Arterial Hypertension Is Associated with Hypalgesia in Humans

SERGIO GHIONE, CATERINA ROSA, LORENA MEZZASALMA, AND ELISABETTA PANATTONI

SUMMARY An association between increased blood pressure and hypalgesia has been reported in several studies in animals and in a few reports in humans. We investigated the relationship between hypertension and pain perception by comparing the response to graded electrical stimulation of the tooth pulp, which is thought to represent an exclusively nociceptive system. The test was performed with a commercial tooth pulp tester in a large series of subjects with borderline or established hypertension and in three groups of normotensive controls: volunteers, nonhypertensive patients, and medical students with a well-established or no family history of hypertension. Subjects had to report when they started to feel pulp stimulation (sensory threshold) and when this became painful (pain threshold). Sensory and pain thresholds were obtained as means of the measurements on four healthy, unfilled teeth. Sensory thresholds were significantly higher in subjects with borderline or established hypertension than in two of the three normotensive groups (volunteers and normotensive patients), whereas no significant difference was observed between the two hypertensive groups. The results for the pain threshold were qualitatively similar but less clear and less amenable to statistical analysis because this parameter could not be determined with accuracy in a number of subjects in whom the subjective pain threshold was above the upper range of stimulation of the instrument. The association between blood pressure levels and pain perception was further confirmed by the highly significant correlation found for the overall data between mean arterial blood pressure and both thresholds. On the other hand, no significant correlation was found with heart rate and no significant effects could be detected by analysis of variance for sex, age, and family history of hypertension. Furthermore, no changes in pain sensitivity were observed in a subgroup of patients studied after 3 months of diuretic or β-blocking treatment or of low salt diet, despite significant reductions of arterial blood pressure. Taken together, our findings provide further confirmatory evidence for an increased tolerance to pain in hypertensive humans and suggest that this may be a feature of arterial hypertension irrespective of the prevailing blood pressure levels. (Hypertension 12: 491-497, 1988)

KEY WORDS • pain • hypalgesia • arterial hypertension • tooth pulp test

SEVERAL lines of evidence indicate that increased arterial blood pressure is associated with a decreased perception of pain.1 Psychophysiological studies in the rat2-9 have demonstrated the association of hypalgesic behavior (delayed response to noxious stimuli such as a hot plate, an electric shock, or a mechanical force applied to a limb) to arterial hypertension. In hypertensive humans, an increased tolerance to pain, as assessed by the measurement of the pain threshold to graded electrical tooth pulp stimulation, has been reported by Zamir and Shuber10 and confirmed in preliminary studies by our group.11, 12

Put into a broader perspective, the phenomenon of hypertension-associated hypalgesia may provide some insight into the involvement of the endogenous opioid system(s) in the pathogenesis of hypertension.13 In fact, several studies have demonstrated that the opiate antagonist naloxone normalizes the increase in pain threshold in spontaneously hypertensive rats (SHR),2-6, 8 suggesting the implication of the opioid peptides in this form of hypalgesia. Numerous biochemical and pharmacological studies in experimental animals have provided convincing evidence of the presence of opioid peptides and their receptors in brain nuclei involved in cardiovascular control14, 15 and, more generally, of a role for these neurotransmitters in cardiovascular regulation.13 Furthermore, a role for the central opioid system in the pathogenesis of hypertension in humans has been supported by the studies of Farsang and colleagues,16, 17 who showed that the
antihypertensive effect of clonidine involves an opioid-mediated inhibition of the central sympathetic outflow and that this mechanism appears to be more pronounced in hypertensive patients with hyperactivity of the adrenergic system.

Because of its simplicity, noninvasiveness, and acceptability, tooth pulp stimulation (a technique used in clinical dentistry for assessing pulp vitality) is a convenient test in experiments designed to investigate pain mechanisms. The dental pulp represents an exclusively sensory system, and a good agreement between intradental nerve activity and pain perception in response to graded stimulation applied to the teeth has been reported. The pain threshold determined by this test is fairly reproducible within the same individual and can be altered by a variety of manipulations known to affect pain perception in the experimental animal such as L-tryptophan supplementation, acupuncture, and transcutaneous stimulation.

We report the results obtained with this test in a series of 156 hypertensive and normotensive subjects. These results confirm and extend previous preliminary reports by us and studies by others indicating that arterial hypertension is associated with an increased tolerance to pain in humans.

Subjects and Methods
We studied 156 subjects over a period of 2.5 years. Eighty were normotensive and 76 had either borderline or established hypertension. The normotensive group comprised three different subgroups: normal volunteers who were recruited either from the medical and paramedical staff of the hospital (Group A1) or from a selected medical student population (Group A2) chosen on the basis of having a well-established family history of hypertension (defined as at least one parent with arterial hypertension—i.e., having measured high blood pressure levels or receiving antihypertensive treatment, or both) or no family history of hypertension (defined as blood pressure values below 140/90 mm Hg in both parents and at least three grandparents), and nonhypertensive patients (Group B) who were recruited from several outpatient clinics.

All hypertensive subjects, except two who were selected from the normal control population but turned out to have borderline blood pressure values, were recruited from the same outpatient clinic. Thirty-four subjects were classified as having borderline hypertension (systolic blood pressure between 140 and 160 mm Hg or diastolic blood pressure between 90 and 95 mm Hg, or both) and 42 as having established hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg or both), according to World Health Organization recommendations. All patients had discontinued drug treatment at least 2 weeks before the study began, and the routine diagnostic workup excluded secondary forms of hypertension in all but two subjects, who had renovascular hypertension. None of the subjects had a history of lung disease, stroke, diabetes, or psychiatric disturbances. All subjects were questioned about their family history of hypertension and smoking habits. The major characteristics of the various subgroups are reported in Table 1.

The procedure was explained to all the hypertensive subjects and to Group B as representing a test that could be of some minor utility since it explored a psychophysiological aspect that might be related to their disease. The procedure was explained to all volunteers as a test to assess pain sensitivity that could be of further clinical or scientific usefulness.

Before the study was initiated, the test was repeatedly performed on the investigators themselves and found to be readily acceptable. All subjects were thus reassured that the test was only lightly painful and, since the evaluation was going to be performed on four teeth, that they could withdraw their consent at any step during the examination. Nine subjects (2 normotensive and 7 hypertensive subjects) who displayed extreme anxiety toward the odontoiatric chair and toward any odontoiatric procedure were excluded from the study. In no case was the test interrupted, and all subjects declared themselves willing to repeat it if required.

A commercial, noninvasive tooth pulp tester (American Analytic Technology, Missoula, MT, USA) was used. This instrument gives automatic intermittent bursts of electrical stimuli of negative polarity at

### Table 1. Characteristics of the Subgroups Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Volunteers</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staff (A1) (n=18)</td>
<td>Students (A2) (n=19)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33.1±8.4 (26–54)</td>
<td>23.9±1.4 (22–26)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14:4</td>
<td>19:0</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>120.1±78.8</td>
<td>130.7±75.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>±10.6/5.7</td>
<td>±8.7/10.7</td>
</tr>
<tr>
<td>Heart rate of family history of hypertension (n)</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are means ± SD. Age range is shown in parentheses.
increasing voltage, with a peak output voltage ranging from 15 to 300 V and 2-MΩ load impedance. The intensity of the stimuli, expressed in arbitrary units (AU) on a relative scale between 0 and 80 was indicated on a digital reader in the instrument, not visible to the subject under examination. The performance of the instrument was checked every 4 months and remained stable throughout the study.

All determinations were done in the morning between 0900 and 1100, with the patient sitting on an odontoiatric chair, and always by the same dentist, who applied a probe to the tooth under examination. The subjects had to indicate, by lifting a hand, when they started to feel pulp stimulation (as a prickling sensation) and when this became painful enough to require the interruption of stimulation, and the corresponding values on display were taken as the sensory and pain thresholds. In several instances the subjects did not report notable pain even at the highest stimulus intensity of the instrument. For these subjects in whom the pain threshold was not measurable since it was above the upper range of stimulation, the highest available value (80 AU) was arbitrarily given. In no case was the sensory threshold above the upper range of stimulation. In most subjects, four healthy, unfilled teeth (two incisors [the right medial inferior and the left lateral superior] and two bicuspids [the first right inferior and the second left superior]) were studied, always in the same order. In 17% of the subjects in whom one tooth was not considered healthy, only three teeth were studied. In no case were less than three teeth studied, and in all cases the average value of the measurements was used for subsequent analysis. All measurements were done blindly (i.e., without the dentist’s knowledge of the subject’s blood pressure).

In all subjects heart rate and casual blood pressure were measured in the sitting position in a quiet room by an automatic recorder (Dinamap 845 Vital Signs Monitor, Critikon, Tampa, FL, USA), and the mean of three successive measurements obtained over 5 minutes was used. The measurements were done 15 to 30 minutes before the tooth pulp stimulation test.

The test was repeated after 3 months in 25 hypertensive patients; 14 were receiving antihypertensive treatment (7: atenolol, 100 mg/day; 7: diuretics [spironolactone, 25 mg/day, and hydrochlorothiazide, 25 mg/day]), and 11 were on moderate sodium restriction.

Statistical evaluation was made by analysis of variance, Kruskal-Wallis test, t test, Wilcoxon test, and regression analysis, using the SPSS (Statistical Package for the Social Sciences) computing package (Chicago, IL, USA) implemented on an IBM 370 computer (Armonk, NY, USA).

**Results**

As shown in Table 2, on average, the highest values of sensory and pain thresholds were observed for the hypertensive subjects (borderline and established), whereas variable results were obtained in the three normotensive subgroups, the lowest values being those of Group A1 (the volunteers recruited from the hospital staff). No subjects in Group A1 (hospital staff) and various percentages of subjects in the other groups had one to four pain threshold values above the upper range. Because of the presence of these out-of-range values, the data distribution of the pain threshold was not normal (Figure 1). Therefore, different statistical techniques had to be applied: one-way analysis of variance showed significant differences between the various groups for the sensory threshold ($F_{4,156} = 8.819, p < 0.0001$); for pain threshold, the equivalent nonparametric Kruskal-Wallis test also confirmed the existence of significant differences between groups (chi square $= 29.411, p < 0.0001$). For the sensory threshold, comparison of the means by Scheffe’s method (see Table 2) showed significant differences ($p < 0.05$) between the normotensive groups (A1 and B) on the one hand and between the borderline and established hypertensive groups (Al and B) on the other hand.

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**Table 2. Sensory and Pain Thresholds, as Assessed by Tooth Pulp Stimulation, and Number of Out-of-Range Values in the Subgroups Studied**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staff (A1)</td>
<td>Students (A2)</td>
</tr>
<tr>
<td>Sensory threshold (AU)</td>
<td>29.4±6.4</td>
<td>34.7±8.3</td>
</tr>
<tr>
<td>Pain threshold (AU)</td>
<td>39.2±7.9</td>
<td>56.1±15.2</td>
</tr>
<tr>
<td>No. of subjects with pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>threshold values out of range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For one tooth</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>For two teeth</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>For three teeth</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>For four teeth</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are means ± SD. AU = arbitrary units.

The horizontal lines below the means of sensory threshold connect the homogeneous subsets obtained with Scheffe’s multiple range test; significance level: $p < 0.05$. The test was not applied to pain threshold values (see text).
The presence of an association between arterial blood pressure and pain sensitivity was confirmed when the pooled data were analyzed for significant correlations between mean arterial blood pressure and sensory \( r = 0.326, p < 0.0001 \) and pain thresholds \( r = 0.270, p < 0.001 \); Figure 2, A and B). On the other hand, no significant correlation was observed with heart rate (Figure 2, C and D), nor was any significant effect on either threshold found by multivariate analysis of variance for sex and age. The lack of possible influences on the results of age and sex distribution was confirmed when age-matched and sex-matched subgroups were compared (Table 3). No effect of family history was found by analysis of variance and the Kruskal-Wallis test on the pooled data or when Group A2 was analyzed alone. In this homogeneous subgroup of subjects with either well-established or no family history of hypertension, no difference was present for sensory \((35.7 \pm 10.1 \text{ vs } 33.0 \pm 5.3 \text{ AU})\) or pain thresholds \((57.4 \pm 16.9 \text{ vs } 54.3 \pm 13.4 \text{ AU})\).

Finally, as shown in Table 4, no significant changes in sensory and pain thresholds were observed in the patients restudied after various antihypertensive treatments, despite significant reductions of arterial blood pressure in most instances.

**Discussion**

The present study confirms and extends previous observations\(^6\)\(^\text{10-12}\) that in humans increased arterial

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**FIGURE 1.** Histogram representing the frequency distribution for the pain threshold (averaged over four teeth) to tooth pulp stimulation in the 156 subjects studied. The apparent bimodal distribution is due to the presence, in the highest classes, of an increasing number of subjects with one or more out-of-range values (to which the cutoff value of 80 arbitrary units was assigned).

**FIGURE 2.** Sensory and pain thresholds related to mean arterial blood pressure (A and B) and to heart rate (C and D) in the 156 subjects studied. A positive significant correlation was found for mean arterial blood pressure \((r = 0.326, p < 0.0001, \text{ and } r = 0.270, p < 0.001, \text{ respectively, for the sensory and pain threshold}), \text{ but not for heart rate (} n = 125; r = 0.084, \text{ NS, and } r = 0.100, \text{ NS).}
blood pressure is associated with reduced pain perception, as assessed by tooth pulp stimulation. Unfortunately, a cutoff value for the pain threshold had to be assigned for a number of subjects. This made the estimation of this parameter less accurate and its distribution nonnormal, thus rendering it impossible to apply standard techniques for multiple comparison. However, in this study, as in that of Zamir and Shuber, the sensory threshold to pulp stimulation was elevated. Although it cannot be ruled out that the perception of other sensations besides pain are reduced in hypertension, most evidence indicates that, from a sensory point of view, the human tooth is an exclusively nociceptive system and that both pain and the so-called prepain elicited by electrical stimulation are mediated by the same type of afferents. The finding of a strong correlation between sensory and pain thresholds observed for the pooled data is also in keeping with a close functional relation of the two measurements.

In this study different subgroups of normotensive subjects were investigated to exclude the possible confounding effects due to the choice of control groups. Taken together, our results suggest that the differences observed between normotensive and hypertensive subjects were not due to the selection of the control group, although they indicate that nonnegligible differences in pain sensitivity may be present between different control groups.

An increasing amount of anatomical, physiological, and pharmacological evidence supports the existence of a relationship between cardiovascular and pain regulatory systems and, in particular, a relationship between arterial blood pressure and pain modulation. Anatomical and physiological studies have shown that the brain stem areas participating in the regulation of blood pressure and those involved in the modulation of pain transmission are closely associated or may even partially overlap. A behavioral hypalgesia has been reported by several authors in SHR. On the other hand, it is less clear whether experimentally induced hypertension also is associated with hypalgesia. In fact, various authors have reported a reduced nociceptive responsiveness in animals after long-term and short-term increases in arterial blood pressure were induced, whereas Sitsen and de Jong did not observe such changes in rats with renal deoxycorticosteroid-acetate-salt hypertension.

Although the underlying mechanisms responsible for this form of hypertension-associated hypalgesia remain to be fully identified, several important aspects have been elucidated in recent years. The observation that this hypalgesia can be suppressed in the experimental animal by naloxone, but not by its exclusively peripherally acting analogue, N-methyl-naloxone, clearly indicates an involvement of the endogenous opioid systems within the central nervous system. However, the effect of these systems on the development and maintenance of hypertension is less clear. Interestingly, a role for the opioid peptides has been supported by several studies, both in animals and in humans, in the mediation of the hypotensive effect induced by central α-adrenergic receptor activation. The relevance of these obser-

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**Table 3. Characteristics, Sensory Thresholds, and Pain Thresholds of Subjects Matched for Age and Sex**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=16)</th>
<th>Borderline (n=16)</th>
<th>Established (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34.88 ± 9.17</td>
<td>34.63 ± 9.42</td>
<td>34.75 ± 9.15</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9 : 7</td>
<td>9 : 7</td>
<td>9 : 7</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125.25 ± 11.54</td>
<td>145.75 ± 7.75</td>
<td>163.00 ± 20.19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77.06 ± 6.94</td>
<td>94.06 ± 2.32</td>
<td>109.63 ± 18.24</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.00 ± 12.67</td>
<td>74.33 ± 12.33</td>
<td>75.93 ± 10.70</td>
</tr>
<tr>
<td>Sensory threshold (AU)</td>
<td>29.40 ± 9.40</td>
<td>39.63 ± 7.58</td>
<td>41.38 ± 7.06</td>
</tr>
<tr>
<td>Pain threshold (AU)</td>
<td>47.81 ± 18.73</td>
<td>62.83 ± 12.86</td>
<td>65.34 ± 12.33</td>
</tr>
</tbody>
</table>

Values are means ± SD. AU = arbitrary units.

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**Table 4. Effect of Antihypertensive Treatment on Blood Pressure and Pain Sensitivity**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of subjects</th>
<th>Arterial blood pressure (mm Hg)</th>
<th>Sensory threshold (AU)</th>
<th>Pain threshold (AU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>7</td>
<td>156±12/100±8</td>
<td>42±5</td>
<td>60±13</td>
</tr>
<tr>
<td>β-blocker</td>
<td></td>
<td>146±11/92±6</td>
<td>41±8</td>
<td>60±15</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7</td>
<td>142±12/98±7</td>
<td>38±5</td>
<td>60±10</td>
</tr>
<tr>
<td>Basal</td>
<td>11</td>
<td>146±11/92±12</td>
<td>40±6</td>
<td>63±9</td>
</tr>
<tr>
<td>Low salt</td>
<td></td>
<td>141±15/85±12</td>
<td>37±9</td>
<td>58±13</td>
</tr>
</tbody>
</table>

Values are means ± SD. AU = arbitrary units.

* t = 4.23, p < 0.01; † t = 3.08, p < 0.02; ‡ t = 2.7, p < 0.05; †† t = 2.76, p < 0.02 (by paired t test for arterial blood pressure and sensory threshold and by Wilcoxon test for pain threshold).
vations in the finding of hypertension-associated hypalgesia in humans remains to be established.

A further aspect of possible importance is represented by the role of the carotid sinus and cardiopulmonary baroreceptor pathways. In fact, hypalgesia can be induced by baroreceptor activation in the hypertensive rat and it can be attenuated by carotid sinus baroreceptor denervation and by reducing the cardiopulmonary baroreceptor afferent input. As pointed out by Zamir and Maixner in a recent review, activation of baroreceptor afferents may play an important part in hypertension-associated hypalgesia, and this mechanism may represent part of an adaptive somatosensory response of the body to stressful events.

Since the majority of patients in this study had essential hypertension, our study provides no indication as to whether reduced pain perception is a characteristic feature of essential hypertension or whether it is also present in secondary forms. On the other hand, the finding that a reduced perception to pain is already present in borderline hypertension and does not appear to increase in established hypertension suggests that hypalgesia is not simply related to the extent of the blood pressure elevation. The observation that reductions of arterial blood pressure by various treatments apparently are not associated with changes in pain sensitivity, as observed in our study, lends support to this suggestion. This finding confirms the observations of Sitsen and de Jong, who reported that the diminished responsiveness to noxious stimuli in SHR was not altered by long-term treatment with hydralazine or captopril, and of Morley et al., who reported elevated pain tolerance to graded electrical stimulation of the finger in diabetic patients treated for hypertension and normotensive at the time of estimations in the finding of hypertension-associated hypalgesia.

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Hypertension. 1988;12:491-497
doi: 10.1161/01.HYP.12.5.491

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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