Treatment With Enalapril Modifies the Pain Perception Pattern in Hypertensive Patients

Luigina Guasti, Paola Grimoldi, Alessio Diolisi, Maria Rosaria Petrozzino, Giovanni Gaudio, Anna Maria Grandi, Maria Grazia Rossi, Achille Venco

Abstract—The cardiovascular system shares numerous anatomic and functional pathways with the antinociceptive network. The aim of this study was to investigate whether angiotensin-converting enzyme (ACE) inhibitor treatment could affect hypertension-related hypalgesia. Twenty-five untreated hypertensive patients, together with a control group of 14 normotensive subjects, underwent dental pain perception evaluation by means of a pulpar test (graded increase of test current applied to healthy teeth). After the evaluation of the dental pain threshold (occurrence of pulp sensation) and tolerance (time when the subjects asked for the test to be stopped), all the subjects underwent a 24-hour ambulatory blood pressure monitoring. The hypertensive group then was treated with 20 mg/d enalapril, whereas the normotensive subjects remained without any treatment. After a time interval of 6±2 months, the dental pain sensitivity was retested in all the subjects, and ambulatory blood pressure was recorded during treatment in the hypertensive patients. At the first assessment, hypertensive patients showed a higher pain threshold than normotensive subjects (P<.001). On retesting of pain sensitivity in hypertensive patients, a significant decrease of both pain threshold and tolerance, leading to their normalization, was observed during treatment (P<.001 and P<.005, respectively), in the presence of reduced 24-hour and office blood pressure values. A slight, though significant, correlation was observed between variations in pain tolerance and baseline blood pressure changes occurring during treatment. During follow-up, the normotensive subjects did not show any significant pain perception or office blood pressure changes. Hypertension-related hypalgesia was confirmed. Mechanisms acting both through lowering of blood pressure and specific pharmacodynamic properties may account for the normalization of pain sensitivity observed in hypertensive patients during treatment with ACE inhibitors. (Hypertension. 1998;31:1146-1150.)

Key Words: hypertension, essential § blood pressure monitoring § angiotensin-converting enzyme inhibitors § enalapril § pain threshold

C omplex mechanisms and numerous pathways underlie the pathophysiology of pain perception. The cardiovascular control network shares with the antinociceptive system various central and peripheral neurotransmitters, as well as anatomic nuclei and projections. Experimental studies have also demonstrated a link between the baroreceptor function and pain perception. Modulatory interactions between pain sensitivity and the cardiovascular system have been reported both in physiological conditions and in patients with various cardiovascular syndromes. Alterations in pain sensitivity and circulating β-endorphin, an endogenous opioid-like peptide, were found in hypertensive subjects, patients with shock and heart failure, and subjects with silent myocardial ischemia. Both in animal and human studies, hypertension has been associated with a reduced perception of painful stimuli. However, the effect of cardiovascular-acting agents on pain perception has been poorly investigated. Antihypertensive drugs could influence pain sensitivity through blood pressure reduction and/or by specific pharmacodynamic mechanisms. In patients with hypertension, no significant change in pain sensitivity was reported after the use of diuretics or β-blockers, whereas ketanserin tended to decrease or reverse the reduced pain perception associated with high blood pressure values. Moreover, interactions between β-endorphins, pain sensitivity, and central α2-stimulating agents have been reported.

The aims of this study were to (1) investigate whether the antihypertensive treatment with enalapril could modify the dental pain threshold and tolerance in human hypertensive subjects and (2) find whether changes in blood pressure levels during treatment could account for possible variations in pain sensitivity.

Methods

Thirty-nine consecutive subjects (mean age, 43±4 years) with the following characteristics were enrolled in the study: male sex, age between 30 and 50 years, no pharmacological treatment or washout of an antihypertensive therapy for at least 3 weeks, no concomitant diseases (diabetes, neuropathies, cardiac or lung diseases, obesity, stroke, or psychiatric disturbances), dental formula suitable for the pulpar test (see below) as indicated by a previous dental checkup (subjects with tooth fractures, abrasions, caries lesions, fillings, and marked periodontal diseases were excluded), and informed consent to the study. Twenty-five of 39 subjects were hypertensives who were either sent from the general practitioner for blood pressure monitoring on a regular basis or were seen in the hypertension clinic of the authors during that period. The remaining 14 subjects were normotensive and were recruited among friends and colleagues of the authors. Twenty-five hypertensive subjects without clinical and/or radiologic signs of cardiovascular disease were selected for the study. The remaining four subjects were hypertensive subjects with clinical and/or radiologic signs of cardiovascular disease and were not administered with enalapril.
evaluation or followed up by our center because of a history of hypertension. The 14 healthy normotensive subjects were studied during a general clinical checkup of Italian post office employees and were considered as the control group. A routine diagnostic workup excluded secondary forms of hypertension in all the subjects. Normotensive and hypertensive subjects were similar regarding mean age (44.5 ± 5 and 43 ± 4 years in normotensive and hypertensive subjects, respectively), smoking habits (2 mild smokers in the normotensive group, 4 mild smokers in the hypertensive group), and body mass index (24.6 ± 1.9 versus 24.7 ± 1.7 kg/m² in normotensives and hypertensives, respectively). The study was approved by the ethics committee of our department.

In all subjects, dental pain perception was determined twice (time interval, 6 ± 2 months) by a pulpar test (performed by the same operator who was blinded to the pressure level of the subjects). The first evaluation (first assessment) was done without any pharmacological treatment. It consisted of a pulpar test preceded by automatic office blood pressure measurements (see “Baseline Blood Pressure”) and followed by 24-hour ambulatory monitoring. At the second assessment, the hypertensive patients were receiving angiotensin-converting enzyme (ACE) inhibitor treatment (which was started after the first assessment) while the normotensive subjects remained without any treatment. After a trituration period, all the hypertensive patients were given enalapril, 20 mg/d, at 7 AM, which was also given the day of the second assessment. In addition to the pulpar test, automatic office blood pressure measurements were repeated at the second assessment in all subjects. Moreover, the hypertensive group underwent additional ambulatory blood pressure monitoring, whereas the normotensive group did not. All subjects were studied at the two assessments after an overnight fast (in particular, the subjects were asked to avoid coffees, teas, cola-containing drinks, alcoholic beverages, chocolate, and smoking during the 12 hours preceding the tests).

**Baseline Blood Pressure**

In the morning, between 9 and 11 AM, the subjects were kept at rest in a supine and comfortable position for a 30-minute period. Blood pressures were automatically measured by a Hewlett-Packard 78352A recorder every 3 minutes. The blood pressure value of the measurement preceding the pulpar test was defined as baseline blood pressure. If the value differed >5 mm Hg from the previous measurement, another measure was taken until two were close.

**Pain Perception Assessment**

After the 30-minute rest, dental pain perception was investigated by means of a pulpar tester. The method has been previously described.14,27 Briefly, the pulp stimulator (Medi-tester, Medic-Al) allows the delivery of automatic intermittent bursts of electrical stimuli, with negative polarity at linearly increasing intensity from 0 to 0.03 mA (maximal tension, 6500 mV; burst frequency, 5 Hz). The stimulator was applied to the enamel surface of the tooth through a metal cylinder. The switching on and off occurred automatically when the contact with the tooth was made or excluded, respectively. The hand of the operator in contact with the lips of the subject closed the circuit. As the test current increased from 0 to 0.03 mA, a number from 0 to 80 (relative units [rU]) was displayed on a digital reader of the instrument (not visible to the subject under examination).

The subjects had been previously instructed to raise their right hand at the occurrence of any pulp sensation (pain threshold, rU). At this point the stimulation was interrupted. Pain tolerance (rU) was obtained by reapplication of the test current immediately afterward and keeping up the stimulation until the subjects asked for the test to be stopped.14,27 The pulpar test was performed on three healthy teeth (two upper incisors and one inferior incisor, always in the same order). Mean values (of the three) of pain threshold and tolerance were used in subsequent analysis.

**Ambulatory Blood Pressure**

After pain perception evaluation, ambulatory blood pressure was recorded by means of a Takeda TM 2421 (A&D Co) set to take a measurement every 15 minutes for a period of 24 hours. In two subjects, the quality of the monitoring was not sufficient (valid measurements <80%) and was repeated successfully the following day. The reading, editing, and analysis of the data were performed by a software system as previously described.14,27 The following parameters were taken into consideration in subsequent analysis: 24-hour systolic and diastolic pressures, 24-hour heart rate, and daytime (7 AM to 10 PM) and nighttime (10 PM to 7 AM) systolic and diastolic pressures.

### Statistical Analysis

Data are presented as mean±SD. The qualitative variable (smoking habit) was compared between normotensive and hypertensive subjects by a χ² test, and possible variations of this variable between the first and second assessment were tested by a McNemar test. Student’s t test was used to compare parametric variables between normotensive and hypertensive subjects. A Mann-Whitney U test was performed to compare pain threshold and tolerance between the normotensive and hypertensive groups. Hemodynamic data obtained at the time of the two assessments were compared by a paired t test. A Wilcoxon rank test was used to compare the results of pain perception evaluation at baseline and during follow-up. Possible relations between blood pressure variations and pain sensitivity changes occurring during follow-up were tested by Spearman rank correlation analysis.

The percentage of change of both arterial pressures and pain perception variables between the two assessments were obtained by the following formula: First Assessment Value–Second Assessment Value/First Assessment Value×100 (%). The statistical analysis was performed with the computerized Statistical Package for the Social Sciences (SPSS). A value of P<.05 was considered significant.

### Results

The 24-hour blood pressure was 141±11/93±11 and 123±12/74±6 mm Hg in hypertensive and normotensive subjects, respectively (P<.001). The dental pain threshold was significantly higher in the 25 hypertensive patients than in the 14 normotensive subjects (29±6 versus 22±4 rU in hypertensives and normotensives, respectively, P<.001). The pain tolerance also tended to be higher, although not significantly, in the hypertensive group (48±18 versus 44±20 rU, NS).

### Follow-up

No difference was found in smoking habits and body mass index between subjects at the first and second assessment. On retesting of hypertensive patients during chronic treatment with ACE inhibitors, a significant reduction was observed in both 24-hour and baseline blood pressure values (Table).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Treatment</th>
<th>Enalapril</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>24-h SBP, mm Hg</td>
<td>141±11</td>
<td>134±15</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>93±11</td>
<td>84±11</td>
<td>&lt;.002</td>
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<tr>
<td>24-h HR, bpm</td>
<td>74±8</td>
<td>75±9</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>147±11</td>
<td>140±16</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>97±10</td>
<td>88±10</td>
<td>&lt;.001</td>
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<tr>
<td>Nighttime SBP, mm Hg</td>
<td>126±14</td>
<td>121±16</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime DBP, mm Hg</td>
<td>81±14</td>
<td>77±12</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>144±8</td>
<td>135±14</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg</td>
<td>88±12</td>
<td>80±11</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>67±8</td>
<td>65±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.
A significant decrease of pain threshold and tolerance was found when the dental pain sensitivity was retested during pharmacological treatment ($P < .001$ and $P < .005$, respectively) (Fig 1).

As expected, the control group of normotensive subjects, who remained untreated during follow-up, did not show any significant variation with respect to baseline systolic and diastolic blood pressures or baseline heart rate (first versus second assessment: $136 \pm 13/82 \pm 10$ versus $139 \pm 15/83 \pm 11$ mm Hg, NS; and $64 \pm 13$ versus $65 \pm 11$ bpm, NS).

Moreover, both pain threshold and tolerance remained unchanged at the second evaluation (Fig 2).

When pain threshold and tolerance of the normotensive subjects were compared with those of hypertensive patients obtained during treatment with enalapril, no significant difference (previously observed between normotensives and untreated hypertensives) was found. Baseline arterial systolic and diastolic blood pressures were similar in normotensive and enalapril-treated patients. However, although a reduction in 24-hour pressure was observed in the treated hypertensive patients, the ambulatory values remained higher than those recorded in normotensive subjects at the first assessment ($P < .05$ for 24-hour systolic pressure; $P < .005$ for diastolic pressure).

In the hypertensive group, the Spearman rank correlation showed no significant relations between changes (arithmetic difference and percent change) in pain threshold and tolerance and changes in 24-hour blood pressure. However, the baseline systolic and diastolic blood pressure variations were slightly, although significantly, correlated with pain tolerance changes ($P < .05$).

**Discussion**

**Hypalgesia in Hypertension**

Hypertension and reduced pain perception have been repeatedly associated in animals and in humans. In humans, various experimental techniques have been used to identify the pain threshold, with similar results. Hypertensive patients show a reduced sensitivity to pain that is independent of the method used to provoke the painful stimuli. Hypalgesia in hypertension has been observed during the follow-up in pain threshold (top) and tolerance (bottom), expressed in relative units (rU).

**Figure 1.** Pain sensitivity changes in hypertensive patients during ACE inhibitor treatment. The pain threshold (top) and tolerance (bottom), expressed in relative units (rU), are shown before and during treatment with enalapril. A significant reduction of both pain threshold and tolerance was observed during treatment ($P < .001$ and $P < .005$, respectively).

**Figure 2.** Pain sensitivity measured in normotensive untreated subjects at two assessments. No significant difference was observed during the follow-up in pain threshold (top) and tolerance (bottom), expressed in relative units (rU).
hypertensive patients, although the difference did not reach statistical significance. It is a matter of discussion whether hypalgesia is triggered by mechanisms related to increased arterial pressure or it is a feature of hypertension related to the complex alterations of central functions associated with hypertension. However, at least in part, the high pressure values per se seem to have a role in hypalgesia. Hypalgesic behaviors have been associated with various forms of experimental hypertension independently of the method used to induce blood pressure elevation. On reduction of blood pressure, after the removal of the constricted kidney, a normalization of pain threshold was reported in renal hypertensive rats, although occurring with a delayed pattern with respect to blood pressure changes. The lowering of blood pressure in rats by peripherally acting ganglionic blockers reversed hypalgesia in the hypertensive strain and induced hyperalgesia in the control rats.

ACE Inhibitors and Pain Perception

Only a few studies have investigated the possible interactions between antihypertensive agents and pain perception in humans. In this study, the treatment with the ACE inhibitor enalapril was associated with a change in both pain threshold and tolerance, with pain sensitivity being higher during treatment. When the dental pain perception and blood pressure values were retested during follow-up, the control group of untreated normotensive subjects showed unchanged results.

Regarding the effect of ACE inhibitors on pain sensitivity, controversial results have been found in animal studies. Both a significant reduction of hypalgesic behavior and no diminished responsiveness to noxious stimuli were reported in hypertensive animals treated with ACE inhibitors.

Angiotensin II (Ang II) seems to antagonize morphine- and electroacupuncture-induced analgesia. On the other hand, other authors have reported that intracerebroventricular angiotensin produced a large analgesic effect that could be blocked by naloxone. Moreover, the dermorphin-induced antinociception was markedly reduced by coadministration of captopril in mice. In addition, Ang II was found to induce baroreflex resetting independently of blood pressure levels, thus this action on baroreceptor function might affect the perception pattern. At a central level, the activity of Ang II has been reported at the nucleus tractus solitarii and area postrema, which are anatomic regions of primary interest has been reported at the nucleus tractus solitarii and area postrema, and the caudal medulla.

The normalization of pain sensitivity found after treatment in the hypertensive group could be related, at least in part, to the normalization of increased hot-plate latencies normally exhibited by SHR, whereas pain sensitivity was unaffected by hydralazine, otherwise effective in reducing blood pressure. Thus, the authors favored the hypothesis of an interplay between renin-angiotensin mechanisms and intrinsic analgesic modulation in explaining the ACE inhibitor–induced changes in pain sensitivity. Studying spinal nociceptive transmission in rats, Randich and Robert-son found that it was significantly attenuated in SHR and that captopril treatment affected the response properties of SHR neurons. However, the findings of that study could not clarify whether this action was obtained by the lowering of arterial pressure or by an influence of the drug on facilitatory or inhibitory systems. In the present study, we found a mild, though significant, relationship between the changes in baseline blood pressure values and pain tolerance reduction. Although the 24-hour blood pressure relates to pain sensitivity better than the standard blood pressure, no significant relation was found between variations of sustained blood pressure induced by therapy and changes in pain perception. The normalization of pain sensitivity found after treatment in the hypertensive group could be related, at least in part, to the drug-induced lowering of blood pressure. Alternatively, the central effects of ACE inhibition or facilitation to bradykinin may account for the increased sensitivity to pain observed after treatment. In our opinion, the increased pain sensitivity may express both variations in mechanisms by which blood pressure affects pain perception and the pharmacodynamic effects of the ACE inhibitors.

However, some limitations of this study have to be acknowledged: the patient population was relatively small, and the investigation was not designed as a placebo-controlled study.

The individual pattern of pain perception seems to be one relevant factor in the determination of symptoms during myocardial ischemia, and a generalized impaired pain sensitivity has been associated with silent ischemia. Moreover, a role of hypertension in the development of silent ischemia has been reported. These results suggest that ACE inhibitors may facilitate the perception of painful stimuli and, at least in hypertensive patients with coronary artery disease, may possibly interfere with silent episodes.

A recent study investigating pain threshold by hot-plate test in normotensive Wistar-Kyoto and spontaneously hypertensive rats (SHR) after ACE inhibitor treatment found a normalization of the increased hot-plate latencies normally exhibited by SHR, whereas pain sensitivity was unaffected by hydralazine, otherwise effective in reducing blood pressure.

In the same study, the treatment with losartan, an angiotensin type 1 (AT1) receptor antagonist, had no effect on blood pressure at the dose used, in the presence of markedly reduced hot-plate latencies. Thus, the authors favored the hypothesis of an interplay between renin-angiotensin mechanisms and intrinsic analgesic modulation in explaining the ACE inhibitor–induced changes in pain sensitivity. Studying spinal nociceptive transmission in rats, Randich and Robert-son found that it was significantly attenuated in SHR and that captopril treatment affected the response properties of SHR neurons. However, the findings of that study could not clarify whether this action was obtained by the lowering of arterial pressure or by an influence of the drug on facilitatory or inhibitory systems. In the present study, we found a mild, though significant, relationship between the changes in baseline blood pressure values and pain tolerance reduction. Although the 24-hour blood pressure relates to pain sensitivity better than the standard blood pressure, no significant relation was found between variations of sustained blood pressure induced by therapy and changes in pain perception. The normalization of pain sensitivity found after treatment in the hypertensive group could be related, at least in part, to the drug-induced lowering of blood pressure. Alternatively, the central effects of ACE inhibition or facilitation to bradykinin may account for the increased sensitivity to pain observed after treatment. In our opinion, the increased pain sensitivity may express both variations in mechanisms by which blood pressure affects pain perception and the pharmacodynamic effects of the ACE inhibitors.

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