Pindolol, Not Propranolol, Reverses Cardiac Hypertrophy in Renal Hypertensive Rats

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SUMMARY Reversal of cardiac hypertrophy has been obtained by treatment with some antihypertensive drugs but has not been achieved consistently with beta blockers. To investigate whether this difference might be explained by the distinct hemodynamic actions of the drugs, we studied the effects of propranolol and pindolol, beta blockers with distinct modes of action, on cardiac hypertrophy of hypertensive male Wistar rats, two-kidney, one clip (2K1C) Goldblatt model (n = 33) and sham-operated control rats (n = 34). We also assessed the effects of such therapies on the ventricular pumping ability during open-chest, transient aortic occlusion. Four weeks after surgery, propranolol (5 mg/kg/day p.o.) was given to hypertensive rats (n = 8) and control rats (n = 11); pindolol was also given orally (1 mg/kg/day) to similar groups (n = 7 and n = 5, respectively). Untreated animals served as controls for both groups. Cardiac hypertrophy developed with hypertension in the untreated rats of the propranolol (3.38 ± 0.18 vs 2.60 ± 0.08 mg/g; p < 0.01) and pindolol groups (3.93 ± 0.21 vs 2.40 ± 0.03 mg/g; p < 0.001). Treatment reversed cardiac hypertrophy in the pindolol-treated rats (3.01 ± 0.19 vs 3.93 ± 0.21 mg/g; p < 0.001, NS) but not in the propranolol-treated rats (3.24 ± 0.18 vs 3.38 ± 0.21 mg/g; NS). The maximal pressure that developed during aortic occlusion in the propranolol group was similar to that observed in the pindolol group. These results indicate that cardiac hypertrophy is reversed by pindolol but not by propranolol, and that this reversal does not interfere with left ventricular pumping ability. (Hypertension 11 [Suppl I]: I-89-I-92, 1988)

KEY WORDS • cardiac hypertrophy • reversal • propranolol • pindolol • pump function • heart • hypertension

CARDIAC hypertrophy in hypertension can be reversed by surgical or medical treatment. Centrally acting a-blockers,1 converting enzyme inhibitors,2,3 and calcium channel blockers4 induce an effective reduction in cardiac mass, whereas the effect of vasodilators,5 diuretics,6 and /3-blockers7,8 is not as apparent. /3-Blockers are reported to be ineffective in reversing cardiac hypertrophy,4 or their action is noted only after long periods of treatment.8 These contrasting results have led some authors to hypothesize that the regression of cardiac hypertrophy in hypertension is mainly dependent on the duration of treatment.10 This hypothesis is in contrast with the findings of Tarazi et al.,11 who suggest that one of the more important determinants is the hemodynamic mechanism of action of the specific drugs.

To address this question, we studied the effects of propranolol and pindolol, two /3-blockers with distinct mechanisms of action,12 on cardiac hypertrophy in two-kidney, one clip (2K1C) Goldblatt hypertension in rats. We also determined the consequences of these drugs on the performance of the heart, so as to detect possible abnormalities induced by the reversal of cardiac hypertrophy.

Materials and Methods

Male Wistar rats (University Central Bioterium, São Paulo, Brazil) aged 60 to 75 days and weighing 200 to 250 g were operated on. Thirty-three rats had hypertension induced by a silver clip (0.2 mm internal width) placed on the left renal artery (renal hypertensive rats, RHR) and 34 were submitted to sham operation to serve as controls (SC). All rats had tail arterial pressure (TAP) determined weekly. Four weeks after surgery, propranolol (5.0 mg/kg/day p.o.) was given to RHR (RHR-PRO, n = 8) and SC (SC-PRO, n = 10) rats; untreated animals (RHR1, n = 9 and SC1, n = 9)
served as controls. Other subgroups of hypertensive (RHR-PIN, n = 7) and normotensive (SC-PIN, n = 6) rats were treated with pindolol (1.0 mg/kg/day), while untreated animals (RHR2, n = 9 and SC2, n = 9) served as controls. Follow-up was an additional 4 weeks, during which TAP was determined weekly.

At the end of this time the rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.), and a PE-50 catheter (Fischer Laboratories, Medford, MA, USA) was inserted into the left carotid artery; they underwent tracheal intubation and were ventilated with a rodent respirator (Model V5KG, Narco Biosystems, Houston, TX, USA). The sternum and ribs were then excised in a way to expose the heart. The heart was punctured with a 29-gauge needle connected to a Gould-Brush recorder (Model 2.200S, Gould-Brush, Cleveland, OH, USA) through a Statham pressure transducer (Model P-50, Hato Rey, Puerto Rico). The intra-arterial line was also connected to a P-50 Statham pressure transducer.

The rats were allowed to stabilize for 20 minutes with adequate ventilation values. After this, the root of the aorta was clamped for 10 seconds, and the tracings of left ventricular pressure, carotid pressure, as well as an expanded tracing of ventricular pressure for readings of left ventricular end-diastolic pressure, were recorded. We determined left ventricular systolic (LVSP) and end-diastolic pressure (LVEDP), and also maximal developed pressure, defined as LVSP minus LVEDP, during the transient aortic occlusion.

The aorta was clamped three times consecutively, allowing a 5-minute period between each procedure to allow recovery. The hearts were then excised at the atrioventricular groove and weighed on an analytical balance (Metter Instruments Corp., Heightstown, NJ, USA).

Statistical analysis was performed using Student’s t test for unpaired variables and two-way analysis of variance, where applicable. Results are expressed as means ± SEM.

**Results**

**Blood Pressure**

No statistically significant differences were noted in TAP of hypertensive rats or sham controls in the two groups, or in the levels achieved in the treated and untreated subgroups (Figure 1). In the propranolol group, blood pressure increased significantly in those subgroups submitted to renal artery clipping (RHR1, from 112.0 ± 2.0 to 170.3 ± 1.1; RHR-PRO, from 111.0 ± 1.0 to 165.6 ± 5.5 mm Hg at the fourth week; p < 0.001 for both) and did not change significantly in the sham-operated control subgroups (SCI, from 110.0 ± 0.9 to 106.6 ± 0.5; SC-PRO, from 108.1 ± 2.0 to 106.6 ± 0.4 mm Hg at the fourth week; NS for both). During the drug test period, blood pressure de-

**Figure 1.** Effects of pindolol and propranolol on hypertensive Goldblatt II rats (GHII) and sham controls (SC). Treatment was extended from the fourth to the eighth week. (For significance of differences, see text.) TAP = tail arterial pressure.
increased significantly in the treated subgroups (RHR-PRO, 80.0 ± 0.1 mm Hg; p < 0.001; SC-PRO, 82.1 ± 0.4 mm Hg; p < 0.05), but not in the untreated subgroups (RHR1, 182.5 ± 1.9; SC1, 109.1 ± 0.53 mm Hg; NS for both) at the eighth week.

In the pindolol group, TAF also increased in the subgroups submitted to renal arterial clipping (RHR2, from 107.5 ± 0.9 to 155.0 ± 2.4; RHR-PIN, from 106.9 ± 2.3 to 155.3 ± 1.3 mm Hg at the fourth week; p < 0.001 for both) but not in the sham-operated subgroups (SC2, from 105.1 ± 2.4 to 118.3 ± 0.7; SC-PIN, from 112.2 ± 2.4 to 119.0 ± 3.3 mm Hg at the fourth week; NS for both). During the drug test period the blood pressure decreased significantly in the subgroups that received pindolol (RHR-PIN, 80.0 ± 1.2 mm Hg; p < 0.001; and SC-PIN, 79.2 ± 0.2 mm Hg; p < 0.05), but not in the untreated subgroups (SC2, 99.6 ± 2.6; RHR2, 153.3 ± 7.5 mm Hg; NS for both at the eighth week).

Cardiac Hypertrophy

Hypertension was associated with an increase in relative heart weight in experimental groups given propranolol (RHR1, 3.38 ± 0.18; SC1, 2.60 ± 0.08 mg/g; p < 0.001) and pindolol (RHR2, 3.93 ± 0.21; SC2, 2.40 ± 0.03 mg/g; p < 0.001). The two treatments had different effects on heart weight. In the propranolol group, the heart weight/body weight ratio was not significantly affected by treatment in the hypertensive (RHR-PRO, 1.05 ± 0.05) and normotensive subgroups (SC1-PRO, 1.46 ± 0.07; SC, 1.30 ± 0.05 mg/g; p < 0.05). In the normotensive subgroups (SC-Pro, 206.4 ± 10.8 mm Hg; NS; see Table 1).

With pindolol, the hypertensive treated subgroup had significantly lower relative heart weight compared to untreated animals (RHR-PIN, 3.01 ± 0.21; RHR2, 3.93 ± 0.21 mg/g; p < 0.001), but these differences were not observed between treated and untreated animals (SC-PIN, 2.64 ± 0.11; SC, 2.40 ± 0.11 mg/g; NS; Table 2).

Transient Aortic Occlusion

In the propranolol group the maximal developed pressure during transient aortic occlusion was not statistically different between the treated and untreated hypertensive subgroups (RHR1, 228.2 ± 10.3; RHR-PRO, 241.6 ± 12.6 mm Hg; NS) or in the normotensive subgroups (SC1, 212.7 ± 13.2; SC-PRO, 206.4 ± 10.8 mm Hg; NS; see Table 1).

Similarly, in the pindolol-treated rats, no statistically significant differences were observed between the hypertensive (RHR2, 211.9 ± 13.6; RHR-PIN, 210.7 ± 19.7 mm Hg; NS) or the normotensive subgroups (SC2, 193.6 ± 12.2; SC-PIN, 181.3 ± 6.2 mm Hg; NS; see Table 2).

Discussion

Our results show that increased cardiac mass was reversed by pindolol but not by propranolol, and this effect was obtained independent of the duration of treatment or level of blood pressure control. Thus the two β-blockers with distinct hemodynamic mechanisms of action differently influence the evolution of cardiac hypertrophy in hypertension. This fact does not support the hypothesis that the duration of treatment is one of the most important determinants of regression of this condition. On the contrary, our results are in accordance with those showing that propranolol is not as effective as other drugs in reversing hypertensive cardiac hypertrophy. Indeed, Trimarco and Wikstrand showed significant reduction of cardiac mass with metoprolol in humans only after 18 months of treatment.

The fact that pindolol but not propranolol reduces cardiac mass in a short period of treatment favors the idea that the hemodynamic mechanism of action of the different drugs is an important determinant of cardiac hypertrophy during treatment. The contrasting effects of these agents may be due to the vasodilating action of pindolol, because this drug stimulates β2-receptors in vascular tissue; propranolol does not.

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart weight (g)</th>
<th>HW/BW (mg/g)</th>
<th>Maximal developed pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>0.90 ± 0.03</td>
<td>2.60 ± 0.08</td>
<td>212.7 ± 13.2</td>
</tr>
<tr>
<td>SC-PRO</td>
<td>0.81 ± 0.06</td>
<td>2.46 ± 0.07</td>
<td>206.4 ± 10.2</td>
</tr>
<tr>
<td>RHR</td>
<td>1.05 ± 0.05*</td>
<td>3.24 ± 0.18*</td>
<td>228.2 ± 10.3</td>
</tr>
<tr>
<td>RHR-PRO</td>
<td>1.06 ± 0.06*</td>
<td>3.38 ± 0.21*</td>
<td>241.6 ± 12.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. HW/BW = heart weight/body weight ratio; SC = sham controls; SC-PRO = propranolol-treated sham controls; RHR = renal hypertensive rats; RHR-PRO = propranolol-treated renal hypertensive rats.

*p < 0.01, hypertensive vs sham group.

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<tr>
<td>RHR</td>
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<td>RHR-PIN</td>
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<td>3.01 ± 0.19*</td>
<td>210.7 ± 19.7</td>
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Values are means ± SEM. HW/BW = heart weight/body weight ratio; SC = sham controls; SC-PIN = pindolol-treated sham controls; RHR = renal hypertensive rats; RHR-PIN = pindolol-treated renal hypertensive rats.

*p < 0.01, hypertensive vs sham group; †p < 0.05, treated vs untreated group.
have this property. When such stimulation does occur, the unloading conditions of the left ventricle are more favorable, and this possibly accounts for a lesser degree of end-systolic stress during ejection.

A role for the intrinsic sympathomimetic activity of pindolol directly inducing reversal of hypertrophy cannot be ruled out, however, since regression of structural changes of resistance vessels after treatment of hypertension with this drug was reported. A second possibility to explain the different results of the two β-blockers is that a lesser degree of hypertrophy obtained in the untreated hypertensive animals of the propranolol group may have obscured the reversal of hypertrophy.

Although our results indicate no significant differences between the two untreated subgroups (3.38 ± 0.18 vs 3.93 ± 0.21 mg/g; p > 0.05), it is reasonable to assume the possibility that a greater number of animals studied in each group could obviate a statistical error of the second order (β-error) and show statistically significant differences. Alternatively, the failure of propranolol to reverse hypertrophy may be a dose-related phenomenon. We could not test this possibility because we observed marked bradycardia induced by doses of propranolol higher than those that we found to be effective. This might affect the comparability of the two groups, because heart rate is thought to be an important determinant of reversibility of cardiac hypertrophy during treatment.

With respect to the effects of regression of cardiac hypertrophy on the pump function of the heart, we found that the force-generating ability of the heart during transient aortic occlusion was maintained because the maximal pressure development was similar in rats with hypertrophy and in those with normal hearts. These results are similar to those previously reported by Saragoca and Tarazi. Moreover, our results also show that the ability to generate force is not affected by the regression of hypertrophy by pindolol. This finding is in contrast with the results of Ferrario et al.; these discrepancies, although difficult to reconcile, may be attributed to the different experimental loading conditions of the hearts in the two types of experiments.

Our findings may be of importance, since diminution of blood pressure levels without concomitant reductions in cardiac mass was reported to be associated with limitations in the coronary flow reserve, which may impair cardiac performance under stress.

References
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