased significantly to 1.68±0.96 μmol/g wet wt. The β-adrenoceptor density of the left anterior descending coronary artery—perfused myocardium was 36.5±5.8 fmol (−)–[125I]iodocyanopindolol/mg protein under control conditions, and this was unchanged during ischemia and the subsequent dobutamine infusion. Following 90 minutes of ischemia with 85 minutes of dobutamine and 2 hours of reperfusion, infarct size (triphenyl tetrazolium chloride staining) was 26.3±7.5% of the area at risk. With constant hypoperfusion, dobutamine redistributed blood flow away from the subendocardium (0.20±0.08 versus 0.11±0.04 mL·min⁻¹·g⁻¹) toward the subepicardium (0.45±0.13 versus 0.51±0.21 mL·min⁻¹·g⁻¹) as well as to the right ventricle (0.26±0.08 versus 0.32±0.09 mL·min⁻¹·g⁻¹). Therefore, in two other groups of six and five swine, the severity of ischemia increased to achieve an 80% or a 90% reduction in regional function, respectively, and the importance of the severity of blood flow reduction per se for the development of myocardial infarction was studied. The infarct size in the animals undergoing 85 minutes of dobutamine (26.3±7.5%) was increased above the level expected from the blood flow reduction alone (6.3±6.4%, P<.01).

Conclusions. Both the increased severity of ischemia and the enhanced energy expenditure induced by dobutamine impair the development of myocardial short-term hibernation and precipitate myocardial infarction. (Circulation 1993;88:684-695)

Key Words: ischemia • infarction • dobutamine

The extent of contractile dysfunction during acute regional myocardial ischemia closely parallels the severity of the blood flow deficit. Although the contractile dysfunction from a total coronary occlusion suggests metabolic failure and impending cell necrosis, the contractile response to more moderate ischemia can be viewed quite differently. The contractile dysfunction associated with such moderate ischemia

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may serve as a protective mechanism by which reduced myocardial energy demand due to reduced contractile work can prolong the metabolic integrity of the ischemic myocardium. Such ischemia-induced downregulation of contractile function\protectcite{5,6} is characteristic of the clinical condition referred to as “hibernating myocardium.”\protectcite{7}

During moderate ischemia, myocardial creatine phosphate content initially decreases during the first few minutes of ischemia but then returns to near-control values,\protectcite{6,8,9} and the ischemia-induced net lactate production becomes attenuated\protectcite{6,10} despite ongoing hypoperfusion and contractile dysfunction. Such short-term hibernating myocardium retains an inotropic reserve and still responds to short-term intracoronary dobutamine infusion after 85 minutes of ischemia with increased work; however, this inotropic response is at the expense of metabolic recovery.\protectcite{9} Nevertheless, even after 85 minutes of ischemia followed by 5 minutes of dobutamine infusion, the myocardium remains viable, and there is no evidence of necrosis.\protectcite{9}

We hypothesized that the development of myocardial hibernation is a delicate process that, as previously suggested, is easily disturbed by unfavorable alterations of the oxygen supply-demand balance\protectcite{7} such as increasing severity of ischemia or prolonged inotropic stimulation.\protectcite{9,11,12} Therefore, the time course of functional, metabolic, and morphological changes of myocardium subjected to moderate ischemia and continuous inotropic stimulation by intracoronary dobutamine infusion was investigated in anesthetized swine. Because the dobutamine infusion not only increases myocardial function but also induces a redistribution of blood flow from the subendocardium toward the subepicardium of the left ventricle\protectcite{13} as well as the right ventricle,\protectcite{14} the importance of the severity of blood flow reduction per se on the development of myocardial hibernation was assessed in two additional groups of swine.

Methods

The experimental protocols used in this study were approved by the Bioethical Committee of the district of Düsseldorf, and they adhere to the guiding principles of the American Physiological Society.

Experimental Model

Twenty-seven Gottinger miniswine (weight, 20 to 40 kg) of either sex were initially sedated with ketamine hydrochloride (1 g IM) and then anesthetized with thiopental (Trapanal, 500 mg IV). Through a midline cervical incision, the trachea was intubated for connection to a respirator (Dräger, Lübeck, FRG). Anesthesia then was maintained using enflurane (1% to 1.5%) with an oxygen–nitrous oxide mixture (40%:60%). Arterial blood gases were monitored frequently in the initial stages of the preparation until levels were stable and then periodically throughout the study (Radiometer, Copenhagen, Denmark). Rectal temperature was monitored, and hypothermia was prevented by the use of a heated surgical table and drapes.

Through the cervical incision, both common carotid arteries and internal jugular veins were isolated. The arteries were cannulated with polyethylene catheters—one for measurement of arterial pressure and the other to supply blood to the extracorporeal circuit. The jugular veins were cannulated for volume replacement using warmed 0.9% NaCl and for the return of blood to the animal from the coronary venous line (see below).

A left lateral thoracotomy was performed in the fourth intercostal space, and the pericardium was opened. A micromanometer (P7, Königsberg Instr, Pasadena, Calif) was placed in the left ventricle through the apex with a saline-filled polyethylene catheter (used to calibrate the micromanometer in situ). Ultrasonic dimension gauges were implanted in the left ventricular myocardium to measure the thickness of the anterior and posterior (control) walls (System 6; Triton Technologies, Inc, San Diego, Calif).

The proximal left anterior descending coronary artery was dissected over a distance of 1.5 cm, ligated, and cannulated, and the distal left anterior descending coronary artery was perfused from an extracorporeal circuit. Before coronary cannulation, the pigs were anticoagulated with 20 000 IU sodium heparin; additional doses of 10 000 IU were given at hourly intervals. The system included a roller pump, windkessel, and two side ports—one for the injection of radiolabeled microspheres and the other for dobutamine infusion.\protectcite{8,13} Coronary arterial pressure was measured from the sidearm of a polyethylene T-connector (Cole-Parmer, Chicago, Ill) used as catheter tip with an external transducer (type 4-3271; Bell and Howell, Pasadena, Calif). The large epicardial vein parallel to the left anterior descending coronary artery was dissected and cannulated. Coronary venous blood was drained to an unpressurized reservoir and then returned to a jugular vein through use of a second roller pump. Heart rate was controlled throughout the study by left atrial pacing (type 215/T; Hugo Sachs Elektronik, Hugstetten, FRG). The completed preparation was allowed to stabilize for at least 30 minutes before control measurements were made. The constant-flow perfusion pump was adjusted so that the minimum coronary arterial pressure was not less than 70 mm Hg under control conditions to avoid initial hypoperfusion. Therefore, mean coronary arterial pressure exceeded peak left ventricular pressure.

Regional Myocardial Function

End diastole was defined as the point when left ventricular dP/dt started its rapid upstroke after crossing the zero-line. Regional end systole was defined as the point of maximal wall thickness within 20 milliseconds before peak negative left ventricular dP/dt.\protectcite{13} Systolic wall thickening was calculated as end-systolic wall thickness minus end-diastolic wall thickness divided by the end-diastolic wall thickness. In view of the ventricular asynchrony observed during regional ischemia and inotropic activation,\protectcite{16} a “work index” was calculated.\protectcite{5,13}

Regional Myocardial Blood Flow

Radiolabeled microspheres (15-μm diameter; 114Ce, 115mIn, 51Cr, 113Sn, 103Ru, 95Nb, or 46Sc; New England Nuclear–Du Pont Co, Boston, Mass) were injected into the coronary perfusion circuit (1 to 2×106 suspended in 1 mL saline) to determine the regional myocardial blood flow and its distribution throughout the left anterior descending coronary artery perfusion bed. This procedure for the determination of blood flow has been validated extensively.\protectcite{13}
Only the blood flow to the tissue at the site of the ultrasonic crystals is reported, and this piece of tissue was divided into transmural thirds of approximately equal thicknesses. Total myocardial blood flow to the left anterior descending coronary artery–perfused territory was also measured and further subdivided into left (including the septum) and right ventricular blood flow.

**Regional Myocardial Metabolism**

Oxygen content was measured using anaerobically sampled blood drawn simultaneously from the coronary vein and an artery (Cavitron/LexO₂-Con-k; Dr B. G. Schlag, Bergisch Gladbach, FRG). Oxygen consumption of the anterior myocardial wall was calculated by multiplying the arterial-coronary venous oxygen difference by the transmural blood flow at the crystal site.

Lactate was measured in simultaneously drawn 1 mL coronary venous and arterial blood samples using enzymatic dehydrogenation and subsequent photometry of NADH, and lactate consumption was calculated by multiplying the arterial-coronary venous difference by transmural blood flow.

Transmural myocardial biopsies (approximately 10 mg each) were taken with a modified dental drill from the left anterior descending coronary artery perfusion bed for analysis of ATP, creatine phosphate, and glyco- gen contents. Care was taken to ensure that the biopsies originated from within the left anterior descending coronary artery perfusion territory (using epicardial arteries as landmarks) but were distal to the site of the ultrasonic dimension gauges and blood flow measurements. Samples requiring more than 1 to 2 seconds for acquisition were not used for this analysis. The analytical procedures have been described in detail previously.

**Regional β-Adrenoceptor Density**

In six of the animals subjected to 90 minutes of ischemia and continuous dobutamine infusion during the latter 85 minutes of ischemia as well as in four animals subjected to 85 minutes of continuous dobutamine infusion during normoperfusion, the β-adrenoceptor density was determined in transmural biopsies using (−)I[125I]iodocyanopindolol (specific activity, 2200 Ci/ mmol; New England Nuclear, Dreieich, FRG). Details of the procedure have been described elsewhere. In the six animals undergoing myocardial ischemia, biop- sies for the determination of β-adrenoceptor density were taken under control conditions, at 5 minutes of ischemia, and at 5 and 85 minutes of the subsequent dobutamine infusion. In the four animals receiving dobutamine for 85 minutes during normoperfusion, biopsies were taken before and at the end of the dobutamine infusion.

**Morphology**

In 17 pigs subjected to 90 minutes of ischemia with or without the additional infusion of dobutamine and in four animals subjected to 85 minutes of continuous dobutamine infusion during normoperfusion, the heart was removed after 2 hours of reperfusion and sectioned from base to apex into five transverse slices in a plane parallel to the atrophicventricular groove. The tissue slices were immersed in a 0.09 M sodium phosphate buffer (pH 7.4) containing 1.0% triphenyl tetrazolium chloride (Sigma, Deisenhofen, FRG) and 8% dextran (mol wt, 77 800) for 20 minutes at 37°C to identify infarcted tissue. The amount of infarcted tissue is expressed as a percentage of the left ventricular area at risk, as determined by the microsphere technique.

**Experimental Protocols**

Each observation period began with the simultaneous withdrawal of pairs of arterial and coronary venous blood samples. During the blood sampling, microspheres were injected into the left anterior descending coronary artery perfusion system for the measurement of regional myocardial blood flow, and hemodynamic and regional dimension data were recorded. Coronary arterial pressure was continuously monitored during the microsphere injection to ensure that it was unaffected by the injection. Immediately after the microsphere injection, myocardial biopsies were taken. A set of measurements was obtained within 2 to 3 minutes.

**Group 1**

In group 1 (n=12), following control measurements, blood flow to the left anterior descending coronary artery was reduced to a level sufficient to reduce the regional systolic work index by 70%. This adjustment period lasted approximately 3 minutes. After 2 more minutes of steady-state ischemia (5 minutes from the onset of flow reduction), a second set of measurements was begun. Immediately after completion of the second set of measurements at 5 minutes of ischemia, dobutamine hydrochloride (2.5±1 μg/min; Lilly, Giessen, FRG) was infused into the left anterior descending coronary artery perfusion circuit. After an additional 2 to 3 minutes, when a stable response to dobutamine was achieved (after approximately 10 minutes of ischemia), a third set of measurements was made. The effects of the dobutamine infusion were confirmed by changes in regional wall performance and characteristics of left ventricular dp/dt, which displayed an increased peak positive value (dp/dtn) and a decreased peak negative value (dp/dtn). After 85 minutes of dobutamine infusion (ie, 90 minutes of ischemia), a final set of measurements was performed, and the myocardium then was reperfused for 2 hours. Data from all 12 animals of group 1 were used in the analysis of hemodynamics, regional myocardial blood flow, and function. Biopsies for the analysis of myocardial creatine phosphate, ATP, and glycogen contents and the determination of β-adrenoceptor density were obtained in six animals of group 1. In the remaining six animals of group 1, infarct size was determined.

**Group 2**

In group 2 (n=6), following the completion of measurements under control conditions and at 5 minutes of ischemia characterized by a 70% reduction in the regional systolic work index, blood flow to the left anterior descending coronary artery was further decreased to achieve an 80% reduction in the regional systolic work index. After about 5 more minutes when all hemodynamic parameters were stabilized, a third set of measurements was made. A final set of measurements was obtained after 90 minutes of ischemia.
Group 3

In group 3 (n=5), following the completion of the measurements under control conditions and at 5 minutes of ischemia characterized by a 70% reduction in the regional systolic work index, blood flow to the left anterior descending coronary artery was further decreased to achieve a 90% reduction in the regional systolic work index. After about 5 more minutes when all hemodynamic parameters were stabilized, a third set of measurements was made. A final set of measurements was obtained after 90 minutes of ischemia.

The pigs of groups 2 and 3 were somewhat larger than those of group 1. Because no biopsies were taken for the measurement of \( \beta \)-adrenoceptor density and biopsies at 5 minutes of ischemia were omitted, it was possible to simultaneously obtain biopsies and determine infarct size in 10 (five of each group) of 11 animals.

Group 4

Group 4 (n=4) served as a time-control series without ischemia. After the completion of measurements under control conditions, dobutamine was infused into the left anterior descending coronary artery perfusion circuit. To avoid a decrease in subendocardial blood flow during the dobutamine infusion, the left anterior descending coronary artery was perfused at constant perfusion pressure. After 5 minutes, when a stable response to dobutamine was achieved, a second set of measurements was made. After 85 minutes of continuous dobutamine infusion, a final set of measurements was obtained.

At the end of each study, the digital reading of the roller pump was calibrated by collecting arterial blood in a graduated cylinder.

Data Analysis and Statistics

Hemodynamic data were recorded on an eight-channel recorder (MK 200A; Gould, Cleveland, Ohio) and transmitted directly for storage to the hard disk of an AT-type computer. Hemodynamic and functional parameters were digitized and recorded over a 20-second period during each microsphere injection (approximately 33 consecutive beats over at least two complete respiratory cycles) using CORDAT software (Essen, FRG). Calculation of all hemodynamic parameters was done on a beat-to-beat basis, and data then were averaged. Changes in the regional work index, ATP, and creatine phosphate that occurred during ischemia and the continuous dobutamine infusion (group 1) or with the increased severity of ischemia (groups 2 and 3) also were expressed as percentages of the respective control values.

Statistical analysis was performed with SYSTAT software (Urbana, Ill). Data of the four groups of pigs during control conditions were compared using a one-way ANOVA. Changes in the measured variables during the experiment were estimated by a one-way ANOVA for repeated measures. When significant differences were detected, individual mean values were compared using post-hoc tests. Paired comparisons were performed for hemodynamics, regional myocardial blood flow, and function between the subgroups of the six dobutamine-stimulated pigs undergoing biochemical analysis and the six dobutamine-stimulated pigs undergoing morphological analysis. All data are reported as mean±SD values, and \( P<.05 \) was accepted as indicating a significant difference in mean values.

A linear regression analysis between transmural myocardial or subendocardial blood flow to the left ventricular area at risk and infarct size (expressed as percentage of the area at risk) was performed, and the 97.5% confidence interval was determined. Previously published data from five additional animals that underwent 90 minutes of ischemia with a 70% reduction in regional function and subsequent 2 hours of reperfusion were included in these regression analyses. The infarct size predicted by such regression analysis was compared with the actual infarct size observed in group 1 by a paired \( t \) test.

Results

There were no significant differences in any measured parameter under control conditions among the four groups of pigs. At 90 minutes of ischemia, the spontaneous heart rate was increased above the atrial pacing rate in a number of animals in group 1 (n=5) and group 3 (n=1).

Group 1

An original tracing from one of the experiments is shown in Fig 1. Data on hemodynamics, regional myocardial function, blood flow, metabolism, and \( \beta \)-adrenoceptor density are summarized in Table 1 and Figs 2 to 4. Blood flow in the subgroup of six pigs undergoing morphological analysis was somewhat higher than that in the six pigs undergoing biochemical analysis. However, because no significant difference was observed, data of all 12 pigs with prolonged inotropic stimulation were combined in Table 1.

Hemodynamics and blood flow. By decreasing the pump speed, coronary inflow was reduced such that mean coronary arterial pressure decreased to 35±12% of the control value at 5 minutes of ischemia (\( P<.05 \)). Left ventricular end-diastolic pressure remained unchanged, whereas left ventricular peak pressure as well as \( \Delta P/dt_{\text{max}} \) and \( \Delta P/dt_{\text{min}} \) tended to decrease (\( P=\text{NS} \)). Transmural myocardial blood flow to the anterior wall was reduced to 53±16% of control at 5 minutes of ischemia, whereas subendocardial blood flow was decreased to 32±15% (both, \( P<.05 \)). Infusion of dobutamine resulted in no further change in left ventricular end-diastolic and peak pressure within the first 5 minutes of infusion. \( \Delta P/dt_{\text{max}} \) increased from 85±7% to 108±11% of the respective control value (\( P<.05 \) versus 5 minutes of ischemia), whereas \( \Delta P/dt_{\text{min}} \) decreased to 55±17% (\( P<.05 \)) of the respective control value, indicative of left ventricular asynchrony. After 85 minutes of dobutamine infusion, heart rate and end-diastolic left ventricular pressure tended to increase (\( P=\text{NS} \)), whereas peak left ventricular pressure decreased to 83±10% of the respective control value (\( P<.05 \)). \( \Delta P/dt_{\text{max}} \) and \( \Delta P/dt_{\text{min}} \) remained unchanged.

The continuous infusion of dobutamine resulted in no further change in transmural myocardial blood flow. However, at 5 minutes of dobutamine infusion (ie, 10 minutes of ischemia), there was a significant redistribution of blood away from the subendocardium of the left ventricle (subendocardial blood flow decreased further from 32±15% to 18±8% of the respective control value,
P<.05) toward the subepicardium of the left ventricle (from 78±24% to 88±34% of the respective control value, P=NS). Of the left anterior descending coronary artery perfusion territory, 19.8±3.6% was right ventricular myocardium. During the continuous dobutamine infusion, blood flow to the right ventricular left anterior descending coronary artery perfusion territory increased from 0.26±0.08 to 0.32±0.09 mL·min⁻¹·g⁻¹ (P=NS).

**Regional myocardial function.** With the reduction of coronary inflow, systolic wall thickening of the anterior wall decreased to 37±21% of control, whereas the work index was reduced to 31±15% of the control value (both, P<.05). Infusion of dobutamine resulted in no significant change in systolic wall thickening, but the work index increased to 59±21% of control (P<.05 versus control and 5 minutes of ischemia). However, this increase in the work index was only transient (Fig 2), and after 85 minutes of dobutamine infusion, the work index was reduced even below the initial ischemic value. Systolic wall thickening of the posterior (control) wall was 25±9% under control conditions and did not change significantly during ischemia and the subsequent intracoronary dobutamine infusion.

**Regional myocardial metabolism.** Five minutes of moderate ischemia resulted in a decrease in regional myocardial oxygen consumption to 65±19% of the control value (P<.05), which then remained unchanged throughout the subsequent 85 minutes of ischemia with the additional dobutamine infusion. At 5 minutes of ischemia, creatine phosphate content was reduced to 68±32% of the respective control value (P=NS), and lactate consumption was reversed to net lactate production (P<.05). After 5 minutes of dobutamine infusion (ie, 10 minutes of ischemia), a further reduction in creatine phosphate to 36±6% (P<.05 versus control and 5 minutes of ischemia, Fig 3) and an additional increase in lactate production were observed (P<.05 versus control and 5 minutes of ischemia). Myocardial ATP content slightly decreased to 88±26% of the respective control value (P=NS) within the first 5 minutes of ischemia but decreased significantly to 67±16% within the first 5 minutes of the dobutamine infusion (Fig 4). During the remainder of the continuous dobutamine infusion, creatine phosphate remained unchanged (Fig 3), whereas ATP decreased to 37±23% of the respective control value (P<.05 versus control and 5 minutes of dobutamine, Fig 4). Myocardial glycogen content continuously declined during ischemia with the additional dobutamine infusion to 58±35% of the control value (P=NS).

**Regional β-adrenoceptor density.** Myocardial β-adrenoceptor density did not change from control to 5 minutes to ischemia and also remained constant throughout the subsequent 85 minutes of ischemia with the additional...
TABLE 1. Hemodynamics, Regional Myocardial Function, Blood Flow, Metabolism, and \( \beta \)-Adrenoceptor Density During 90 Minutes of Ischemia With Dobutamine Infusion During the Latter 85 Minutes of Ischemia

<table>
<thead>
<tr>
<th>Group 1 (n=12)</th>
<th>Control</th>
<th>5 Minutes of ischemia</th>
<th>10 Minutes of ischemia plus dobutamine</th>
<th>90 Minutes of ischemia plus dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>111±12</td>
<td>113±13</td>
<td>114±11</td>
<td>126±11</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10.6±3.7</td>
<td>12.5±3.5</td>
<td>13.3±6.8</td>
<td>15.6±9.5</td>
</tr>
<tr>
<td>LVPP (mm Hg)</td>
<td>92±8</td>
<td>85±11</td>
<td>87±10</td>
<td>77±14*</td>
</tr>
<tr>
<td>dP/dt(_{\text{max}}) (mm Hg/s)</td>
<td>1297±200</td>
<td>1099±143</td>
<td>1390±192†</td>
<td>1336±335†</td>
</tr>
<tr>
<td>dP/dt(_{\text{min}}) (mm Hg/s)</td>
<td>1484±335</td>
<td>1234±334</td>
<td>836±352*</td>
<td>903±498*</td>
</tr>
<tr>
<td>CAP (mm Hg)</td>
<td>113±18</td>
<td>39±13*</td>
<td>36±12*</td>
<td>35±16*</td>
</tr>
<tr>
<td><strong>Regional myocardial function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT (%)</td>
<td>34.3±1.6</td>
<td>11.8±7.3*</td>
<td>16.9±11.4*</td>
<td>3.8±10.3*†</td>
</tr>
<tr>
<td>WI (mm Hg · mm)</td>
<td>248±59</td>
<td>73±35*</td>
<td>139±34†</td>
<td>42±34††</td>
</tr>
</tbody>
</table>

**HR**, heart rate; bpm, beats per minute; LVEDP, left ventricular end-diastolic pressure; LVPP, left ventricular peak pressure; dP/dt\(_{\text{max}}\), maximum value of the first derivative of left ventricular pressure; dP/dt\(_{\text{min}}\), minimum value of the first derivative of left ventricular pressure; CAP, mean coronary arterial pressure; WT, systolic wall thickness; WI, work index; TMF, transmural myocardial blood flow; ENDO, subendocardial blood flow; MID, midwall blood flow; EPI, subepicardial blood flow; CP, myocardial creatine phosphate content; ATP, myocardial ATP content; GLY, myocardial glycogen content; MVo2, myocardial oxygen consumption; V\(_{\text{LAC}}\), myocardial lactate consumption; \( B_{\text{max}} \), maximal number of \( \beta \)-adrenoceptor binding sites; ICYP, \( (-)\)\[^{125}\text{I} \)iodocyanopindolol; \( K_D \), equilibrium dissociation constant; values are mean±SD.

\*P<.05 versus control; †P<.05 versus previous value.

dobutamine infusion. The same held true for the \( K_D \) values of \( (-)\)\[^{125}\text{I} \)iodocyanopindolol (Table 1).

**Group 2**

Data on hemodynamics, regional myocardial function, blood flow, and metabolism are summarized in Table 2 and Figs 2 to 4.

After 5 minutes of ischemia (comparable to group 1), coronary inflow was further reduced such that mean coronary arterial pressure fell to 34±10% of the respective control value \( (P<.05) \) at 10 minutes of ischemia. Left ventricular end-diastolic pressure remained unchanged, whereas left ventricular peak pressure and dP/dt\(_{\text{max}}\) tended to decrease \( (P=\text{NS}) \). Transmural myocardial blood flow to the anterior wall was reduced to 32±12% of control at 10 minutes of ischemia, whereas subendocardial blood flow decreased to 22±12% (both, \( P<.05 \) versus control). Regional myocardial oxygen consumption was decreased to 38±11% of control, and myocardial lactate consumption was reversed to net lactate production (both, \( P<.05 \) versus control). Both myocardial creatine phosphate and ATP contents were reduced to 26±11% and 74±10% of the respective control value (both, \( P<.05 \) versus control). There was no further change in hemodynamics, regional myocar-

![FIG 2. Plot of regional myocardial work (WI, as a percentage of control) during 90 minutes of ischemia. Left anterior descending (LAD) coronary inflow was initially reduced to achieve a 70% reduction in the work index in groups 1 through 3. The arrow indicates the time point when either the intra-coronary dobutamine infusion was started (group 1) or the blood flow to the LAD was further reduced to achieve an 80% (group 2) or 90% (group 3) reduction in regional work. Infusion of dobutamine resulted in a transient increase in regional work. After 85 minutes of dobutamine infusion, however, regional work was reduced even below the initial ischemic value. *P<.05 versus the previous value.](http://circ.ahajournals.org/content/mechanismsmothers)
After 10 minutes of moderate ischemia, a continuous dobutamine infusion was started in group 1 or left anterior descending coronary artery blood flow was further reduced to achieve an 80% (group 2) or a 90% (group 3) decrease in regional work. After 10 minutes of ischemia with and without dobutamine infusion, ATP was decreased in all groups. Although ATP remained depressed in groups 1 and 3, ATP recovered in group 2 to a value no longer significantly different from control. *P<.05 versus control.

![Graph of myocardial ATP content](image)

**FIG 4.** Bar graphs of myocardial ATP content (as a percentage of control) during 90 minutes of moderate ischemia. Left anterior descending coronary artery coronary inflow was initially reduced to achieve a 70% reduction in regional work in groups 1 through 3. After 5 minutes of moderate ischemia, a continuous dobutamine infusion was started in group 1 or left anterior descending coronary artery blood flow was further reduced to achieve an 80% (group 2) or a 90% (group 3) decrease in regional work. After 10 minutes of ischemia with and without dobutamine infusion, ATP was decreased to a similar extent in all groups. No further change in ATP occurred in group 2 when ischemia was prolonged to 90 minutes. However, ATP was significantly reduced further in groups 1 and 3. *P<.05 versus control; #P<.05 versus 10 minutes of ischemia.

**Group 3**

Data on hemodynamics, regional myocardial function, blood flow, and metabolism are summarized in Table 3 and Figs 2 to 4.

After 5 minutes of ischemia (comparable to group 1), coronary inflow was further reduced such that mean coronary arterial pressure decreased to 31±8% of the respective control value (P<.05 versus control) at 10 minutes of ischemia. Left ventricular end-diastolic pressure increased, whereas left ventricular peak pressure and dP/dt max tended to decrease and dP/dt min was reduced significantly (81±12% of the respective control value, P<.05). Transmural myocardial blood flow to the anterior wall was reduced to 24±10% of control at 10 minutes of ischemia, whereas subendocardial blood flow fell further to 9±8% (both, P<.05 versus control and 5 minutes of ischemia). Regional myocardial oxygen consumption was decreased to 38±19% of control, and myocardial lactate consumption was reversed to net lactate production (both, P<.05 versus control). Both myocardial creatine phosphate and ATP contents were reduced to 22±10% and 71±14% (both, P<.05 versus control), respectively. There was no further change in hemodynamics, regional myocardial blood flow, and myocardial oxygen consumption when ischemia was prolonged to 90 minutes. Myocardial creatine phosphate content slightly recovered to 37±42% of the respective control value (P=NS), and myocardial lactate production tended to be attenuated. Myocardial ATP content decreased further to 22±25% of the respective control value (P<.05 versus 10 minutes of ischemia).

**Group 4**

Data on hemodynamics, regional myocardial function, blood flow, metabolism, and β-adrenoceptor density are summarized in Table 4.

At constant coronary arterial pressure, dobutamine infusion increased systolic wall thickening by 67±48% and the work index increased by 43±26% at 5 minutes of infusion (both, P<.05 versus control). This increase in regional myocardial function remained unchanged throughout the 85 minutes of dobutamine infusion. Associated with the increase in regional myocardial function, transmural myocardial blood flow and regional myocardial oxygen consumption were increased (Table 4). Neither the myocardial contents of creatine phosphate and ATP nor the myocardial β-adrenoceptor density changed throughout the stimulation period. The same increases or lack of change held true for the K<sub>e</sub> values of (-)[<sup>38</sup>II]iodoestanoliodopindolol.

**Myocardial Blood Flow Versus Infarct Size**

There were significant relations between transmural myocardial (Fig 5) and subendocardial (Fig 6) blood flow in the left ventricular myocardium at risk after 10 minutes of ischemia and infarct size (expressed as a percentage of area at risk). With continuous inotropic stimulation by dobutamine, infarct size for a given blood flow was increased (all points are at the boundary or outside of the 97.5% confidence interval). These results were no different when infarct size was plotted versus blood flow after 90 minutes of ischemia rather than after 10 minutes of ischemia.
The results of this study indicate that continuous inotropic stimulation with dobutamine during moderate myocardial ischemia initially increases regional myocardial work, continuously depletes myocardial energy stores, and finally precipitates myocardial infarction. Both the increased severity of ischemia secondary to a dobutamine-induced redistribution of blood flow and the increased energy expenditure during the dobutamine infusion contribute to impair the development of myocardial hibernation and to precipitate myocardial infarction.

**Limitations of Experimental Approach**

The sampling of venous blood from an epicardial coronary vein provides an adequate regional assessment because it is almost unaffected by contamination from coronary venous collateral channels. Because coronary venous blood represents a transmurally averaged blood sample, only transmural myocardial oxygen and lactate consumption were calculated, without attempting transmural differentiation.

Our biopsy technique also sampled transmurally as we could not divide our tissue samples because they became highly distorted by the “freeze-clamping.” Thus, our technique attempted to freeze tissue as rapidly as possible but sacrificed the possibility of dividing it transmurally. Despite marked perfusion heterogeneity, the metabolic response to ischemia appears to be more uniform, thereby minimizing the underestimation of the metabolic consequences of ischemia due to our examining only transmural samples. If anything, however, the more pronounced changes in high-energy phosphates in subendocardial layers were underestimated by only transmural sampling. The fact that ATP continued to decrease whereas creatine phosphate remained unchanged at a greatly reduced level in groups 1 and 3 may be attributed to the problem of transmural sampling and averaging over cells with different metabolic changes. We also could not determine to what extent the biopsies contained noninfarcted and infarcted tissue. In group 2, infarct size was only around 6%, and metabolic recovery was observed in every animal. As the amount of infarcted tissue was increased, biopsies in groups 1 and 3 probably contained a mixture of noninfarcted and infarcted tissue.

In the present study, we did not try to provide a transmural differentiation of regional contractile function because we have previously demonstrated that despite marked flow heterogeneity within the left ventricular wall, no such gradient in contractile function exists during 90 minutes of ischemia and in response to dobutamine.

One limitation of all animal experiments that have studied myocardial hibernation is the limited observation period. Myocardial hibernation, as introduced by Rhahimtoola, is a clinical situation of contractile dysfunction in patients with coronary artery disease that
TABLE 3. Hemodynamics, Regional Myocardial Function, Blood Flow, and Metabolism During 90 Minutes of Ischemia

<table>
<thead>
<tr>
<th>Group 3 (n=5)</th>
<th>Control</th>
<th>5 Minutes of ischemia</th>
<th>10 Minutes of ischemia</th>
<th>90 Minutes of ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>103±3</td>
<td>104±3</td>
<td>104±3</td>
<td>113±20</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>13±4</td>
<td>18±6</td>
<td>21±6</td>
<td>17±7</td>
</tr>
<tr>
<td>LVPP (mm Hg)</td>
<td>98±13</td>
<td>92±14</td>
<td>91±14</td>
<td>86±15</td>
</tr>
<tr>
<td>dP/dt max (mm Hg/s)</td>
<td>164±359</td>
<td>1282±248</td>
<td>1275±200</td>
<td>1269±230</td>
</tr>
<tr>
<td>dP/dt min (mm Hg/s)</td>
<td>-1695±179</td>
<td>-1346±135</td>
<td>-1360±154*</td>
<td>-1304±175*</td>
</tr>
<tr>
<td>CAP (mm Hg)</td>
<td>124±11</td>
<td>56±33</td>
<td>41±10*</td>
<td>36±11*</td>
</tr>
<tr>
<td><strong>Regional myocardial function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT (%)</td>
<td>48.9±7.2</td>
<td>18.4±4.7*</td>
<td>8.6±4.9*†</td>
<td>4.9±3.7*</td>
</tr>
<tr>
<td>WI (mm Hg · mm)</td>
<td>317±86</td>
<td>95±15*</td>
<td>40±12†</td>
<td>29±12*</td>
</tr>
<tr>
<td><strong>Regional myocardial blood flow and metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMF (mL · min⁻¹ · g⁻¹)</td>
<td>0.69±0.08</td>
<td>0.29±0.08*</td>
<td>0.17±0.07*†</td>
<td>0.16±0.07*</td>
</tr>
<tr>
<td>ENDO (mL · min⁻¹ · g⁻¹)</td>
<td>0.71±0.139</td>
<td>0.16±0.07*</td>
<td>0.07±0.06†</td>
<td>0.05±0.03*</td>
</tr>
<tr>
<td>MID (mL · min⁻¹ · g⁻¹)</td>
<td>0.63±0.09</td>
<td>0.26±0.10*</td>
<td>0.13±0.06†</td>
<td>0.14±0.07*</td>
</tr>
<tr>
<td>EPI (mL · min⁻¹ · g⁻¹)</td>
<td>0.72±0.11</td>
<td>0.43±0.12*</td>
<td>0.31±0.12*</td>
<td>0.27±0.13*</td>
</tr>
<tr>
<td>CP (µmol/g wet wt)</td>
<td>8.30±1.34</td>
<td>...</td>
<td>1.79±0.72*</td>
<td>2.92±2.26*</td>
</tr>
<tr>
<td>ATP (µmol/g wet wt)</td>
<td>3.97±0.34</td>
<td>...</td>
<td>2.81±0.61</td>
<td>0.91±1.07†</td>
</tr>
<tr>
<td>GLY (mg/g wet wt)</td>
<td>1.64±0.43</td>
<td>...</td>
<td>1.25±0.57</td>
<td>1.00±0.72</td>
</tr>
<tr>
<td>MVo₂ (µL · min⁻¹ · g⁻¹)</td>
<td>57.9±5.2</td>
<td>34.4±13.1*</td>
<td>20.8±10.7*</td>
<td>18.8±12.2*</td>
</tr>
<tr>
<td>VₗAC (µmol · min⁻¹ · g⁻¹)</td>
<td>1.60±1.60</td>
<td>-2.49±1.04*</td>
<td>-2.75±1.11*</td>
<td>-1.27±0.31*‡</td>
</tr>
</tbody>
</table>

HR, heart rate; bpm, beats per minute; LVEDP, left ventricular end-diastolic pressure; LVPP, left ventricular peak pressure; dP/dt max, maximum value of the first derivative of left ventricular pressure; dP/dt min, minimum value of the first derivative of left ventricular pressure; CAP, mean coronary arterial pressure; WT, systolic wall thickening expressed as a percentage of the end-diastolic wall thickness; WI, work index; TMF, transmural myocardial blood flow; ENDO, subendocardial blood flow; MID, midwall blood flow; EPI, subepicardial blood flow; CP, myocardial creatine phosphate content; ATP, myocardial ATP content; GLY, myocardial glycogen content; MVo₂, myocardial oxygen consumption; VₗAC, myocardial lactate consumption; values are mean±SD.

*P<.05 versus control; †P<.05 versus previous value.

exists for months and longer but is fully reversible on reperfusion. In contrast to the short-term hibernation studied in animal models so far, such long-term hibernation is accompanied by morphological alterations of the ischemic myocardium.23

Dependence of Myocardial Hibernation on the Severity of Ischemia

Moderate low-flow ischemia, such as that produced in the present study, is characterized by less intense regional contractile dysfunction and a marked transmural heterogeneity of blood flow. Unlike total ischemia, such moderate ischemia can be maintained for prolonged periods without the development of irreversible damage. Matsuzaki and colleagues24 subjected dogs to ischemia sufficient to reduce systolic wall thickening by 40% for 5 hours. Although recovery of function on subsequent reperfusion required 1 week, function recovered fully, and necrosis was absent from the left ventricular free wall. In a previous study from our laboratory, a reduction in regional myocardial work by 70% was tolerated for 90 minutes without the development of myocardial infarction.9 In the present study, however, a further reduction of regional myocardial function to 20% (group 2) or 10% (group 3) of the respective control value for 90 minutes progressively increased myocardial infarct size. Thus, the ability of the ischemic myocardium to survive an ischemic insult critically depends on whether sufficient residual blood flow exists.

As long as transmural myocardial blood flow was more than 0.34 mL · min⁻¹ · g⁻¹ and subendocardial blood flow was more than 0.18 mL · min⁻¹ · g⁻¹, no myocardial infarction developed (Figs 5 and 6). Within our experimental model, these flow values appear to represent the lower limit of successful hibernation.

Metabolic Adaptation of Short-term Hibernating Myocardium

Short-term hibernating myocardium is characterized by a recovery of metabolic parameters despite a persistent reduction in blood flow and contractile function. In anesthetized pigs in which a coronary stenosis was maintained for 3 hours, a progressive improvement in coronary venous PCO₂ and pH as well as myocardial lactate metabolism occurred despite constant hypoperfusion and reduced myocardial oxygen consumption.10 During a reduction in myocardial blood flow sufficient to reduce myocardial work by 70%, myocardial creatine phosphate content was almost normalized after 90 minutes of ischemia, and myocardial ATP content remained constant at a slightly reduced level.9 A comparable result was achieved in the present study, when myocardial blood flow was further reduced to achieve an 80% reduction in work. Myocardial creatine phosphate content once again recovered to near-control values, whereas myocardial ATP content decreased only slightly. Only when ischemia was more severe (group 3) was such metabolic adaptation no longer observed, as
TABLE 4. Hemodynamics, Regional Myocardial Function, Blood Flow, Metabolism, and β-Adrenoceptor Density With 85 Minutes of Dobutamine Infusion During Normoperfusion

<table>
<thead>
<tr>
<th>Group 4 (n=4)</th>
<th>Control</th>
<th>5 Minutes of dobutamine</th>
<th>85 Minutes of dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>112±6</td>
<td>113±3</td>
<td>114±7</td>
</tr>
<tr>
<td>LVPP (mm Hg)</td>
<td>89±18</td>
<td>89±17</td>
<td>86±18</td>
</tr>
<tr>
<td>dP/dt max (mm Hg/s)</td>
<td>1563±281</td>
<td>2280±530*</td>
<td>2311±571*</td>
</tr>
<tr>
<td>CAP (mm Hg)</td>
<td>113±4</td>
<td>115±12</td>
<td>111±14</td>
</tr>
<tr>
<td><strong>Regional myocardial function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT (%)</td>
<td>41.5±14.1</td>
<td>63.8±4.6*</td>
<td>65.5±16.2*</td>
</tr>
<tr>
<td>WI (mm Hg·mm)</td>
<td>259±120</td>
<td>341±91*</td>
<td>338±95*</td>
</tr>
</tbody>
</table>

**Regional myocardial blood flow, metabolism, and β-adrenoceptors**

| | | | |
| TMF (mL·min⁻¹·g⁻¹) | 0.82±0.19 | 1.24±0.20* | 1.48±0.33* |
| CP (μmol/g wet wt) | 6.77±0.94 | 5.45±1.29 | 5.15±1.36 |
| ATP (μmol/g wet wt) | 3.89±1.22 | 3.71±1.08 | 3.78±1.24 |
| GLY (mg/g wet wt) | 2.10±0.72 | 2.20±0.65 | 2.20±0.59 |
| MVO₂ (μL·min⁻¹·g⁻¹) | 70.7±18.4 | 97.2±15.5* | 120.2±30.2* |
| V̇LAC (μmol·min⁻¹·g⁻¹) | 1.78±0.09 | 7.00±1.42* | 5.63±4.19 |
| B₀sat (mol ICYP/mg protein) | 57.1±13.1 | ... | 52.4±25.8 |
| K₀ | 18.2±1.8 | ... | 18.5±3.1 |

HR, heart rate; bpm, beats per minute; LVPP, left ventricular peak pressure; dP/dt max, maximum value of the first derivative of left ventricular pressure; CAP, mean coronary arterial pressure; WT, systolic wall thickening expressed as a percentage of the end-diastolic wall thickness; WI, work index; TMF, transmural myocardial blood flow; CP, myocardial creatine phosphate content; ATP, myocardial ATP content; GLY, myocardial glycogen content; MVO₂, myocardial oxygen consumption; V̇LAC, myocardial lactate consumption; B₀sat, maximal number of β-adrenoceptor binding sites; ICYP, (−)[³²P]iodoanopindolol; K₀, equilibrium dissociation constant; values are mean±SD.

*P<.05 versus control.

myocardial ATP content continuously declined and myocardial creatine phosphate content, after a rapid depletion, remained depressed. Thus, the recovery of myocardial creatine phosphate content as well as the persistence of the myocardial ATP content at a slightly reduced level appear to be set by the absolute level of residual blood flow. As long as subendocardial blood flow is more than 0.15 mL·min⁻¹·g⁻¹ (References 8 and 9) (also group 2 of the present study; Table 2), myocardial creatine phosphate content recovers and myocardial ATP content remains constant during ongoing ischemia, whereas a further decrease in myocardial blood flow (group 3) impairs the recovery of myocardial creatine phosphate content and further depletes myo-

![Fig 5. Scatterplots of relation between transmural myocardial blood flow in the left ventricular myocardium at risk (mL·min⁻¹·g⁻¹, x axis) and infarct size (expressed as a percentage of the area at risk, y axis). For a given blood flow, infarct size was increased by stimulation with dobutamine. Group CR consists of previously published data from five animals subjected to 90 minutes of ischemia characterized by a reduction of regional work by 70% without continuous dobutamine infusion.](image1)

![Fig 6. Scatterplots of relation between subendocardial blood flow in the left ventricular myocardium at risk (mL·min⁻¹·g⁻¹, x axis) and infarct size (expressed as a percentage of the area at risk, y axis). For a given blood flow, infarct size was increased by the stimulation with dobutamine. Group CR consists of previously published data from five animals subjected to 90 minutes of ischemia characterized by a reduction of regional work by 70% without continuous dobutamine infusion.](image2)
cardial ATP stores (Table 3). Thus, the lower limit of a continuum of subendocardial blood flows to which the myocardium can adapt metabolically is nearly identical to the level of subendocardial blood flow tolerated without the development of myocardial infarction (see above). Of course, these are statistical threshold values that are not necessarily applicable to each individual animal and are valid only within the framework of our open-chest porcine preparation. Nevertheless, threshold values at which hibernation develops clearly exist.

**Inotropic Challenge and Precipitation of Myocardial Infarction**

The increase in infarct size during inotropic stimulation previously was attributed to the reduction in myocardial blood flow secondary to an increase in heart rate and a decrease in arterial pressure. When both the increase in heart rate and the decrease in arterial pressure were prevented by low-dose intravenous infusion of dobutamine, however, myocardial blood flow was increased and infarct size was reduced compared with control conditions. Although these prior studies addressed alterations in infarct size with the use of inotropic agents in the face of changes in hemodynamics and blood flow, the present study demonstrates that inotropic stimulation per se can impair the development of hibernation and finally precipitate myocardial infarction. In contrast to the above studies, the development of myocardial infarction in the present study cannot be simply attributed to reduced myocardial blood flow. Even for a given blood flow, infarct size was increased in the dobutamine-stimulated compared with the nonstimulated myocardium. Thus, enhanced energy expenditure by transient stimulation of contractile processes and more continuously by stimulation of noncontractile metabolic processes significantly contributes to the development of myocardial infarction in addition to the dobutamine-induced unfavorable redistribution of blood flow, which increases the severity of ischemia.

**Conclusions and Clinical Perspectives**

Successful hibernation of ischemic myocardium critically depends on the level of residual blood flow. Viable ischemic myocardium is characterized by the recovery of metabolic markers of ischemia toward control values. Prolonged inotropic stimulation of ischemic myocardium impairs this delicate adaptation process with further production of lactate and loss of myocardial high-energy phosphates. During continuous inotropic stimulation with dobutamine, both redistribution of blood flow and increased energy expenditure through contractile and noncontractile processes contribute to impair the development of hibernation and to precipitate myocardial infarction.

Of importance to the clinician is the ability to identify viable hibernating or stunned myocardium as opposed to tissue that is also dysfunctional but irreversibly damaged. Clearly, the combined use of imaging techniques that can identify and quantify regional contractile dysfunction together with metabolic imaging using positron emission tomography and assessment of high-energy phosphate concentrations using nuclear magnetic resonance spectroscopy offers the potential for making such differentiations. In addition, the use of a short-term inotropic challenge may be a useful adjunct maneuver to further distinguish hibernating from stunned myocardium, as the recruitment of inotropic reserve in hibernating but not in stunned myocardium is required for noncontractile processes is substantially less and may still be met during moderate ischemia. Although the increase in regional myocardial work was only transient, the increase in dP/dt max persisted throughout the 85 minutes of dobutamine stimulation, presumably secondary to a baroreflex in response to decreased arterial pressure (Table 1).
dium will be accompanied by metabolic deterioration. Although short-term inotropic stimulation thus might be of diagnostic value, more prolonged periods of inotropic stimulation are deleterious, as they impair the development of myocardial hibernation and precipitate myocardial infarction.

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