Aspirin Lowers Blood Pressure in Patients With Renovascular Hypertension

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To clarify the role of renal prostanoid in hyperreninemia and high blood pressure in human renovascular hypertension, we measured prostaglandin E₂ and renin activity in renal venous and abdominal aortic plasma before and after the intravenous administration of the cyclooxygenase inhibitor, aspirin dl-lysine. Subjects were six patients with unilateral renovascular hypertension and six with essential hypertension. In patients with renovascular hypertension, prostaglandin E₂ concentration in renal venous plasma from the stenotic kidney was 9.25 ± 1.48 pg/ml, which was significantly higher (p < 0.01) than the concentration in the renal venous plasma from the normal kidney (4.97 ± 1.02 pg/ml) or in the aortic plasma (2.59 ± 0.15 pg/ml). Plasma renin activity was also higher in the renal vein of the stenotic kidney than in the other two sites. The stenotic side/normal side ratio of the renal venous prostaglandin E₂ correlated significantly with a renin ratio greater than 1.5 (r = 0.8211, p < 0.05). Intravenous injection of aspirin dl-lysine (18 mg/kg) 30 minutes later markedly suppressed prostaglandin E₂ and renin levels at all sites and clearly lowered arterial blood pressure (mean: from 120 ± 6 to 110 ± 5 mm Hg, p < 0.01). The reduction in blood pressure correlated significantly with the suppression of plasma renin activity in the aorta (p < 0.05) and in the renal vein of the stenotic kidney (p < 0.01). Conversely, in patients with essential hypertension, aspirin had little effect on renin levels and increased mean blood pressure. These data indicate that renal prostaglandin plays an important role in the augmented release of renal renin and the pathogenesis of hypertension in human renovascular hypertension. (Hypertension 1989;14:461–468)

Whether the renal synthesis of prostanoids is increased or decreased by ischemia due to renal arterial stenosis is still controversial. However, in human renovascular hypertension (RVH) associated with unilateral renal arterial stenosis, it has been shown that renal venous concentration of prostaglandin E₂ (PGE₂) is higher on the ischemic than on the normal side and that the stenotic side/normal side ratio of renal venous PGE₂ correlates with the renal venous renin activity ratio.¹⁻³ The increase of PGE₂ concentration has been considered to be secondary to stimulation of the renin-angiotensin system.⁴⁻⁵ However, PGs (PGE₂, PGI₂) are known to stimulate renal renin secretion directly or indirectly.⁶⁻⁸ In renin-dependent hypertension such as RVH, renal PGs increase and participate in hyperreninemia, a PG synthesis inhibitor (cyclooxygenase inhibitor) ought to suppress plasma renin activity (PRA) and lower blood pressure (BP). But, surprisingly, it is difficult to find reports of such effects in human RVH, and there are many reports on animals with RVH showing that indomethacin increases BP.⁴⁻⁵ This may be because the outcome depends on 1) the kind of inhibitor used, 2) whether inhibition is acute or chronic, and 3) the balance between inhibition of systemic vascular PGs producing vasodilation and inhibition of renal PGs that stimulate renin release. Recently, intravenously injectable aspirin, aspirin dl-lysine (ASP),⁹ has been made available for clinical use. We used it to produce rapid inhibition of PG synthesis and attempted to clarify the role of renal PG in renin release and BP in human RVH.

Subjects and Methods

Patients

The subjects studied consisted of two groups with normal renal function: six patients with unilateral RVH and six with essential hypertension. The patient
profiles are summarized in Table 1. Renal arterial stenosis was detected by digital subtraction angiography or selective renal arterial angiography. All six patients with RVH had a unilateral renal arterial stenosis of over 75% that was caused by fibromuscular dysplasia in three and arteriosclerosis in three. Six patients with essential hypertension were confirmed to have normal renal arteries by angiography. The BP of patient I (30-year-old man, Table 1) was almost normal when hypertensive changes. All patients were fully confined to bed for 1 hour and then transferred, still supine, to the laboratories for investigation. BP in the left upper arm was measured twice at 4-minute intervals with an automatic ultrasound sphygmonanometer (BP-103, Nippon Colin Co., Ltd., Komaki City, Aichi Prefecture, Japan). Heart rate (HR) and electrocardiogram were also monitored. Thirty minutes after catheterization of the right femoral artery and vein by Seldinger’s method, abdominal aortic and bilateral renal venous blood samples were drawn simultaneously for measurement of PRA and plasma PGE2 concentration. Then, ASP (Venopirin, The Green Cross Corporation, Osaka, Japan) was administered intravenously in a dose of 18 mg/kg (10 mg/kg as aspirin). Thirty minutes later, a second blood sample was taken at the same sites as the control samples. All blood samples were immediately placed in ice-cooled tubes containing EDTA2Na (1 mg/ml) and aspirin (1 mg/ml) for PGE2 assay and EDTA2Na (1 mg/ml) only for PRA assay. The plasma was separated and frozen at −70°C until assay.

We compared the data of average values of BP and HR at 26, 30, and 34 minutes after ASP injection (n=2×3) with those at 8, 4, and 0 minutes before the injection (n=2×3).

### Measurement of Prostaglandin E2 in Plasma

The amount of PGE2 in the plasma was determined by using a [125I]PGE2 radioimmunoassay (RIA) kit (New England Nuclear Research Products, Boston, Massachusetts). We used the modified assay procedure given in the kit manual, as reported.10,11

In brief, for extraction, 2 ml plasma at 4°C were equilibrated with 5,000 dpm [3H]PGE2 (sp. act. 100 Ci/mmol, New England Nuclear Research Products) to monitor recovery and acidified with 0.05 M citrate at pH 3.5. Bond-Elut C-18 extraction cartridge columns (200 mg, Analytichem Intl., Inc., Harbor City, California) were pretreated with 2 ml methanol and 4 ml 0.05 M citrate. The acidified plasma was passed through the cartridge and eluted serially with 2 ml distilled water, 2 ml 10% metha-
nol, 2 ml cyclohexane, and 2 ml ethyl acetate. The last solvent was evaporated at 37°C under a stream of nitrogen. Additionally, Bond-Elut silica columns (500 mg, Analytichem Intl., Inc.) were prepared for further purification of PGE2 using solvent mixtures of increasing polarity: benzene:ethyl acetate:methanol, 60:40:0 (solvent I), 60:40:15 (solvent II), 60:40:20 (solvent III). Extracted and dried residue samples were reconstituted with 1 ml solvent I and applied onto the silica columns washed in advance with solvent III and I. After washing the column with 6 ml solvent I, PGE2 was eluted off with 6 ml solvent II into a siliconized glass vial. The eluted solvent was dried again under nitrogen gas and used in the RIA procedure.

All PGE2 concentrations were determined with corrections made for each loss in extraction and purification. Percentage recovery of the added [3H]PGE2 was 86.6±0.5% (mean±SEM, n=90) throughout the extraction and purification. We also examined the recovery of authentic PGE2 (10 pg/ml) added to PG-free plasma (supplied by New England Nuclear Research Products) using the whole assay procedure described above, and 76.5±1.7% (n=20) was recovered.

**Plasma Renin Activity**

Plasma renin activity was determined by a RIA method reported elsewhere.12,13

**Cyclooxygenase Inhibitor: Aspirin DL-lysine**

ASP (Venopirin, The Green Cross Corporation) was used to achieve cyclooxygenase inhibition. Each vial contained 900 mg ASP, which is the salt of 497 mg aspirin and 403 mg DL-lysine, as the active ingredient. We used ASP (Venopirin) because 1) it is intravenously injectable, 2) indomethacin, a representative PG synthesis inhibitor, is not injectable for clinical use and has many other effects apart from its cyclooxygenase inhibitory action,14,15 and 3) acute inhibition of PG synthesis is necessary to investigate the change of PRA and BP without modification by other factors. After intravenous administration of ASP, the onset of the inhibitory action on cyclooxygenase activity of microsome fractions from renal medulla is rapid.9 Inhibition is approximately 60% after 5 minutes, reaches a peak at 1 hour, and slowly reduces thereafter (83% inhibition after 2 hours), when given in a dose of 10 mg/kg as aspirin.9

Because ASP contains DL-lysine and we could find no information about its nonspecific action on BP or PRA in human subjects, the subjects with essential hypertension were used as a control group for the subjects with RVH.

**Statistical Analysis**

Statistical assessment of the data was done by analysis of variance and Scheffe’s method for simultaneous multiple comparison.16 Student’s paired t test was also used to compare control and treatment values of BP, HR, PRA, and PGE2. In addition, the relation between renal vein PGE2 ratio and PRA ratio, and between PRA and mean BP were subjected to linear regression analysis. Data are expressed as mean±SEM.

**Results**

**Prostaglandin E2 Concentration in Plasma**

The data for plasma PGE2 concentration in patients with RVH are presented in Figure 1 (I). Pretreatment PGE2 concentrations in aortic plasma (A) and in renal venous plasma from the stenotic (S) and normal (N) side were 2.59±0.15, 9.25±1.48 (p<0.01 compared with values in A and N), and 4.97±1.02 pg/ml, respectively. Thirty minutes after the intravenous administration of ASP, the PGE2 concentration in A, S, and N decreased to 1.95±0.25 (p<0.05 compared with control), 1.50±0.31 (p<0.01 compared with control), and 1.36±0.14 (p<0.05 compared with control) pg/ml, respectively. These results indicate the almost complete inhibition of renal PGE2 synthesis by ASP. In patients with RVH, the pretreatment and posttreatment renal vein PGE2 ratios (stenotic side/normal side) were 1.96±0.20 and 1.02±0.04 (p<0.01 compared with pretreatment values), respectively (Figure 2).

In patients with intact renal arteries, the renal venous PGE2 concentration was significantly higher than the aortic PGE2 concentration, and there was no difference in level between the right and the left side as shown in Figure 1 (II) (aortic PGE2 concentration, 1.50±0.31; right side, 3.36±0.63 [p<0.05]; left side, 3.73±0.49 [p<0.01] pg/ml). ASP clearly inhibited renal PGE2 production, as shown in Figure 1 (II) (aortic PGE2 concentration, 1.14±0.22 [p<0.05 compared with control]; right side, 0.87±0.13 [p<0.05 compared with control]; left side, 1.04±0.21 [p<0.01 compared with control]) pg/ml.

When analyzed by Student’s t test, pretreatment aortic PGE2 levels in the renovascular hypertensive patients were significantly higher than those in the essential hypertensive patients (p<0.05).

**Plasma Renin Activity**

In patients with RVH the PRA in A, S, and N was 5.28±0.88, 9.51±1.63 (p<0.05, S compared with values in A and N), and 5.39±0.86 ng/ml/hr, respectively [Figure 3 (I)]. This enhanced renin release from the ischemic kidney was markedly suppressed by ASP; PRA in A, S, and N decreased to 3.32±0.71, 4.55±0.94, and 3.49±0.69 ng/ml/hr (p<0.01, respectively [Figure 3 (I)]. Renal vein PRA ratio (stenotic side/normal side) was reduced from 1.76±0.12 to 1.29±0.03 (p<0.05, Figure 2). In patients with essential hypertension, PRA in the aorta, the right and the left renal vein was 2.70±0.89, 3.80±1.22, and 3.98±1.45 ng/ml/hr, respectively. These values tended to be decreased by injection of ASP, but there was statistically no significant suppression except in aortic PRA (aorta, 2.21±0.82 (p<0.05);
right renal vein, 2.92±0.90; left renal vein, 3.16±1.09 ng/ml/hr) as shown in Figure 3 (II).

**Hemodynamics**

Figure 4 gives the data for BP and HR before and after the inhibition of PG synthesis. Intravenous administration of ASP significantly lowered BP in patients with RVH (systolic, \( p<0.05 \); diastolic, \( p<0.01 \); mean, \( p<0.01 \)). In patients with essential hypertension, there was a small but significant increase in mean BP (\( p<0.05 \)). HR was not changed by ASP in either group.

**Correlation Between Prostaglandin E\(_2\) and Plasma Renin Activity in Patients With Renovascular Hypertension**

The renal venous stenotic side/normal side ratio of PGE\(_2\) significantly correlated with the ratio of PRA under basal conditions (\( r=0.8211, p<0.05 \)) (Figure 5). ASP inhibited renal PGE\(_2\) synthesis and eliminated the stenotic side–normal side difference of PGE\(_2\) (Figures 1 and 2). The difference in PRA between S and N was diminished, but still remained (Figure 2). The correlation of stenotic side/normal side ratio between PGE\(_2\) and PRA disappeared after PG synthesis inhibition.

**Relation Between Blood Pressure and Plasma Renin Activity in Patients With Renovascular Hypertension**

The correlation between mean BP and aortic PRA of each patient with RVH was not significant. So, as ASP suppressed PRA and lowered mean BP, we assessed the relation between the reduction of mean BP (Δ mean BP) and the suppression of PRA (Δ PRA) in A or S (Figure 6). The Δ mean BP was significantly correlated with the Δ PRA in A (\( r=0.8205, p<0.05 \)), and more closely correlated with the Δ PRA in S (\( r=0.9224, p<0.01 \)).

**Discussion**

It remains uncertain whether the production of prostanoids is increased or decreased in kidneys.
with significant renal arterial stenosis. There are few reports in human RVH and there is no unanimity of opinion about the change of renal prostanoids in experimental animals with RVH.\(^4\)\(^{17-19}\) Recently, however, in two-kidney, one clip (2K1C) hypertensive rats, only PGE\(_2\) formation was found to be significantly increased in the glomeruli of the clipped kidney.\(^20\) Anderson et al\(^21\) reported that the production of PGs and thromboxane was increased in ischemic renal cortical slices from humans with RVH, though it was decreased in the ischemic medulla. Although we did not measure renal blood flow and, therefore, could not assess the secretion rate of PGE\(_2\), the present data suggest that PGE\(_2\) synthesis is increased in the stenosed kidney of

![Figure 3](image)

**FIGURE 3.** Panel (I): Renovascular hypertensive patients' plasma renin activity in aorta (A) and renal vein of stenotic (S) and normal (N) side before and 30 minutes after the intravenous (iv) injection of aspirin DL-lysine (ASP) (18 mg/kg) (n=6). Panel (II): Essential hypertensive patients' plasma renin activity in aorta (A) and renal vein of right (R) and left (L) side before and 30 minutes after the intravenous injection of ASP (18 mg/kg) (n=6). RVH, renovascular hypertension; EHT, essential hypertension. *p<0.05, simultaneous multiple comparisons using Scheffe's method. **p<0.01; comparing treatment values with controls by paired \(t\) test.

![Figure 4](image)

**FIGURE 4.** Blood pressure (BP) and heart rate of the subjects with renovascular hypertension (RVH) and with essential hypertension (EHT) before and 30 minutes after the injection of aspirin DL-lysine.

![Figure 5](image)

**FIGURE 5.** Correlation between renal venous stenotic side/normal side (S/N) ratio of prostaglandin \(E_2\) (PGE\(_2\)) and the S/N ratio of plasma renin activity (PRA) in each patient with renovascular hypertension.
RVH. We base this suggestion on 1) the renal vaso-arterial difference in PGE_2 concentration (about three times higher in S-A than in N-A), 2) the higher aortic levels of PGE_2 in RVH compared with essential hypertension (despite the effects of avid pulmonary extraction), and 3) the significant correlation of renal venous stenotic side/normal side ratios between PGE_2 and PRA and the suppression of excessive renin release by ASP.

Angiotensin II is known to stimulate the production of PGs, but PGE_2 and PGl_2 are also known to accelerate renin secretion. Both systems must be able to act on each other in RVH, but our data indicate that renal PGE_2 acts as one mediator in stimulation of renin release from the ischemic kidney.

PGl_2 is also active in release of renin and is abundantly produced by the vascular endothelium. Unfortunately, plasma 6-keto-PGF_1alpha, a stable metabolite of PGl_2, was not measured in the present study; thus, we cannot comment on the part played by PGl_2 in the observed results. It is likely that the changes of PGE_2 are paralleled by changes of PGl_2 synthesis in the ischemic kidney.

It is possible that ASP further decreased renal blood flow to the stenotic kidney. However, the reduction in aortic PRA was not simply caused by the decrease of renal blood flow to the stenotic kidney because renal venous PRA on that side was markedly suppressed. If blood flow to the ischemic kidney had decreased drastically, PRA in the renal vein should have increased because of secretion of renin into a much reduced volume of blood. We believe it is reasonable to conclude that the suppression of PRA level resulted from the inhibition of renal PG synthesis by ASP.

The effect of PG synthesis inhibitors on BP in patients with RVH has not been confirmed. In 2K1C hypertensive animals, both indomethacin and aspirin accelerate hypertension after long-term oral administration. This acceleration in hypertension is considered to be attributable to a reduction of vascular PG (PGl_2) biosynthesis and to be unrelated to renal PG production. In contrast, when indomethacin was acutely and intravenously injected, the inhibitor showed a vasodepressor action in 2K1C rats. Jackson et al reported that, in rats under the severe hyperreninemic condition caused by complete aortic ligation between the origin of the renal arteries, hypertension was reduced by indomethacin. In human unilateral RVH, our current study showed that intravenously injected ASP reduced hypertension, and the reduction appeared highly correlated with a substantial decrement in PRA. The discrepancy of the inhibitors' action on BP may be because of the difference in administration route (orally or intravenously), that is, the effect of indomethacin or aspirin on BP depends on whether the suppressive effect on renin release or the attenuation of systemic vasodilatory PGs is dominant. Several years ago, a PG synthesis inhibitor could not be intravenously administered to human subjects with safety. Now it is possible to use injectable ASP, and by this means we have demonstrated the vasodepressor effect of a PG synthesis inhibitor as a result of PRA suppression in unilateral RVH.

In patients with essential hypertension, ASP produced a small increment in mean BP as was also noted with indomethacin. Acute administration of ASP appears to cause an acute reduction in vascular PG synthesis, thus leading to a pressor response in essential hypertension. In contrast, the dominant effect appears to be suppression of excessive renin release and a depressor response in RVH. These different responses of BP to ASP may be useful for differential diagnosis of unilateral RVH from essential hypertension.

Two of the six patients with RVH could not discontinue /-blocker or isosorbide dinitrate therapy because of ischemic heart disease. However, the dosage used was small, and several investigators have already confirmed that the /-adrenergic mechanism of renin release is independent of the PG system. In fact, /-blocker and

![Graph](http://hyper.ahajournals.org/)

**Figure 6.** Top panel: Relation between the reduction of mean blood pressure (BP) (Δ mean BP) and the suppression of plasma renin activity (PRA) in the aorta (Δ PRA in A) in each patient with renovascular hypertension (RVH). Bottom panel: Relation between the Δ mean BP and the suppression of PRA in the renal vein of stenotic side (S) (Δ PRA in S) in each patient with RVH.
dinitrate slightly lowered the basal PRA and BP in these two patients compared with the other four patients (Table 1, Figure 4), but ASP obviously and independently suppressed their PRA and showed a depressor action. These results imply that the action of the cyclooxygenase inhibitor was independent of the medication.

In conclusion, the present data provide evidence that renal PG (PGE₂) plays an important role in acceleration of renal renin secretion and in the pathogenesis of BP elevation in the vasodilator. The vasodilator action of ASP in unilateral RVH may be helpful for differential diagnosis of RVH from other types of hypertension.

References

18. Imaheni et al Prostaglandin in Renovascular Hypertension 467


**KEY WORDS** • renin • renovascular hypertension • aspirin • prostaglandins
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M Imanishi, M Kawamura, S Akabane, Y Matsushima, M Kuramochi, K Ito, M Ohta, K Kimura, M Takamiya and T Omae

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