This study was undertaken to examine whether prostaglandin (PG) inhibition with indomethacin interferes with angiotensin II receptor blockade (losartan) during treatment for arterial hypertension. In a double-blind crossover design 10 patients with essential arterial hypertension and treated with losartan were randomized to supplementary treatment with indomethacin or placebo for 1 week, with a 2-week washout period interposed. At the end of each treatment period the following examinations were performed, preceded by 4 days on sodium-fixed diet: 24-h blood pressure (BP), 24-h sodium excretion (UNaV), supine BP, glomerular filtration rate (GFR), renal resistive index (RRI), extracellular fluid volume (ECV), sodium clearance (ClNa), body weight, peripheral blood flow (PBF), and plasma concentrations of aldosterone, renin (PRC), and atrial natriuretic peptide (ANP). Indomethacin did not change BP. Indomethacin increased weight ($P < .05$) and ECV ($P < .05$). A nonsignificant decrease in UNaV was seen after indomethacin, as in 24-h ClNa. Conversely, in the laboratory in the supine position ClNa increased after indomethacin ($P = .05$). Indomethacin increased plasma ANP ($P < .01$). No changes were observed in GFR, RRI, PBF, PRC, or plasma aldosterone. Thus indomethacin did not attenuate the antihypertensive effect of losartan, neither was peripheral blood flow affected. Indomethacin caused sodium retention in the nonresting situation, which was not counterbalanced by the increased ClNa in the resting supine position. The observed changes during prostaglandin (PG) inhibition seem most likely due to lack of PG “protection” of renal function, when the sympathetic nervous system is activated throughout the day. Am J Hypertens 1999; 12:209–216 © 1999 American Journal of Hypertension, Ltd.

**KEY WORDS:** Hypertension, angiotensin II receptor antagonism, blood pressure, sodium clearance, losartan, indomethacin.
nal prostaglandins (PG) decreases sodium and water excretion either directly by a reduced tubular PG effect or indirectly by a decrease in glomerular filtration rate (GFR). Glomerular filtration rate is regulated by angiotensin II (ANG II)-induced vasoconstriction of efferent arterioles, whereas prostaglandins protect afferent glomerular arterioles against ANG II vasoconstriction, and thus contribute to the maintenance of GFR when the renin angiotensin system (RAS) is activated.\(^8\) The physiologic importance of this protection is still unclear, although studies in intact animals suggest that even physiologic levels of ANG II may markedly reduce GFR, in parallel with reduced renal blood flow, when synthesis of PG is impaired.\(^9,10\) Elimination of this protection of PG with NSAID could decrease renal blood flow and GFR and enhance sodium and water retention.

Recently an increase in renal endothelin production with chronic indomethacin treatment has been demonstrated,\(^5\) making an increase in peripheral vascular resistance by endothelin a possible explanation for an increase in blood pressure during treatment with NSAID.

Losartan potassium is the first of a new class of orally active nonpeptide ANG II receptor antagonists.\(^11\) It is highly selective and specific for the ANG II receptor subtype 1 (AT\(_1\)) without agonistic activity.\(^12\) It shows similar blood-pressure-lowering efficacy to that of enalaprilat at trough, and presents fewer adverse side effects.\(^13,14\) The present study was undertaken to examine whether indomethacin (100 mg/day for 1 week) interferes with the antihypertensive effect of losartan (50 to 100 mg/day), as well as with the effects of losartan on peripheral vasculature and renal function.

**MATERIALS AND METHODS**

**Patients and Study Protocol** Ten patients with mild to moderate essential hypertension, with no signs of congestive heart failure and no other chronic diseases, were included in the study. Informed consent was obtained from each patient, and the protocol was approved by the local Ethical Committee of Copenhagen County. Secondary hypertension was excluded by standard investigations. If not treated, sitting diastolic blood pressure (Korotkoff phase V) would be between 95 and 125 mm Hg at two measurements separated by at least 1 week. If previously treated, medication was stopped and treatment with losartan initiated at a dose of 50 mg once a day, and gradually increased over 4 weeks to 100 mg, if necessary. If diastolic blood pressure was > 110 mm Hg at two separate measurements after 6 weeks, the patient was excluded. Blood pressure and heart rate (HR) were measured at least every second week. After at least 6 weeks’ treatment with a constant dose of losartan, the patients were randomized, in a double-blind crossover design, to additional treatment with the PG inhibitor indomethacin 50 mg twice a day or placebo tablets for 7 days. Then, preceded by 24-h blood pressure monitoring, the following investigations were performed 2 to 3 h after the usual morning dose of losartan and indomethacin or placebo tablets: blood pressure; heart rate; weight; serum electrolytes; concentrations of plasma renin, plasma aldosterone, plasma atrial natriuretic peptide, and plasma endothelin; peripheral blood flow; GFR; sodium clearance; and renal resistive index. Patients were eating their normal diet until 4 days before the study day, but instructed to avoid excessive sodium intake during the study. The last 4 days before the examinations listed earlier, the patients were eating a sodium-fixed diet (100 mEq/day). Twenty-four-hour urine was collected during the last 3 days for sodium and creatinine determination. After these procedures there was at least a 2-week washout period before indomethacin treatment or placebo was crossed over, and an identical study was performed on day 7.

**Experimental Procedures and Methods** At the ambulatory visits blood pressure and heart rate were measured in triplicate using a standard Takeda AM 2021 apparatus (A & D, Tokyo, Japan), after resting for 10 min supine. Twenty-four-hour blood pressure was measured by oscillometry using a Takeda 2421 apparatus. Measurements were performed every 30 min during the day (07:30 to 23:00) and every hour during the night (23:00 to 07:00).

On the examination day the patients met at 08:00, after an 8-h overnight fast. However, losartan and indomethacin or placebo was taken at 06:00. The patients abstained from smoking, tea, and coffee during the same period. A cannula was inserted in a cubital vein for drawing blood samples and injection of radioactive isotopes. During the examination the patients were in the supine position from 08:00 to 12:30. After 1 h rest blood pressure and heart rate were measured, and blood samples drawn for electrolyte and hormone analyses. Then peripheral blood flow was measured, using venous occlusion plethysmography with strain gauge strips on the lower limb.\(^15,16\) Glomerular filtration rate was determined by \(^{51}\)Cr-ethylendiaminetetraacetic acid (EDTA) (Amersham International, Amersham, Buckinghamshire, England) clearance using the single-injection technique,\(^17\) and extracellular fluid volume (ECV) was evaluated by simultaneous measurement of \(^{51}\)Cr-EDTA distribution space, a method described by Brøchner-Mortensen.\(^18\) Sodium clearance was performed after water loading with 200 mL of tap water every 20 min for 2 h before and during the investigational procedure. Urine (U) was collected during three 20-min periods for determination of volume (V), potassium, sodium (Na) and
creatinine. In the middle of each period plasma (P) samples were drawn for similar electrolyte determinations. CLNa was calculated from CLNa = UNa × V/PNa. The patients were allowed to void in the sitting or standing position. At the end of each clearance period urine volume was corrected for the residual urine, measured by determining the radioactivity over the bladder region before and after voiding, with correction for background radioactivity determined over the chest. Twenty-four–hour CLNa was calculated using mean UNaV from the three 24-h urine collections. Renal resistive index was studied by means of echo-Doppler technique. Each kidney of the patients was examined three times with the translumbar approach as described by Veglio et al. and renal resistive index (RRI) calculated using the following formula: (peak systolic frequency shift − lowest diastolic frequency shift)/peak systolic frequency shift. The presented data are the means of the three measurements.

Sodium and potassium in plasma and urine were measured using flame photometry. Plasma aldosterone concentration was measured using radioimmunoassay, as described by Lund et al. Plasma renin concentration was determined as the amount of produced angiotensin I (radioimmunoassay) after incubation with angiotensinogen and calibrated against a renin standard, a modified method of that described by Giese et al. Plasma endothelin and plasma atrial natriuretic peptide were determined by radioimmunoassay after extraction of plasma, as described by Rasmussen et al.

**Statistical Calculations**

Twenty-four–hour blood pressure was measured as means of measurements during day time (07:30 to 16:00), evening (16:30 to 23:00), and night time (24:00 to 07:00). Statistical comparisons were made using Wilcoxon’s test for paired observations and Student’s unpaired t test where appropriate. Five percent was accepted as the level of statistical significance. Data are presented as median value (M) and range in parenthesis.

**RESULTS**

Ten patients, three women and seven men, age 46 years (range, 36 to 63 years), serum creatinine 95 (74 to 106) μmol/L, mean dose of losartan 91 mg/day, entered the study. No adverse effects of either drug were recorded and no patients dropped out of the study. Due to technical errors 24-h BP was obtained in only eight patients. After indomethacin treatment, blood pressure measured supine in the laboratory after 1 h rest did not show any significant change in systolic or diastolic blood pressure (Table 1). Twenty-four–hour BP did not disclose any significant effect on BP induced by indomethacin, even though there was a tendency to an increase in systolic BP during the day (08:00 to 16:00), and a tendency towards lower blood pressure during evening and night time with indomethacin treatment (Table 1, Figure 1). Peripheral blood flow did not change. After indomethacin body weight increased from 83.8 (62 to 115) kg to 85.5 (62.5 to 116) kg (P < .05), in accordance with a significant increase in ECV from 13.9 (6.2 to 17.8) L to 14.9 (8.8 to 18.1) L (P < .05). There was a tendency to a decrease in 24-h urine sodium excretion, from 112 (56 to 137) mmol to 82 (75 to 132) mmol. Mean 24-h CLNa was significantly lower than the CLNa measured in the laboratory in the supine resting position during placebo and indomethacin as well. However, in the supine resting position CLNa increased after indomethacin, from 0.92 (0.48 to 1.97) to 1.28 (0.71 to 9.29), whereas a tendency towards a decrease in the 24-h CLNa after indomethacin treatment was seen, from placebo (0.55 [0.27 to 0.68] mL/min) to indomethacin treatment (0.41 [0.36 to 0.65] mL/min)(Table 2, Figure 2). No significant changes were seen in GFR, RRI (Table 2), PBF, HR, serum electrolytes, hematocrit, plasma renin, plasma aldosterone, or plasma endothelin (Figure 3). Indomethacin significantly increased plasma ANP from 16 (7 to 45) pg/mL to 21.5 (13 to 56) pg/mL (Figure 3).

**DISCUSSION**

In patients with essential hypertension treated with angiotensin II receptor antagonism, 1-week treatment with indomethacin did not change BP in the resting supine position. Neither was any significant change in 24-h ambulatory blood pressure found. Thus the results rule out that short-term indomethacin treatment blunts the antihypertensive efficacy of losartan.
Our 24-h blood pressure results may appear to be in contrast to the findings of Polonia et al in 18 patients treated with enalapril, disclosing an increase in 24-h systolic blood pressure after 1 week with supplementary indomethacin. Polonia et al did not show an increase in body weight. The length of time receiving indomethacin treatment was comparable to ours, as were those of several other studies with ACEI and PG inhibition, which have demonstrated an attenuating effect of indomethacin on the hypotensive effect of ACEI. Other studies with ACEI or other antihypertensive agents and PG inhibition for 1 to 4 weeks have disclosed an increase in weight during PG inhibition, similar to our finding (0.7 to 1.0 kg), combined with an increase in BP. Therefore it is conceivable that the duration of our study would allow for disclosure of a possible increase in blood pressure. However, due to Guyton et al’s concept of pressure control by the kidney-blood volume system, we cannot exclude the possibility that the persistence of a volume expansion over the course of weeks would cause an increase in blood pressure.

Why short-term treatment with indomethacin interferes with blood pressure control during ACE inhibition and not during angiotensin II receptor blockade is not fully understood. It is, however, well known that bradykinin increases during ACE-inhibitor treatment. This deserves consideration, as bradykinin can increase prostaglandins through an increase in phospholipase A2. An increase in PG may be part of the antihypertensive effect of ACEI. Consequently, the inhibition of PG may reduce the part of the antihypertensive effect of ACEI related to prostaglandins. In opposition to ACEI, angiotensin II receptor antagonists do not interfere with bradykinins. We did not measure PG concentrations in our study, and it is unknown whether PG are changed during ANG II receptor blockade. However, according to previous studies indomethacin 100 mg/day, as used in our study, will reduce renal prostaglandin synthesis by 54% to 70%.

Indomethacin treatment increased extracellular fluid volume and body weight, disclosing a slight but significant sodium and fluid retention. In accordance,

| TABLE 2. EFFECT OF INDOMETHACIN ON RENAL FUNCTION, BODY WEIGHT, AND EXTRACELLULAR VOLUME IN HYPERTENSIVE PATIENTS TREATED WITH LOSARTAN |
|-------------------------------------------------|-------------------------------------------------|
| L+ Placebo | L+ Indomethacin |
| ECV (L) | Median | Range | Median | Range |
| 13.96 | 6.23–17.82 | 14.89 | 8.75–18.13* |
| Body weight (kg) | 85.8 | 62.0–115.0 | 85.5 | 62.5–116.0* |
| Supine Na clearance (mL/min) | 0.92 | 0.48–1.97 | 1.28 | 0.71–9.29* |
| 24-h Na clearance (mL/min) | 0.55 | 0.27–0.68 | 0.41 | 0.37–0.65 |
| Urinary Na (mmol/24 h) | 112 | 56–137 | 82 | 75–132 |
| 51Cr-EDTA clearance (mL/min) | 98 | 64–140 | 103 | 73–148 |
| Renal resistive indices | 0.59 | 0.48–0.76 | 0.59 | 0.45–0.79 |

L, losartan; Cl, clearance; Na, Sodium; ECV, extracellular volume.
*P < 0.05.
a tendency to a decrease in 24-h sodium excretion and 24-h sodium clearance was seen despite the fact that an increase in sodium clearance was measured in the laboratory during resting in the supine position. It is well known that in normal humans sodium excretion is reduced when changing position from supine to erect. In the present study this response seems to be augmented by indomethacin. An explanation for this could be that in the erect position—with sympathetic activation—the PG have a renal effect that maintains sodium excretion, but in the resting situation with little activation of the sympathetic nervous system the renal PG play little functional role in counterbalancing any tendency towards sodium retention. This is supported by the results summarized by Dunn and colleagues, who concluded that whenever vasoconstrictor agents such as adrenergic catecholamines are augmented, renal function becomes “prostaglandin dependent.” The observed increase in sodium clearance found in the resting state could be caused by other renal mechanisms trying to compensate for the sodium retention that had occurred during daily activity.

Previous studies have shown that prostaglandins protect the afferent arteriole against the vasoconstrictor effect of angiotensin II in dogs and in normal humans during angiotensin II infusion. Thus infusion of angiotensin II in dogs pretreated with the prostaglandin inhibitor meclophenamate significantly decreased GFR and renal blood flow due to a significant increase in afferent arteriolar resistance. The significance of PG for renal function when the RAS is blocked is unknown. However, as previously mentioned, even at physiologic levels of ANG II PG may be important to maintain afferent arteriolar dilation, GFR, and renal blood flow. In the present study we used RRI as an indicator for changes in total renal vascular resistance. Because there was no change in GFR, we assumed that no change in RRI indicated that renal blood flow was unaltered during the examination. These hemodynamic parameters were obtained with the patients in the resting supine position with ANG II blocked, a state of little activation of the sympathetic nervous system. In this setting PG seemed to play little role in the regulation of renal hemodynamics. This is in agreement with Dunn and colleagues’ statement, and also with Ruilope et al’s study. They found in normotensive patients during prolonged treatment (42 days) with indomethacin that PG are important to maintain GFR and renal excretory function when the RAS is activated during sodium depletion, a situation that may resemble that of activation of the sympathetic nervous system.

A significant increase in plasma ANP (P < .01) during indomethacin treatment is probably caused by volume expansion. The secretory stimuli of ANP have been shown previously to be mainly atrial stretch and volume expansion.

Johnson et al have reported an increase in renal
endothelin production with chronic (1 month) indomethacin treatment in healthy, elderly individuals. However, we did not find any change in plasma endothelin levels after indomethacin treatment in the present study. Previous studies have investigated the effects of ACE inhibitors on peripheral blood flow. The majority of these studies showed no change or a slight increase in PBF with systemic administration of drugs. We did not study the effect of losartan alone on PBF. Indomethacin added to losartan treatment did not change PBF.

In summary, in the present study we could not demonstrate that 1 week of indomethacin treatment interferes with the antihypertensive efficacy of losartan in patients with essential hypertension, despite the fact that indomethacin caused a significant increase in weight and extracellular fluid volume. Glomerular filtration rate remained unchanged. Indomethacin did not adversely influence peripheral hemodynamics. This is in contrast to the reported effect of indomethacin during ACE inhibition, leading to an increase in blood pressure. It might indicate that prostaglandins in part mediate vasodilation during ACE inhibition, a mechanism that is not shared by angiotensin II antagonists such as losartan.

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