Effects of diltiazem on cardiac function and regional blood flow at rest and during exercise in a conscious rat preparation of chronic heart failure (myocardial infarction)

HELMUT DREXLER, M.D., JOSEPH W. DEPENBUSCH, M.D., ARNOLD G. TRUOG, M.D., ROBERT ZELIS, M.D., AND STEPHEN F. FLAIM, PH.D.

ABSTRACT The effects of intravenous infusion of diltiazem on regional blood flow (radioactive microspheres), hemodynamics, and maximum rate of oxygen consumption were evaluated in conscious rats with congestive heart failure caused by large myocardial infarction (n = 10, infarct size 41.8% of left ventricle) and compared with data obtained from rats subjected to sham surgical procedures (n = 9). In both groups data were obtained at rest and during submaximal treadmill exercise during alternate infusion of diltiazem and saline. In the group with heart failure, diltiazem increased stroke volume at rest and during exercise (p < .05), reduced heart rate (p < .05), and improved cardiac output during exercise (p < .05) without increasing left ventricular end-diastolic pressure in any of the animals. Blood flow to renal and splanchnic circulations was reduced in the group with heart failure but was increased by diltiazem to values similar to those observed in sham-operated animals. Although skeletal muscle flow during exercise was significantly increased by the drug, maximal rate of oxygen consumption was not, indicating unchanged oxygen availability within working muscle. Thus diltiazem caused redistribution of blood flow to kidney and gut in animals with myocardial infarction and failure, thereby restoring blood flow to circulatory beds known to be impaired in this setting.


ALTHOUGH BENEFICIAL hemodynamic effects of calcium blockers in heart failure have been demonstrated,1–3 their use in this setting is still somewhat controversial because of the negative inotropic effects produced by these agents.4,5 In chronic heart failure caused by congestive cardiomyopathy, the dilated left ventricle may be sensitive to changes in inotropic function, and, in high output states (e.g., mitral regurgitation), impaired left ventricular performance may reduce the limit to which systemic ejection can increase in response to peripheral arterial vasodilation as reported recently.6 By contrast, calcium blockers may be of particular interest in chronic heart failure caused by coronary artery disease because of their positive effects on coronary blood flow, their antiarrhythmic potential, and their arterial vasodilator capacity.

Although vasodilators are widely used to improve central hemodynamics in patients with heart failure, limited information on the regional vascular effects produced by these agents in the setting of chronic heart failure is available. Nevertheless, the importance and potential of vasodilator therapy to alter the fractional distribution of cardiac output in congestive heart failure have been recognized.7 In particular, their ability to augment nutritional skeletal muscle blood flow and, in turn, to increase exercise capacity has been viewed with increasing interest.8–10 Redistribution of blood flow to regional circulations known to be impaired in heart failure may have beneficial effects after long-term therapy. For example, improved renal blood flow may increase diuresis and thereby reduce sodium content. In this context, it has been speculated that one
beneficial effect of long-term nitroglycerin therapy may be related to a vasodilator effect in the renal, splanchnic, and cutaneous beds rather than to a vasodilator effect in the skeletal muscle bed.\textsuperscript{11} Recent data from this laboratory indicate that calcium blockers act as potent renal vasodilators and increase skeletal muscle blood flow in conscious rats during exercise.\textsuperscript{12, 13}

Accordingly, in this study we examine the effect of diltiazem, the least negative inotropic calcium blocker in isolated tissues,\textsuperscript{14, 15} currently available, on cardiac function and regional blood flow in a rat preparation of heart failure secondary to large myocardial infarction. To investigate whether oxygen availability within working skeletal muscle is improved, blood flow measurements were complemented by determinations of maximum rate of oxygen consumption.

Methods

Experimental preparations. Male Sprague-Dawley rats weighing 334 ± 10 g were anesthetized with 0.3 g/kg chloralhydrate (intraperitoneally), intubated via tracheotomy, and placed on a Harvard respirator (Harvard Apparatus Model 665). A thoracotomy was performed in the left fifth intercostal space and the left coronary artery was ligated approximately 2 mm from its origin with a 6-0 suture. In the sham-operated animals, the suture was tied loosely so as not to obstruct coronary flow. The rats were awake within 5 to 30 min after coronary ligation. With this method, the 24 hr mortality rate was 35% for the group with infarction and 5% for the sham-operated group. The surviving rats were maintained on standard rat chow, and subsequent experimental procedures were started 42 days after surgery. During this postsurgical period, the mortality rate in the group with infarction was approximately 15%.

Instrumentation. With animals under halothane anesthesia (1% to 2% in oxygen), polyethylene catheters (PE 50) were placed in the left ventricle (via the right carotid artery), in the caudal artery, and in the right jugular vein. Catheter positions were determined by pressure waves (typical left ventricular pressure tracing upon entering the left ventricle) detected by Statham P23Gb pressure transducers and displayed on an Electronics for Medicine recorder (AR-6). The left ventricular and right jugular catheters were brought through a subcutaneous tunnel to the dorsal cervical region. After closure, animals were allowed to recover for a minimum of 3 hr before experimental procedures were initiated. This recovery period has been found to be of sufficient duration to ensure a return to steady-state conditions in the rat.\textsuperscript{16}

Regional blood flow. Radioactive microspheres (3M Co., St. Paul, MN), 15 ± 5 µm in diameter, were used to measure regional blood flow according to the reference sample technique,\textsuperscript{17, 18} as adapted for use in the rat.\textsuperscript{19, 20} A detailed presentation of the radioative microsphere technique as used in this study has been described previously.\textsuperscript{16, 21, 22} Four different radionuclide-labeled (\textsuperscript{141}Ce, \textsuperscript{85}Sr, \textsuperscript{95}Nb, \textsuperscript{48}Sc) microsphere species, with specific activities of approximately 12 mcCi/g, suspended in normal saline plus 0.01% polysorbate 80 (TWEEN 80; Sigma Chemical Co., St. Louis, MO) were used in rotating sequence. TWEEN 80, which was added to retard microsphere aggregation, did not cause hemodynamic changes in any of the animals studied. Similar results have been reported previously from studies on conscious rats\textsuperscript{23} and dogs.\textsuperscript{24} The final specific activity of the microsphere suspension was approximately 0.01 mCi/ml of suspending agent. The microsphere suspension was thoroughly mixed by agitation and sonication (Heat Systems Ultrasonics Sonicator Model W 200 R) immediately before each injection. One-half milliliter of microsphere suspension, approximately 150,000 microspheres, was then injected in the left ventricle through the catheter over a 15 sec period, followed immediately by a 1 ml heparinized saline flush over a 15 sec period. One minute before the injection, withdrawal of blood was begun via the caudal arterial catheter at a rate of 0.2 ml/min with a Harvard pump (Model 907). The total withdrawal period equaled 4 min for each injection and blood obtained at this time was used as the blood flow reference sample. At the end of the study, animals were killed by injection of pentobarbital in the left ventricle; organs as well as tissue samples were then removed. All samples were blotted, weighed, and transferred to a two-channel gamma scintillation counter (Packard Auto-Gamma Spectrometer Model 5230) for determination of radioactivity levels. Sample size and height were altered to obtain, as nearly as possible, equal total counts in all samples, thereby reducing error due to nonuniform counting efficiency over large ranges in emission rates. The average weight of tissue samples was approximately 0.5 g. However, this value was varied to ensure that both the coincident counting was avoided and that a sufficient number of microspheres were present to provide accurate flow measurement. Except for the tissue samples from the adrenals, biceps, and soleus, the number of microspheres present in the samples was greater than 200 as estimated by comparison with the counts of the reference tubes. This number of microspheres has been found to be sufficient for accurate determination of blood flow.\textsuperscript{24} Each channel was set to record emissions at the peak energy level of a single isotope for 5 min through a window of 50 keV. A Digital Equipment Corp. PDP 11/40 computer was programmed to calculate regional blood flow as well as total cardiac output according to the method of Wagner et al.\textsuperscript{18}

Random samples of microspheres were periodically analyzed under a microscope equipped with an optical micrometer to measure actual microsphere diameter and to determine the effects of sonication. The position of the peak emission energy levels for each radionuclide-tagged microsphere species was periodically checked to avoid counting errors caused by drift in the detecting apparatus. The total injected counts were estimated from the average number of counts in 10 tubes, each containing the same known dilution of the total volume of each microsphere injection.

For regions where total flow was not measured (skin, skeletal muscle, gastrointestinal tract), estimates for each animal were made on the basis of measured flow per 100 g of tissue and projected body weight percentages for each tissue in the rat (skin, 320; skeletal muscle, 454; gastrointestinal tract, 53 g/kg of body weight).\textsuperscript{25} Bilateral samples of eight different leg and dorsal muscles weighing at least 10 g were used for measurement of skeletal muscle blood flow.

Blood flow to the free wall of the right ventricle was used as a measure of noninfarcted coronary blood flow, since microsphere trapping in noninfarcted left ventricular tissue was not determined separately.

Hemodynamics. Cardiac output at the time of the injection was determined by the use of the radioactive microsphere technique described by Heymann et al.\textsuperscript{17} Cardiac output and stroke volume data are expressed as flow per kilogram of body weight. Tracings from the left ventricular catheter were used to obtain heart rate as well as left ventricular peak systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP). Stroke volume was calculated from cardiac output and heart rate. Total vascular resistance was determined from cardiac output and mean arterial pressure data. Stroke work was esti-
mated by the following formula: stroke work = (stroke volume) 
× 0.0144 × (LVSP − LVEDP). With the exception of cardiac output, hemodynamic data were collected immediately before the microsphere injection.

**Determination of infarct size.** After the rats were killed, the left ventricle and ventricular septum were separated, weighed, and fixed in 10% formalin. The left ventricle was cut in four transverse slices from apex to base. Five micrometer sections were cut and stained with Masson’s trichrome stain and mounted.26 With a planimeter Digital Image Analyzer (MOP 3, Carl Zeiss), the endocardial circumference of the infarcted and noninfarcted portions of the left ventricle were determined. The infarcted circumference of all four slices was summed and then expressed as ratio of the summed circumference of the left ventricle. For all animals with infarction, myocardial infarction was transmural with a mature scar located at the left anterior free wall. Area measurements of infarct size were not made because these have been shown to underestimate infarct size as a result of resorption of necrotic tissue and subsequent wall thinning26 and late development of compensatory myocardial hypertrophy.27

**Oxygen consumption.** Maximum rate of oxygen consumption (VO2max) was measured by the flow-through mask technique.28 Room air was drawn through the mask by a vacuum pump at 4 liters/min. A fraction of expired flow (250 ml/min) was drawn through a flowmeter (Model R-1, Applied Electrochemistry) and connected to an oxygen analyzer (N-22M 3A-unit, Applied Electrochemistry, Sunnyvale, CA), which was calibrated with room air. Both H2O and CO2 absorbers were imposed in the line before the flowmeter and analyzer. Thus VO2 was calculated by the equation VO2 = V E × (FlO2 − FEO2) × (1 − FlO2)−1, where VE = expired minute volume, FlO2 = fraction of inspired O2, and FEO2 = fraction of expired O2. Maximal VO2 (VO2max) was marked by a point at which higher physical workload did not result in a further increase in VO2. VO2max was generally achieved at the fourth exercise stage (105% of maximal exercise capacity determined on the previous day by standardized incremental steps). Submaximal VO2 was marked at 80% of VO2max and the respective workload was applied for subsequent blood flow studies.

**Experimental protocol.** Maximal exercise capacity of all animals was determined during progressive treadmill exercise (35, 50, and 140 ft/min), with increasing workload every 2 min, 42 days after myocardial infarction or sham operation. After a 24 hr recovery period, a PE 50 catheter was placed in the right jugular vein and the animals were allowed to recover for a minimum of 3 hr before experimental procedures were initiated.16 At this time, either diltiazem (Marion Laboratories, Kansas City, MO) in saline (0.4 mg/ml) or 0.9% saline (at similar infusion rates) were infused. Diltiazem was infused at a rate of 0.067 mg/kg/min for 15 min and then at a rate of 0.013 mg/kg/min until the end of the exercise period. The total dose of diltiazem was approximately 1 mg/kg, which has been found to reduce mean arterial pressure by approximately 10% in normal rats.12 Fifteen minutes after starting the infusion of diltiazem or saline, submaximal and maximal VO2 values were determined during progressive treadmill exercise. The initial speed of the treadmill was 30% of the maximal exercise capacity (determined the day before) and was increased after 2 min each to 55%, 80%, and 105%. This protocol was applied to ensure similar exercise time for all rats. The protocol was repeated with the alternate infusion (diltiazem and saline) after a recovery period of 3 hr. This period has been found to be sufficient for return of hemodynamics to baseline and for repetition of VO2 measurements. The selection of animals with infarction was based on a VO2max of less than 70 ml/kg/min, a criterion that has been noted previously to indicate impaired left ventricular function and large myocardial infarction (unpublished observations). Five animals, which did not meet this inclusion criterion, were excluded from blood flow measurements. After 24 hr, PE 50 catheters were placed in the left ventricle and caudal artery under halothane anesthesia and, after recovery, diltiazem or saline was again administered as described above. Fifteen minutes after drug infusion, hemodynamic values were determined and microspheres were injected. Submaximal exercise (80% of maximal exercise capacity) was then begun and measurement of hemodynamics and injection of microspheres were again performed during the last minute of the exercise period. The protocol was repeated with alternate infusion after a recovery period of 3 hr.

**Statistical analysis.** Results are reported as mean ± SEM. All data were evaluated with three-way analysis of variance of repeated measures applying one grouping (infarction and sham) and two trial factors29 (rest/exercise and saline/diltiazem) followed by calculation of the simple main effects.30

**Results**

Effect of myocardial infarction and diltiazem on hemodynamics. Hemodynamic and blood flow data were determined in nine sham-operated rats and 10 animals with infarction. The average infarct size, determined histologically at postmortem examination, was 41.8 ± 1.6% of the left ventricular circumference (range 35% to 50%).

Hemodynamic data for both groups of animals during administration of saline and diltiazem are given in table 1. Arterial pressure was significantly decreased and LVEDP was significantly elevated, and neither parameter changed further with exercise. At rest, baseline cardiac output was not reduced in rats with infarction; however, at exercise, cardiac output, stroke volume, and stroke work were significantly lower in animals with infarction compared with sham-operated animals.

In sham-operated animals at rest, diltiazem significantly increased cardiac output, stroke volume, and stroke work with concomitant reduction in systemic vascular resistance. In animals with infarction, mean arterial pressure, LVSP, and heart rate were significantly lower with diltiazem. In sham-operated animals, only mean arterial pressure was reduced by diltiazem. Diltiazem increased cardiac output in sham-operated animals but not in animals with infarction. This difference was probably related to the fact that diltiazem reduced heart rate in animals with infarction but not in sham-operated animals. The fact that diltiazem increased stroke volume in both groups supports this conclusion.

In both groups during exercise, diltiazem significantly increased cardiac output, stroke volume, and stroke work compared with saline. In the animals with infarction, systemic vascular resistance, mean arterial
TABLE 1
Effects of heart failure and diltiazem on hemodynamics (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Sham-operated animals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113 ± 5</td>
<td>103 ± 5\textsuperscript{a}</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>168 ± 4</td>
<td>164 ± 3</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>447 ± 10</td>
<td>437 ± 11</td>
</tr>
<tr>
<td>CO (ml/min/kg)</td>
<td>221 ± 16</td>
<td>264 ± 26\textsuperscript{a}</td>
</tr>
<tr>
<td>SV (ml/beat/kg)</td>
<td>0.50 ± 0.04</td>
<td>0.60 ± 0.05\textsuperscript{a}</td>
</tr>
<tr>
<td>SVR (mm Hg/kg/min/ml)</td>
<td>0.53 ± 0.05</td>
<td>0.49 ± 0.06\textsuperscript{a}</td>
</tr>
<tr>
<td>SW (g/kg)</td>
<td>1.11 ± 0.08</td>
<td>1.32 ± 0.11\textsuperscript{a}</td>
</tr>
</tbody>
</table>

| Animals with infarction|                       |                        |                       |                        |
| MAP (mm Hg)            | 98 ± 4\textsuperscript{a} | 88 ± 4\textsuperscript{a, b} | 91 ± 5\textsuperscript{a} | 85 ± 4\textsuperscript{a, b} |
| LVSP (mm Hg)           | 153 ± 5\textsuperscript{a} | 140 ± 4\textsuperscript{a, b} | 149 ± 6\textsuperscript{a} | 143 ± 5\textsuperscript{a, b} |
| LVEDP (mm Hg)          | 27 ± 4\textsuperscript{a} | 28 ± 4\textsuperscript{a} | 28 ± 4\textsuperscript{a} | 27 ± 4\textsuperscript{a} |
| HR (beats/min)         | 435 ± 12              | 403 ± 9\textsuperscript{a, b} | 498 ± 9               | 482 ± 13               |
| CO (ml/min/kg)         | 204 ± 14              | 213 ± 16               | 239 ± 16\textsuperscript{a} | 295 ± 21\textsuperscript{b} |
| SV (ml/beat/kg)        | 0.47 ± 0.03           | 0.53 ± 0.04\textsuperscript{a} | 0.48 ± 0.03\textsuperscript{a} | 0.61 ± 0.05\textsuperscript{b} |
| SVR (mm Hg/kg/min/ml)  | 0.43 ± 0.03           | 0.44 ± 0.05            | 0.40 ± 0.03\textsuperscript{a} | 0.30 ± 0.03\textsuperscript{b} |
| SW (g/kg)              | 0.88 ± 0.11           | 0.87 ± 0.10\textsuperscript{a} | 0.85 ± 0.10\textsuperscript{a} | 1.01 ± 0.09\textsuperscript{a, b} |

MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; SW = stroke work.

\textsuperscript{a}Statistically significant compared with respective data from sham-operated animals.

\textsuperscript{b}Statistically significant compared with respective data during infusion of saline.

pressure, and LVSP were significantly reduced during infusion of diltiazem and exercise (table 1).

Effect of myocardial infarction and diltiazem on regional blood flow. Data for skeletal muscle blood flow and vascular resistance are presented in figure 1. At rest, diltiazem significantly increased skeletal muscle blood flow in sham-operated rats but not in animals with infarction, whereas systemic vascular resistance was reduced in both groups by the drug. During exercise, blood flow to working muscle was reduced in animals with infarction compared with sham-operated animals. Diltiazem increased skeletal muscle blood flow during exercise in both groups; however, this increase was statistically significant only for the group with heart failure.

Skeletal muscle vascular resistance was substantially reduced by exercise in both groups. Diltiazem caused a slight but nonsignificant further augmentation of this response in both groups.

The effects of diltiazem on renal blood flow and vascular resistance are given in figure 2. Renal blood flow at rest was significantly lower in the group with infarction compared with the sham-operated group. Diltiazem increased renal blood flow in the group with infarction to levels similar to those of the sham-operated animals during infusion of saline. Renal vascular resistance at rest was significantly reduced in both groups by diltiazem. During exercise, a similar response to the drug was observed; however, these changes were statistically significant for renal vascular resistance only in the group with infarction.

Blood flow to the right ventricle was similar for both groups at rest and during exercise (table 2). Diltiazem increased right ventricular blood flow at rest, but not during exercise, in both groups. In general, right ventricular coronary resistance demonstrated the opposite pattern, but the change was statistically significant for the group with infarction only at rest (table 3). In contrast to right ventricular blood flow, atrial blood flow at rest was elevated for the group with infarction compared with the sham-operated group (table 2), which may indicate increased oxygen demand due to congestive heart failure. Diltiazem further increased atrial blood flow and reduced vascular resistance at rest in the group with infarction.

Data for cutaneous blood flow and vascular resistance are presented in figure 3. Data from two different cutaneous beds were obtained: the dorsal cervical region and the lateral hind limb region. At rest, diltiazem increased cutaneous blood flow in both groups. These changes were significant for blood flow to dorsal skin in the sham-operated group and in both regions in the group with infarction. During exercise, no significant effect of diltiazem on cutaneous blood flow was ob-
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FIGURE 1. Average skeletal muscle blood flow and vascular resistance at rest and during exercise in sham-operated rats (n = 9) and rats with infarction (n = 10) during infusion of saline (SAL) and diltiazem (DZ). Asterisks indicate statistical significance (p < .05) between comparable data for the two groups. Daggers indicate statistical significance comparing respective saline and diltiazem data. Data are plotted as mean ± SEM.

served. In general, cutaneous vascular resistance was reduced by the drug; the difference was significant for the hind limb (at rest) and dorsal regions (at exercise) of the group with infarction only.

Total gastrointestinal blood flow in sham-operated animals was only slightly increased by diltiazem at rest and during exercise (rest/exercise: saline 202/104, diltiazem 237/120 ml/min/100 g). However, gastrointestinal blood flow was significantly augmented in animals with infarction at rest (rest/exercise: saline 164/85, diltiazem 211/107 ml/min/100 g; p < .05). Gastrointestinal vascular resistance was significantly reduced by diltiazem in animals with infarction at rest and during exercise (rest/exercise: saline 6.27 ± 0.46/11.2 ± 0.83, diltiazem 4.82 ± 0.8/9.12 ± 1.16 mm Hg/100 g/min/ml, p < .05) but no effect was seen in the sham-operated group (rest/exercise: saline 5.76 ± 0.43/10.6 ± 1.26, diltiazem 4.69 ± 0.57/8.97 ± 0.54 mm Hg/min/ml). Hepatic arterial blood flow was reduced in the group with infarction compared with the sham-operated group and was increased with diltiazem both at rest and during exercise in the animals with infarction. Concomitantly, hepatic arterial vascular resistance decreased but the difference was statistically significant only for the exercise data. In the sham-operated group, hepatic arterial blood flow and vascular resistance were unchanged by the drug.

Blood flow to the spleen was not affected by diltiazem either in sham-operated animals or in animals with infarction, although vascular resistance was significantly reduced by diltiazem at rest in both groups.

Data for blood flow and vascular resistance obtained from other circulatory beds are presented in tables 2 and 3. These data indicate that diltiazem had little effect in the sham-operated group. In the group with infarction, adrenal blood flow was significantly reduced compared with the sham-operated group and increased significantly with diltiazem both at rest and during exercise. Concomitantly, adrenal resistance decreased with diltiazem. Blood flow to the brain was augmented by diltiazem at rest and, in part, during exercise in the group with infarction while vascular resistance in the brain decreased. Although similar changes were observed in the sham-operated group, these differences did not reach statistical significance except for cerebral vascular resistance at rest.

Effect of diltiazem on submaximal and maximal VO2. Diltiazem did not effect submaximal or maximal VO2 values, either in sham-operated animals (submaximal/ maximal: saline 64.8 ± 1.8/74.4 ± 1.9, diltiazem

KIDNEY

FIGURE 2. Renal blood flow and vascular resistance at rest and during exercise in sham-operated rats and rats with infarction during infusion of saline (SAL) and diltiazem (DZ). See legend to figure 1 for definition of symbols.
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Table 2
Effects of heart failure and diltiazem on regional blood flow (ml/min/g, mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated animals</th>
<th>Animals with infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Diltiazem</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Atria</td>
<td>2.16 ± 0.21</td>
<td>3.01 ± 0.61</td>
</tr>
<tr>
<td>RV</td>
<td>5.30 ± 0.55</td>
<td>8.14 ± 1.39</td>
</tr>
<tr>
<td>Lungs</td>
<td>1.61 ± 0.25</td>
<td>2.08 ± 0.32</td>
</tr>
<tr>
<td>Adrenals</td>
<td>4.94 ± 0.59</td>
<td>5.68 ± 0.96</td>
</tr>
<tr>
<td>Liver</td>
<td>0.93 ± 0.33</td>
<td>1.12 ± 0.57</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.92 ± 0.37</td>
<td>2.71 ± 0.44</td>
</tr>
<tr>
<td>Testes</td>
<td>0.28 ± 0.03</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.03 ± 0.06</td>
<td>1.22 ± 0.13</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>1.23 ± 0.13</td>
<td>1.42 ± 0.11</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.81 ± 0.06</td>
<td>0.89 ± 0.11</td>
</tr>
</tbody>
</table>

RV = right ventricle.

*Statistically significant compared with respective control data from sham-operated animals.

*Statistically significant compared with respective control data during infusion of saline.

65.4 ± 1.9/74.9 ± 1.3 ml/kg/min) or in animals with infarction (submaximal/maximal: saline 55.8 ± 2.1/61.9 ± 1.9, diltiazem 56.7 ± 2.2/63.8 ± 2.6 ml/kg/min). However, submaximal and maximal VO₂ values were significantly reduced in the group with infarction compared with the sham-operated group (p < .01 for submaximal and p < .005 for maximal VO₂).

Discussion

It is evident, particularly when comparing the exercise data of both groups, that heart failure occurred in this animal preparation of large myocardial infarction. Depressed cardiac performance is documented by elevated resting LVEDP, depressed resting LVSP, and reduced cardiac output and stroke work during exercise. Because of the concomitant reduction in mean arterial pressure, total and, in part, regional vascular resistances were not increased. A similar observation has recently been reported for rats with large myocardial infarctions.[31]

Redistribution of blood flow in the animals with infarction included reduced flow to kidney, gut, and liver, circulatory beds known to be impaired in heart failure. The results of the present study indicate that the "calcium channel blocker" diltiazem increased blood flow to the renal, splanchnic, and cutaneous circulations of rats with heart failure under resting conditions. These effects were attenuated during exercise. Reports of vasodilation of hepatic, mesenteric, and renal arteries by diltiazem in anesthetized dogs[32,33] and normal rats[12] are available. By comparing data from both groups of animals, it appears that the effects of diltiazem on those circulations under a high degree of sympathetic control are more pronounced in the infarction group. This may indicate a capacity of diltiazem to override and attenuate the increased sympathetic tone that occurs in these circulatory beds in the setting of congestive heart failure. It has been suggested that diltiazem interacts with the sympathetic reflex constrictor mechanisms that are induced by the systemic hypotensive effect of the drug.[34] These results obtained from conscious animals are supported by the results of studies in isolated preparations, which suggest that diltiazem inhibits the norepinephrine release from sympathetic nerve terminals.[35,36] Thus the mechanism by which diltiazem limits reflex vasoconstriction may be related in part to an inhibition of norepinephrine release.[37]
TABLE 3
Effects of heart failure and diltiazem on regional vascular resistance (mm Hg/g/min/ml)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Sham-operated</td>
<td>Saline</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>animals</td>
<td>Saline</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Atria</td>
<td>38.2 ± 3.9</td>
<td>26.4 ± 3.0b</td>
</tr>
<tr>
<td>RV</td>
<td>18.1 ± 1.4</td>
<td>12.5 ± 1.0b</td>
</tr>
<tr>
<td>Lungs</td>
<td>33.0 ± 10.7</td>
<td>331.1 ± 30.0</td>
</tr>
<tr>
<td>Adrenals</td>
<td>71.6 ± 9.3</td>
<td>50.2 ± 5.7b</td>
</tr>
<tr>
<td>Liver</td>
<td>71.6 ± 9.3</td>
<td>50.2 ± 5.7b</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>103.7 ± 7.1</td>
<td>74.0 ± 11.4b</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>103.7 ± 7.1</td>
<td>74.0 ± 11.4b</td>
</tr>
<tr>
<td>Midbrain</td>
<td>120.7 ± 7.6</td>
<td>89.1 ± 12.9b</td>
</tr>
</tbody>
</table>

RV = right ventricle.

Statistically significant compared with respective control data from sham-operated animals.

Statistically significant compared with respective control data during infusion of saline.

In the setting of congestive heart failure, blood flow to the renal, cutaneous, and gastrointestinal circulations is generally reduced. A redistribution of blood flow by diltiazem appears to restore the circulation to these beds and therefore may improve diuresis and gastrointestinal function in this setting. It is clear from the data for hepatic arterial blood flow both at rest and, in particular, during exercise, that this beneficial effect of diltiazem is limited by the excessive exercise-induced sympathetic activation in congestive heart failure.

It should be noted that diltiazem did not result in overt precipitation of congestive heart failure in any of the animals with infarction, although mean arterial pressure and LVSP were consistently reduced by the drug. Indeed, the significant reduction of heart rate, particularly in comparison to the sham-operated group, suggests that the hemodynamic state of the animals with infarction was improved by the drug. However, it should be noted that part of the negative chronotropic effect of the drug may have been due to the known inhibitory action of diltiazem on the slow inward current of pacemaker cells. LVEDP was unchanged by diltiazem both at rest and during exercise and stroke volume was increased, indicating that a reduction of afterload resulted in an augmentation of cardiac output. In contrast to the present findings, left ventricular function was found to be depressed by diltiazem in a preparation of chronic volume overload and high output failure. The ability of diltiazem to improve hemodynamics by afterload reduction in states of high output failure (such as that which develops secondary to chronic mitral regurgitation) may be offset by the negative inotropic effect of calcium-channel blockade. However, the results of the present study suggest that afterload reduction caused by diltiazem is capable of improving congestive heart failure in the setting of coronary artery disease. Indeed, improvement of left ventricular performance in response to diltiazem has been demonstrated recently in patients with congestive heart failure secondary to coronary artery disease. In one of these studies substantial augmentation of stroke volume occurred during exercise. Similarly, in the present study stroke volume during exercise was significantly increased with diltiazem. The primary benefit of this diltiazem-induced augmentation of stroke volume and cardiac output during exercise appears to be an improvement in skeletal
muscle blood flow, since little effect of the drug was observed in other circulatory beds.

The improvement of maximal exercise capacity, a major goal of vasodilator therapy in coronary heart disease and heart failure, depends on the capability of the vasodilators to increase blood flow to working muscles. The question of whether or not vasodilators improve skeletal muscle blood flow has been addressed in a number of recent reports. Recent data obtained from patients with severe coronary heart failure indicate that hydralazine increases blood flow to skeletal muscle but does not improve oxygen availability within working muscle, since \( \text{VO}_2 \text{max} \) and peak femoral venous lactate were unchanged by the drug. Similarly, the increase in blood flow to working muscle produced by diltiazem observed in this study, does not appear to increase oxygen availability in skeletal muscle. During control exercise, \( \text{VO}_2 \text{max} \) was reduced in the group with infarction compared with the sham-operated group, suggesting impaired oxygen delivery to working muscle. Administration of diltiazem did not increase \( \text{VO}_2 \) either at submaximal or maximal workloads. This suggests that oxygen delivery to working muscle was unchanged. However, the possibility remains that diltiazem improved working skeletal muscle oxygen uptake but the effect was masked by a reduction in oxygen uptake by nonexercising tissues. Since studies with hydralazine as well as dobutamine demonstrated similar results, it has been speculated that an impediment of oxygen exchange at the capillary level may be responsible for the unchanged oxygen availability to working muscle despite the increase in blood flow. For example, increased vascular stiffness caused by elevated sodium content of the vascular wall may limit oxygen exchange.

At present, we do not know the long-term effects of vasodilators on regional blood flow and oxygen consumption. Nevertheless, recent data obtained after long-term therapy with nitrates or captopril suggest that these agents can improve \( \text{VO}_2 \text{max} \) in patients with congestive heart failure. Nevertheless, both of these agents appear not to increase skeletal muscle blood flow after short-term administration. Since nitrates and captopril are capable of increasing renal perfusion and diuresis, it is possible (although highly speculative) that a diuretic effect during long-term treatment with these agents may alter vascular stiffness through tissue sodium loss, thereby increasing oxygen exchange within working muscle. Since diltiazem appears to restore blood flow to the renal, splanchnic, and coronary circulations at rest in a myocardial infarction model of heart failure, this agent merits further investigation in this setting. Further studies, including long-term trials with calcium-channel blockers such as diltiazem, are warranted to investigate the usefulness of these drugs in the clinical management of congestive heart failure.

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H Drexler, J W Depenbusch, A G Truog, R Zelis and S F Flaim

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