Serial Renin-Angiotensin Studies in Spontaneously Hypertensive and Wistar-Kyoto Normotensive Rats

Transition from Normal- to High-Renin Status During the Established Phase of Spontaneous Hypertension

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SUMMARY

To characterize the renin-angiotensin system in the Aoki-Okamoto spontaneously hypertensive rat (SHR) more fully, serial measurements of plasma renin activity (PRA), plasma renin concentration (PRC), renin reactivity (as relative index of circulating modifiers of the renin reaction) and renin substrate concentration were made in 6- to 64-week-old SHR and in age-matched Wistar-Kyoto normotensive rats (WKY). In the evolving phase of SHR hypertension (6 and 13 weeks of age), PRA was comparable to WKY control values, whereas mature SHR with established hypertension developed, between 13 and 35 weeks of age, a high-PRA state persisting through 64 weeks of age. In 64-week-old SHR, increased plasma volume (3.54 ± 0.91 in SHR vs. 3.18 ± 0.90 ml/100 g body weight in WKY, *p < 0.025), together with increased PRA (24.9 ± 3.8 in SHR vs. 13.1 ± 2.2 ng Al/ml plasma/hr in WKY, *p < 0.025), suggest that volume decrease cannot explain increased PRA. In 42-week-old SHR, PRA was incompletely suppressed by deoxycorticosterone acetate plus 1% saline orally for 4 days: 4.9 ± 1.2 in SHR vs. 0.6 ± 0.8 ng angiotensin I/ml plasma/hr in WKY, *p < 0.001. Modestly increased renin reactivity of plasma was observed in SHR at all ages studied, supporting the ubiquity of increased circulating accelerators (or decreased inhibitors) of the renin reaction in hypertensive states. However, elevated renin reactivity did not account for the transition from normal to high PRA observed in mature SHR, nor did renin substrate concentration, which was consistently lower in SHR than in age-matched WKY. Temporal patterns of, and strain differences in PRA were closely paralleled by variations in PRC but not by other reaction components. Significant elevation of serum creatinine in old SHR support the presence of renal injury. We conclude that PRA and PRC are normal in evolving SHR hypertension and progress to abnormally elevated levels after hypertension is established. We postulate that "high-renin" hypertension may develop as a consequence of the hypertensive state per se, perhaps due to nephrosclerotic vascular disease. (Hypertension 1: 347-354, 1979)

KEY WORDS • spontaneously hypertensive rat • plasma renin activity • plasma renin concentration • renin reactivity • renin substrate • renin-volume relationship

The Aoki-Okamoto spontaneously hypertensive rat (SHR) is a potentially valuable model for the study of human essential hypertension. However, correlation with clinical hypertension has been limited by major discrepancies in reports of renin-angiotensin activity in SHR. Plasma renin activity (PRA) has been found to be low, and high in SHR with established hypertension, and reported patterns of change in PRA with age are similarly conflicting. Use of different control strains and in vitro methods hinders resolution of these conflicts.

Additionally, circulating modifiers of the in vitro renin reaction (accelerators or lack of inhibitors) have been reported in a wide variety of hypertensive states but have not been examined in SHR hypertension. We have accordingly evaluated serial renin-angiotensin indices in young (6- and 13-week-old) and mature (35- to 64-week-old) SHR, using the genetically related Wistar-Kyoto normotensive rat (WKY) as control and employing in vitro methods developed and validated specifically for the SHR/WKY strains.
Methods and Materials

Beginning at 4 weeks of age, male Aoki-Okamoto spontaneously hypertensive rats (SHR) and Wistar-Kyoto normotensive rats (WKY) (Laboratory Supply Co., Indianapolis, Indiana) were maintained on a basal chow containing 0.5% sodium chloride (0.085 mEq Na+/g chow) and tap water. Rats were serially studied in two temporally separate groups; Group I data spanning 14–60 weeks of age and Group II data spanning 4–64 weeks of age.

Systolic blood pressure was determined by tail sphygmomanometry (Narco Biosystems, Houston, Texas) according to standard methods. Four readings were averaged for each rat at each time point. Twenty-four hours after pressure determinations, animals were gently immobilized in a towel, the tail tip quickly amputated, and 1 cc of blood obtained on ice in EDTA (1 mg/cc blood) for renin-angiotensin studies. Plasma was separated and stored at −20°C.

Rat renin was extracted by the method of Lucas et al. and standardized in a WKY control plasma pool. That concentration of renin (in plasma) generating a reaction velocity increment of 5 ng angiotensin I/ml plasma/hr was arbitrarily designated as 1 × 10^4 units/ml plasma. Stock renin contained 58 units/ml and was without detectable angiotensinase activity in the concentrations used.

Within each age group, equal numbers of plasmas from each strain were incubated and assayed concurrently. Based on previously validated incubation methodology, each plasma sample (containing 0.005 M EDTA) was pretreated by adding diisopropylfluorophosphate (DFP) and 2–3 dimercaptopropanol (BAL) to final concentrations of 0.016 M and 0.007 M respectively, and by adjusting pH to the optimum range of 6.0–6.4 using 0.38 M citric acid. Plasma was then aliquoted for determination of plasma renin activity (PRA), renin reactivity, and renin substrate concentration (vida infra). After incubation, angiotensin I was measured by radioimmunoassay utilizing AI standard from the Medical Research Council (Research Standard A, code 71/328). Each incubated aliquot was assayed in triplicate at least twice.

Plasma Renin Activity

One hundred-μl aliquots of pretreated plasma were incubated at 37°C for 15 minutes and the AI concentration was determined. Results are expressed as ng AI/ml plasma/hr.

Renin Reactivity

Renin reactivity of plasma, defined as the increment in reaction velocity produced by addition of a known small amount of exogenous renin to plasma, has been used to estimate relative activity of circulating modifiers of renin-reaction velocity. The effect of differences in endogenous renin concentration among plasmas compared is offset by using change in veloc-

ity above baseline. However, renin reactivity is theoretically influenced both by circulating modifier activity and by renin substrate concentration. Accordingly, renin reactivity values can be taken as relative measures of modifier activity only if 1) substrate concentrations are equal in plasmas compared, or 2) substrate levels, although different, vary within a range wherein reaction velocity is independent of substrate concentration (i.e., zero-order kinetics with respect to substrate). Otherwise, renin reactivity must be viewed as a summation of substrate and circulating modifier effects.

Ten μl of the appropriate rat renal dilution (in tris lysozyme buffer) was added to a 100-μl aliquot of pretreated plasma to achieve final renin concentrations of approximately 5 × 10^4 and 2.5 × 10^4 units exogenous renin/ml plasma. Linearity of reaction velocity with increasing renin concentration was thus confirmed. Substrate utilization did not exceed 5% of the total available. Aliquots were incubated at 37°C for 15 minutes; AI generated was measured by radioimmunoassay. For each plasma sample, a 3-point linear regression analysis was performed using exogenous renin concentration vs. reaction velocity, the PRA value representing reaction velocity at zero concentration of added renin. Renin reactivity is represented by the slope of the regression line and is expressed as ng AI/ml plasma/hr/1 × 10^4 units renin/ml.

Plasma Renin Concentration

Plasma renin concentration (PRC) is a value derived from PRA and renin reactivity measurements: PRC = PRA × renin reactivity. Intuitively, if a known concentration of added renin, acting under the same substrate and modifier conditions as endogenous renin, generates a given increment in reaction velocity, then the endogenous renin concentration responsible for the baseline reaction velocity (i.e. for PRA) can be determined. Given the conditions employed for renin reactivity measurement (vida supra) and assuming similarity of endogenous and exogenous renin, this method of deriving PRC yields values that, unlike PRA, are theoretically independent of in vitro differences in substrate and modifier concentrations among plasmas. Results are expressed as units renin × 10^4/ml plasma.

Renin Substrate Concentration

Renin substrate concentration was measured by adding 10 μl of a renin solution (0.08 units/ml) to each of two 50-μl aliquots of pretreated plasma. These were incubated at 37°C for 40 and 70 minutes, respectively. Incubates were diluted 1:100 before assay. In all cases, the AI generated was comparable at the two time points, demonstrating both complete conversion of substrate to AI and adequate inhibition of angiotensinases. Results were corrected for dilution factors and expressed as ng AI/ml plasma.
DOCA-Saline Suppression

In the 42-week-old rats of Group II, 20 mg of desoxycorticosterone acetate (DOCA) in 100 μl of oil was injected subcutaneously and 1% saline drinking water instituted on Day 0. On Day 4, tail-blood samples were obtained and processed for measurement of PRA as described above.

Blood Urea Nitrogen, Creatinine

In two rat batches (unrelated to Groups I and II) aged 9 weeks and 56–78 weeks, plasma or serum was obtained by decapitation for determination of urea nitrogen and creatinine by standard methods.23, 24

Plasma Volume

In 64-week-old rats of Group II, just prior to anesthetization, 1 cc of tail-blood was obtained for PRA and a tourniquet applied to the tail tip to prevent further blood loss. Iodine-131-serum albumin was injected via the exposed right jugular vein in pentobarbital-anesthetized rats. At 5, 10, and 15 minutes post-injection, 600-μl samples were withdrawn from the similarly exposed left jugular vein. Sample counts per minute were plotted against time and extrapolated to zero-time for plasma volume calculation.

Statistical Analysis

Analysis of variance was applied to data shown in figures 1–3. Student's t test or Mann-Whitney U test were used for analysis of all other data.

Results

Body Weight and Systolic Blood Pressure

Serial mean values for body weight of all Group I and Group II rats are shown in figure 1. The rate of weight gain in SHR declined at 30–35 weeks of age in both groups; SHR body weight became significantly less than WKY controls by 39 weeks of age in Group I and by 35 weeks of age in Group II.

Changes in systolic blood pressure (BP) with age for all rats are shown in figure 2. While pressure was similar in 6-week-old SHR and WKY rats of Group II, systolic BP was significantly higher in SHR (Group II) at 4 weeks (F, 1100 = 5.45, p < 0.01) and 8 weeks of age (F, 1100 = 27.76, p < 0.001) and at all subsequent ages for both groups. Plateau BP was apparent by 14 weeks of age in Group I SHR.

Renin-Angiotensin Parameters

Serial mean values for PRA, plasma renin concentration, renin reactivity, and renin substrate concentration are shown in figure 3. During the developing phase of hypertension (6 and 13 weeks of age), PRA in SHR was comparable to WKY control values (F, 124 = 0.42, NS). In contrast, mature SHR (35 weeks of age) exhibited significant elevation of PRA (F, 1124 = 46.81, p < 0.001), a difference demonstrable in Group I rats at 35, 39 and 52 weeks of age and in Group II rats at 42 weeks of age (fig. 3A). Further confirming elevation of PRA in mature SHR are values in 64-week-old rats of Group II (table 1) and in 60-week-old Group I rats: 24.0 ± 1.7 (n = 6) in SHR (Group 1) vs. 16.8 ±
FIGURE 2. Serial systolic blood pressures in SHR and WKY of Groups I and II. Values are means ± se obtained via tail-cuff method. See text for statistical comments.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Plasma volume (cc/100 g body wt)</th>
<th>PRA (ng Al/ml/hr)</th>
<th>Body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>3.54 ± 0.91</td>
<td>24.9 ± 3.8</td>
<td>413 ± 12</td>
</tr>
<tr>
<td>WKY</td>
<td>3.18 ± 0.91</td>
<td>13.1 ± 2.2</td>
<td>499 ± 17</td>
</tr>
<tr>
<td>no.</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

*Values are means ± se. PRA = plasma renin activity; Al = angiotensin I; SHR = spontaneously hypertensive rat; WKY = Wistar-Kyoto normotensive rat. Group II rats were fed basal chow.

**TABLE 2. Urea Nitrogen and Creatinine Values in Young and Old Spontaneously Hypertensive (SHR) and Wistar-Kyoto (WKY) Rats**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (wks)</th>
<th>Urea nitrogen (mg%)</th>
<th>Creatinine (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma&lt;br&gt;WKY</td>
<td>7</td>
<td>19.5 ± 1.4</td>
<td>0.30 ± 0.01</td>
</tr>
<tr>
<td>SHR</td>
<td>9</td>
<td>24.8 ± 1.2</td>
<td>0.29 ± 0.03</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.025</td>
<td>&lt; 0.025</td>
<td>NS</td>
</tr>
<tr>
<td>Serum&lt;br&gt;WKY</td>
<td>12</td>
<td>16.2 ± 6.0</td>
<td>0.52 ± 0.02</td>
</tr>
<tr>
<td>SHR</td>
<td>12</td>
<td>24.0 ± 2.2</td>
<td>0.81 ± 0.03</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.002</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

All values are means ± SEM from samples obtained by decapitation.

1.2 ng Al/ml/hr (n = 7) in WKY (Group I), p < 0.005.

Plasma renin concentration in SHR (fig. 3B), exhibiting a temporal pattern identical to that of PRA, was also comparable to WKY controls in the developing phase of SHR hypertension and showed abnormal elevation only in mature (35-week-old) SHR (F,19 = 15.72, p < 0.001).

Renin reactivity (fig. 3C) was increased over WKY controls by an average of 20% in SHR of all ages when compared to WKY controls. While there was considerable overlap of values between strains within each age group, a statistically significant strain difference was apparent when all age groups were combined (F,19 = 8.25, p < 0.005).

Renin substrate concentration (fig. 3D) was lower in SHR at all ages studied (F,118 = 43.73, p < 0.001). In both strains, renin substrate values increased significantly with age up to 39 weeks and declined thereafter. (Age effect for each strain: F,118 = 11, p < 0.001).

Suppressibility of PRA by DOCA plus 4 days of 1% saline loading in 42-week-old rats of Group II is shown in figure 4. While highly significant suppression of PRA was achieved in both WKY (p < 0.001) and SHR (p < 0.001) rats, post-suppression PRA was significantly higher in SHR (4.9 ± 1.2 vs. 0.6 ± 0.8 ng Al/ml plasma/hr, p < 0.001). Expressed as percent decrease, the mean of 86.4 ± 3.0% for SHR was significantly less than the mean of 97.5 ± 0.3% for WKY rats (p < 0.001). There was no correlation between initial PRA and post-suppression PRA for either strain.

**Plasma Volume**

Results of plasma volume determinations with corresponding PRA and body weights in 64-week-old rats...
of Group II are shown in table 1. Expressed as percent body weight, plasma volume was significantly higher in SHR. PRA was also significantly elevated. The lower body weight in SHR conforms to the trend identified in the younger rats.

**BUN and Creatinine Values**

Values for urea nitrogen and creatinine in young (9-week-old) and mature (56- to 78-week-old) rats of both strains are shown in table 2. Although urea nitrogen in plasma was slightly and significantly higher in young SHR, plasma creatinine did not differ from that of age-matched WKY controls. By contrast, both urea nitrogen and creatinine in serum were significantly elevated in mature SHR averaging 62 weeks of age as compared to mature WKY averaging 73 weeks of age.

**Mortality**

Mortality records were maintained for Group I rats. With the exception of two of the 10 WKY controls dying of pneumonia at 40 weeks of age, rats of both strains appeared healthy through 52 weeks of age. There were no additional WKY deaths through 72 weeks of age. In the nine SHR, cumulative mortality at 72 weeks was 56%. Ages at death ranged from 56-68 weeks.

**Discussion**

Prior studies of the renin-angiotensin system in SHR do not agree, presumably a reflection of differences both in control strains chosen and in methodologic approaches. The critical importance of selecting an appropriate control rat to minimize genetic differences unrelated to blood pressure has been amply documented. Our results are based both on the genetically related Wistar-Kyoto rat as normotensive control and on in vitro methods specifically validated in the SHR and WKY strains.

We find that plasma renin activity (PRA) in SHR is comparable to age- and weight-matched controls in the developing phase of hypertension (6 and 13 weeks of age), whereas PRA is abnormally high in mature SHR (35-64 weeks of age) with established hypertension when referenced to age-matched WKY controls.

Our findings differ in one or more respects from all prior reports. Only one published study has matched our own both in specifically examining peripheral PRA by radioimmunoassay and in using the WKY strain as control: Freeman et al., obtaining plasma by decapitation, found suppression of PRA in six SHR at 8 weeks of age.

Among those studies evaluating the time-course of PRA changes in SHR, all based on non-WKY controls, results are again inconsistent. Forman and Mulrow and Czyzewski and Pettinger found basal PRA values in SHR comparable to standard Wistar controls at ages spanning 1-11 months. Sen et al. reported high PRA (relative to standard Wistar controls) in young SHR and suppressed values by 9-10
Influence of Renin-Reaction Components on PRA

According to the reaction formula:

\[ \text{Renin} \rightarrow \text{Renin Substrate} \rightarrow \text{Angiotensin I}, \]

\[ \text{Modifiers} \]

PRA reflects the net velocity of angiotensin I generation in vitro and is influenced by the concentration of each of the three reaction components. In theory, strain differences in substrate or modifier concentrations as well as in renin concentrations could account for differences in PRA. In order to assess their respective influences on PRA, we measured renin substrate concentration and renin reactivity (a relative index of circulating modifier activity) and derived plasma renin concentration (see Methods section).

Our findings of lower renin substrate concentrations in SHR of each age group studied contrasts with earlier reports. DeJong et al.\(^6\) and Sen et al.\(^6\) found elevated renin substrate concentrations in SHR that were 4–35 weeks of age. However, these results are based on a standard Wistar rat as control rather than on the WKY strain. Lower renin substrate levels in our SHR indicate that this reaction component cannot account for the abnormally high PRA observed in mature SHR.

Renin reactivity was modestly elevated in SHR in each age group studied, achieving statistical significance when analysis of variance was performed on pooled data. Increased renin reactivity has now been reported in a wide variety of hypertensive states, including human essential hypertension,\(^6\) renovascular hypertension,\(^6\) primary aldosteronism,\(^6\) and experimental coarctation hypertension.\(^6\) Our present findings extend this phenomenon to SHR hypertension and further support its ubiquity in hypertensive disease of diverse etiology.

In the past,\(^6\) comparison of renin reactivity values among plasma with equal renin substrate concentrations permitted viewing the reactivity as a relative index of modifier effects alone. In the present study, the unequal renin substrate values require interpreting the renin reactivity differences as a summation of substrate plus modifier effects on PRA. The relationship between substrate concentration and reaction velocity is nonlinear and can be quantitatively assessed only if kinetic constants are known.\(^7\) The contribution of the substrate concentration to the renin reactivity values determined herein could thus vary from nil (i.e., SHR vs. WKY substrates differ but fall within a concentration range which has no influence on reaction velocity, as under-zero-order kinetic conditions) to a direct linear effect (i.e., substrates differ and fall within a concentration range appropriate to first-order kinetic conditions). In the absence of kinetic information, it is not possible to choose between these alternatives. However, in either case, it can be concluded that, given lower renin substrate levels in SHR, substrate concentration cannot account for the observed increase in renin reactivity. This suggests that the strain difference observed is most likely due to net increase in accelerating modifiers in SHR. Furthermore, lower substrate concentrations would, if non-zero-order kinetics were operative, lead to underestimation of accelerating modifier effects in SHR.

Net increase in accelerator activity would theoretically serve to augment PRA at any given renin concentration in SHR. However, the relatively constant magnitude of renin reactivity elevation in SHR of all ages suggests that modifier factors cannot explain the transition from normal to high PRA observed in maturing SHR.

Plasma renin concentration, the third reaction component influencing PRA, has not been previously examined in SHR by the method we have used. This value, calculated from PRA measured independently and renin reactivity, is theoretically independent of any differences in other reaction components.\(^6\) Plasma renin concentration followed a pattern identical to that for PRA in that 1) both were normal in 6-
and 13-week-old SHR and abnormally elevated in mature SHR (fig. 3B), and 2) PRC and PRA showed parallel changes with age within each strain. This concordance suggests that PRC may be the reaction component primarily responsible for the observed strain differences in, and temporal pattern of, PRA. That renin in these strains is of predominantly renal origin is supported by our finding of PRA below the limits of quantitative detection at 24 hours post-nephrectomy in both SHR and WKY rats (S. Bagby, unpublished observations).

Thus, the transition from a normal-PRA to a high-PRA state observed in SHR, as compared to age-matched WKY controls, is associated with parallel increases in PRC (and presumably renal renin release) while the remaining reaction components appear to vary independently of PRA.

Our finding of normal PRA and PRC in 6- and 13-week-old SHR, whether conditions are basal or stimulated, excludes absolute hyperactivity of the renin-angiotensin system in the developing phase of SHR hypertension. As noted above, because of the possibility that the renin response in SHR is preferentially augmented by tail-cutting stress, our findings do not exclude the existence of chronically suppressed PRA in the basal state. Since normality of PRA can be precisely defined only in relation to body fluid volume, our data do not eliminate a primary imbalance of the renin-angiotensin-volume relationship in the evolving phase of SHR hypertension.

In all mature (35-week-old) SHR, we found consistent elevation of PRA and PRC. Possible explanations for this transition from a normal- to a high-renin state might include 1) decrease in plasma volume, 2) development of an accelerated form of hypertension, 3) appearance of (or increase in) sympathetic hyperreactivity with increasing age in SHR, and 4) development of renal microvascular lesions yielding impaired renal perfusion.

Plasma volume in a small group of 64-week-old SHR, expressed as percent of body weight, was increased over age-matched WKY values (table 1). We do not take this as definitive evidence for excess plasma volume but rather as evidence that overtly decreased plasma volume does not contribute to elevation of PRA and PRC in mature SHR.

That transition from a normal- to a high-renin state in SHR is not due to development of an accelerated form of hypertension is suggested by the fact that the earliest deaths in our Group I SHR occurred a full 23 weeks following the PRA/PRC rise and that blood pressure remained stable over this period (fig. 2).

In order for sympathetic hyperresponsiveness to tail-cutting stress to account for the normal-to-high PRA/PRC transition in SHR, appearance or exacerbation of this feature must have occurred between 13 and 35 weeks of age. However, the findings of Hallback indicate a comparable degree of sympathetic hyperresponsiveness in SHR of 2 and 7 months of age and thus do not support this alternative.

Nephrosclerosis is amply documented in SHR hypertension. Moreover, Feld et al. have recently described the temporal evolution of these lesions in SHR, with the earliest nephrosclerotic changes appearing in kidneys of 30- to 40-week-old SHR and progressing in severity through 65 weeks of age; age-matched WKY control kidneys were histologically normal. The appearance of a high-renin state in our SHR between 13 and 35 weeks of age thus coincides with the development of histological markers of renal parenchymal and vascular damage in SHR hypertension. Additionally supportive of renal injury in our mature SHR is the finding of elevated serum creatinine in old hypertensive rats (average 62 weeks of age) as compared to WKY (average 72 weeks of age). These results are in quantitatively close agreement with those of Feld et al., who additionally demonstrated decreased creatinine clearances in SHR over 50 weeks of age.

Our demonstration of incomplete suppressibility of PRA in 42-week-old SHR subjected to DOCA-saline treatment provides additional evidence for a renin-angiotensin-volume disturbance. However, the implicit assumption that the final volume achieved in SHR was at least equal to that in WKY controls requires direct confirmation, particularly in view of the possibility of exaggerated natriuresis reported to occur in SHR as in hypertensive man. Unfortunately, neither plasma volume nor sodium balance data were obtained during our DOCA-saline suppression studies.

Incomplete suppression of PRA by volume-expanding maneuvers has been noted in a variety of hypertensive states including the essential and renal categories in man. This observation in our 42-week-old SHR, while not suggestive of specific etiology, qualitatively supports the findings of Czyzewski and Pettinger and strengthens the analogy between human and SHR hypertension. However, the above authors reported total lack of PRA suppression in SHR of identical age, a quantitative discrepancy for which we have no explanation.

In summary, we find that the developing phase of SHR hypertension is a "normal-renin" state apparently comparable to that reported in the majority of human essential hypertensives. In contrast, SHR with established hypertension develop, between 13 and 35 weeks of age, a persistently high-renin state which may be similar to that observed in 9–16% of essential hypertensive patients. Our observations in SHR hypertension support the view that "high-renin" hypertension may develop as a consequence of the hypertensive state per se. We further speculate that secondary PRA elevation may serve as an early marker of nephrosclerotic disease.

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