LABORATORY INVESTIGATION
VENTRICULAR PERFORMANCE

Elimination of exercise-induced regional myocardial dysfunction by a bradycardiac agent in dogs with chronic coronary stenosis

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ABSTRACT We have previously demonstrated that the beneficial effect of cardioselective β-blockade on exercise-induced ischemia is due entirely to negative chronotropism. Therefore we studied the effect of a new bradycardiac agent (UL-FS 49) in 10 dogs with chronic coronary artery stenosis produced by an ameroid constrictor. Regional myocardial function (sonomicrometers, wall thickness) and blood flow (microspheres) were measured during a control treadmill exercise bout and an identical run 3 hr later after the administration of UL-FS 49 (1.0 mg/kg iv). In the control run, heart rate increased from 114 ± 20 to 230 ± 19 beats/min and systolic wall thickening (%WT) in the poststenotic myocardium decreased from 23.3 ± 5.2% at rest to 9.3 ± 5.0%, a 60% reduction. Subendocardial blood flow in the ischemic area decreased from 1.04 ± 0.30 to 0.55 ± 0.40 ml/min/g, blood flow per beat decreased from 9.1 × 10⁻³ to 2.5 × 10⁻³ ml/g, and mean transmural flow failed to increase (1.06 ± 0.30 vs 1.08 ± 0.39 ml/min/g). During exercise with UL-FS 49, heart rate increased from 89 ± 10 to only 139 ± 10 beats/min. End-diastolic left ventricular pressure was increased compared with that during the control run (35.7 ± 3.0 vs 28.9 ± 5.5 mm Hg) but left ventricular peak systolic pressure and dP/dt were unchanged. %WT in the ischemic zone did not change significantly during exercise with UL-FS 49 (23.3 ± 7.9% at rest, 21.5 ± 8.4% during the run), and in the nonischemic zone it increased to the same extent as during the control run. Absolute subendocardial blood flow (0.75 ± 0.32 ml/min/g) and flow per beat (5.3 ± 2.0 × 10⁻³ ml/g) were significantly increased compared with those during the control run (p < .05), and transmural blood flow per beat increased to 9.8 ± 1.7 × 10⁻³ ml/g (p < .01). These data demonstrate that UL-FS 49 is an effective bradycardiac agent that can markedly attenuate exercise-induced ischemic dysfunction and improve regional perfusion without compromising contractile function of nonischemic areas or global left ventricular contractility.


CARDIOSELECTIVE β-adrenergic blockade with atenolol was shown by this laboratory to reduce exercise-induced regional myocardial ischemia and wall dysfunction in dogs with chronic, single-vessel coronary artery stenosis.¹ More recently, we used the same experimental preparation to demonstrate that the beneficial effect of atenolol is dependent on the reduction of heart rate during exercise. Atrial pacing during exercise to prevent the bradycardiac effect of atenolol eliminated all of the improvements observed at the reduced heart rate.² These findings stress the importance of heart rate control for reducing stress-induced myocardial ischemia and suggest the use of a specific bradycardiac agent for reducing exercise-induced ischemia and wall dysfunction to avoid the negative inotropic effect associated with β-blockade during exercise.¹

Specific bradycardiac agents are a chemically diverse group of compounds, but all are characterized by the production of sinus bradycardia at dosages that result in minimal secondary cardiovascular effects such as negative inotropism, membrane depressant antiarrhythmic effects, or hypotension.³ One such agent, UL-FS 49, has been shown to effectively reduce heart rate in conscious dogs without changes in blood pressure⁴ and was shown to increase ischemic myocardial...
perfusion and function in open-chest dogs. Therefore we used a conscious dog preparation of single-vessel coronary artery stenosis to test the effectiveness of the bradycardiac agent UL-FS 49 for reducing exercise-induced regional myocardial ischemia and wall dysfunction.

**Methods**

**Animal preparation.** The animals used in this study were handled in accordance with the animal welfare regulations of the University of California, San Diego, and the experimental protocol was approved by the Animal Subjects Committee of this institution.

Data from 10 adult mongrel dogs (20 to 35 kg) are reported. Before surgery, each dog received extensive training so that it could run comfortably on a motor-driven treadmill with minimal restraint and lie quietly on a table. On the day of surgery, dogs were initially tranquilized with acepromazine maleate (0.5 mg/kg im) and atropine (0.04 mg/kg im). Anesthesia was provided by sodium pentobarbital (30 mg/kg iv) and further analgesia was produced by morphine sulfate (0.5 mg/kg iv). A left lateral thoracotomy was then performed in the fifth intercostal space. A silicone rubber catheter (1.57 mm inner diameter, 3.18 mm outer diameter) was inserted into the descending thoracic aorta for later use in withdrawing arterial reference blood samples during microsphere injections. The pericardium was opened and sutured to the chest wall to cradle the heart and a second silicone rubber catheter was implanted in the left atrium through the appendage for microsphere injections. A stab wound was made in the left ventricular apex for insertion of a micromanometer (Königsberg P?) and a Tygon fluid-filled catheter (1.27 mm inner diameter, 2.29 mm outer diameter), both secured with a purse-string suture. Left ventricular pressure was measured through the fluid-filled catheter by an external transducer (Statham P23Db) at the estimated level of the right atrium to calibrate the micromanometer in situ.

The proximal left circumflex coronary artery was dissected free from surrounding tissue for a distance of approximately 2 cm. A single crystal (10 MHz) Doppler flow probe was placed around the vessel and an amniotic constrictor was positioned distal to the flow probe. The constrictor was designed to produce gradual constriction of the coronary artery and consists of a slotted casein ring encased in stainless steel (5 mm wide, diameter 8 mm). The original internal diameter of the constrictor was 2.3 to 3.0 mm and was matched to the size of the artery to provide a nonconstrictive fit at the time of implantation. A pneumatic occlusive cuff was placed distal to the amniotic constrictor to allow complete but reversible occlusion of the coronary artery.

Regional myocardial function was assessed with sonomicrometers (Triton Technologies) to measure left ventricular wall thickness. Two pairs of ultrasonic crystals (5 MHz) were implanted in each dog according to standard techniques. One pair of crystals was implanted in the posterolateral wall to measure a region in the potentially ischemic myocardium. The proper position of this pair was confirmed during surgery by performing a brief occlusion of the left circumflex artery to observe the prompt development of cyanosis and wall dysfunction. The other pair of crystals was implanted in the anterior wall of the left ventricle near the intraventricular septum to measure wall thickening in an area not rendered ischemic during circumflex coronary artery occlusion. Stainless-steel wires were sewn to the left atrium for subsequent electrical pacing.

The pericardium was left open and all wires and catheters exited the thorax through intercostal spaces adjacent to the thoracotomy and then run subcutaneously to the dog's back, where they were exteriorized and anchored with sutures. The thoracotomy was repaired in layers and the pneumothorax was evacuated through a chest tube. Ampicillin (6.6 g/day im) was administered throughout the surgery and for 3 days postoperatively.

**Experimental protocol.** Dogs were studied when a brief run on the treadmill eliciting a heart rate greater than 200 beats/min produced regional myocardial dysfunction such that systolic wall thickness (%WT) in the posterolateral wall decreased to less than 60% of the resting control value. %WT was defined as the difference between end-systolic and end-diastolic wall thickness, expressed as a percentage of the end-diastolic thickness.7 End-diastole was defined as the time when the first derivative of left ventricular pressure (dP/dt) crossed zero immediately before its positive peak value, and end-systole was defined as the time of maximum wall thickening within the period beginning 20 msec before peak negative left ventricular dP/dt and ending at peak negative dP/dt.8 Once this amount of exercise-induced regional myocardial dysfunction was observed, the study was performed on the same day.

Control measurements were made with the dog standing quietly on the treadmill, including the injection of microspheres (15 μm diameter) labeled with one of the following radionuclides: 141Ce, 153Gd, 111In, 51Cr, 133Sn, 103Ru, 95Nb, and 46Sc. Details of the measurement of blood flow in this laboratory have been published previously9 and follow the methods outlined by Heymann et al.10 Measurements of left ventricular pressure, wall thicknesses, and circumflex coronary artery flow velocity were made throughout the microsphere injection and the 2 min arterio- nal blood withdrawal to document a hemodynamic steady state. Dogs were then run at the speed (5 to 7 mph) and inclination (5% to 15%) determined previously to elicit the appropriate heart rate response and regional myocardial dysfunction. Once a steady state was observed, microspheres with a second radionuclide label were injected into the left atrium during arterial blood withdrawal. Dogs ran at least throughout the arterial withdrawal period, and data were collected for 30 min after the run with the dogs standing on the treadmill.

A second, identical run (same speed and inclination) was performed 3 hr after the control run. This interval period was chosen because we have previously demonstrated that repeated runs 3 hr apart without intervention are completely reproducible.11 Dogs were given UL-FS 49 (1,3,4,5-tetrahydro-7,8-dimethoxy-3-(2-(3,4-dimethoxyphenyl)ethyl) methylmimo)(propyl)-2H-3-benzazepin-2 on) (1.0 mg/kg iv), kindly supplied by Dr. Juergen Daemmgen (Dr. K. Thomae GmbH, Biberach, F.R.G.), 1 hr before the second run. Hemodynamic measurements were again made with the dogs standing on the treadmill before initiating the run. Once a steady state was apparent during the run with UL-FS 49, a third injection of microspheres was made. After the last withdrawal of arterial blood, seven of the dogs continued to run with the heart rate paced by atrial stimulation to match the rate observed during the control run (total run time 6 min). The run and atrial pacing were then stopped at a time to make both runs of equal duration and the dogs were again monitored for 30 min after the run.

At the end of the study, after euthanization, the hearts were removed with the instrumentation intact, cleaned, and placed in 10% formalin. Later, the atria, right ventricle, and epicardial fat were removed and the left ventricle was sliced perpendicularly to the long axis to produce a 2 cm wide ring of myocardium containing the ischemic zone sonomicrometer. The position of the ultrasonic crystals was carefully mapped to confirm proper orientation across the left ventricular wall and to ensure that the subendocardial crystal was near the endocardial surface (all crystals lay within the inner third of the ventricular wall). A transmural plug was then cut to include both ultrasonic crystals.
This was then cut into transmural thirds and weighed, and the gamma radiation was determined by a Packard Autogamma Spectrometer. The remainder of the ring was divided into additional transmural plugs and processed in a similar manner. We report only the blood flow at the two sonomicrometer locations (ischemic and control walls), but the remainder of the left ventricular ring was analyzed to ensure that the sonomicrometers were not in a perfusion border zone.

Data acquisition and analysis. Data were recorded on a Brush forced-ink recorder (Model 202) and on one-half inch magnetic tape with a Hewlett-Packard tape system. Data recorded on tape were played back for digitization and beat averaging with a Honeywell (Model 7600) tape recorder interfaced with an analog-to-digital converter and a PDP/11/03 computer. Twenty consecutive cardiac cycles were digitized at 5 msec intervals and averaged for each observation.

Statistical analysis was performed on data from three points in each run: (1) resting control, (2) steady-state running at the time of microsphere injection (approximately 3 min into the run), and (3) at the end of the run, at which time the heart rate was electrically paced during the run with UL-FS 49 to match the heart rate observed during the control run. Analysis of these data was done with an analysis of variance for repeated measures, and Tukey’s least significant difference test was used to determine which individual means differed when an overall difference was detected. A paired t test was applied to the regional blood flow data to compare specifically the control run flows with the flows during the UL-FS 49 run.

Results

Dogs were studied 16 ± 6 days postoperatively at a time when the ameroid constrictor produced a significant reduction of resting flow velocity (six dogs) or had completely occluded the left circumflex coronary artery (four dogs). In the dogs with an open circumflex artery, exercise did not produce an increase in coronary flow velocity. Thus antegrade blood flow through the circumflex artery was either absent or severely limited. An original recording from one study is shown in figure 1.
TABLE 1

Hemodynamics during a control run and an identical run after administration of UL-FS 49

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Mid-run</th>
<th>End run</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>114 ± 20</td>
<td>230 ± 19</td>
<td>231 ± 17</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>UL-FS run</td>
<td>89 ± 10</td>
<td>139 ± 10</td>
<td>230 ± 17</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>3227 ± 762</td>
<td>5027 ± 715</td>
<td>5122 ± 692</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UL-FS run</td>
<td>3372 ± 717</td>
<td>4803 ± 636</td>
<td>5382 ± 557</td>
</tr>
<tr>
<td>PSLVP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>138 ± 17</td>
<td>167 ± 19</td>
<td>171 ± 14</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UL-FS run</td>
<td>146 ± 15</td>
<td>160 ± 24</td>
<td>169 ± 28</td>
</tr>
<tr>
<td>EDLVP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>14.0 ± 5.0</td>
<td>28.9 ± 5.5</td>
<td>31.5 ± 4.8</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>UL-FS run</td>
<td>21.0 ± 5.1</td>
<td>35.7 ± 3.0</td>
<td>12.8 ± 7.8</td>
</tr>
<tr>
<td>PSLVP × heart rate (mm Hg/min × 10⁻³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>16.2 ± 4.3</td>
<td>40.2 ± 6.5</td>
<td>39.3 ± 4.1</td>
</tr>
<tr>
<td>p value</td>
<td>.08</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>UL-FS run</td>
<td>13.3 ± 2.2</td>
<td>23.7 ± 4.5</td>
<td>39.6 ± 6.0</td>
</tr>
</tbody>
</table>

Measurements made before start of run (Rest), during steady-state running when blood flow determination was made (Mid-run), and near the end of the runs when heart rates were matched by atrial pacing during the UL-FS 49 run (End run).

LV dP/dt = first derivative of left ventricular pressure; PSLVP = peak systolic left ventricular pressure; EDLVP = end-diastolic left ventricular pressure.

*p < .05 vs Rest; **p < .01 vs Rest; †p < .05 vs Mid-run; ANOVA, n = 10.

Hemodynamic variables. The hemodynamic data from all 10 dogs are summarized in Table 1. UL-FS 49 produced significant reductions of both resting and exercise heart rates (both p < .01); exercise heart rate was reduced by 91 beats/min. The diastolic interval during the control run was 100 ± 13 msec and significantly increased during the run with UL-FS 49 to 230 ± 39 msec (p < .01). Peak systolic left ventricular pressure was not affected by administration of UL-FS 49 but end-diastolic left ventricular pressure was significantly increased after UL-FS 49 both at rest and during exercise (both p < .01: Table 1). Left ventricular pressure at peak positive dP/dt (estimating arterial pressure at the onset of ventricular ejection) increased from a resting value of 83 ± 12 mm Hg to 99 ± 8 mm Hg (p < .05) during the control run and was not different during the run with UL-FS 49 (102 ± 15 mm Hg).

With the addition of atrial pacing, both heart rate (230 ± 17 beats/min) and diastolic interval (105 ± 15 msec) were identical to those observed during the control run. End-diastolic left ventricular pressure fell significantly and was substantially less than that observed during the control run (p < .01; Table 1). Left ventricular pressure at peak positive dP/dt was 102 ± 22 mm Hg thus being unchanged by atrial pacing.

Regional myocardial function. Regional %WT for both the control (anterior) wall and ischemic (posterior) wall is presented in Table 2, and %WT is presented in Figure 2.

Control wall. Absolute systolic wall thickening increased significantly during the control run (p < .05; Table 2, Figure 2). The administration of UL-FS 49 did not affect %WT at any observation, including the addition of atrial pacing at the end of the run.

Ischemic wall. Absolute systolic wall thickening in the posterior wall was 23.3 ± 5.2% at rest. Although somewhat less than resting %WT in the anterior wall, this does not indicate the presence of regional ischemic dysfunction since this value is not significantly different from %WT in the posterior wall measured 1 week postoperatively when the left circumflex artery was not constricted. (The difference between anterior and posterior wall function likely reflects the more basal placement of the posterior wall crystal pair and the apical placement of the anterior wall crystal pair; regional

TABLE 2

Regional wall thickening during exercise before and after administration of UL-FS 49

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Mid-run</th>
<th>End run</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norm. EDWT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>10.00</td>
<td>9.83 ± 0.31</td>
<td>9.80 ± 0.29</td>
</tr>
<tr>
<td>p value</td>
<td>.05</td>
<td>NS</td>
<td>10</td>
</tr>
<tr>
<td>%WT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>23.3 ± 5.2</td>
<td>9.3 ± 5.0</td>
<td>8.7 ± 5.5</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.021</td>
</tr>
<tr>
<td>Control wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norm. EDWT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>10.00</td>
<td>9.74 ± 0.46</td>
<td>9.79 ± 0.45</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.19</td>
</tr>
<tr>
<td>%WT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control run</td>
<td>37.7 ± 12.9</td>
<td>50.1 ± 19.6</td>
<td>46.1 ± 16.5</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Norm. EDWT = end-diastolic wall thickness normalized to a control resting value of 10.00; %WT = systolic wall thickening.

p value compares Control run with UL-FS run: *p < .05 vs Rest; **p < .01 vs Rest.
systolic function has been shown to increase significantly from the base to apex.\textsuperscript{14}

During the control run, \%WT decreased markedly in the posterior wall to 9.3 \pm 5.0\% (p < .01), a 60\% decrease, and remained unchanged throughout the run (table 2). Resting \%WT was not changed after administration of UL-FS 49, but \%WT during the subsequent run was significantly improved compared with that during the control run (p < .001) and not reduced from the resting value.

Increasing the heart rate to match that of the control run reduced \%WT in the posterior wall substantially to 12.6 \pm 8.3\%, but this was still significantly greater than \%WT during the control run at the same heart rate (p = .021).

Regional myocardial blood flow. Regional myocardial blood flow measured at the sites of the ultrasonic crystal pairs in the ischemic and control walls is summarized in table 3 and figure 3.

Control wall. During the control run, blood flow in the anterior wall increased transmurally (p < .01; figure 3). Blood flow in the subendocardium and mean transmural flow, when expressed as flow per beat, did not change from rest to exercise in the control run (table 3).

During the run after administration of UL-FS 49, blood flow still increased transmurally but was reduced compared with that during the control run (figure 3). Blood flow per beat increased compared with that at rest and during the control run (subendocardial flow/beat, p = .06; transmural flow/beat, p = .05) (table 3).

Ischemic wall. Mean transmural blood flow in the ischemic posterior wall did not change during the control run from the resting value. A marked transmural redistribution resulted in a significant reduction of subendocardial blood flow and increase in subepicardial blood flow (table 3 and figure 3). Subendocardial and mean transmural blood flow expressed as flow per beat were reduced significantly (table 3). Blood flow expressed as a fraction of flow to the control wall (“normalized” blood flow) was also significantly reduced during the control run.

During the run after administration of UL-FS 49, subendocardial blood flow was no longer significantly reduced compared with that at rest and was increased compared with that during the control run (p < .05, paired t test). Blood flow per beat (both subendocardial and mean transmural) was approximately doubled during the run with UL-FS 49; the change in transmural blood flow per beat was significant (p < .01) and it was no longer different from the resting value. “Normalized” blood flows changed similarly to blood flows per beat (table 3).

Discussion

This study documents the importance of tachycardia in causing exercise-induced regional myocardial ischemia and wall dysfunction and demonstrates the dramatic improvement in regional function possible when the tachycardia of exercise is controlled. This was accomplished with the new bradycardic agent UL-FS 49, which reduced both resting heart rate and the heart rate during treadmill exercise in a canine preparation of chronic single-vessel coronary artery stenosis. The 91 beat/min reduction of heart rate during exercise was accompanied by a substantial improvement in systolic wall thickening in the poststenotic myocardium so that it no longer decreased from the resting value. Furthermore, this marked bradycardia was not associated with reduced myocardial contractility, as shown by the unimpaired function of the nonischemic anterior wall and the lack of a decrease in left ventricular dP/dt before and during exercise. The ability to create significant

![Graph](http://circ.ahajournals.org/)

FIGURE 2. Regional myocardial function summarized for the ischemic posterior wall (top) and the control anterior wall (bottom). Control run data are represented by the gray bars, and data for the run after UL-FS 49 are represented by the striped bars. p values compare mean values of the two runs at the time of microsphere injection (RUN) and later in the run during atrial pacing in the UL-FS 49 run (END RUN). *p < .05; **p < .01 vs REST. Mean values given with standard deviation.
bradycardia during exercise without compromising myocardial contractility appears to largely prevent the development of regional contractile dysfunction in a collateral-dependent region of myocardium that exhibits severe exercise-induced ischemia before drug administration. However, the efficacy of UL-FS 49 may not be due entirely to its property as a specific bradycardic agent, since a small but persistent improvement in systolic wall thickening was observed during atrial pacing to prevent the bradycardia, suggesting the possibility that the drug could also have a vasodilatory effect. Nevertheless, the major beneficial effect of UL-FS 49 was observed when its bradycardic effect was intact, thereby supporting the conclusion that reduction of heart rate is its primary mode of action.

Brady cardia has multiple beneficial actions for the prevention of regional myocardial ischemia during exercise. The increase in the diastolic interval provides enhanced myocardial perfusion especially to the deeper layers. Also, reduced heart rate causes reduced oxygen demand per minute. As estimated by the product of left ventricular peak systolic pressure and heart rate (table 1), oxygen consumption was reduced by 42% during the run with UL-FS 49 compared with an identical run before its administration. If one views myocardial ischemia as an imbalance between oxygen delivery and oxygen demand, bradycardia serves to both increase delivery (increased diastolic perfusion time) and reduce demand. Recently, however, exercise-induced, steady-state ischemia has been preferentially described as an “absolute” ischemia rather than a “relative” ischemia in which oxygen demand exceeds supply, even though demand exceeds supply during the onset of exercise. In this view, the amount of regional wall thickening is directly dependent on, and matched to, the absolute subendocardial blood flow and oxygen delivery to the ischemic myocardium when in the steady state. Regional wall function (and presumably regional oxygen demand) decreases to a level compatible with the limited oxygen delivery, thereby making absolute blood flow to the ischemic myocardium the primary determinant of regional myocardial contraction. In this study, the absolute blood flow per beat (subendocardial) in the poststenotic myocardium during the run with UL-FS 49 was 204% of that observed in the control run, while regional wall thickening was increased by 212%. These data are consistent with the concept that exercise-induced regional ischemia represents an absolute reduction of regional perfusion with an associated reduction of regional function and suggest that increased perfusion results in increased regional wall function.

Despite the marked improvement in regional contractile function and blood flow during exercise after the administration of UL-FS 49, there was still hypoperfusion of the subendocardium in the ischemic zone.
The development of a transmural blood flow gradient has been well documented during regional ischemia at rest, during isoproterenol-induced ischemia, and during exercise-induced ischemia. Restricted coronary inflow to a region of myocardium associated with perfusion pressures below the range of autoregulation results in preferential perfusion of the outer wall on the basis of the transmural gradient of intramyocardial compressive forces. Since a primary determinant of the transmural wall stress is left ventricular pressure, the significant increase in diastolic left ventricular pressure during the UL-FS 49 run may have offset some of the potential improvement of blood flow to the subendocardium because of increased diastolic perfusion time. Furthermore, the substantial prolongation of the diastolic interval caused by UL-FS 49 may have compromised myocardial perfusion if the diastolic coronary arterial pressures were not adequate throughout the lengthened diastolic interval. Thus the combination of an elevated left ventricular end-diastolic pressure together with the possibility of reduced end-diastolic arterial perfusion pressure may have limited subendocardial blood flow during the exercise with UL-FS 49. A more moderate reduction in heart rate than the large decrease in the present study may be more advantageous in regulating the improvement associated with prolongation of diastole to compensate for the potential problem of reduced perfusion pressure and increased diastolic wall stress.

$\beta$-Adrenergic blockade with propranolol or atenolol has been shown to reduce exercise-induced regional myocardial ischemia and to improve wall dysfunction modestly in the same experimental preparation. More recently, the beneficial effect of atenolol was shown to depend on the reduction of exercise heart rate. Both propranolol and atenolol improved ischemic zone wall function but depressed regional function in nonischemic regions, while significantly reducing peak left ventricular systolic pressure and $dP/dt$. Thus the overall left ventricular performance and cardiac output after $\beta$-blockade are compromised to a greater extent than would be expected with reduced heart rate alone. Furthermore, the increased wall performance in the ischemic region during exercise with $\beta$-blockade may not be caused entirely by enhanced regional contractility, since there are significant decreases in peak systolic left ventricular pressure and therefore afterload. Conversely, the increases in systolic wall thickening in the ischemic zone during exercise with UL-FS 49 were at an unchanged systolic left ventricular pressure, suggesting enhanced contractility in the ischemic myocardium. In the control region,
normal enhancement of contractility during exercise and use of the Frank-Starling mechanism are suggested by the thinner wall at end-diastole and a trend toward increased %WT compared with that during the control run (table 2). Additionally, global left ventricular function during the run with UL-FS 49 was associated with utilization of the Frank-Starling mechanism, as shown by the significant increase in left ventricular end-diastolic pressure (table 1). Thus the bradycardiac agent UL-FS 49 increased ischemic regional wall performance by improving contractility (by increasing regional perfusion) and maintained or enhanced control wall function by utilizing preload reserve.

It has been shown that vasodilatory reserve exists in acutely ischemic myocardium\textsuperscript{22-24} and that this reserve can be utilized by means of adenosine,\textsuperscript{22-24} calcium-channel blockers,\textsuperscript{24} or $\alpha_2$-adrenergic blockade.\textsuperscript{26, 27} Recent clinical studies suggest that $\alpha$-adrenergic blockade can reduce regional myocardial ischemia.\textsuperscript{28, 29} In this context, it is interesting that atrial pacing at the end of the run with UL-FS 49 did not completely eliminate the beneficial effect on function in the ischemic wall observed at the reduced heart rate, as noted earlier. This finding is in sharp contrast to that reported previously with a similar protocol, in which the cardioselective $\beta$-adrenergic blocker atenolol was studied and regional function deteriorated with the onset of atrial pacing to a level below that observed during the control run.\textsuperscript{2} The beneficial effect of UL-FS 49 not associated with bradycardia suggests the possibility of a coronary vasodilator effect. UL-FS 49 is a chemical congener of verapamil, which has such vasodilator properties.\textsuperscript{30} However, Daemmgen et al.\textsuperscript{5} reported no bradycardia-independent improvement in regional ischemic dysfunction in an anesthetized dog preparation in which a related compound, AQ-AH 208, exhibited a beneficial effect even without reduced heart rate. The small beneficial effect of UL-FS 49 remaining during the pacing protocol may be due to the significant reduction in end-diastolic left ventricular pressure observed at that time (left ventricular end-diastolic pressure was significantly increased by UL-FS 49 when its bradycardiac action was intact). The reduced end-diastolic pressure was associated with slightly increased wall thickness (table 2), thus suggesting a smaller heart size and reduced myocardial oxygen consumption.\textsuperscript{31} Using this experimental preparation, Kumada et al.\textsuperscript{32} reported a significant reduction in end-diastolic left ventricular pressure and a small decrease in peak systolic left ventricular pressure during exercise with isosorbide dinitrate without a heart rate effect. Thus the small beneficial effect remaining after pacing had prevented bradycardia may be a result of preload reduction in the exercising dog.

The calcium-channel blockers verapamil and diltiazem have been studied in this animal preparation and had similar effects.\textsuperscript{11, 33} Both reduced exercise heart rate by approximately 20 beats/min and had minimal effects on left ventricular peak or end-diastolic pressures and $dP/dt$. Verapamil improved ischemic systolic wall thickening from 5.9% to 11.5%,\textsuperscript{33} whereas diltiazem improved it from 5.2% to 10.2%.\textsuperscript{11} The 91 beat/min reduction in heart rate observed with UL-FS 49 is substantially greater than that reported for verapamil or diltiazem. Although UL-FS 49 caused a significant increase in end-diastolic left ventricular pressure at the reduced heart rate during exercise, this likely reflects the prolonged diastolic interval and increased filling. The greater bradycardia produced by UL-FS 49 also was associated with a larger improvement in ischemic zone systolic wall thickening. However, the degree of dysfunction reported during the control run in the present study is slightly less than that in previous studies employing diltiazem and verapamil. Thus the action of UL-FS 49 is similar to both verapamil and diltiazem except for the greatly accentuated bradycardia.

This study has demonstrated the dominant role of tachycardia in the genesis of exercise-induced regional myocardial ischemia and contractile dysfunction. With the new bradycardiac agent UL-FS 49, the tachycardia of exercise was significantly attenuated, resulting in increased regional blood flow and elimination of the regional dysfunction observed in the control run. The specificity of UL-FS 49 for bradycardia provided a significant reduction of heart rate without compromising contractility of the nonischemic myocardium, the systolic left ventricular pressure, or left ventricular $dP/dt$, thereby preserving overall left ventricular performance. Potential application of this therapeutic strategy to the treatment of effort angina pectoris may have distinct advantages over $\beta$-adrenergic blockade, since the beneficial effect of reduced exercise heart rate is retained without loss of ventricular contractility.

We thank Margaret R. Hill, Denice Jio, Sergio Martinez, and Kathy Kohlhaas for their technical assistance in performing these studies. In addition, we express our gratitude to Thomas Widmann, M.D., and Mark Miller for their computer and electronics support of this work and to Elizabeth Gilpin for providing the statistical analyses of these data.

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LABORATORY INVESTIGATION—VENTRICULAR PERFORMANCE

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Circulation. 1987;75:661-669
doi: 10.1161/01.CIR.75.3.661

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