Responses of the Stenosed and Contralateral Kidneys to [Sar\(^1\), Thr\(^8\)] All in Human Renovascular Hypertension

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SUMMARY To better define the intrarenal hemodynamic effects of angiotensin in human renovascular hypertension, 10 patients underwent renal hemodynamic and functional measurements before and during infusion of a competitive angiotensin analog, [Sar\(^1\), Thr\(^8\)] All. Eight had technically satisfactory split function studies. Despite a fall in mean arterial pressure (132 ± 6 to 121 ± 6 mm Hg, \(p < 0.05\)) and humoral changes consistent with angiotensin-mediated hypertension, the intrarenal effects of this analog were commonly those of an angiotensin agonist, producing vasoconstriction and sodium retention. This was quantitatively greatest in the contralateral kidney, whose preinfusion sodium excretion (86 ± 30 μEq/min vs 25 ± 9 μEq/min, \(p < 0.02\)) and glomerular filtration rate (76 ± 7 ml/min vs 41 ± 7 ml/min, \(p < 0.01\)) were higher than the stenotic kidney. In some cases, an increase in renal blood flow and rise in sodium excretion were evident during angiotensin blockade, suggesting a tonic intrarenal action of angiotensin. Although renin vein renin values differed markedly between the stenotic and contralateral kidney (ratio = 2.05 ± 0.30), relative changes in effective renal plasma flow were correlated (\(r = 0.84; p < 0.01\)) during infusion of this analog. These results underscore the differences in sensitivities between vascular beds to the effects of angiotensin II and the major role of the contralateral kidney in renal function and sodium homeostasis in human renovascular hypertension. (Hypertension 5: 796–804, 1983)

KEY WORDS • [Sar\(^1\), Thr\(^8\)] All • renovascular hypertension • angiotensin antagonists • renal hemodynamics

ALTHOUGH unilateral renal artery stenosis regularly produces hypertension in both animals and humans, the relative roles of the stenotic and contralateral kidney in this process remain incompletely defined. It has been suggested that the unaffected kidney may play a contributory role by failing to excrete salt and water despite rising arterial pressure.\(^1\)\(^4\) Several lines of evidence do suggest, in fact, that sodium retention participates in human renovascular hypertension. Intravascular volume measurements are no different from those observed in essential hypertension.\(^3\) Second, “angiotensin-dependence” of blood pressure as defined by changes induced by interruption of the renin-angiotensin system by competitive antagonists may not be evident without prior administration of diuretics.\(^6\)\(^4\) Third, demonstration of lateralization of renal vein renin production to the stenotic side often requires prior sodium depletion.\(^9\)

Experimental studies in renovascular (two-kidney, one clip) hypertension have demonstrated functional changes in the contralateral kidney (CLK), which is often hypertrophied due to the reduction of nephron mass following loss of perfusion to the stenotic side. In addition to systemic vasoconstrictor effects, angiotensin II (All) generated by ischemia appears to have direct intrarenal effects in animal models that limit sodium excretion and reduce renal blood flow.\(^2\)\(^3\)

The questions of sodium homeostasis and renal hemodynamics in human renovascular hypertension have been less frequently addressed, in part because of the technical difficulties in obtaining separate renal function studies and because most studies emphasized abnormalities on the stenotic side. Furthermore, the progression of human renovascular disease is more gradual than in experimental models, and renal ischemia sufficient to induce renin release and hypertension may occur without drastic reduction of nephron mass. There is little information regarding the relative roles and sensitivities of the stenotic (STK) and CLK kidneys to intrarenal effects of angiotensin II in humans. It is recognized that the renal vascular bed is particularly sensitive to the vasoconstrictor effects of All,\(^10\) but it is less certain what the effects of local
concentrations of renin in the stenotic kidney and its virtual absence in the CLK might have in modifying these effects.

The present investigation was undertaken to better define the functional differences and sensitivities of the separate kidneys in human renovascular hypertension. After basal measurements of renal function, patients were studied during intravenous infusion of [Sar¹, Thr⁸] All, an angiotensin analog with minimal agonist activity in the peripheral vascular and adrenal beds, compared to other available analogs. Within the renal vascular bed, this analog was found to possess both agonist and antagonist effects. This provided the opportunity to measure side-to-side agonist sensitivity as well as to demonstrate a tonic role of angiotensin in regulating the renal vascular tone and sodium excretion in the contralateral kidney in humans.

Methods

Patients
Ten hypertensive patients previously diagnosed as having renovascular hypertension selected for renal artery revascularization or transluminal angioplasty were studied. Ages ranged from 22 to 65 years (mean, 45 years). Selection for corrective repair was made on the basis of a marked unilateral stenosis on angiogram with relatively short duration of hypertension and/or lateralization of renin release during sampling for renal vein renins (mean ratio: stenotic/contralateral = 2.05 ± 0.30). All had been treated with multiple medications previously and were judged to be cured or markedly improved following the procedure (blood pressure less than 150/90 mm Hg without medication or with diuretic therapy only). A single patient developed recurrent severe hypertension after angioplasty; subsequent nephrectomy of the stenotic kidney led to normal blood pressures. The procedures involved in the study were explained, and written informed consent was obtained. [Sar¹, Thr⁸] All is an investigational drug approved for use in this Institution. Its administration was approved by the Institutional Review Board of the Cleveland Clinic Foundation.

Protocol
Antihypertensive medications were withheld as tolerated, at least 48 hours before the study. Patients were given hospital diets containing 80–120 mEq sodium. On the morning of the study, cystoscopy was performed utilizing light narcotic anesthesia, and ureteral catheters were placed bilaterally of such a dimension as to occlude the ureteral orifice as completely as possible and passed to the ureteropelvic junction. Catheter position was verified by fluoroscopy. A bladder catheter was placed, and all three were connected to closed drainage. Adequate flows were established with prior oral hydration (15 ml/kg) and administration of 5% dextrose solution. After allowing at least 60 minutes of equilibration and recovery from catheter placement, three baseline collections for renal hemodynamics and function as described below were obtained. Thereafter, three 15- to 20-minute collections were obtained during intravenous infusion of [Sar¹, Thr⁸] All, beginning with 300 ng/kg/min and reaching 3000 ng/kg/min. These dosages have been determined to maximally block the pressor effects of angiotensin II in previous studies. Subsequently, 45 minutes were allowed for washout of the angiotensin analog, and one to two final collections were obtained. Blood pressure was measured by cuff sphygmomanometer at 5- to 10-minute intervals throughout the procedure. Blood samples for plasma renin activity, plasma aldosterone, and serum electrolytes were obtained from an indwelling venous catheter before, during, and after the infusion. Samples for hormones were placed in prechilled tubes (0°C), separated promptly and stored at −40°C.

Renal Hemodynamics and Function

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by the clearances of ¹³¹iodohippuran and ¹²⁵iothalamate, respectively, administered by constant infusion pump. Following a loading dose of 0.5 μCi/kg each, a maintenance solution prepared in 5% dextrose in water was infused at 1 ml/min to deliver 0.5 μCi/min for iohippuran and 0.25 μCi/min of iothalamate. After an equilibration period of 40 minutes, serum levels were obtained at the beginning and end of each period; the mean value was used in calculating clearances. Urine was collected separately from each ureteral catheter and the bladder catheter. Eight subjects had technically satisfactory collections from both ureters without leakage, such that both total and individual renal function measurements were obtained. Studies in two patients were technically inadequate for separate renal function studies due to leakage into the bladder from both sides. They were included in measurements of total renal function. Functional measurements in normotensive and hypertensive subjects were made under the same conditions with the exception of split function studies and analog infusion. Levels of urine and serum isotopes were determined by liquid gamma scintillation counting in a double-well counter with correction for spillover of ¹³¹I into the ¹²⁵I channel. Clearances were calculated as UV/P. Renal blood flow was calculated as ERPF/(1-hematocrit).

Renal vascular resistance (RVR) in the contralateral kidney was expressed as MAP/RBFc where RBFc is the flow to that kidney and MAP is mean arterial pressure derived as (systolic-diastolic)/3 + diastolic pressure (units = mm Hg/ml/min). Urinary sodium and potassium were determined in each sample. Fractional excretion was calculated as amount excreted/amount filtered, where UV = amount excreted and P GFR = amount filtered. When comparisons were made with normotensive and essential hypertensive subjects, ERPF and GFR were expressed as ml/min/1.73 m².

Plasma volume was determined by ¹²⁵I-radiiodinated serum albumin (RISA). Total blood volume was calculated from the plasma volume and simultaneously determined hematocrit as previously described. Re-
TABLE 1. Clinical Characteristics and Renal Hemodynamic Data for Renovascular Hypertensive Patients

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Sex</th>
<th>Vascular disease</th>
<th>Age (yrs)</th>
<th>Pre-Rx (mm Hg)</th>
<th>AIIA (mm Hg)</th>
<th>PRA (ng/ml/hr)</th>
<th>PA (ng/dl)</th>
<th>ERPF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>PV (% NL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>ASO</td>
<td>65</td>
<td>208/100</td>
<td>204/99</td>
<td>12</td>
<td>35.4</td>
<td>164</td>
<td>51</td>
<td>269</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>ASO</td>
<td>52</td>
<td>155/96</td>
<td>147/87</td>
<td>7.0</td>
<td>44</td>
<td>339</td>
<td>103</td>
<td>669</td>
<td>64.2</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>ASO</td>
<td>56</td>
<td>245/111</td>
<td>167/80</td>
<td>15</td>
<td>79</td>
<td>164</td>
<td>52</td>
<td>278</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>FMD</td>
<td>28</td>
<td>195/135</td>
<td>188/125</td>
<td>2.5</td>
<td>10</td>
<td>440</td>
<td>122</td>
<td>731</td>
<td>82.9</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>FMD</td>
<td>50</td>
<td>202/115</td>
<td>206/116</td>
<td>4.3</td>
<td>29.2</td>
<td>449</td>
<td>149</td>
<td>718</td>
<td>153.8</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>ASO</td>
<td>60</td>
<td>211/103</td>
<td>196/101</td>
<td>5.0</td>
<td>13.5</td>
<td>349</td>
<td>102</td>
<td>598</td>
<td>92.8</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>ASO</td>
<td>40</td>
<td>181/110</td>
<td>173/105</td>
<td>23</td>
<td>23.3</td>
<td>402</td>
<td>111</td>
<td>670</td>
<td>79.8</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>FMD</td>
<td>22</td>
<td>140/93</td>
<td>130/86</td>
<td>15</td>
<td>60.6</td>
<td>410</td>
<td>109</td>
<td>644</td>
<td>71.4</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>FMD</td>
<td>36</td>
<td>169/97</td>
<td>133/79</td>
<td>13</td>
<td>23.4</td>
<td>323</td>
<td>87</td>
<td>551</td>
<td>72.7</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>FMD</td>
<td>41</td>
<td>150/97</td>
<td>135/89</td>
<td>3.5</td>
<td>32.7</td>
<td>822</td>
<td>174</td>
<td>1265</td>
<td>94.2</td>
</tr>
</tbody>
</table>

Mean (22-65) 182 ± 11, 168 ± 10, 10.0 ± 6.6, 35.1 ± 7, 386 ± 61, 106 ± 13, 639 ± 92, 89 ± 10

ASO = Atherosclerosis obliterans; FMD = Fibromuscular dysplasia; PRA = plasma renin activity; PA = plasma aldosterone; ERPF = effective renal plasma flow; GFR = glomerular filtration rate; RBF = renal blood flow; PV = plasma volume; TBV = total blood volume; CLK = contralateral kidney; STK = stenosed kidney.

Results

Clinical features including sex, pathologic diagnosis, age, blood pressures, plasma renin activity, plasma aldosterone, plasma and total blood volumes, renal plasma flows, GFR, and individual stenotic and contralateral kidney hemodynamics under baseline preinfusion conditions are presented in Table 1. There were eight women and two men, with a mean age of 45 years (range = 22-65 years). Half of these subjects had some form of fibromuscular dysplasia causing the renal lesion. Plasma renin activity was generally elevated (10.0 ± 2.2 ng/ml/hr) (normal = 0.6 - 2.6 ng/ml/hr) as was plasma aldosterone (34.3 ± 7.5 ng/dl) (normal = 10 ± 4 sp, ng/dl). Intravascular volumes were slightly reduced, plasma volume being 89% ± 10% of normal.

Table 2 A summarizes the baseline renal functional measurements and mean arterial pressure in subjects with renovascular hypertension as compared to normal subjects and untreated essential hypertensive patients of comparable age and urinary sodium excretion under similar conditions. ERPF, GFR, and RBF have been corrected for body surface area. Although there is a discernible diminution of total ERPF in the RVH group, it is small, and total GFR was not appreciably affected. Thus, overall renal function appeared well preserved, despite sufficient unilateral ischemia to cause renovascular hypertension. Panel 2 B presents the basal comparison of the stenosed and contralateral kidney in eight subjects with satisfactory split renal function studies. As expected, there was a marked difference between kidneys, reflecting diminished flow and GFR on the stenotic side. Average sodium excretion was more than threefold higher from the contralateral kidney (86 ± 30 vs 25 ± 9 μEq/min, p < 0.02). Consequently, fractional sodium excretion was higher in the contralateral kidney. Hence, although overall renal function appeared well-preserved, there were differences between contralateral and stenotic kidneys with the CLK accounting for the major portion of filtration and excretion under these conditions. In some instances, this suggested a functional hypertrophy by the CLK, which is illustrated in Panel 2 C. Data from normal subjects and essential hyperten-
sives are calculated from total renal function measurements, assuming equal function from both kidneys. Although approximate, these data suggest that renal plasma flow, and GFR were increased in the CLK compared to either hypertensive or normal subjects. Filtration fraction was comparable in all groups and single kidney renal vascular resistance was at an intermediate level between normal subjects and hypertensives.

Response to [Sar1, Thr8] All Infusion

As shown in figure 1, mean arterial pressure fell during [Sar1, Thr8] All infusion (132 ± 6 to 121 ± 6 mm Hg, \( p < 0.01 \)) while plasma renin activity rose, consistent with an angiotensin antagonist effect in the peripheral vasculature. During the short period of the

![Figure 1](https://hyper.ahajournals.org/)

**Figure 1.** Blood pressure, plasma renin activity (PRA), and aldosterone level before and during intravenous infusion of a synthetic angiotensin II analog (AIIA), [Sar1, Thr8] All, in patients with renovascular hypertension. The fall in pressure and rise in PRA are consistent with peripheral angiotensin blockade.

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**Table 1.** (Continued)

<table>
<thead>
<tr>
<th>TBV (% NL)</th>
<th>CLK</th>
<th>STK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERPF (ml/min)</td>
<td>GFR (ml/min)</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>70.8</td>
<td>197</td>
<td>64</td>
</tr>
<tr>
<td>78.9</td>
<td>281</td>
<td>80</td>
</tr>
<tr>
<td>149</td>
<td>313</td>
<td>104</td>
</tr>
<tr>
<td>95.8</td>
<td>305</td>
<td>81</td>
</tr>
<tr>
<td>80.1</td>
<td>246</td>
<td>75</td>
</tr>
<tr>
<td>74.7</td>
<td>233</td>
<td>73</td>
</tr>
<tr>
<td>87.9</td>
<td>453</td>
<td>93</td>
</tr>
</tbody>
</table>

(Continued)

**Table 2.** Baseline Renal Functional Measurements and Mean Arterial Pressure in Patients with Renovascular and Essential Hypertension Compared to Normal Subjects

**A.** Mean arterial pressure, total ERPF, and GFR (corrected for 1.73 m²) in renovascular (RVH), essential hypertensive (EH), and normal subjects (NS).

<table>
<thead>
<tr>
<th></th>
<th>RVH (n)</th>
<th>EH (n)</th>
<th>NS (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>45</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>131±6</td>
<td>131±5</td>
<td>98±4</td>
</tr>
<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>390±69</td>
<td>372±21</td>
<td>462±24</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>106±14</td>
<td>100±8</td>
<td>117±8</td>
</tr>
<tr>
<td>( U_{NaV} ) (µEq/min)</td>
<td>162±44</td>
<td>214±42</td>
<td>173±25</td>
</tr>
</tbody>
</table>

**B.** Contralateral vs stenotic kidney in renovascular hypertensive patients.

<table>
<thead>
<tr>
<th></th>
<th>Contralateral</th>
<th>Stenotic</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>271±40</td>
<td>151±40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>76±7</td>
<td>41±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( U_{NaV} ) (µEq/min)</td>
<td>86±30</td>
<td>25±9</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>FE (%)</td>
<td>0.95±0.37</td>
<td>0.58±0.25</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**C.** Comparison of renovascular contralateral kidney and estimated single renal hemodynamics in essential hypertensive and normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>RVH-CLK</th>
<th>EH</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>271±40</td>
<td>186±13*</td>
<td>231±13</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>76±7</td>
<td>50±5†</td>
<td>59±4*</td>
</tr>
<tr>
<td>FF (%)</td>
<td>28</td>
<td>26.9</td>
<td>25.4</td>
</tr>
<tr>
<td>RBF (ml/min/1.73 m²)</td>
<td>446±58</td>
<td>310±21*</td>
<td>380±24</td>
</tr>
</tbody>
</table>

\( *p < 0.05; †p < 0.01; \) compared to contralateral kidney (RVH). See table 1 for abbreviations.
Infusion, average aldosterone levels did not change. During the recovery phase from the All analog, blood pressure returned toward preinfusion levels.

By contrast, the [Sar¹, Thr⁸] All caused constriction of the renal vasculature, producing a fall in total ERPF as illustrated in figure 2, which reversed upon discontinuing the infusion. This was associated with a rise of renal vascular resistance from 0.2 ± 0.05 to 0.53 ± 0.10 mm Hg/ml/min (p < 0.05). Total GFR and UₘV changed in parallel fashion.

Responses in The Stenosed and Contralateral Kidney

Figure 3 illustrates the differential effects on the stenosed and contralateral kidneys during infusion of [Sar¹, Thr⁸] All. Flow diminished in both kidneys, although quantitatively the greatest effect was observed in the CLK. When the infusion was stopped, these values returned toward preinfusion levels. Despite being quantitatively largest in the CLK, relative changes in ERPF were symmetric between the two sides when expressed as percent change from initial value (R =

\[ N=8 \]
\[ R=0.84 \]
\[ p<.01 \]

**Figure 2.** Total effective renal plasma flow (ERPF) decreased during infusion of the angiotensin analog, demonstrating intrarenal vasoconstriction and the marked sensitivity of the renal vasculature to the agonist properties of this agent, in contrast to other vascular beds.

**Figure 3.** Preinfusion effective renal plasma flow (ERPF) was higher in the contralateral kidney (CLK) than in the stenotic kidney. The response to the angiotensin analog was proportionately symmetric in both, however, despite the major quantitative changes in the CLK.

**Figure 4.** Changes in effective renal plasma flow (ERPF) during All A infusion are compared in the stenosed and contralateral kidneys, expressed as relative change from preinfusion values. The line of regression is indistinguishable from the line of identity.
STENOTIC AND CONTRALATERAL KIDNEY RESPONSES TO [Sar\(^1\), Thr\(^8\)] All/Textor et al. 801

![Graph showing contralateral and stenotic kidney responses to [Sar\(^1\), Thr\(^8\)] All](image)

**Figure 5.** Preinfusion sodium excretion was nearly threefold higher in the contralateral kidney; this was more than could be explained by differences in glomerular filtration, thus reflecting relatively enhanced fractional excretion of sodium by the contralateral side (p < 0.05). There was wide variability in sodium excretion during infusion of the angiotensin analog, [Sar\(^1\), Thr\(^8\)] All, but changes observed tended to parallel changes in ERPF (r = 0.85, p < 0.01).

0.84, p < 0.01; fig. 4). The effects on urinary sodium excretion were quite similar, as illustrated in figure 5. Dispersion of urinary sodium values was such that sequential changes in mean values did not achieve statistical significance, although individual changes correlated well with changes in ERPF (r = 0.85, p < 0.01).

The occurrence of renal vasoconstriction and sodium retention during [Sar\(^1\), Thr\(^8\)] All administration was not universal. Three patterns of renal hemodynamics are illustrated in figures 6–8, with differing preinfusion levels of PRA. In figure 6, the most commonly observed fall in ERPF was paralleled by a fall in GFR, and \( U_{Na} \) and was associated with the lowest PRA (2.5 ng/ml/hr). The subject in figure 7 had a higher PRA (11.3 ng/ml/hr). There was a slight increase in ERPF and GFR observed in both kidneys, and most notably, a large increment in urinary sodium excretion, all of which reverted to preinfusion levels after stopping infusion of the All analog. The patient in figure 8 had a PRA value of 23 ng/ml/hr and demonstrated a marked increase in ERPF, GFR, and \( U_{Na} \) during [Sar\(^1\), Thr\(^8\)] All infusion. In all cases, the hemodynamic and functional responses to [Sar\(^1\), Thr\(^8\)] All were similar in direction between the contralateral and stenotic kidneys, although quantitatively the contralateral kidney was most affected.

**Figure 6.** Average changes in blood pressure, ERPF, GFR, and urinary sodium excretion in a renovascular hypertensive patient during infusion of [Sar\(^1\), Thr\(^8\)] All, demonstrating a pattern of changes most commonly observed in the group overall.
Discussion

The current study was undertaken to better define the functional roles of both the stenotic and contralateral kidneys in human renovascular hypertension, in particular, their relative sensitivities to a specific AII analog, [Sar¹, Thr⁸] AII. This compound was utilized because of its previously demonstrated antagonist properties in the peripheral and adrenal receptor beds, relatively less agonist properties compared to other substituted AII analogs and its short half-life. Both antagonist and agonist actions were evident in the renal vascular bed in this study and provided a useful means of distinguishing renal and peripheral circulatory effects.

In this series of patients, total renal perfusion and glomerular filtration were well preserved, despite demonstrable loss of function on the stenotic side. The flows and function were often enhanced on the contralateral side, denoting functional hypertrophy.

Although renal hypertrophy is commonly observed after unilateral nephrectomy and in experimental models, it is not universally mentioned in series of patients with renovascular hypertension. This may be due in part to the gradual loss of function on the stenotic side, which may not stimulate hypertrophy or to the occurrence of hypertensive vascular damage to the opposite side. As is evident from table 1, not every patient had contralateral hypertrophy. On average, however, there was higher flow and GFR in the CLK when compared to estimates of single kidney function of a comparably aged group of essential hypertensive subjects. These figures are admittedly approximate, as previous measurements of split renal function in essential hypertension have indicated that renal function may not be always symmetric. Nonetheless, these figures do reflect a marked discrepancy in function between stenotic and contralateral kidneys and provide an explanation of remarkably well-preserved overall function despite unilateral ischemic renal atrophy.

Baseline fractional sodium excretion in these patients was nearly twofold higher on the contralateral kidney, consistent with both enhanced excretion on that side and avid sodium retention by the stenotic kidney.

Connor et al. reported that ischemic kidneys reabsorbed sodium and water to a greater degree than the opposite kidney, a finding that has been confirmed and expressed in various numerical forms by Stamey and
Renin activity during infusion of \([\text{Sar}^1, \text{Thr}^8]\) All in our study were varied. In several instances it has been described to explain "pressure natriuresis." 

Taken together, our findings suggest that the CLK in humans responds to a loss in nephron mass and to elevated systemic pressures in a manner similar to that observed in experimental animals.

Recent work in experimental forms of renovascular hypertension has indicated that the contralateral kidney may undergo vasodilation and natriuresis following inhibition of angiotensin converting enzyme with captopril, leading to the suggestion that All may be exerting direct renal hemodynamic effects modulating sodium excretion.

Although it has been demonstrated that low levels of angiotensin may in fact induce sodium retention in humans and animals, there has been, heretofore, scant information on the differential sensitivities of ischemic and contralateral kidneys in humans.

The fall in blood pressure and changes in plasma renin activity during infusion of \([\text{Sar}^1, \text{Thr}^8]\) All in our study were similar to several previous reports employing other angiotensin antagonists. Hemodynamic studies of this agent have indicated that changes in blood pressure reflect alterations of total peripheral resistance. However, the vasocostriction in the renal vascular bed (fig. 2) is at variance with the rest of the circulation and suggested a markedly exaggerated sensitivity of this receptor bed to the agonist effects of this agent. Such a differential sensitivity within the kidney has been observed during studies with All and other analogs.

It is unlikely that the fall in systemic pressure alone would produce vasoconstriction; on the contrary, a fall in renal resistance due to autoregulation and vasodilation is typically observed. The rise in single kidney resistance in our patients is in contrast to the vasodilation occurring during infusion of antihypertensive doses of nitroprusside over a similar blood pressure range.

Individual renal responses during \([\text{Sar}^1, \text{Thr}^8]\) All infusion were varied. In several instances it was possible to demonstrate increases in renal perfusion and sodium excretion, during angiotensin blockade suggesting a release from tonic vasoconstriction and sodium retention attributable to All. These were qualitatively symmetric between the stenotic and contralateral kidneys, but quantitatively largest on the contralateral side. Taken together, these findings underscore the differences between vascular, adrenal, and renal receptor sensitivity to angiotensin analogs.

Perhaps least expected was the symmetry of hemodynamic responses during the \([\text{Sar}^1, \text{Thr}^8]\) All infusion between the stenotic and contralateral kidneys, despite marked local differences in renin production as reflected by renal vein renin levels. Animal studies have shown marked hypercellularity of the juxtaglomerular cells and high local concentrations of renin in ischemic kidneys and virtual suppression of renin production in the CLK. The fact that renal venous and arterial renin are nearly identical in the CLK in humans, whereas there is evident increase in venous levels on the stenotic side, suggests that similar events are obtained in man. One might anticipate that local activation of All on the stenotic side might modify the response to exogenously infused angiotensin analogs compared to that in the contralateral kidney.

The fall in blood pressure and changes in plasma renin activity during infusion of \([\text{Sar}^1, \text{Thr}^8]\) All in our study were similar to several previous reports employing other angiotensin antagonists. Hemodynamic studies of this agent have indicated that changes in blood pressure reflect alterations of total peripheral resistance. However, the vasocostriction in the renal vascular bed (fig. 2) is at variance with the rest of the circulation and suggested a markedly exaggerated sensitivity of this receptor bed to the agonist effects of this agent. Such a differential sensitivity within the kidney has been observed during studies with All and other analogs.

It is unlikely that the fall in systemic pressure alone would produce vasoconstriction; on the contrary, a fall in renal resistance due to autoregulation and vasodilation is typically observed. The rise in single kidney resistance in our patients is in contrast to the vasodilation occurring during infusion of antihypertensive doses of nitroprusside over a similar blood pressure range.

Individual renal responses during \([\text{Sar}^1, \text{Thr}^8]\) All infusion were varied. In several instances it was possible to demonstrate increases in renal perfusion and sodium excretion, during angiotensin blockade suggesting a release from tonic vasoconstriction and sodium retention attributable to All. These were qualitatively symmetric between the stenotic and contralateral kidneys, but quantitatively largest on the contralateral side. Taken together, these findings underscore the differences between vascular, adrenal, and renal receptor sensitivity to angiotensin analogs.
Taken together with the recent clinical study by Fiorentini et al.39 demonstrating that transient complete occlusion of the renal artery during transluminal angioplasty produces unilateral renin release and the humoral pattern typical of renovascular hypertension, but does not elevate blood pressure, it may be postulated that renal ischemia is a necessary but possibly not sufficient condition for renovascular hypertension to develop. A further condition may be incomplete excretion of sodium, in part by the contralateral kidney.

This formulation would help explain the relative insensitivity of both lateralization of renal vein renin measurements and diagnostic tests utilizing All antagonists without prior sodium depleting maneuvers. Although sodium retention was manifest in both kidneys, our data suggest that the contralateral kidney excretes the majority of sodium and demonstrates the largest absolute changes to the sodium retaining stimulus of angiotensin. It is likely that tonic sodium retention is mainly a functional defect of this side. Revascularization procedures on the stenotic kidney not only remove the systemic pressor action of angiotensin and its effects on the adrenal gland, but may well release the contralateral kidney from direct renal actions of angiotensin which limited its ability to excrete sodium as systemic pressures were rising.

Taken together, these data are consistent with a direct intrarenal hemodynamic role for All in the pathogenesis of human renovascular hypertension.

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