Quinapril, an Angiotensin Converting Enzyme Inhibitor, Prevents Cardiac Hypertrophy During Episodic Hypertension

Stevo Julius, Ying Li, David Brant, Lisa Krause, and David Taylor

Six control dogs, six dogs treated with 1.5 mg/kg b.i.d. quinapril, and six dogs treated with 8 mg/kg q.d. minoxidil underwent 6 hours daily of hindquarter compression for 9 weeks. Minoxidil significantly decreased baseline blood pressure (—17 mm Hg; p<0.01), whereas quinapril decreased baseline blood pressure 11 mm Hg but not significantly (p=0.15). Hindquarter compression elicited blood pressure increases in all three groups (control +18, quinapril +13, minoxidil +19 mm Hg). After 9 weeks, left ventricular mass in control dogs increased 22% (p<0.001); a similar increase was seen in minoxidil-treated dogs (+22%, p<0.0001) but not in the quinapril-treated group (+4%, p<0.15). The increase in left ventricular mass in control dogs was concentric (increased epicardial volume only), whereas in the minoxidil group, the hypertrophy was eccentric (both epicardial and endocardial volumes increased). The minimal hypertrophy in the quinapril group was concentric (no change in epicardial, but a decrease in endocardial volume). Quinapril had little hypotensive effect, but prevented the development of left ventricular hypertrophy, whereas minoxidil did not prevent hypertrophy in spite of its hypotensive effect. The mechanism of this differential effect of direct vasodilation versus converting enzyme inhibition on left ventricular hypertrophy is not fully elucidated. The results with quinapril suggest that some antihypertensive agents may positively affect left ventricular hypertrophy in spite of the absence of a large effect on baseline blood pressure or on blood pressure reactivity. (Hypertension 1991;17:1161-1166)

The original report from Sen et al1 that not all drugs that lower blood pressure (BP) reverse left ventricular hypertrophy (LVH) generated considerable interest in factors that moderate the effect of high BP on cardiac hypertrophy. Of particular interest have been differences in the mechanisms by which drugs lower BP and the intensity of elicited counterregulatory sympathetic and renin-angiotensin responses. It now is recognized that activation of the renin-angiotensin1-3 and the sympathetic nervous1-6 systems can stimulate cell growth. The baseline levels of the sympathetic7 and renin-angiotensin8 systems frequently are elevated in hypertension, and coexistence of these two abnormalities in the same patient has been described.7 Laragh et al8 suggested that higher renin levels negatively affect the cardiovascular prognosis of patients with hypertension, and Devereux et al9 demonstrated that the recurrent BP elevations that occur at work are more closely related to LVH than BP at any other period of the day.

We developed a model in which repeated pressor episodes can be produced in dogs by hindquarter compression.10-12 This pressor response can be abolished by ganglionic blockade and spinal anesthesia and therefore is neurogenic. Hindquarter compression increases plasma norepinephrine levels,11 enhances the renal sympathetic drive,13 and causes a neurogenic increase of plasma renin levels.11 When elicited over a prolonged period of time, these recurrent neurogenic pressor episodes cause substantial LVH.13 As with many other central nervous pressor responses,14 hypotensive agents do not abolish the pressor response to hindquarter compression. It therefore is possible to treat animals with antihypertensive agents while subjecting them to bouts of BP elevation.15 In this article we report how quinapril, a converting enzyme inhibitor, and minoxidil, a direct vasodilator, affect the development of cardiac hypertrophy in this model. It will be shown that quinapril prevents, whereas minoxidil does not prevent, development of LVH.
Methods

Studies were performed in 18 adult mongrel dogs. Six dogs (three males, three females) did not receive medication, six (two males, four females) received quinapril (1.5 mg/kg b.i.d. orally), and six (four males, two females) received minoxidil (8 mg/kg q.d. orally). The average weight (±SEM) of the various groups were control, 24.5±1.3 kg; quinapril, 25.1±1.5 kg; and minoxidil, 28.9±2.1 kg (p=NS). The weight of the quinapril-treated and control groups did not change appreciably during the experiment, but the minoxidil group lost 2.3 kg, a change that was significant (p<0.04).

The animal preparation is described in detail elsewhere. Intra-arterial BPs were obtained from a subcutaneous port connected to a catheter implanted in the infrarenal aorta. Data were stored on a magnetic tape and analyzed off-line as average BP and heart rate values for a time period.

During a 3-week period, the animals were trained to rest in a sling, after which they were acclimated to compression with a suit (Jobst Institute, Toledo, Ohio) for 1 week. The suit encompassed the hind limbs and the gluteal region, but the abdomen was not compressed.

After training, the three groups were brought from the kennels to the laboratory every day for 3 hours of 30-mm Hg compression in the morning and 3 hours in the afternoon for 9 weeks. At the end of each week, the intra-arterial BP was monitored for 40 minutes before compression, throughout the 3 hours of compression, and for 40 minutes after deflation of the suit.

Cardiac dimensions were assessed by a two-dimensional echocardiographic exam before compression (two times) and at the end of the 3rd, 6th, and 9th weeks of compression according to a protocol previously described in detail. All echocardiographic exams were performed by the same technician; the echo measurements of cardiac mass were practically identical to cardiac weights measured at autopsy.

The protocol was approved by the Institutional Review Board for use of animals in research. Statistical analysis included analysis of variance with correction for repeated measures and Student's t test. A value of p<0.05 was considered significant.

Results

Table 1 gives BP values during the run in period after training but before compression (average of two monitoring sessions) and an average of 9 weeks of BP readings during compression. These findings are illustrated in Figure 1. Compared with the pretreatment period, both quinapril- and minoxidil-treated dogs had lower baseline BPs, attesting to the mild hypotensive action of both regimens. The significance of this hypotensive action was tested in two ways. First, for each group the average baseline before compression during the active experimentation period (average of 9 weeks) was compared with the average BP during the pretreatment run in period (average of 2 weeks) using a paired t test. The BP of the minoxidil group was significantly decreased

![Figure 1. Line graph showing average of mean blood pressure (MBP) levels over 9 weeks of the experiment. Pressure was monitored 40 minutes before inflation of a suit, 3 hours during inflation, and 40 minutes after inflation. Bars represent SEM. ++, p<0.01, within-group difference of precompression baseline on treatment to pretreatment baseline. x, p<0.05; xx, p<0.01; xxx, p<0.001, difference from control group by analysis of variance.](http://hyper.ahajournals.org/)}
TABLE 2. Change in Mean Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Quinapril</th>
<th>Control</th>
<th>Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>-2±1</td>
<td>2±3</td>
<td>NA</td>
</tr>
<tr>
<td>Sham</td>
<td>0±2</td>
<td>-1±4</td>
<td>NA</td>
</tr>
<tr>
<td>Week 1</td>
<td>14±4</td>
<td>22±6</td>
<td>20±4</td>
</tr>
<tr>
<td>Week 2</td>
<td>12±3</td>
<td>24±4</td>
<td>22±3</td>
</tr>
<tr>
<td>Week 3</td>
<td>7±4</td>
<td>16±7</td>
<td>20±6</td>
</tr>
<tr>
<td>Week 4</td>
<td>13±4</td>
<td>24±4</td>
<td>14±5</td>
</tr>
<tr>
<td>Week 5</td>
<td>15±8</td>
<td>20±4</td>
<td>13±6</td>
</tr>
<tr>
<td>Week 6</td>
<td>11±2</td>
<td>16±3</td>
<td>22±3</td>
</tr>
<tr>
<td>Week 7</td>
<td>19±4</td>
<td>17±4</td>
<td>17±4</td>
</tr>
<tr>
<td>Week 8</td>
<td>14±5</td>
<td>19±5</td>
<td>22±2</td>
</tr>
<tr>
<td>Week 9</td>
<td>15±2</td>
<td>12±5</td>
<td>19±2</td>
</tr>
<tr>
<td>Weekly average</td>
<td>13±2</td>
<td>19±3</td>
<td>18±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM and denote the difference between baseline and average pressure from the 30th through 180th minute of compression.

(p<0.001). During the treatment, baseline BP of the quinapril group was 11 mm Hg lower than the run in baseline, but the difference was not statistically significant (p=0.15). In the control group, the run in and baseline BPs were practically identical. Second, between-group BP differences during the experimental period were evaluated by an analysis of variance and a contrast test for various time points. Compared with the control and quinapril group, the minoxidil-treated group had lower BPs at baseline (p<0.001 versus control; p<0.01 versus quinapril) and during compression (p<0.001 versus control; p<0.06 versus quinapril). In comparison with the control dogs, the quinapril-treated group did not have a significantly lower BP at baseline, but the BP during compression was significantly lower (p<0.05).

BP response to compression expressed as change from baseline to peak values during compression through the 9 weeks is shown in Table 2, and the average values over 9 weeks are illustrated in Figure 2. All three groups continued to respond to hindquarter compression throughout the 9-week period.

The percent changes in the left ventricular mass are shown in Figure 3. There is a clear trend for an increase of the left ventricular mass in control and in minoxidil-treated animals but no such trend in animals treated with quinapril. Repeated measures analysis of variance in each group showed a significant time effect in the control group (p<0.0001) and in the minoxidil-treated group (p<0.0005), whereas the time effect in the quinapril-treated group was only marginally significant (p<0.06). The groups were contrasted by analysis of variance and covariance with repeated measures for all possible pairs. A comparison of the control and minoxidil-treated groups showed marginal group difference (p<0.06), no group/time interaction (p<0.40), and a strong time effect (p<0.0001). Comparing the quinapril-treated group with the controls revealed a group difference (p<0.005), time effect (p<0.0000), and a group/time interaction (p<0.0001). Similar differences were obtained when the quinapril group was compared with the minoxidil-treated group; a group difference (p<0.006), a time effect (p<0.0003), and a time/group interaction (p<0.001) were found.

The actual cardiac weight from which the percentage changes were calculated is given in Table 3. The change in cardiac weight index in the minoxidil group is exaggerated because of a simultaneous loss of body weight. The percent changes shown in Figure 3 are based on changes in the uncorrected cardiac weight.

The change in epicardial and endocardial volumes for all groups is given in Table 4. As shown in a previous article,13 the hindquarter compression in
control dogs induced an increase of the epicardial volume without a change in endocardial volume, a classical hypertensive pattern of concentric hypertrophy without a change in the chamber size. Conversely, animals treated with minoxidil developed true eccentric hypertrophy; the endocardial volume, the epicardial volume, and the overall wall thickness increased. In the quinapril-treated group, the overall cardiac weight was only marginally increased (a time effect by analysis of variance at p<0.06, Figure 3). This was due to a significant decrease of the endocardial volume without a change in the external diameter of the heart—a pattern of mild concentric hypertrophy combined with a smaller chamber size.

### Discussion

**Methodology of the Measurement of Cardiac Size**

In the previous experiment in our laboratory, we obtained a good correlation between the calculated weight by echocardiography and the weight of the left ventricle at autopsy, but the slope of the relation suggested that overestimation may occur at higher cardiac weights. In the present experiment, the minoxidil-treated dogs started with a larger baseline cardiac weight. The question arises whether some of the larger weight at the end of the 9 weeks is an overestimate due to measurement error. This was addressed by analyzing whether there is any correlation between the baseline size and the change in cardiac size at 9 weeks. None was found (p>0.3). Although the baseline did not affect later measurements, it is possible, due to the echocardiographic tendency to overestimate the larger ventricles, that the actual changes in both the control and the minoxidil-treated groups may have been anatomically somewhat smaller. However, the comparison of relative changes of the left ventricular mass across groups in this paper is reasonable.

#### Left Ventricular Hypertrophy

A considerable body of the literature now confirms the original observation that various antihypertensive treatments have different effects on the regression of preexisting LVH. Regression of LVH has been documented with sympatholytic drugs, β-blocking agents, α-adrenergic blockers, calcium antagonists, and angiotensin converting enzyme inhibitors. Hydralazine and minoxidil do not cause LVH regression. The effect of diuretics on LVH regression is less clear cut, but they probably are less effective than other treatment modalities. It is presumed that lack of an effect on LVH regression by diuretics and hydralazine or minoxidil is due to drug-induced activation of the renin-angiotensin or sympathetic nervous system. Volume retention with minoxidil may play an additional role.

By contrast, little is known about the role of antihypertensive compounds in primary prevention of LVH. Linz et al. showed that ramipril, a converting enzyme inhibitor, prevented LVH in rats with banding of the abdominal aorta. The present study is, to our knowledge, the second to explore the question of primary prevention of ventricular hypertrophy. In addition, our study addresses a hitherto unanswered question: Does antihypertensive treatment, by lowering the baseline BP but not affecting the magnitude of pressor response, prevent cardiac hypertrophy induced by regularly reoccurring pressor episodes? This question is of considerable interest as most of the presently used antihypertensive agents lower BP but do not affect stress-induced BP variability. Clinical evidence suggests that such BP variability may be a major risk factor for the development of LVH and cardiovascular damage in humans. The results show that some antihypertensive agents may, and others may not, prevent cardiac hypertrophy in this model. The study does not fully elucidate the mechanism of this differential effect of the antihypertensive drugs on cardiac hypertrophy.

The increase of BP during hindquarter compression is associated with a substantial increase of plasma renin and norepinephrine values, but the primary factor in this model appears to be sympathetic activation. An increase of plasma nor-

### Table 3. Cardiac Weight During the Experiment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of 9th week</th>
<th>Paired t test (baseline vs 9th week within group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac weight (g)</td>
<td>Weight index</td>
<td>Cardiac weight (g)</td>
</tr>
<tr>
<td>Quinapril (n=6)</td>
<td>92 ±2.3</td>
<td>7.22 ±17</td>
<td>95.8±2.0</td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>82 ±13.7</td>
<td>3.38 ±24</td>
<td>101±6.8</td>
</tr>
<tr>
<td>Minoxidil (n=6)</td>
<td>133±22.8</td>
<td>4.64±0.20</td>
<td>161±14.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM

### Table 4. Changes in Myocardial Volume (cm³) After 9 Weeks of Compression

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>9 Weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume <em>EPI</em></td>
<td>142.05±6.14</td>
<td>140.3±5.69</td>
<td>&gt;0.507</td>
</tr>
<tr>
<td>Volume <em>ENDO</em></td>
<td>55.00±4.98</td>
<td>48.33±5.18</td>
<td>&lt;0.041</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume <em>EPI</em></td>
<td>124.75±11.73</td>
<td>146.72±11.01</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Volume <em>ENDO</em></td>
<td>46.73±3.93</td>
<td>47.41±4.69</td>
<td>&lt;0.800</td>
</tr>
<tr>
<td>Minoxidil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume <em>EPI</em></td>
<td>168.49±13.01</td>
<td>222.13±21.84</td>
<td>&lt;0.028</td>
</tr>
<tr>
<td>Volume <em>ENDO</em></td>
<td>59.18±7.38</td>
<td>68.64±7.35</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

Values are mean±SEM. EPI, epicardial, ENDO, endocardial.
epinephrine values was found both in anesthetized\textsuperscript{11} and conscious animals,\textsuperscript{13} whereas the plasma renin activity during compression was elevated only in anesthetized animals.\textsuperscript{11} Consequently, three factors or a combination of them could be involved in the development of cardiac hypertrophy during repeated hindquarter compression: BP increase, sympathetic activation, and activation of the renin-angiotensin system. The present study suggests that yet a fourth factor, the mode of BP lowering, may affect the development of cardiac hypertrophy during hindquarter compression in dogs.

Our study is similar in design to other studies\textsuperscript{1,2,3,4,5}, that is, we compared a drug expected not to prevent cardiac hypertrophy with a drug that might be efficacious in preventing hypertrophy. In that context, the minoxidil group in this study was conceived as "positive control" for the quinapril group. If two drugs lower the BP to the same degree but only one prevents cardiac hypertrophy, BP lowering per se may not be the major factor in the prevention of myocardial hypertrophy. In the present study, the comparison of minoxidil to quinapril therefore was intended to elucidate the importance of antagonizing the renin-angiotensin system and possibly the importance of the renin-mediated attenuation of the sympathetics. However, minoxidil is not a neutral agent; while lowering BP, the compound promotes the development of dilated eccentric cardiac hypertrophy. Because this type of hypertrophy is radically different from the concentric type seen in control dogs, the finding suggests that monotherapy with minoxidil in its own right favors cardiac hypertrophy. Our data support the hypothesis proposed by Tsopoulos and Leenen\textsuperscript{30} that a combination of sympathetic activation with fluid retention may be responsible for the eccentric hypertrophy seen with minoxidil.

The failure of the minoxidil group to serve as a neutral positive control for the effects of the BP lowering precludes firm conclusions about the exact mechanism of the "cardioprotective" action of quinapril. Nevertheless, we favor the interpretation that quinapril prevented development of cardiac hypertrophy through a mechanism different than its depressor action. First, the data in this study are similar to the results with aortic banding.\textsuperscript{31,40} Linz et al\textsuperscript{31} demonstrated that in this model of high renin hypertension, nonhypotensive doses of ramipril induced regression of preexisting ventricular hypertrophy. Second, we chose small doses of quinapril and expected them not to lower the BP. This expectation was only partially fulfilled. The effect of quinapril on the baseline pressure was not statistically significant; nevertheless, the average BP was 11 mm Hg lower. The pressor response to suit inflation was similar in all three groups when all 9 weeks were averaged. However, a perusal of Table 2 suggests that during the first 6 weeks of compression, the response of the quinapril may have been lower.\textsuperscript{*} The achieved BP level during compression and the postcompression BPs in the quinapril-treated group were significantly lower than in the control group. It also is appropriate to acknowledge that we measured the BP only once a week, and the BP on other days could have been different. Consequently, we cannot rule out that the modest degree of BP lowering by quinapril could have had biological effects.

The third argument favoring the nonhypotensive protective action of quinapril against LVH is in the type of cardiac changes observed in quinapril-treated dogs. After 9 weeks of compression and quinapril, the epicardial volume did not change, but the endocardial volume became smaller. Such a concentric restructurin of the heart suggests that the pressor effects were still present, but their cardiac impact was attenuated by some other mechanism. Had the effect been due to only hypotension, one would expect a proportionally symmetric decrease of all cardiac diameters.

Final resolution of the mechanism by which quinapril inhibits and minoxidil favors cardiac hypertrophy will require complex experimentation. Comparative studies with other drugs, investigation of multiple doses of converting enzyme inhibitors causing substantial angiotensin converting enzyme inhibition but no BP lowering, and studies of reflex-activating vasodilators without compression would be necessary to resolve these issues. This is beyond the scope of one laboratory, and we hope other investigators will use our dog model to resolve some of these outstanding issues.

Conclusions from the dog hindquarter compression model are very similar to conclusions regarding the effect of sympathetically mediated pressor episodes in humans. We demonstrated earlier\textsuperscript{13} that in dogs, repeated neurogenic pressor episodes can cause cardiac hypertrophy. Devereux et al\textsuperscript{10} reported that job stress–related BP elevations at work correlate more strongly to cardiac hypertrophy than BPs from any other period of the day or night. Presently available antihypertensive medication does not decrease stress-induced BP elevations,\textsuperscript{32,33,34,35} and obtaining a smooth BP control in such patients is a difficult clinical problem. Our study illustrates an important new pharmacotherapeutic action; in spite of their inability to affect the magnitude of the BP response to stress, and while having only a minimal effect on the prevailing average BP, some antihypertensive agents may offer protection against stress-related cardiac hypertrophy. This assumption could be tested easily in future clinical trials.

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