Hemodynamic Mechanism of Blood Pressure Response to Captopril in Human Malignant Hypertension

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SUMMARY The hemodynamic mechanism of blood pressure response to angiotensin blockade is well established in "benign" but not in human malignant hypertension. We studied the changes in mean arterial pressure (MAP), cardiac index (CI), pulmonary wedge pressure (PWP), and in plasma volume (PV) induced by a single oral dose of captopril (150 mg) in 11 patients with malignant hypertension. Two hours after captopril, MAP fell from 178.5 ± 5.8 to 151.8 ± 7.8 mm Hg (p < 0.001) (X ± SEM) due to a fall in total peripheral resistance (TPR) (from 54.8 ± 6.8 to 46.4 ± 1.6 arbitrary units, p < 0.001). However, there was a simultaneous increase in CI (from 3.29 ± 0.13 to 3.70 ± 0.15 liter/min/m², p < 0.001), and a decrease in PWP (from 15.3 ± 3.5 to 11.0 ± 2.5 mm Hg, p < 0.001), while PV remained unchanged (from 4.02 ± 0.26 to 4.12 ± 0.12 liters, n.s.). Our data show that, in human malignant hypertension, blood pressure response to captopril is due to a decrease in TPR, but in contrast to benign hypertension, there is also a simultaneous increase in CI. Our results suggest that, in malignant hypertension, potentially high CI levels are artificially normalized by the increased TPR and may be fully disclosed by vasodilation.

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KEY WORDS • malignant hypertension • captopril • total peripheral resistance • cardiac index • vasodilation • plasma renin activity • plasma volume • mean arterial pressure • pulmonary wedge pressure • heart rate

MALIGNANT and severe hypertension have often been associated with elevated plasma renin activity (PRA). More recently, captopril has also been proposed by Case et al., and ourselves for the treatment of this clinical emergency. Although severe and malignant levels of blood pressure have been thought to be maintained by increased total peripheral resistance in association with low cardiac output, more recent clinical and experimental studies have shown that this hemodynamic pattern is not always present. Instead, both low and high cardiac output has been described in experimental malignant hypertension in dogs by Ferrario and McCubbin. In that work, the question remains unsolved whether these two different hemodynamic patterns correspond to different mechanisms or if they are stages of the same pathophysiologic mechanism. On the other hand, Kim et al., studying patients with end-stage renal disease, showed that patients with malignant hypertension had a normal cardiac output, which was significantly increased after nephrectomy. In those studies, this contrasted with patients with non-malignant hypertension in whom cardiac output did not change. The authors then suggested a vasopressor substance of renal origin that might be responsible for the relative impairment of cardiac function in the malignant form of hypertension. Thus, it may not be warranted to extrapolate the well-established results of studies of the blood pressure (BP) response to angiotensin blockade in nonmalignant hypertension to the malignant forms of hypertension because of possibly different hemodynamic mechanisms underlying the two forms of the disease.

Therefore, we studied the hemodynamic responses to angiotensin blockade by the oral administration of captopril in malignant hypertensive patients, in order to clarify the mechanism of action of this drug in lowering BP.
Material and Methods

Patients

The patients included in this study were referred to the emergency rooms of the University Hospital (Hospital São Paulo) because of hypertensive crisis. All patients had symptoms and clinical signs of hypertensive encephalopathy, such as torpor and diminution of alertness. In all but two patients, fundus oculi examination revealed papilledema and retinal hemorrhages; two patients had only papilledema and no hemorrhages. Diastolic BP at admission was 140 mm Hg or higher, and plasma creatinine levels varied from 0.7 to 11.5 mg/dl. Clinical data on admission are detailed in table 1.

Protocol of Study

After physical examination and routine blood sample collections, patients under local anesthesia had a flow-directed Swan-Ganz catheter passed under fluoroscopy by a modified Seldinger technique into either the cephalic or basilic vein. Blood pressure was monitored using auscultatory sphygmomanometry at 3-minute intervals. Pulmonary artery pressure (PAP) and right atrial pressure (RAP) were recorded directly through the Swan-Ganz catheter at regular intervals of 15 minutes for 1 hour on a Gould-Brush recorder 2400S (Gould Instruments, Cleveland, Ohio) using a Gould-Statham P50 transducer. Cardiac output (CO) was measured by thermodilution using a computer (Edwards Laboratories, Model 9502) at intervals of 15 minutes for 1 hour. Plasma volume (PV) was also determined by a modified radioimmunoassay in samples collected immediately before and 2 hours after captopril administration.

Statistical Analysis

Student t test for paired comparisons was used to assess the significance of changes from control to test periods; correlation between variables was assessed by linear regression analysis. Results are expressed as means ± standard error of the mean (SEM).

Results

Two hours after captopril administration, PRA was significantly increased compared to control (5.14 ± 1.37 to 8.96 ± 2.82 ng/ml/hr, p < 0.01).

Table 1. Clinical and Laboratory Data on the Patients Upon Hospital Admittance

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood pressure (mm Hg)</th>
<th>Fundoscopy (KW)</th>
<th>Serum creatinine (mg/dl)</th>
<th>PRA (ng/ml/hr)</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>260 × 168</td>
<td>G IV</td>
<td>2.0</td>
<td>9.0</td>
<td>32</td>
</tr>
<tr>
<td>02</td>
<td>195 × 138</td>
<td>G IV</td>
<td>3.4</td>
<td>1.3</td>
<td>35</td>
</tr>
<tr>
<td>03</td>
<td>230 × 142</td>
<td>G IV</td>
<td>11.5</td>
<td>7.0</td>
<td>26</td>
</tr>
<tr>
<td>04</td>
<td>244 × 160</td>
<td>papilledema</td>
<td>0.7</td>
<td>0.4</td>
<td>39</td>
</tr>
<tr>
<td>05</td>
<td>234 × 142</td>
<td>G IV</td>
<td>2.6</td>
<td>6.2</td>
<td>35</td>
</tr>
<tr>
<td>06</td>
<td>246 × 156</td>
<td>G IV</td>
<td>6.1</td>
<td>6.5</td>
<td>25</td>
</tr>
<tr>
<td>07</td>
<td>220 × 138</td>
<td>G IV</td>
<td>4.5</td>
<td>4.4</td>
<td>30</td>
</tr>
<tr>
<td>08</td>
<td>198 × 166</td>
<td>G IV</td>
<td>3.7</td>
<td>2.6</td>
<td>36</td>
</tr>
<tr>
<td>09</td>
<td>236 × 146</td>
<td>papilledema</td>
<td>0.9</td>
<td>0.1</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>250 × 150</td>
<td>G IV</td>
<td>9.0</td>
<td>3.3</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>250 × 188</td>
<td>G IV</td>
<td>11.0</td>
<td>15.7</td>
<td>23%</td>
</tr>
</tbody>
</table>

Correlates of Blood Pressure Response

In eight of the 11 patients, BP was reduced after captopril administration by 10 mm Hg or more, and consequently MAP was reduced from 178.5 ± 5.8 to 151.8 ± 7.8 mm Hg (p < 0.001), while heart rate (HR) remained unchanged (from 89.7 ± 4.5 to 89.3 ± 4.5 bpm n.s.). Blood pressure response was associated with a fall in TPRI (from 4458.8 ± 304.1 to 3379.4 ± 251.7 dyn sec · cm⁻³ · m⁻², p < 0.001), and a highly significant correlation was observed between these two variables (y = 2 + 0.02x, r = 0.95, p < 0.001). Also, BP responses were significantly correlated with pretreatment PRA (y = -11.8 - 16.7x, r = 0.72, p < 0.01).

Changes in Cardiac Index

Cardiac index was within the normal limits in seven patients, decreased in one, and increased in three. We considered as increased output those values two standard deviations above the average for normals in our laboratory (3.19 ± 0.19 liter/min/m²). Two hours after captopril administration, CI increased from 3.29 ± 0.13 to 3.68 ± 0.15 liter/min/m² (range, from -2 to 24%) (p < 0.001). Captopril showed peak action on CI 30 minutes after administration, when it reached 3.78 ± 0.15 liter/min/m² (p < 0.001). In all but one patient, cardiac indices were increased, and at the end of the study in six of the 11 patients they were increased by two or more standard deviations above the average normal standards (fig. 1).

Furthermore, no correlation was found between hematocrit and CI both before (r = 0.42, n.s., fig. 2) and after captopril (r = 0.06, n.s.), but a significant inverse correlation was found between control CI and the magnitude of the fall in MAP (y = 1.22 - 28.9x, r = -0.71, p < 0.01) (fig. 3). No correlation was found between control PRA and baseline TPRI (r = 0.56, n.s.), and a weak, although significant, inverse correlation was observed between control PRA and baseline
BLOOD PRESSURE RESPONSE TO CAPTOPRIL/Saragoça et al.  

CI \( (l/min) \)

\[
\begin{array}{c}
4.5 \\
4.0 \\
3.5 \\
3.0 \\
2.5 \\
\end{array}
\]

CONTROL 2Hrs

NORMAL RANGE \( (X \pm 2\text{SD}) \)

![Graph showing increases in cardiac index observed in malignant hypertension between control and 2 hours after captopril. Single lines represent individual changes; heavy line and bars represent means ± SEM; shaded area represents average normal ± 2 SD from average.](image)

CI \( (l/min) \)

\[
\begin{array}{c}
4.5 \\
4.0 \\
3.5 \\
3.0 \\
2.5 \\
\end{array}
\]

![Graph showing relationship between control cardiac index and hematocrit in the patients studied.](image)

![Graph showing influence of control cardiac index on the magnitude of the blood pressure fall with captopril in malignant hypertensive patients.](image)

Stroke volume was not significantly reduced in the control period (37.4 ± 1.8; range 29–45 ml/beat/m²) and increased significantly with captopril (41.6 ± 1.7, range 39 to 53 ml/beat/m², \( p < 0.001 \)). Figure 4 shows the association between pulmonary wedge pressure (PWP) and CI before and after captopril administration.

Blood Volume and Venous Hemodynamics

Mean pulmonary artery pressure and pulmonary diastolic artery pressure were significantly reduced by captopril administration (from 21.9 ± 4.3 to 17.8 ± 3.5, \( p < 0.01 \); and from 15.2 ± 3.5 to 10.4 ± 2.4 mm Hg, \( p < 0.01 \), respectively). Also, right atrial pressure was significantly decreased after the drug (from 3.5 ± 1.4 to 1.5 ± 1.4 mm Hg, \( p < 0.001 \)). However, pulmonary arteriolar resistance did not change significantly during the study (from 112.0 ± 24.0 to 114.5 ± 27.0 dyn sec · cm⁻⁵ · m⁻², n.s.) and PV was also unchanged by captopril (from 4.02 ± 0.26 to 4.12 ± 0.12 liters, n.s.).

Discussion

Captopril has been successfully used to reduce BP in several forms of nonmalignant hypertension. ²⁵ ²⁶ This study confirms our previous results⁶ ⁹ and those of others¹ that captopril is also effective in acutely reducing BP in malignant hypertensive patients, thus suggesting the participation of elevated PRA in the maintenance of these high BP levels. Although some studies have failed to demonstrate an association between PRA and the magnitude of BP fall with captopril,¹⁹ ²⁰ our data are in accordance with a number of others¹³ ¹⁸ ¹⁹ ²⁸ showing that the reduction in arterial pressure in our patients was due to the decrease in TPR and that it was closely correlated with pretreatment levels of PRA. These facts support the concept that the
action of captopril in reducing BP is due to a large extent to the blockade of angiotensin generation. They also are in agreement with the hypothesis that PRA levels are important in determining the increased TPR in human malignant hypertension.1-3

On the other hand, our data also show that, following angiotensin blockade, the CI increased significantly. These results are in sharp contrast with all previous studies on the hemodynamic response to captopril in nonmalignant forms of hypertension.15,16,18-20 These studies invariably show that BP response to captopril in benign hypertension is due to a fall in TPR and that the CI remains unchanged. Some factors could be responsible for this important difference: 1) acute increases in preload due to acute increases in PV or to central redistribution of blood volume induced by the drug; and 2) increased sympathetic cardiac stimulation due to baroreflex.

The possibility of changes in PV or in its distribution has been focused in several studies. The acute effects of captopril on PV have not yet been reported, but the administration of the drug for several days induces little19 or no change19 in PV. Our data show that there were no significant changes in PV with captopril in malignant hypertensive patients that could be responsible for increasing preload and CO. On the other hand, CO may have risen because of a central redistribution of an unchanged blood volume. Data concerning blood volume distribution with captopril in hypertension are scarce, but Tarazi et al.30 have shown that captopril administration in patients with congestive heart failure induces peripheral pooling instead of central relocation of blood, thus indicating a diminution rather than an increase in venous return. Although we did not measure the changes in cardiopulmonary volume induced by captopril, indirect evidence from our data is in accordance with those results because right atrial and pulmonary diastolic pressures decreased significantly while pulmonary vascular resistance and blood volume did not change significantly during the study. Thus, the decreased venous and pulmonary pressures in the presence of an unchanged PV are also suggestive of increased venous compliance and possibly associated with peripheral venous pooling of blood. For that reason, it is unlikely that the increases in CO observed in our patients were due to increases in preload secondary to angiotensin blockade.

A second possibility to explain our findings is an increase in sympathetic drive in response to the fall in arterial pressure. Against this possibility, our results show that no increase in HR occurred following administration of the drug. This fact is in accordance with many previous studies, including those of Fouad et al.18 and others,15,19 in which longer term therapy showed that no tachycardia followed captopril administration, suggesting that this drug may blunt baroreceptor function.31 Thus, the increases in CO observed in our patients remain unexplained in the light of our data and those of others.

An alternative explanation for our findings could be that CO increased after captopril because of the reduction in arterial pressure and in resistance to left ventricular ejection.32 This might happen in failing hearts when their afterload is reduced.33 However, there was no evidence of cardiac decompensation in our patients since pulmonary diastolic pressure was normal in most (7/11). However, this conclusion is not fully warranted without the analysis of stroke index and its relation to the left ventricular filling pressure. Figure 4 depicts such individual relationships both before (black dots) and after (open dots) captopril. The arrows show that captopril induced a change of the individual points to higher levels, implying improvement to a higher Frank-Starling relation. However before captopril, only four of the patients showed modestly depressed stroke volume as compared to patients with congestive heart failure.33-M Only three of these four patients had elevated PWP, indicating depressed cardiac pump function; moreover, this depression was apparently a moderate one.35,36 Therefore, these facts imply that the other eight patients had at least normal pump function, and that this function was improved in most of the patients after captopril. Therefore, it is more reasonable to suggest that malignant hypertension in our patients involved a 'mechanical' overload to the heart rather than myocardial failure, for when the overload was reduced, the output increased to high levels.
The observed normal or high CO could, otherwise, be related to the low hematocrit values in these patients and consequently be part of the well-established hemodynamic pattern of chronic renal failure. This is probably not the case, because we did not observe any correlation between serum creatinine levels and CO at rest in our patients. More importantly, no correlation was found between hematocrit and CO either before (control) or after vasodilatation with captopril. These findings are in contrast with the reports of Neff and colleagues and Kim et al. in patients with chronic renal failure, but since our patients had low hematocrits irrespective of whether their renal function was preserved or decreased, their low hematocrit may possibly reflect the microangiopathic anemia of malignant hypertension, rather than the anemia of chronic renal failure. However, our data do not allow exclusion of the anemia of malignant hypertension as responsible in part for the increases in CO with captopril.

The high levels of CI could also be attributable to volume expansion in these patients; however, the inverse correlation demonstrated between their PV and CI suggests that volume expansion is probably not the cause of the high output. After captopril administration, CO rose to levels higher than normal. Similar results were obtained by Kim et al. in their population of end-stage renal disease, CO increased after nephrectomy in patients with malignant forms. This is in contrast with the report of Safar et al. who observed that the increase in CI was paralleled by a parallel increase in peripheral resistance. Furthermore, inhibition of angiotensin generation may be at least part of the mechanism of the action of captopril since a correlation was observed between pretreatment PRA and the percent increase in CI; however, other mechanisms of action may also be involved in this response.

Thus, in patients with malignant hypertension, CO was either high or normal; the first condition was found in patients with relatively well-preserved renal function and normal or low PRA. In those with high PRA, the increased peripheral resistance lowered output to normal levels; the high output was “unmasked” when captopril reduced resistance to flow. This fact is reflected by the highly significant correlation between the percentual changes in TPRI and CI (y = 6.9 − 1.3x, r = −0.84, p < 0.01). This may also help to explain the resistance to treatment with sodium nitroprusside recently described in malignant hypertensive patients.

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