Mortality After Coronary Artery Occlusion in Different Models of Cardiac Hypertrophy in Rats

Frans H.H. Leenen, Baoxue Yuan

Abstract—Chronic treatment with minoxidil induces cardiac trophic and sympathetic responses, which may increase the propensity for lethal arrhythmias. To test this hypothesis, acute coronary artery occlusion was performed in conscious normotensive rats treated for 2 or 5 weeks with minoxidil with the use of a 2-stage approach to cause a myocardial infarction. For comparison, rats with aortocaval (A-V) shunts and spontaneously hypertensive rats (SHR) were studied. Minoxidil increased left ventricular and right ventricular weights by 15% to 20%, and the A-V shunt increased these weights by 30% to 40%. In SHR, left ventricular weight was increased by 50%, and right ventricular weight was increased by 25%. In rats treated with minoxidil for 5 weeks, coronary artery occlusion caused a rapid and marked mortality, and 4 hours after myocardial infarction, only 18% of these rats were alive versus 61% of the control rats. In rats with the A-V shunt, coronary artery occlusion was also associated with increased mortality, and after 6 hours, 33% were still alive compared with 59% of the control rats. In contrast, SHR with marked hypertension and cardiac hypertrophy showed only a minor increase in mortality (survival rates were 53% versus 60% in SHR versus Wistar-Kyoto rats, respectively). Mortality was preceded by high arrhythmia scores, and ventricular fibrillation was the cause of death. Discontinuation of minoxidil for 1 week, sympathetic blockade with nadolol or clonidine, or blockade of the renin-angiotensin system with enalapril or losartan did not improve minoxidil-induced excess mortality. We conclude that ventricular stretch and other mechanisms (eg, cardiac vagal activity) in rats appear to be more potent than hypertension-induced left ventricular hypertrophy in predisposing for lethal arrhythmias in the setting of acute ischemia.

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Key Words: hypertrophy ■ mortality ■ minoxidil ■ occlusion ■ rats ■ arrhythmias

Cardiac hypertrophy is a well-established major risk factor for cardiovascular disease, including sudden death.1,2 In hypertensive humans, event rates may be higher in patients with concentric hypertrophy compared with patients with eccentric hypertrophy.3–5 Most antihypertensive drugs lower blood pressure (BP) and also cause regression of left ventricular (LV) hypertrophy (LVH).6 However, the classic arterial vasodilators, hydralazine and minoxidil, cause minimal regression7 and can increase LV mass in hypertensive rats and humans.8–10 Moreover, we showed that in normotensive rats and also in humans, the vasodilator minoxidil actually induces cardiac hypertrophy of the eccentric type.11,12 Cardiac overload, cardiac sympathetic hyperactivity, and the renin-angiotensin system have been implicated in these cardiac effects.5,11,13,14 The relevance for outcome of the changes in cardiac structure and the persistent increase in cardiac sympathetic activity induced by arterial vasodilators in normotensive and hypertensive individuals has so far not been assessed. In hypertensive dogs with LVH, short-term treatment with the β-blocker metoprolol normalized the increased incidence of sudden cardiac death after coronary artery occlusion observed in these dogs compared with control dogs but not treatment with the ACE inhibitor enalapril, despite similar lowering of BP.15 The authors hypothesized that the decreased incidence of ventricular fibrillation (VF) by metoprolol may be related to the antagonism of sympathetic influences that potentiate conduction delay in the ischemic zone, particularly in hypertrophied cardiac muscle. Increased sympathetic activity has been implicated in the mortality after myocardial infarction (MI) due to lethal dysrhythmias as well as the extension of ischemic injury.16 In dogs, stellate stimulation markedly enhanced the lowering of the VF threshold after acute coronary occlusion.17 Therefore, a persistent increase in cardiac sympathetic tone, as we previously have shown to be caused by chronic minoxidil treatment,8–11 may also enhance the propensity for VF after acute coronary occlusion. To test this hypothesis, the incidence of sudden death after coronary artery occlusion was evaluated in conscious normotensive rats treated for 2 or 5 weeks with minoxidil, and this incidence was related to infarct size and risk area. Conscious rats were studied to negate confounding effects of anesthetic agents and surgical trauma.18,19 Normotensive rats were studied to diminish the possible protective effects of BP lowering20 induced by minoxidil, which is

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present in hypertensive but not normotensive rats during chronic therapy.8 For comparison purposes, acute coronary artery ligation was also performed in rats with eccentric hypertrophy induced by aortocaval (A-V) shunt21 and in spontaneously hypertensive rats (SHR) with combined concentric and eccentric hypertrophy.8

Methods

Animals

Three rat models were used in the present study: (1) For minoxidil studies, male Wistar rats weighing 225 to 250 g (Charles River Breeding Laboratories, Montreal, Canada) were randomized into control or minoxidil treatment. Minoxidil was administered via the drinking water (120 mg/L).8 Treatment lasted 2 or 5 weeks, and the coronary occluder was implanted at the end of the first or fourth week of treatment. (2) For A-V shunt studies, an A-V shunt was opened in male Wistar rats (body weight 225 to 250 g) with an 18-gauge needle.21 The coronary occluder was implanted 5 weeks after shunt surgery. (3) Male SHR and Wistar-Kyoto rats (WKY, Taconic, Germantown, NY) were studied at 28 weeks of age without pretreatment. All rats were housed 2 per cage on a 12-hour dark-light cycle.

Drug Protocols in Minoxidil-Treated Rats

After it became apparent that minoxidil-treated rats exhibit marked mortality after MI, treatment protocols were designed to assess possible mechanisms. As mentioned above, minoxidil was administered via the drinking water at 120 mg/L for 5 weeks. An occluder was again implanted at the end of the fourth week of treatment. In 1 group of rats, minoxidil treatment was discontinued at this time, ie, 1 week before the actual ligation. In other groups of rats, other drugs were added 2 days before the coronary artery ligation: nadolol (10 mg/kg SC BID) or clonidine (150 µg/kg SC BID) to assess the possible role of sympathetic tone and enalapril (20 mg/kg SC BID) or losartan (5 mg/kg SC BID) to assess the possible role of the renin-angiotensin system. The last dose of these drugs was administered 2 to 3 hours before ligation.

Surgery

The coronary occluder was made from a 5.0-gauge atraumatic prolene suture (8720H, Ethicon Inc), which passed through a PE-10 polyethylene guide tubing (Clay Adams). Rats were anesthetized with 4% halothane and intubated with a No. 14 catheter (Innys, Becton Dickinson), through which 1.0% halothane in oxygen/nitrous oxide was ventilated at 10 mL/kg body wt, 60 times per minute (Harvard Apparatus), to maintain anesthesia. After opening the thorax at the fourth or fifth left intercostal space, the occluder was passed around the left coronary artery 2 to 3 mm from the origin by inserting the needle into the LV wall under the overhanging left atrial appendage and bringing it out high on the pulmonary conus. The guide tubing with the other end of the occluder was then exteriorized at the back of the neck.22,23 Seven days after the open-chest surgery, the left carotid artery was cannulated as described previously.11 Permanent ECG leads (10 to 14 cm of polytetrafluoroethylene [Teflon]-coated stainless-steel wire, 0.005 in, A-M Systems Inc) were implanted through a needle trocar into the pectoralis muscle and in the left hind limb and both forelimbs. Animals were then allowed to recover for 24 hours.

Coronary Artery Ligation and BP and ECG Measurements

The left carotid catheter and ECG leads were connected to a Grass 7D polygraph (Grass Instruments). After resting BP and heart rate (HR) were recorded for 30 minutes, the occluder was carefully pulled until it was no longer possible to move the occluder in relation to the outer guide. The exposed occluder was melted down with a cautery to form a bubble adjacent to the distal end of the outer guide tubing, fixing it in place.

BP and ECG were monitored continuously and recorded at 15 minutes and 2, 4, 6, and 24 hours after coronary ligation. During the first 6 hours, if VF did not spontaneously revert within 10 seconds, precordial taps were used to try to obtain sinus rhythm. If resuscitation for 2 minutes failed to revive the rat, the rat was considered dead, and its heart was excised for occluded zone estimation. The criteria for scoring arrhythmias were modified from the method described by Johnston et al22: 0 for normal sinus rhythm, 1 for premature ventricular contractions, 2 for ventricular tachycardia (VT), 3 for spontaneously reversible VT or VF, 4 for reversible VT and/or VF, 5 for irreversible VF causing death within 6 hours after ligation, and 6 for fatal VF within 15 minutes after ligation.

Determination of Ischemic and Infarcted Zones

At the conclusion of measurement of BP and HR 24 hours after coronary ligation, the rats were euthanized with an overdose of pentobarbital injected into the arterial line. With the occluder intact, the heart was removed and perfused retrogradely with 10 mL of 0.9% saline to wash out blood before 1 mL methyl blue (1 mg/mL in 0.9% saline, Sigma Chemical Co) was used to differentiate perfused from occluded tissue. Thereafter, the occluded tissue was sliced transversally into 1.0-mm sections and incubated in tetrazolium dye (10 mg 2,3,5-triphenyltetrazolium chloride/mL of 70 mmol/L sodium phosphate buffer, pH 8.5, Sigma) at 37°C for 30 minutes. This procedure stains only the vital tissue and thus within the occluded zone differentiates the infarcted myocardium from the ischemic myocardium. Their weights were expressed as percentages of the LV weight.22,23

Rats that died after coronary artery ligation mostly died within the first hours. Because the infarct does not fully develop so quickly, in these rats the whole occluded zone was determined as described above, but no separation between ischemic and infarcted myocardium was attempted.

Data Analysis

The survival rates between the groups (minoxidil-treated versus control, shunt versus sham-operated, and SHR versus WKY) at 15 minutes and 1, 2, 4, 6, and 24 hours were compared. The product-limit method was used to estimate the survivorship or time to death. Nonparametric methods (Gehan’s generalized Wilcoxon test) were used to compare the survivorship distributions for the 2 groups in each experiment. Differences for other variables between groups were evaluated by ANOVA. A value of P<0.05 was considered statistically significant.

Results

Survival Rates After Coronary Ligation

Treatment with minoxidil for 2 weeks tended to decrease the survival rate (Figure 1, left panel). The survival rates showed a modest difference between the 2 groups within the first 6

Figure 1. Survival rates after acute coronary artery occlusion in control rats and in rats treated for 2 weeks (left) or 5 weeks (right) with minoxidil. Numbers of animals at time 0 were as follows: for 2-week experiment, n=21 for control and n=22 for minoxidil; for 5-week experiment, n=18 for control and n=22 for minoxidil. *P<0.05 vs control.

BP and ECG were monitored continuously and recorded at 15 minutes and 2, 4, 6, and 24 hours after coronary ligation. During the first 6 hours, if VF did not spontaneously revert within 10 seconds, precordial taps were used to try to obtain sinus rhythm. If resuscitation for 2 minutes failed to revive the rat, the rat was considered dead, and its heart was excised for occluded zone estimation. The criteria for scoring arrhythmias were modified from the method described by Johnston et al22: 0 for normal sinus rhythm, 1 for premature ventricular contractions, 2 for ventricular tachycardia (VT), 3 for spontaneously reversible VT or VF, 4 for reversible VT and/or VF, 5 for irreversible VF causing death within 6 hours after ligation, and 6 for fatal VF within 15 minutes after ligation.
hours and had decreased to 67% in the control group and 45% in the minoxidil-treated group at 24 hours after ligation \((P>0.05)\). After 5 weeks of treatment, the survival rate in the minoxidil group was significantly and markedly lower compared with that in the control group \((P<0.01)\): rats on minoxidil died very quickly, and 4 hours after coronary artery occlusion, only 18% were alive versus 61% of the control rats. Eighteen percent of the rats in the minoxidil group survived 24 hours after ligation compared with 56% of the control group (Figure 1, right panel).

In rats with an A-V shunt for 6 weeks, acute coronary artery occlusion was also associated with enhanced mortality (Figure 2, left panel). A significant difference in the survival rate between the control and shunt groups was seen as early as 15 minutes after coronary artery ligation. Six hours later, the survival rates in control and shunt rats had decreased to 59% and 33%, respectively \((P<0.05)\). The difference was not significant at 24 hours after ligation (56% versus 33%, respectively).

In SHR 6 hours after ligation, the survival rate was only slightly \((P=NS)\) lower compared with the survival rate in WKY (Figure 2, right panel): 24 hours after ligation, the survival rates for SHR and WKY were 60% and 53%, respectively.

**Reversal of Minoxidil-Induced Excess Mortality After MI**

Treatment of control rats with either nadolol or enalapril for 2 days nearly doubled the mortality at 24 hours after MI. Minoxidil-treated rats again showed excess mortality relative to untreated control rats. Treatment of minoxidil-treated rats with nadolol or enalapril did not prevent this excess mortality compared with untreated control rats (Table 1).

In preliminary studies, the effects of discontinuation of minoxidil for 1 week or treatment with clonidine or losartan were evaluated. None of these interventions appeared to offer a protective effect compared with minoxidil alone (Table 1).

**Ventricular Weights, Ischemic Zone, and Infarct Zone**

**Ventricular Weights**

Table 2 shows ventricular weights in rat groups. Minoxidil treatment for 2 weeks induced a modest \((P=NS)\) increase in LV weight but a significant increase in right ventricular (RV) weight. After 5 weeks of minoxidil treatment, LV and RV weights had increased by 16% and 20%, respectively \((P<0.05)\). Six weeks after opening an A-V shunt, LV weight had increased by 33%, and RV weight had increased by 40%. In 28-week-old SHR, increases in LV weight by 51% and in RV weight by 62% were as follows: n = 28-week-old WKY and SHR (right). Numbers of animals at time of treatment for 2 weeks induced a modest \((P<0.01)\) decrease in LV weight, whereas RV weight had increased by 40%.

**Table 2. Ventricular Weights in Minoxidil-Treated Rats, Rats With A-V Shunt, and SHR Compared With Their Controls**

<table>
<thead>
<tr>
<th>Study n</th>
<th>LV Weight, mg/100 g BW</th>
<th>RV Weight, mg/100 g BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con-s 14</td>
<td>243±6</td>
<td>44±1</td>
</tr>
<tr>
<td>Con-d 7</td>
<td>243±13</td>
<td>51±2</td>
</tr>
<tr>
<td>Min-s 10</td>
<td>261±10</td>
<td>54±3†</td>
</tr>
<tr>
<td>Min-d 12</td>
<td>264±6</td>
<td>61±3†</td>
</tr>
<tr>
<td>Con-s 10</td>
<td>230±5</td>
<td>49±2</td>
</tr>
<tr>
<td>Con-d 8</td>
<td>248±12</td>
<td>50±1</td>
</tr>
<tr>
<td>Min-s 4</td>
<td>263±7*</td>
<td>57±5</td>
</tr>
<tr>
<td>Min-d 18</td>
<td>271±5†</td>
<td>61±2†</td>
</tr>
<tr>
<td>Con-s 15</td>
<td>231±7</td>
<td>49±2</td>
</tr>
<tr>
<td>Con-d 12</td>
<td>229±10</td>
<td>52±3</td>
</tr>
<tr>
<td>Shunt-s 7</td>
<td>300±14*</td>
<td>70±5*</td>
</tr>
<tr>
<td>Shunt-d 14</td>
<td>312±12†</td>
<td>70±4†</td>
</tr>
<tr>
<td>WKY-s 10</td>
<td>225±6</td>
<td>41±1</td>
</tr>
<tr>
<td>WKY-d 9</td>
<td>229±6</td>
<td>44±3</td>
</tr>
<tr>
<td>SHR-s 12</td>
<td>339±7*</td>
<td>54±2*</td>
</tr>
<tr>
<td>SHR-d 8</td>
<td>349±7†</td>
<td>53±2†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BW indicates body weight; Con, control rats; Min, minoxidil-treated rats; s, surviving rats; and d, dead rats.

\(\*P<0.05\) vs con-s or WKY-s; †\(P<0.05\) vs con-d or WKY-d.
RV weight by 26% were noted. There were no differences in LV or RV weights between the rats that survived and those that did not within each group.

Occluded Zone and Ischemic Versus Infarct Zone
Minoxidil treatment for 2 weeks did not affect the extent of the occluded zone in surviving or nonsurviving rats, nor did the extent of ischemic versus infarct zone in surviving compared with control rats (Figure 3). In contrast, after 5 weeks of treatment, the occluded zone was significantly larger in the nonsurviving rats in the minoxidil group compared with the nonsurviving rats in the control group. In surviving rats, the occluded zone and ischemic versus infarct zones were similar for control and minoxidil groups (Figure 3).

In nonsurviving rats with the A-V shunt, the occluded zone was similar to that of the nonsurviving rats in the control group. Similarly, in surviving rats, the occluded zone and ischemic versus infarct zones did not differ between shunt and control groups (Figure 4).

In nonsurviving WKY rats and SHR, the occluded zone was similar. In surviving WKY rats and SHR, the occluded zone and the ischemic versus infarct zones were also similar (Figure 4).

Arrhythmia Score
In all models, the nonsurviving rats had significantly higher arrhythmia scores than did the surviving rats (Table 3, Figure 5). In minoxidil-treated Wistar rats, the arrhythmia score was similar to that of the control rats in both surviving and nonsurviving subgroups (Figure 5). In rats with A-V shunt and in SHR, severe and fatal arrhythmias occurred early in the nonsurviving rats (Table 3), consistent with their early mortality, compared with the more gradual mortality in the control rats (Figure 2).

BP and HR

Blood Pressure
In control rats, coronary artery ligation caused only minor changes in BP both in survivors and nonsurvivors (Table 4). Minoxidil treatment for 2 or 5 weeks did not affect the resting BP. In both experiments, treatment did not substantially alter the effect of coronary ligation on BP in surviving and nonsurviving rats. Opening an A-V shunt decreased BP significantly. After coronary artery ligation, BP changes in the shunt rats were similar to BP changes in the control rats. At 28 weeks of age, SHR had significantly higher resting BP than did the WKY. In surviving SHR, BP decreased gradually after coronary ligation, and it was down by 50% at 24 hours. A more marked drop of BP was seen in the nonsurviving SHR immediately after coronary artery ligation. Coronary artery ligation did not cause obvious BP changes in surviving and nonsurviving WKY.

Heart Rate
SHR had a higher ($P<0.05$) resting HR ($\approx425$ bpm) than did WKY ($\approx360$ bpm). Treatment with minoxidil for 2 or 5 weeks or opening an A-V shunt did not affect the resting HR. Coronary artery ligation did not cause obvious or consistent HR changes in any group (data not shown).

Discussion
The present results demonstrate that different models of cardiac hypertrophy affect mortality after MI to a varying degree: there was little impact in SHR versus a marked impact in minoxidil-treated rats, and the impact on rats with the A-V shunt fell in between. Induction of an MI in conscious rats caused a marked decrease of BP in the surviving and nonsurviving SHR but had only a minimal impact on the BP and HR of control rats, rats with an A-V shunt, or rats treated with minoxidil. Mortality within 24 hours after MI was primarily due to fatal arrhythmias (ie, VF).
Minoxidil and Mortality After MI

In previous studies, we showed that chronic treatment with minoxidil causes cardiac volume overload,11 cardiac sympathetic hyperactivity,8 and increased cardiac angiotensin II.14 As a result, RV and LV weights increase, with a clear increase in LV internal diameter and minor change in LV wall thickness,11 indicative of LV eccentric hypertrophy. These changes in cardiac morphology are qualitatively similar to those caused by minoxidil, but they are clearly quantitatively larger. In contrast, the A-V shunt also caused enhanced mortality early after MI, but mortality was not as bad as that caused by minoxidil. Thus, if LV dilation with stretch of cardiac tissue plays a major role in the fatal arrhythmias, one would expect the reversed (ie, higher mortality in A-V shunt versus minoxidil). Thus, although increased stretch may explain the more rapid and excess mortality in rats with an A-V shunt, this cannot be the primary mechanism for the large excess mortality in rats treated with minoxidil. Resting autonomic tone and its responses to coronary occlusion and resulting ischemia may differ, leading to the observed differences in fatal arrhythmias.

In contrast to the occluded zone in rats treated with minoxidil, the occluded zone was not larger in rats with the A-V shunt compared with control rats. This suggests that LV growth in this model did not preferentially occur in the area supplied by the left coronary artery.

A-V Shunt and Mortality After MI

By 6 weeks after opening an A-V shunt with a 18-gauge needle, plasma and cardiac angiotensin II have returned to normal levels,30 but modest increases in LV end-diastolic pressure persist, with clear increases in LV and RV weight by 40% to 50%, as well as LV internal diameter, consistent with LV eccentric hypertrophy. These changes in cardiac morphology are qualitatively similar to those caused by minoxidil, but were preceded by high arrhythmia scores, and VF was the cause of death in both the control and minoxidil-treated rats. To identify the mechanisms contributing to the excess mortality after MI caused by minoxidil, several approaches were tried. Blockade of the renin-angiotensin system by losartan or enalapril did not provide any protection, nor did blockade of the sympathetic nervous system by nadolol or clonidine. In control rats treated with nadolol or enalapril, mortality after MI was actually enhanced, suggesting that the function of these systems is actually important for survival in this setting (as also suggested previously by Botting et al24). On the other hand, it is possible that in parallel with enhanced cardiac sympathetic drive, cardiac vagal activity is diminished and unresponsive, leading to an increased risk of sudden death after MI.25 The doses used are effective for treatment of hypertension or prevention/reversal of cardiac hypertrophy. Whether higher or lower doses may exert some protective effect can obviously not be excluded. Somewhat surprisingly, discontinuing minoxidil for 1 week after 4 weeks of treatment was also ineffective in lowering the excess mortality. In previous studies, we have shown that after discontinuation for 2 weeks, LV end-diastolic pressure has normalized, but LV and RV weight and LV internal diameter are still significantly increased.26 On the basis of these findings, it is tempting to speculate that stretch of cardiac tissue by chronic minoxidil treatment enhances the propensity for fatal arrhythmias during the immediate post-MI period. Chronic ventricular stretch may create an electrophysiological milieu that facilitates life-threatening arrhythmias via several mechanisms.27 Whether minoxidil, per se, contributes as well cannot be assessed from the present studies, but it is unlikely that much minoxidil remains in the heart after 1 week.

The larger occluded zone in rats treated with minoxidil for 5 weeks is unexpected and may suggest that dilatation of the LV preferentially happened in the area supplied by the left coronary artery, thereby leading to a larger relative occluded zone. This larger occluded and presumably ischemic zone in minoxidil-treated rats may contribute to a higher incidence of VF and death in these rats.22,28,29

### TABLE 3. Arrhythmia Scores Over 24 Hours After Coronary Artery Ligation in Rats With A-V Shunt and SHR vs Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Arrhythmia Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>A-V shunt (6 weeks)</td>
<td></td>
</tr>
<tr>
<td>Con-s</td>
<td>0.5±0.3</td>
</tr>
<tr>
<td>Con-d</td>
<td>2.5±0.6*</td>
</tr>
<tr>
<td>Shunt-s</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td>Shunt-d</td>
<td>3.7±0.9*</td>
</tr>
<tr>
<td>SHR (28 weeks of age)</td>
<td></td>
</tr>
<tr>
<td>WKY-s</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>WKY-d</td>
<td>1.3±0.9</td>
</tr>
<tr>
<td>SHR-s</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>SHR-d</td>
<td>4.0±1.3*†</td>
</tr>
</tbody>
</table>

Values are mean±SEM (for numbers of animals, see Table 2). Numbers in parentheses indicate rats remaining at this time-point. 

*P<0.05 vs surviving rats within group; †P<0.05 vs WKY-d.
SHR and Mortality After MI

By 28 weeks of age, the SHR had developed severe hypertension and marked LVH, which was more marked than in the rats with an A-V shunt. In contrast, mortality was only modestly accelerated and not higher than in the control WKY rats. The latter showed a pattern similar to that observed in control Wistar rats. Thus, the model with the worst LVH had the least excess mortality after MI. The occluded zone as a percentage of the LV was similar in SHR versus WKY, but in absolute terms, it would be nearly 50% larger in SHR versus WKY, with an accordingly larger interface between ischemic and normal myocardium. Despite this and the presence of severe hypertension, only SHR had severe and fatal arrhythmias early on, but mortality overall did not increase (only occurred earlier). These findings are consistent with findings in isolated hearts of SHR showing increased ischemia-induced arrhythmias, but in contrast, they show that these arrhythmias do not lead to increased rates of cardiac death. These findings in SHR also differ from the findings in dogs with renovascular hypertension and LVH, which show an increased incidence of sudden cardiac death after coronary artery occlusion.

In conclusion, these findings in 3 rat models of cardiac hypertrophy challenge the concept that hypertension-induced LVH increases ischemia-induced lethal arrhythmias and sudden death. However, it is possible that these findings are specific for SHR, and other findings may be obtained in different hypertension models in rats or other species, such as dogs. Nonetheless, in conscious rats after MI, other mechanisms, such as chronic ventricular stretch and perhaps cardiac vagal activity, appear to be more potent in this regard. Arterial vasodilators, such as hydralazine and minoxidil, cause similar cardiac trophic and sympathetic responses in rats and humans. Therefore, it is possible that the minoxidil-induced propensity for lethal arrhythmias in the setting of acute ischemia also occurs in humans.

Acknowledgments

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