Heart rate reduction by zatebradine reduces infarct size and mortality but promotes remodeling in rats with experimental myocardial infarction

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Heart rate reduction by zatebradine reduces infarct size and mortality but promotes remodeling in rats with experimental myocardial infarction. Am J Physiol Heart Circ Physiol 286: H1281–H1288, 2004; 10.1152/ajpheart.00390.2003.—The importance of heart rate for left ventricular remodeling and prognosis after myocardial infarction is not known. We examined the contribution of heart rate reduction by zatebradine, a direct sinus node inhibitor without negative inotropic effects on left ventricular function and dilatation, on mortality, energy metabolism, and neurohormonal changes in rats with experimental myocardial infarction (MI). Thirty minutes after left coronary artery ligation or sham operation, the rats were randomized to receive either placebo or zatebradine (100 mg·kg−1·day−1 per gavage) continued for 8 wk. Mortality during 8 wk was 33.3% in the placebo and 23.0% in the zatebradine group (P < 0.05); MI size was 36 ± 2% and 30 ± 1% (means ± SE, P < 0.05), respectively. Zatebradine improved stroke volume index in all treated rats but increased left ventricular volume in rats with small MI (2.43 ± 0.10 vs. 1.81 ± 0.10 ml/kg, P < 0.05) but not in rats with large MI (2.34 ± 0.09 vs. 2.35 ± 0.11 ml/kg, not significant). Zatebradine reduced left and right ventricular norepinephrine and increased left and right ventricular 3,4-dihydroxyphenyl ethylene glycol-to-norepinephrine ratio suggesting aggravation of cardiac sympathetic activation by zatebradine after MI. Creatine kinase and lactate dehydrogenase isoenzymes in rats with MI remained unchanged by zatebradine. Lowering heart rate per se reduces mortality and MI size in this model but induces adverse effects on left ventricular remodeling in rats with small MI.

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under ether anesthesia at 3, 12, and 24 h with ECG in rats with various treatment protocols. A dose of 100 mg·kg⁻¹·day⁻¹ reduced heart rate by 20% over 24 h and was chosen for the main study.

**Hemodynamic Measurements and LV Volume**

Hemodynamic measurements were performed 8 wk after coronary artery ligation as described previously in detail (19, 20). LV systolic pressure (LVSP) and end-diastolic pressure (LVEDP), the maximum rate of rise of LV systolic pressure (dP/dt max), mean arterial pressure, heart rate, and mean right atrial pressure were measured under light ether anesthesia and spontaneous respiration via a short segment of fluid-filled PE-50 tubings connected to a microtip manometer (Millar). A midsternal thoracotomy was performed to expose the aorta, and a precalibrated electromagnetic flow probe (2.0 mm; Statham Gould Instruments; Hato Rey, Puerto Rico) was placed on the ascending aorta for measurement of aortic flow (cardiac output excluding coronary flow), as previously described (20). Total peripheral resistance index was calculated as (mean arterial pressure − right atrial pressure/cardiac index) (CI) and was expressed as millimeters of mercury per milliliter per minute kilogram body weight. After baseline measurements, peak CI and peak stroke volume index were obtained by an acute infusion of warmed (39–40°C) Tyrode solution into a femoral vein at a rate of 40 ml·kg⁻¹·min⁻¹ for 45 s or until maximal flow was achieved. The passive pressure-volume curves of the LV were then obtained by a double-lumen catheter, as previously described (5). Briefly, the heart was arrested by potassium chloride and a double-lumen catheter (PE-50 inside PE-200) was inserted into the LV via the ascending aorta. The right ventricular free wall was incised to avoid fluid accumulation. The atrioventricular groove was ligated, and isotonic saline was infused at a rate of 0.76 ml/min via one lumen while intraventricular pressure was continuously recorded through the other lumen from negative pressure to 30 mmHg. At least three reproducible pressure-volume curves were obtained within 10 min of cardiac arrest, well before the onset of rigor mortis. Operating LV end-diastolic volume was derived from the LV pressure-volume curve (19). It was defined as the volume on the pressure-volume curve corresponding to a filling pressure equal to in vivo end-diastolic pressure.

For rats assigned to biochemical measurements, on the following day after in vivo hemodynamic (heart rate, LVSP, LVEDP, and dP/dt max) measurements, the rat hearts were isolated and perfused in the Langendorff mode at a constant pressure of 100 mmHg at 37°C, as previously described (13). A water-filled colored latex balloon in the LV, hearts were rapidly freeze clamped with Wollenberger tongues, as previously described (17). With the colored latex balloon in the LV, hearts were rapidly freeze clamped with Wollenberger tongues, as previously described (17). With the balloon fixed in distended form in 10% buffered formalin for 24 h and coronary flow (ml buffer/min) divided by dry heart weight (g). Pressure-volume area (PVA) was calculated and MVO₂-PVA relation was obtained at the different filling levels (0.2–0.8 ml at 0.05-ml intervals), as described previously (28). Linear regression analysis was used to determine the slope and the MVO₂ intercept of each MVO₂-PVA relation.

**HPLC Measurements of High-Energy Compounds**

High-energy compounds were measured with the method described by Sellevold et al. (24) with a HPLC system. Briefly, powdered viable LV tissue was homogenized in 0.42 M perchloric acid using the homogenizer Potter S (Braun Melsungen; Melsungen, Germany), keeping the sample temperature at 4°C. Aliquots for protein were measured with Peterson’s modification of the Lowry method (15). After the addition of 2 M KOH to set a pH of ~5, the sample was centrifuged, filtered, and injected into the HPLC system. The chromatography was run at room temperature, and the wavelength of the detector was set to 206 nm. The mobile phase consisted of KH₂PO₄ (215 mM), tetrabutylammoniumhydroxide sulfate (2.3 mM), and acetontile (3.5%).

**Isoenzyme Measurements**

Total CK and lactate dehydrogenase (LDH) activities of LV samples were measured using an Ultraspex III spectrophotometer (Pharmacia Biosystems; Freiburg, Germany), and the isoenzymes of LDH were determined with the TITAN GEL LD Isozyme System (Helena Diagnostika; Hartheim, Germany) using agarose gel electrophoresis as previously described (13). The CK isoenzyme distribution was measured with the Rapid Electrophoresis System (REP, Helena Diagnostika) as separation unit and the REP CK Isofronis Kit (Helena Diagnostika) for agarse gel and incubation solution. The agarse gel contained a Tris-barbital buffer with sodium azide as preservative.

Quantification of the separated isozyme bands was done automatically by the Electrophoresis Data Center (Helena Diagnostika).

**Hormone Measurements**

**Sample collection.** Eight weeks after coronary ligation, rats assigned to neurohormonal studies were anesthetized with an injection of pentobarbital sodium (80 mg/kg ip). A PE cannula was inserted into the trachea for artificial ventilation and a PE-50 catheter was inserted into the right carotid artery to withdraw blood. Blood samples were collected into a prechilled tube containing potassium EDTA (2 ml/g blood). Plasma was separated by centrifugation at 1,700 g for 10 min at 4°C and stored at −80°C for later measurements of endothelin-1 and plasma renin activity, as previously described (6). Plasma samples (500 μl) for catecholamine determination were extracted on aluminum oxide (pH 8.6) and the catecholamines were eluted with 0.1 mol/l perchloric acid (50 μl) and assayed by HPLC with electrochemical detection. The limit of detection was 2 pg. The heart was subsequently removed, rinsed in ice-cold saline, and divided into the right ventricle and the LV, including the septum. After infarct size determination, the scarred area was removed from residual myocardium, separately weighed, rapidly frozen in liquid N₂, and stored at −80°C. Tissue samples were homogenized in 0.2 mol/l perchloric acid for catecholamine determination and the homogenate was centrifuged for 20 min at 15,000 g for 4°C. The supernatant was collected and the extraction was performed as described for plasma samples.

**Infarct size determination.** The method used to process the heart for the measurement of infarct size in rats that underwent the hemodynamic studies was similar, as previously described (10). The hearts were fixed in distilled form in 10% buffered formalin for 24 h and...
then dissected into the LV plus interventricular septum and right ventricular free wall, which were weighed separately. The whole LV was dehydrated in alcohol, cleared in xylene, and embedded in paraffin. Transverse serial sections of 20 μm thickness were obtained in 1-mm intervals from apex to base, mounted, and stained with sirius red (0.1% solution in saturated aqueous picric acid) to provide a clear discrimination between fibrous scar and noninfarcted tissue. Infarct size was determined by planimetric measurement with a digital image system (Mocha computer digitizing program) and calculated by dividing the sum of the planimetered endocardial and epicardial circumferences occupied by the infarct by the sum of the total epicardial and endocardial circumferences of the LV. Rats in hemodynamic studies were grouped as sham-operated, small myocardial infarction (MI) (≤35% of LV), and large MI (≥35% of LV). Rats in energy metabolism studies were “matched” by in vivo LVEDP levels with rats in hemodynamic studies for group classification. An alternative approach was used to evaluate infarct size of rats for hormone measurements, as previously described (6). Briefly, incisions were made in the LV so that LV tissue could be pressed flat. A clear macroscopic boundary of scar could be seen, which allowed the identification of infarcted area. The endocardial and epicardial infarcted and total area were drawn onto a superimposed glass. Infarct size was determined by planimetry with a digital imaging system (Mocha computer digitizing program) and calculated as [epicardial MI area/epicardial area + endocardial MI area/endocardial area] × 100. Because this method systematically underestimates MI sizes (14), rats were grouped as sham-operated, small MI (<30% of LV), and large MI (≥30% of LV).

**LV shape.** After separation from the right ventricle, external apex to basis distance and the maximal diameter of the LV were measured with a vernier caliper and maximal LV circumference with both a 2-0 suture and a vernier caliper. Internal LV diameter was measured as the maximal distance from the endocardial surface of the septum to the endocardial surface of the free LV wall along a line perpendicular to the septum and, accordingly, was used as a measure of aneurysmal shape distortion. LV free wall thickness, which represents scar thickness in rats with infarction, was measured at the point where the LV diameter reached the free LV wall. Average septal thickness was determined as the septal area enclosed by two lines originating from the center of gravity of endocardial circumference, which connected the two origins of right ventricular surface length. These measurements were performed with a digital imaging system (Mocha digitizing computer program).

**Data Analysis**

The results are expressed as means ± SE. Multiple comparisons among various groups were evaluated by two-factor (MI size and treatment) factorial ANOVA (SuperANOVA, Abacus Concepts; Berkeley, CA). The mortality difference in placebo and zatebradine-treated rats was determined by χ² and Fisher’s exact test. *P < 0.05 was considered to indicate statistical significance.

**RESULTS**

**Mortality**

A total of 537 rats underwent coronary artery ligation, and 116 died within 30 min postoperation. The remaining 421 rats were randomized to receive either placebo (n = 186) or zatebradine (n = 235). Mortality during 8 wk was 33.3% in the placebo group and 23.0% in the zatebradine group (P < 0.05). As shown in Fig. 1, the survival benefit of zatebradine occurred on the first day after coronary ligation.

**General Characteristics**

Body weights (286 ± 2) were not different among various protocols or groups of MI sizes or treatments, respectively. MI sizes and LV and RV weights were similar in the hemodynamic and neurohormonal study and pooled data are given in Table 1. MI size was substantially reduced by zatebradine in the total group. LV and right ventricular weights increased in placebo-treated rats in proportion to infarct size. Zatebradine increased LV and right ventricular weights.

**Table 1. General characteristics**

<table>
<thead>
<tr>
<th>Animal numbers</th>
<th>Infarction</th>
<th>Sham</th>
<th>Small</th>
<th>Large</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI size, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>22±2</td>
<td>44±1</td>
<td>36±2</td>
<td></td>
</tr>
<tr>
<td>Zatebradine</td>
<td>0</td>
<td>20±1</td>
<td>40±1</td>
<td>30±1†</td>
<td></td>
</tr>
<tr>
<td>LV/BW, mg/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2.26±0.06</td>
<td>2.50±0.05*</td>
<td>2.60±0.06*</td>
<td>2.48±0.04</td>
<td></td>
</tr>
<tr>
<td>Zatebradine</td>
<td>2.74±0.07†</td>
<td>2.70±0.05</td>
<td>2.70±0.05</td>
<td>2.71±0.03‡</td>
<td></td>
</tr>
<tr>
<td>RV/BW, mg/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.56±0.03</td>
<td>0.69±0.04</td>
<td>0.96±0.05†</td>
<td>0.77±0.03</td>
<td></td>
</tr>
<tr>
<td>Zatebradine</td>
<td>0.68±0.02‡</td>
<td>0.80±0.02†</td>
<td>1.16±0.04‡</td>
<td>0.93±0.03‡</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. MI, myocardial infarction; LV, left ventricular weight; RV, right ventricular weight; BW, body weight. *P < 0.05 vs. sham in the same treatment group; †P < 0.05 vs. placebo; ‡P < 0.05 vs. rats with small MI in the same treatment group; ‡P < 0.05 vs. placebo.

![Cumulative survival curves for rats treated with placebo (dotted line) and zatebradine (solid line). Mortality was significantly (P < 0.05) reduced in zatebradine-treated animals.](http://ajpheart.physiology.org/DownloadedFrom)
SVI in rats with MI (Fig. 2). Total peripheral resistance index tended to be higher post MI and was not affected by zatebradine (data not shown).

LV Shape and Volume

Table 3 and Fig. 3 show that LV length (LV apex-basis), width (LV maximal diameter and circumference), and volume increased in rats with MI. Zatebradine further increased diameters, circumference, and volume in sham and rats with small MI but not in rats with large MI. Free wall and septal thickness were not changed by zatebradine.

Study on Energy Metabolism

In vitro hemodynamics. As shown in Table 4, heart rate remained decreased in the isolated heart. Coronary flow (CF) increased in zatebradine-treated rats with large MI.

Pressure-volume relations. LV developed pressure or dP/dt max (performance) were related to volume (preload). These relations were shifted to the lower right in proportion to MI size (less performance at more preload). Zatebradine shifted the curves to the right in sham rats and rats with small MI but shifted the curves to the left in hearts with large MI (Fig. 4, A and B). MV˙O2-PVA relations shifted to the right after MI.

Table 2. Hemodynamics before thoracotomy for hemodynamic and energy metabolism studies

<table>
<thead>
<tr>
<th>Infection</th>
<th>Sham</th>
<th>Small</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>410±1</td>
<td>403±8</td>
<td>394±9</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>346±14</td>
<td>297±8*‡</td>
<td>289±8*‡</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>141±3</td>
<td>131±3</td>
<td>117±7*†</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>147±5</td>
<td>138±2</td>
<td>123±1*†</td>
</tr>
<tr>
<td>dP/dt max, mmHg/s × 10³</td>
<td>14.2±0.6</td>
<td>10.8±0.5*</td>
<td>9.4±0.7*</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>16.3±1.1</td>
<td>10.9±0.5*</td>
<td>8.1±0.4*†</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>6.8±0.8</td>
<td>10.7±1.4</td>
<td>23.5±2.2*†</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>5.0±0.5</td>
<td>16.9±1.7*‡</td>
<td>25.6±1.6*‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt max, maximum rate of rise of LV systolic pressure. *P < 0.05 vs. sham in the same treatment group; ‡P < 0.05 vs. rats with small MI in the same treatment group; †P < 0.05 vs. placebo rats with comparable MI size.

Table 3. Shape measurements

<table>
<thead>
<tr>
<th>Infection</th>
<th>Sham</th>
<th>Small</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV apex-basis length, mm</td>
<td>14.9±0.2</td>
<td>14.2±0.3</td>
<td>15.2±0.2†</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>15.1±0.3</td>
<td>15.3±0.2</td>
<td>15.4±0.1</td>
</tr>
<tr>
<td>LV median diameter, mm</td>
<td>11.2±0.3</td>
<td>12.1±0.2*</td>
<td>12.4±0.2*</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>11.8±0.4</td>
<td>13.1±0.2*†</td>
<td>12.8±0.1*</td>
</tr>
<tr>
<td>LV circumference, mm</td>
<td>35.4±0.7</td>
<td>37.2±0.5</td>
<td>38.5±0.7*</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>37.3±1.3</td>
<td>40.1±0.7*†</td>
<td>39.3±0.6</td>
</tr>
<tr>
<td>Free wall thickness, mm</td>
<td>1.1±0.1</td>
<td>0.8±0.1</td>
<td>0.4±0.0*†</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>0.9±0.2</td>
<td>0.7±0.1</td>
<td>0.5±0.1*</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>1.3±0.1</td>
<td>1.0±0.1</td>
<td>0.9±0.1*</td>
</tr>
<tr>
<td>Zatebradine</td>
<td>1.2±0.2</td>
<td>0.9±0.1</td>
<td>0.9±0.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. sham in the same treatment group; †P < 0.05 vs. rats with small MI in the same treatment group; ‡P < 0.05 vs. placebo rats with comparable MI size.
Parameters of Energy Metabolism

After MI, CK, CK-BB, and CK-MB isoenzymes increased, CK-mito and total creatine decreased in proportion to MI size (data not shown). CK-MB increased from 15 ± 1% of total CK (placebo) to 20 ± 1% (zatebradine, P < 0.05 vs. placebo) in sham-operated hearts; it remained unchanged in animals with large MI (placebo 21 ± 1%, P < 0.05 vs. sham; zatebradine 19 ± 1%, not significant vs. placebo). The LDH5-to-LDHl ratio increased after large MI and was not changed by zatebradine. Myocardial ATP values decreased after large MI both in placebo and in zatebradine-treated rats (Table 5).

Hormone Study

Plasma hormone and catecholamine measurements. Plasma norepinephrine, epinephrine, and endothelin-1 tended to be higher and plasma renin activity increased in proportion to MI sizes but were not affected by zatebradine (data not shown). Circulating NH2 terminal pro-ANP was increased in proportion to MI size and by zatebradine (Table 5). LV norepinephrine remained unchanged post-MI but was decreased by zatebradine in MI rats. Right ventricular norepinephrine decreased in proportion to MI size and was further decreased by zatebradine in sham rats and rats with small MI. LV and right ventricular 3,4-dihydroxyphenyl ethylene glycol (DHPG)-to-norepinephrine ratio increased post MI and were further increased by zatebradine (Table 5).

DISCUSSION

The major results of this study were that zatebradine reduced “acute” mortality and MI size and improved LV performance post MI, but induced LV dilatation in sham rats and rats with small MI. Accordingly, a shift of myocardial CK isoenzymes toward an “embryonic” pattern and shift of LDH isoenzymes toward the “hypoxic” enzymes were induced by zatebradine in sham rats as observed in models of hypertrophy or failure (13,
17). The ambivalent effect of zatebradine is underlined by an increase in NH$_2$ terminal pro-ANP, which is a marker for late prognosis in patients with LV dysfunction post MI (8). In addition, LV and right ventricular norepinephrine was decreased and the DHPG-to-norepinephrine ratio was increased by zatebradine.

**Mortality**

In a recent study, Opitz and collaborators (18) demonstrated that acute and subacute death in this model was an arrhythmic event (ventricular fibrillation). Bril and coworkers (1) studied the effects of zatebradine (750 mg/kg iv) 20 min after left circumflex coronary artery ligation in rabbit and found that the incidence of ventricular fibrillation was reduced by zatebradine by ~50%. Because this effect was completely reversed by atrial pacing to the predrug heart rate (1), direct antiarrhythmic effects of zatebradine were unlikely. In animals with large MI, zatebradine improved global CF. Thus the reduction of acute mortality by lowering heart rate might be related to an improvement of energy balance by reducing O$_2$ consumption and improving coronary flow at longer diastoles. In addition, MI size for the total group was reduced by zatebradine, thus most likely contributing to the lower mortality rate. Reduction of acute mortality by zatebradine was in part outweighed by later excess mortality. Early survival of animals with infarcts, which would not have survived without treatment, might be an explanation or the adverse effect of zatebradine on remodeling in animals with small MI. Moreover, in agreement with a previous study in this model (9), norepinephrine levels were reduced in tissue from the right ventricle in MI rats. The DHPG-to-norepinephrine ratio was also increased in these rats, reflecting an increased norepinephrine turnover (9). Because this ratio was further increased by zatebradine in MI hearts, a further increased norepinephrine turnover is suggested. Thus sympathetic activation could contribute to the late deaths by zatebradine.

### Remodeling and Performance

Zatebradine increased LV weight and volume in sham-operated rats and rats with small MI at a constant ratio of LV weight to volume and an unchanged wall thickness (“eccentric hypertrophy”). In fact, animals with small MI treated with zatebradine ended up with an increased filling pressure and the same LV volumes as animals with large MI. The exact mechanism of LV dilation by heart rate reduction remains unknown.

![Fig. 4. Relations between performance left ventricular (LV) developed pressure (LVDP, A) or maximum rate of rise of LV systolic pressure (dP/dt$_{max}$, B) and preload (volume) in rats treated with placebo (open symbols) and zatebradine (solid symbols). These relations were shifted to the lower right in proportion to MI size (less performance at more preload). Zatebradine shifted the curves to the right in sham-operated hearts (circles) and rats with small MI (triangles) but shifted the curves to the left in hearts with large MI (squares).](image)
But it was also recently reported as an acute effect of zatebradine in patients with LV dysfunction (25). The fundamental variables like blood pressure and cardiac output were not altered despite lower heart rate. In acute experiments, zatebradine reduces, along with heart rate, cardiac output and intraventricular pressure (29). The increase in chamber volume probably contributed to normalize cardiac output and thus blood pressure by the geometric advantage of a larger ventricle (11). In addition, however, isolated MI hearts even at the same preload and working isovolumetrically, developed more pressure when pretreated with zatebradine. Zatebradine shifted developed pressure-diastolic volume relations to the left. Thus, in sham and small MI rats, LV enlargement appeared to be an adaptation to lower heart rate. However, MVO₂-PVA relations were shifted to the left by chronic zatebradine treatment, suggesting reduced efficiency of electromechanical coupling or increased basal MVO₂ in these hearts (Fig. 5) (28), which was another unexpected fundamental difference to the acute effects of lowering heart rate (25). Zatebradine did not change the slope of the MVO₂-PVA relations at least in infarcted hearts. Thus an effect on contractile efficiency appears not to be a mechanism of action of zatebradine.

It remained unclear why LV dilatation was not aggravated by zatebradine in the animals with large MI. An extensive MI promoting LV dilatation in rats with small MI. Additional effects of β-blockers independent of lowering heart rate, such as an increase in myocardial creatine content (13), may be more important for long-term processes. Future experimental studies are needed comparing directly drugs only lowering heart rate with β-blockers. The biochemical effects of β-blockers on the myocardium not shared by zatebradine suggest superiority of β-blockers for the treatment of heart failure. Especially, large infarcts maintain their stroke volume at lower heart rate?

In rats with large MI, zatebradine did not change mean arterial pressure or total peripheral resistance index. Thus afterload appeared to be unchanged. Ejection fraction was increased and dP/dt max unchanged despite lower heart rate. One explanation might be a beneficial effect of longer ejection time in these enlarged hearts.

**Zatebradine Versus β-Blocker**

Previous studies (4, 10) have shown that β-blockers may promote LV dilatation in rats with MI. The effect is dependent on MI size similar to that of zatebradine observed in the present study. Cardiac output was also maintained despite reduction of heart rate by β-blockers. Finally, promotion of LV dilatation by β-blockers was also not seen in rats with large MI (10). There were, however, distinct effects of β-blockers not observed with zatebradine. The β-blocker bisoprolol prevented the shift of CK isoenzymes to an embryonic pattern, the shift of LDH isoforms to a hypoxic pattern, and increased total myocardial creatine (13). All of these effects were not observed with zatebradine. Thus lowering heart rate per se reduces early mortality and MI size but induces adverse effects on LV remodeling in rats with small MI. Additional effects of β-blockers independent of lowering heart rate, such as an increase in myocardial creatine content (13), may be more important for long-term processes. Future experimental studies are needed comparing directly drugs only lowering heart rate with β-blockers. The biochemical effects of β-blockers on the myocardium not shared by zatebradine suggest superiority of β-blockers for the treatment of heart failure. Especially,
changes of cardiac neurotransmitters and their metabolites after zatebradine suggest caution with an uncritical application of this therapy to patients with heart failure.

Clinical Relevance

Zatebradine has not been further developed to clinical use for various reasons. The successor drug ivabradine is, however, now evaluated in phase III studies (26). The present study may contribute to a better understanding of this therapeutic principle. So far, no clinical experience exists on the chronic use of pure heart rate-lowering drugs in patients with heart failure. Short-term use appears promising (25).

ACKNOWLEDGMENTS

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REFERENCES


