Enhanced Blood Pressure Response to Cyclooxygenase Inhibition in Salt-Sensitive Human Essential Hypertension

Claudio Ferri, Cesare Bellini, Alfonso Piccoli, Antonio Carlomagno, Maria Simona Bonavita, Anna Santucci, and Francesco Balsano

To evaluate the influence of salt sensitivity on the blood pressure response to oral indomethacin treatment, we studied 35 hospitalized essential hypertensive patients (24 men and 11 women, aged from 40 to 55 years). During a normal NaCl intake (120 mmol Na⁺ per day), patients were assigned to receive in a randomized double-blind fashion either 200 mg indomethacin (25 patients) or placebo (10 patients) for 5 days. Two weeks after the interruption of indomethacin treatment, during which the normal NaCl intake was continued, salt sensitivity was assessed by giving each patient a high (220 mmol Na⁺ per day for 10 days) and then a low (20 mmol Na⁺ per day for 10 days) NaCl diet. Blood pressure changes were evaluated, and the measurement taken at the end of the 2 weeks under normal sodium intake was considered baseline blood pressure. Patients were classified as salt sensitive when a diastolic blood pressure change of 10 mm Hg or more occurred after both low and high periods of sodium intake. In salt-resistant patients treated with indomethacin (n = 12, nine men and three women, mean age 50.5 ± 3.7 years), neither blood pressure (systolic blood pressure from 150.8 ± 11.2 to 154.6 ± 9.2 mm Hg, NS; diastolic blood pressure from 95.1 ± 4.4 mm Hg, NS) nor the urinary Na⁺ excretion (from 108.1 ± 20.9 to 97.9 ± 9.1 mmol/24 hr, NS) was significantly affected by the drug. On the contrary, when compared with patients receiving placebo (five men and five women, mean age 44.4 ± 4.1 years), salt-sensitive hypertensive patients (n = 13, 10 men and three women, mean age 47.9 ± 6.5 years) showed significantly higher levels (p < 0.004) of diastolic blood pressure after indomethacin therapy. According to these data, compared with pretreatment values blood pressure significantly increased in salt-sensitive patients after indomethacin treatment (systolic blood pressure from 156.9 ± 9.7 to 163.5 ± 10.8 mm Hg, p < 0.001; diastolic blood pressure from 98.5 ± 2.1 to 105.7 ± 5.7 mm Hg, p < 0.006) despite a marked plasma renin activity (from 0.18 ± 0.14 to 0.10 ± 0.09 ng/L per second, p < 0.02) and aldosterone (from 390.5 ± 154.9 to 299.3 ± 169.5 pmol/L, p < 0.002) decrease. Salt-sensitive patients also showed a significant indomethacin-related decrease of urinary Na⁺ excretion (from 108.1 ± 11.6 to 90.9 ± 10.1 mmol/24 hr, p < 0.04). Our results indicate that the blood pressure response to indomethacin depends on salt sensitivity in human essential hypertensive patients. The increase of blood pressure, observed in salt-sensitive hypertensive patients, is followed by a significant reduction in urinary Na⁺ excretion. This finding suggests that the indomethacin-induced decrease in Na⁺ excretion is responsible for the blood pressure increase showed by salt-sensitive patients after oral indomethacin treatment. (Hypertension 1993;21:875–881)

KEY WORDS • sodium-dependent prostaglandins • prostaglandin-endoperoxide synthase • hypertension, acute or chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can have a deleterious impact on blood pressure levels in both normotensive and hypertensive individuals (see References 1 and 2 for review). Furthermore, NSAIDs can antagonize the effects of many antihypertensive drugs such as thiazide.4 and loop diuretics,5 B-adrenergic6–8 and α-adrenergic blockers,9 and angiotensin converting enzyme inhibitors.10–13 The mechanisms of the blood pressure effects of NSAIDs are related to their inhibitory action on the cyclooxygenase pathway of the arachidonic acid metabolism, with the consequent blockade in the synthesis of prostaglandins (PGs).14,15

The vasculature and the kidney are the main sites of vasodilatory PG synthesis (see Reference 16 for review). Extrarenal synthesized PGs take part in the regulation of blood pressure. These substances act directly on vascular smooth muscle function or indirectly in modulating the vascular smooth muscle response to other vasopressor agents.17 Systemic vascular resistance increases after treatment with NSAIDs.18 However, the increase in total peripheral resistance is usually followed by compensatory mechanisms resulting in reduced cardiac output such that blood pressure changes are often minimal.18

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Since the action of newly generated PGs is rapidly terminated by local catabolism, it is likely that these substances may act as paracrine factors rather than as circulating hormones (see Reference 16 for review). Thus, although the potential role of systemic PGs in blood pressure homeostasis cannot be neglected, researchers have often focused their attention on the kidney to evaluate the pathogenetic mechanisms of the prohypertensive effects of cyclooxygenase inhibition.1,2,5,14-17,19-26

At the renal level, the inhibition of the PG system results in a decrease in sodium excretion.2,5,12,14-17,19,20,24-26 Furthermore, the decrease of blood pressure that follows a low sodium intake is completely reversed by cyclooxygenase inhibition.27 Thus, it has been hypothesized that the NSAID-related decrease in sodium excretion could represent a main contributor to the increase in blood pressure.1,4,17,19 According to this hypothesis, salt sensitivity should be combined with an unfavorable blood pressure response to NSAID administration.

Despite the potential interest of this hypothesis, the influence of salt sensitivity on the blood pressure response to NSAID treatment has never been investigated. Thus, we planned a study to evaluate the blood pressure effect of cyclooxygenase inhibition in essential hypertensive patients who were divided into groups according to their blood pressure response to changes in NaCl intake.

Methods

The protocol was approved by the Ethics Committee of the Andrea Cesalpino Foundation. All patients gave their informed consent.

The study was performed in 46 never-treated white essential hypertensive patients (31 men and 15 women) aged from 40 to 55 years (mean 46.8±5.2) who were hospitalized in our institute. Hypertension was mild to moderate, with the diastolic blood pressure between 95 and 114 mm Hg. Patients with either a smoking or alcohol habit or a body mass index <18 or >25 kg/m² were screened out. Serum creatinine was <110 µmol/L; proteinuria was absent; microalbuminuria was <0.300 µmol/24 hr. Both renal echography and [¹²⁵I]orthoiodohippurate scintirenography were normal. No patient had a positive history or clinical evidence of gastrointestinal diseases. None of the patients showed any cardiovascular alterations as evaluated on the basis of clinical and ultrasound studies. Hypertensive retinopathy was grade II or less. All patients had normal glucose and lipid metabolisms. The absence of impaired glucose tolerance was confirmed by the following criteria: fasting glucose levels <6.7 mmol/L, fructosamine levels <280 µmol/L, absence of glycosuria, and normal plasma glucose response to orally administered glucose (1 g/kg body wt). The patients who showed fasting insulin levels >110 pmol/L or abnormal insulin response to oral administered glucose (1 g/kg body wt) were excluded from our study. All patients had plasma cholesterol levels between 3.8 and 5.2 mmol/L and plasma triglyceride levels between 1.1 and 1.7 mmol/L. The secondary forms of hypertension were excluded by clinical and laboratory assessments. No patients took NSAIDs in the 2 years preceding this study.

After hospitalization, all patients were given a normocaloric diet (1 g/kg protein, 2 g/kg carbohydrate, and 0.6 g/kg fat per day) with constant sodium and potassium intakes (120 mmol Na⁺ and 60 mmol K⁺ per day). Sodium was given as sodium chloride. Urinary sodium excretion was measured every day. Patients with a urinary sodium excretion <80 or >130 mmol/day were excluded from the study. All patients were advised to drink 1.5 L water per day.

After 2 weeks of normal sodium intake, an oral placebo was given twice a day to each patient for a further week. At the end of this period, the patients who showed a diastolic blood pressure <95 or >114 mm Hg (n=9 patients, five men and four women) were excluded from the study. The remaining patients (n=37, 25 men and 12 women) were assigned to receive oral indomethacin (100 mg at 8:00 AM, and 100 mg at 8:00 PM) or identical tablets containing placebo for a period of 5 days, in a double-blind randomized fashion (Figure 1).
Blood pressure and heart rate were controlled every day during the placebo run-in period and the active treatment periods. Blood pressure was evaluated with a standard Riva-Rocci sphygmomanometer at 7:45 AM while the patient was in a supine position 30–45 minutes after awakening. Systolic blood pressure was taken at Korotkoff phase I, and diastolic blood pressure was taken at Korotkoff phase V. The first measurement of blood pressure and heart rate was excluded; the average of the following three measures, taken at 3-minute intervals, was considered baseline measurement. The last measurements were taken on the 13th day of our study, 12 hours after the last indomethacin or placebo administration (Figure 1).

Blood samples for plasma renin activity (PRA), aldosterone (PAC), atrial natriuretic factor (ANF), and serum Na⁺ and K⁺ were withdrawn with the patients in supine position, at the beginning and at the end of the period of either indomethacin or placebo administration. Serum Na⁺ and K⁺ were assayed immediately after blood collection by standard laboratory methods. Plasma samples were immediately stored at −80°C. All the assays were performed no later than 4 days after blood sampling (mean 2 days).

Plasma ANF was evaluated by a commercially available human ANF-(99–126) radioimmunoassay (Peninsula Laboratories, Belmont, Calif.). Synthetic human ANF-(99–126) was used as standard. Mean recovery was 89%, and interassay and intra-assay variations were less than 8%. PRA and PAC were assayed by radioimmunoassay (Sorin Biomedica, Vercelli, Italy).

**Dietary Regimens and Salt Sensitivity Assessment**

At the end of either indomethacin or placebo administration, patients continued the normal sodium diet and did not take any medication for 2 weeks. After this period, patients were blindly assigned to receive first a high sodium diet (220 mmol Na⁺ per day for 10 days) and then a low sodium diet (20 mmol Na⁺ per day for another 10 days) (Figure 1). Sodium was given as sodium chloride. Potassium intake (60 mmol K⁺ per day) did not change.

To achieve the different sodium diets, on the day of hospitalization patients were given a standard diet (see above) containing 20 mmol Na⁺ and 60 mmol K⁺ per day. When patients were on normal sodium intake, a daily supplement of 4 capsules (each capsule containing 25 mmol Na⁺) was given to each patient. To achieve a high or a low sodium intake, patients were given identical capsules containing either sodium chloride (50 mmol/capsule) or dextrose, respectively, for two consecutive periods of 10 days. In all patients, the high sodium intake period preceded the low sodium intake one (Figure 1). Throughout the study, compliance was assessed by measuring the daily sodium excretion by standard laboratory methods. Patients were considered compliant when 24-hour sodium excretion was between 80 and 130 mmol for those on the normal, >200 mmol for those on the high, and <30 mmol for those on the low sodium intake. All the patients were compliant, and the salt sensitivity assessment was then completed in 37 patients (27 in the active treatment group and 10 in the placebo group).

Every morning, during the salt sensitivity assessment, the body weight and the blood pressure of each patient (as described above) were measured by researchers who were aware of the diet assigned to each patient. Hypertensive patients were classified as salt sensitive when a diastolic blood pressure change of 10 mm Hg or more occurred after both periods of low and high sodium intake (i.e., when diastolic blood pressure decreased on a low and increased on a high sodium intake). Blood pressure changes were evaluated, considering as baseline blood pressure the measurement taken at the end of the 2 weeks under normal sodium intake (i.e., before starting the salt sensitivity evaluation) (Figure 1). Two patients (one man and one woman) showed an “indeterminate” response to changes in sodium intake (both patients showed a 10 mm Hg diastolic blood pressure fall during low sodium diet, but their blood pressure did not change at all during the high sodium diet). These two patients were not considered in the following “Results” section.

The statistical evaluation was performed by a PC Olivetti M-380 XPI. The statistical software PRIMER OF BIOSTATISTICS (McGraw-Hill, New York) was used. To evaluate intragroup statistical significance we used the paired Student’s t test; to establish the differences among groups, we used unpaired Student’s t test and one-way analysis of variance with Bonferroni’s test. Linear regression and correlation were used to evaluate the relation between two variables.

Statistical significance was considered for values of p < 0.05. All results are given as mean±SD.

**Results**

We started with 46 patients, but only 35 completed the study. Among these patients, 25 (19 men and six women, mean age 49.2±5.6 years) received the active treatment and 10 (five men and five women, mean age 44.4±4.1 years) received placebo. The oral treatment with the cyclooxygenase inhibitor was in general well tolerated. In particular, none of the patients complained of gastrointestinal troubles during indomethacin treatment, and all of them received the total daily dose of 200 mg for 5 days.

When all patients in the active-treated group were considered, indomethacin treatment produced a significant increase in both systolic (from 153.9±10.2 to 159.1±15.5 mm Hg, p < 0.05) and diastolic (from 98.8±2.1 to 103.4±5.4 mm Hg, p < 0.01) blood pressure (Figure 2). Body weight slightly increased (from 74.8±2.5 to 75.4±2.7 kg, NS) whereas PRA (from 44.4±4.1 pmol/mL, NS) or urinary volume (from 1,304.4±348.2 mL/24 hours, NS), but it significantly lowered urinary Na⁺ excretion (from 108.1±16.7 to 94.0±10.1 mmol/L, p < 0.001) after the active treatment.

Indomethacin therapy did not induce any variation in plasma ANF levels (from 14.31±5.53 to 15.54±6.73 fmol/mL, NS) or urinary volume (from 1,338.8±386.3 to 1,304.4±348.2 mL/24 hours, NS), but it significantly lowered urinary Na⁺ excretion (from 108.1±16.7 to 94.0±10.1 mmol/L, p < 0.01). Compared with placebo, indomethacin treatment induced a significant increase in diastolic blood pressure (p < 0.002) (Figure 2) and a significant reduction in the urinary Na⁺ excretion (p < 0.01) (Figure 2). Also PRA (p < 0.004) and PAC (p < 0.03) levels were significantly reduced by the cyclooxygenase inhibitor.
After the salt sensitivity evaluation, 13 patients (10 men and three women, mean age 47.9±6.5 years) were classified as salt sensitive and 12 (nine men and three women, mean age 50.5±3.7 years) as salt resistant. The general characteristics of each group, as evaluated before indomethacin administration, are given in Table 1. As it is shown, plasma ANF levels were significantly higher (p<0.004) in salt-sensitive patients than in salt-resistant ones. Moreover, baseline plasma ANF levels were significantly correlated with diastolic blood pressure in both groups (salt resistant, p<0.04; salt sensitive, p<0.05). No other significant correlations were found.

In salt-resistant patients, both systolic (from 150.8±11.2 to 154.6±9.3 mm Hg, NS) and diastolic (from 99.3±2.1 to 101.1±4.4 mm Hg, NS) blood pressure levels were not affected by indomethacin therapy (Figure 3). Moreover, the circulating levels of PRA (from 0.27±0.21 to 0.14±0.08 ng/L per second, p<0.05) and PAC (from 313.6±85.9 to 235.3±86.6 pmol/L, p<0.05) decreased after indomethacin treatment, whereas plasma ANF (from 12.68±5.69 to 10.6±1.7 pmol/mL, NS), body weight and diuresis did not significantly change. Placebo group (3) was composed of 10 patients. Standard deviations were omitted for clarity.

As compared with placebo, indomethacin treatment did not induce significant blood pressure changes in salt-resistant patients. At variance with the salt-resistant group, indomethacin treatment in the salt-sensitive group induced a significant increase of both the systolic (from 156.9±9.7 to 163.5±10.8 mm Hg, p<0.001) and the diastolic (from 98.5±2.1 to 105.7±5.7 mm Hg, p<0.006) blood pressure (Figure 3). Although not significantly, body weight increased during the active treatment phase (from 75.1±2.7 to 75.6±2.8 kg, NS). Both PRA (from 0.18±0.14 to 0.10±0.09 ng/L per second, p<0.02) and PAC (from 390.5±154.9 to 299.3±169.5 pmol/L, p<0.002) decreased during cyclooxygenase inhibition, but ANF did not change at all (from 16.15±5.97 to 18.05±6.62 fmol/mL, NS). Urinary volume remained unchanged (from 1275.0±331.1 to 1223.0±354.2 mL/24 hours, NS), but urinary Na⁺ excretion decreased.

### Table 1. Comparison Between Salt-Resistant and Salt-Sensitive Hypertensive Patients Before Oral Indomethacin Treatment

<table>
<thead>
<tr>
<th></th>
<th>Salt resistant (n=12)</th>
<th>Salt sensitive (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> (M/F)</td>
<td>9/3</td>
<td>10/3</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>50.5±3.7</td>
<td>47.9±6.5</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.7±1.2</td>
<td>23.2±1.0</td>
</tr>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>150.8±11.2</td>
<td>156.9±9.7</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>99.3±2.1</td>
<td>98.5±2.1</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>72.4±8.2</td>
<td>74.1±6.8</td>
</tr>
<tr>
<td><strong>Serum creatinine (μmol/L)</strong></td>
<td>88.4±9.7</td>
<td>79.5±16.6</td>
</tr>
<tr>
<td><strong>Creatine clearance (mL/sec)</strong></td>
<td>1.6±0.2</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td><strong>Blood urea (mmol/L)</strong></td>
<td>10.8±1.1</td>
<td>10.6±1.7</td>
</tr>
<tr>
<td><strong>Serum Na⁺ (mmol/L)</strong></td>
<td>138.8±4.5</td>
<td>140.2±4.7</td>
</tr>
<tr>
<td><strong>Serum K⁺ (mmol/L)</strong></td>
<td>4.1±0.6</td>
<td>4.5±0.5</td>
</tr>
<tr>
<td><strong>Plasma glucose (mg/dL)</strong></td>
<td>4.8±0.6</td>
<td>4.9±0.6</td>
</tr>
<tr>
<td><strong>Plasma insulin (μg/mL)</strong></td>
<td>74.4±40.8</td>
<td>70.2±51.0</td>
</tr>
<tr>
<td><strong>Serum cholesterol (mg/dL)</strong></td>
<td>4.8±0.3</td>
<td>4.9±0.6</td>
</tr>
<tr>
<td><strong>Serum triglycerides (mg/dL)</strong></td>
<td>1.5±0.1</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td><strong>PRA (ng/L per second)</strong></td>
<td>0.27±0.21</td>
<td>0.18±0.14</td>
</tr>
<tr>
<td><strong>PAC (pmol/L)</strong></td>
<td>313.6±85.9</td>
<td>390.5±154.9</td>
</tr>
<tr>
<td><strong>ANF (fmol/mL)</strong></td>
<td>12.68±5.69</td>
<td>16.15±5.97</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PRA, plasma renin activity; PAC, plasma aldosterone concentration; ANF, atrial natriuretic factor. All data (presented as mean±SD) were obtained at the end of the placebo run-in period, on a normal NaCl intake (120 mmol NaCl daily). *p<0.004 salt-sensitive vs. salt-resistant group.
increase of blood pressure in salt-sensitive hypertensive patients, whereas no blood pressure changes were observed in salt-resistant ones. The reasons for these qualitative differences are not clear.

Renin status has been indicated as a main contributor to the variability of the blood pressure response to NSAID therapy (see Reference 15 for review). According to this hypothesis, in both animal and human models of renin-dependent hypertension, blood pressure decreased after indomethacin treatment. On the other hand, a marked blood pressure increase after NSAID treatment has often been reported in adult white hypertensive patients having a low renin activity (see Reference 15 for review).

However, although both decreased PRA and increased ANF levels have already been described in salt-sensitive hypertension, only the second characteristic was present in our salt-sensitive patients (Table 1). Therefore, it seems likely that the blood pressure response to indomethacin has been influenced more by the salt-sensitive status than by the renin one.

The possible explanation of our findings could be related to the PG system itself. It has been hypothesized that some environmental factors, mainly represented by sodium intake, could cause hypertension in subjects who have a peculiar genetic susceptibility. In particular, it has often been suggested that environmental factors such as an "inappropriate" salt intake can lead to hypertension in subjects with unknown abnormalities of some intrarenal systems involved in tubular sodium handling (see Reference 35 for review). According to this hypothesis, we have recently demonstrated a re-
duced urinary excretion of active kallikrein in human salt-sensitive essential hypertension.32

With regard to PGs, Luft et al36 showed in animal models that the urinary excretion of the thromboxane (Tx) derivative TxB2, but not of PGE2, increased in Sprague-Dawley rats during an angiotensin II infusion. According to these findings, Tobian et al37 showed an imbalance of prohypertensive versus antihypertensive prostanooids in both the vasculature and the kidney of Dahl salt-sensitive rats (i.e., TXA2 synthesis was increased while PGE2 and prostacyclin were reduced). Furthermore, when Dahl salt-sensitive rats switched from a normal sodium to a high sodium diet, the increment of PGE2 was approximately 50% of that observed in Dahl salt-resistant rats.38 Similar findings have been indicated by Surstarcic et al39 and by Shimamoto et al,40 who showed a reduced urinary excretion of PGE2 in the Dahl salt-sensitive rats before salt loading and the consequent development of hypertension.

In human hypertension, more than 10 years ago Goldstone et al41 studied the effects of indomethacin and ibuprofen on the blood pressure response to a single dose of captopril. A complete reversal of the antihypertensive action of captopril was obtained only when the patients were on a high salt diet.41 No significant reversal of captopril’s hypotensive effect was observed when patients were on a low sodium diet.41 These data were seen in the view of the renin dependence of the prohypertensive effects of NSAIDs.14,31 However, although low renin hypertensive patients are reported to be particularly sensitive to sodium intake,21,32 the influence of salt sensitivity on their enhanced blood pressure responsiveness to NSAIDs was not investigated.41 Thus, an alternative (although merely speculative) explanation of the data of Goldstone et al could be that salt sensitivity more than the renin profile influenced the NSAID-related inhibition of the hypotensive effects of captopril.

On the other hand, a preliminary report by Gomi et al42 recently showed that the urinary excretion of 6-keto-PGF1α, a PG originating from prostacyclin catabolism, increased at a lesser extent than TXA2 excretion in salt-sensitive essential hypertensive patients after dietary salt load. These data are in agreement with the hypothesis that a possible PG-related defect in sodium excretion has been revealed in our salt-sensitive hypertensive patients by the use of indomethacin. According to this hypothesis, salt-sensitive patients showed an indomethacin-related negative effect on both blood pressure and urinary Na+ excretion. However, although the presence of an indomethacin-related volume expansion is further supported by the slight increase in plasma ANF and body weight observed in salt-sensitive hypertensive patients after cyclooxygenase inhibition, we cannot offer support for this hypothesis, since we did not evaluate the urinary excretion of renal or extrarenal PG metabolites.

In conclusion, this is the first report demonstrating that the prohypertensive effect of indomethacin is strongly dependent on salt sensitivity in human essential hypertension. The reasons leading to this phenomenon are unclear. However, the inhibition of renal PG synthesis impairs sodium excretion in salt-sensitive but not in salt-resistant hypertensive patients, suggesting that the indomethacin-related reduction in the renal capa-

bility to excrete NaCl is responsible for the rise in blood pressure.

Acknowledgment

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References


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