Renal Blood Flow and Renin Activity in Renal Venous Blood in Essential Hypertension

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ABSTRACT

The intrarenal distribution of blood flow measured by the $^{183}$Xenon washout method and the renin activity of renal venous blood were determined in 16 patients with early essential hypertension. None of the patients had evidence of systemic disease except for the elevation in blood pressure (> 150/100 mm Hg). Fifteen of the subjects received a controlled sodium diet during 7 to 9 days before study, at the time of renal angiography. An inverse relationship was noted between the cortical component of the renal blood flow and renin activity of renal venous blood ($r = 0.64$, $P < 0.02$). Renin secretion rates were also calculated in 12 patients confirming the inverse relationship between cortical distribution of blood flow and renin secretion ($r = 0.763$, $P < 0.01$).

The cortical renal blood flow in 10 patients on a low salt intake was $79.6 \pm 2.6$ (mm) of the total renal blood flow. The cortical blood flow in five patients on a high salt diet was $87.68 \pm 1.9$ (mm); the statistical difference between the two groups is significant ($P < 0.05$). A direct relationship was noted between cortical blood flow and the logarithm of the 24-hour urinary sodium excretion from the day preceding the study ($r = 0.54$, $P < 0.05$). Renin secretion rate and renin in renal venous blood were directly correlated ($r = 0.813$, $P < 0.01$). Changes in corticomedullary distribution of flow were inversely related to the changes in cortical distribution. The degree of reduction of cortical renal blood flow correlated with the degree of increase in renin secretion and in renin activity in renal venous blood. Our data are compatible with reduced cortical renal blood flow mediating renin release or vice versa. Either mechanism would result in more efficient conservation of salt and water by the kidney.

ADDITIONAL KEY WORDS

renin release human hypertension low salt intake sodium excretion xenon washout cortical blood flow corticomedullary blood flow

The majority of pathologic conditions which are accompanied by consistent alterations in renal blood flow are also associated with changes in peripheral renin activity. Renovascular hypertension (1), acute renal failure (2), and hemorrhagic hypertension (3) are each associated with increased peripheral renin activity and with a reduction in the total renal blood flow. Recently Nash et al. (4) have demonstrated that changes in renin activity of renal venous blood may be produced in the experimental animal with no concomitant change in the total renal blood flow. This apparent dissociation of renin secretion from renal hemodynamics is confusing in view of the previously anticipated close relationship in both the experimental and clinical situations. The common denominator between renin secretion and renal blood flow may be the intrarenal distribution of blood flow rather than the total flow. This possibility is not excluded by the work of Nash et al. (4). Attempts to define the intrarenal distribution...
of blood flow in conditions that have been correlated with changes in renin activity have been limited previously by methods which are indirect and may be unreliable (5, 6). Such measurements may detect only very large changes. The recent introduction of a clinically applicable method for the measurement of the partition of the renal blood flow utilizing a gas washout technique (7) provides a means to reassess the intrarenal distribution of blood flow and to explore further a possible relation to renin secretion. It is possible theoretically for significant changes to occur in the distribution of the renal blood flow with little or no detectable change in the total flow. This may explain why it is possible to provoke changes in renin activity with no change in renal blood flow as measured by an electromagnetic flowmeter. An alternative explanation is that there may be no relationship between renal blood flow and renin secretion and that the changes in renin activity noted in renal artery stenosis, acute renal failure and hemorrhagic hypotension are mediated entirely through variations in the delivery of sodium to the macula densa either as postulated by Thurau and Schnermann (8) or by Vander and Miller (9). Changes in perfusion pressure also may occur without simultaneous changes in blood flow and may serve as a regulating factor in renin secretion.

In the present study we have evaluated the relationship between the intrarenal distribution of blood flow and renin activity of renal venous blood in man under varying conditions of sodium intake in an effort to obtain some of the answers to these questions.

Methods

Sixteen patients with essential hypertension were included in the study. Patients with heart disease or other systemic disease, proteinuria or grade III or IV hypertensive retinopathy (Keith-Wagener) were excluded from the study. The mean age of the group was 37 years (23 to 52) with eight males and eight females. Seven of the patients were white and nine were Negro. They were selected from the renal-hypertension clinic with eight males and eight females. Seven of the patients were white and nine were Negro. They were selected from the renal-hypertension clinic of the Bronx Municipal Hospital Center at random on admission, using only the above criteria. Each patient in this group was admitted for studies to rule out the possibility of renovascular hypertension and was subsequently shown by renal angiography to have no evidence of renal artery stenosis. All of the subjects were shown to have blood pressure readings consistently higher than 150/100 mm Hg at the time of study. Fifteen of the patients were admitted to the Clinical Research Center of Van Etten Hospital and were placed initially on a high sodium diet (200 mEq/day) containing approximately 90 to 100 mEq of potassium and adequate caloric value. After approximately 7 to 9 days, aortography and selective renal angiography were performed in five of the patients. Ten other subjects were switched to a calculated low sodium intake (<30 mEq/day) on the fifth day and were maintained on this intake for 7 to 9 days at which time aortography and selective renal angiography were performed. The remaining patient was studied while on a normal sodium intake (about 100 mEq/day). Daily 24-hour urine collections were obtained for determination of sodium, potassium and creatinine while the subjects were on the metabolic ward. Adherence to the diet was confirmed by the urinary sodium excretion. The blood pressure of each patient was measured four times a day during hospitalization and a nonantihypertensive therapy was administered until the completion of the study.

On the day of aortography, each patient lay supine for about 3 hours before the procedure. The initial procedure consisted of retrograde catheterization of the renal veins through the femoral vein with an end-hole Kifa catheter. The placement of the catheter was confirmed with an injection of 3 to 5 ml of sodium diatrizoate and the renal venous blood was then sampled. The ovarian or testicular vein was carefully excluded. Approximately 20 ml of whole blood were collected from each renal vein in iced test tubes containing 1 ml of 3.8% ammoniated EDTA. The blood was immediately centrifuged in the cold and the pH of the plasma was adjusted to 5.5 with hydrochloric acid. The plasma was then frozen to be analyzed later for renin activity. Measurement of renin activity was performed by the method of Boucher (10) as modified by Hickler (11) using a bioassay system. Each sample was assayed in duplicate in two test animals by two observers. Duplicate samples in this laboratory agree within ± 10%. Plasma renin activity was expressed as nanograms of angiotensin II/100 ml.

Immediately after renal vein catheterization, retrograde aortography and selective renal arteriography were performed to rule out renal artery stenosis. At the time of aortography and arteriography, renal arterial samples were obtained for determination of renin activity in 12 patients. The catheter was left in one renal artery and approximately 15
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minutes after the completion of renal arteriography, 1 mc of 133 xenon in 5 ml of normal saline was injected rapidly as a bolus. The catheter was withdrawn immediately into the iliac artery after the injection and was flushed of radioactivity by withdrawing 10 ml of blood. The washout of radioactivity from the kidney was monitored by a 6 inch Na I (Tl) crystal with photomultiplier tube connected to a Picker Dual-Rate Computer powered by a Packard high voltage supply. A 6 inch cylindrical collimator was used. Data were recorded on a four-track electromagnetic tape recorder using Scotch brand recording tape. This was subsequently played back and printed on a Franklin Printout. The count rate versus time was plotted on semilogarithmic graph paper at 2-second intervals for the first 200 seconds and at 10-second intervals during the remainder of the study. Curves were analyzed as previously reported (7, 12). Intrarenal distribution of the renal blood flow was calculated from the relative intercepts of the components of the washout curve. Blood flow per gram of kidney tissue was calculated from the slopes of the components of the curve after correction for the renal arterial hematocrit, using the formula of Ladefoged (13) to correct the partition coefficient. Only the first and second components of the curves were analyzed as having physiologic meaning. The first component was interpreted as a measure of cortical blood flow and the second as a measure of corticomedullary flow (7, 12-14).

The mean renal blood flow was determined from integration of the experimentally obtained xenon washout curve according to the method of Zierler (15) where:

\[
f = \frac{\lambda \text{Height}}{\text{Area}} \times 100
\]

\(f\) = blood flow (ml-min\(^{-1}\)-100 g\(^{-1}\)), \(\lambda\) = partition coefficient, Height =maximum height of the curve, Area =area of the curve (this includes an initial rising portion of the curve which is not included in the curve peeling method). The blood flow was corrected for hematocrit and the mean renal plasma flow was calculated from the product of the mean blood flow and \(1 - \text{hematocrit}\). The renal secretion rate of renin was estimated from the renal plasma flow multiplied by the arteriovenous difference in renin activity and was expressed as ng angiotensin II \(\cdot\) min\(^{-1}\)-100 g\(^{-1}\).

Results

Each xenon washout study yielded a four-component curve on analysis. No three-component curves or technical failures were encountered in this group of subjects. Component I (cortical flow) in the five patients receiving a calculated high salt intake represented 87.6% ±1.9 (SE) of the total renal blood flow and the flow rate determined from component I was 533 ml\(\cdot\)min\(^{-1}\)-100 g\(^{-1}\) ±32 (SE). Component II (Corticomedullary flow) accounted for 8.3% ± 1.2 (SE) of the total renal blood flow and the flow rate to the corticomedullary nephrons was 105 ml\(\cdot\)min\(^{-1}\)-100 g\(^{-1}\) ±19 (SE) in this group. The mean renin activity of renal venous blood in these subjects, expressed as angiotensin II, was 259 ng/100 ml ± 50 (SE), which is within the normal range for patients with essential hypertension in this laboratory. The data obtained from the group of patients receiving a low salt intake revealed a significantly reduced fraction of the total renal blood flow represented by component I and an increased fraction of the flow represented by component II when compared to the results from the group which received a high salt diet. Component I was 79.6% ±2.6 (SE) \((P < 0.05)\). Component I in the group on a low salt diet yielded a mean flow rate of 470 ml\(\cdot\)min\(^{-1}\)-100 g\(^{-1}\) ±42 (SE) and the mean for component II was 142 ml\(\cdot\)min\(^{-1}\)-100 g\(^{-1}\) ±24 (SE). The mean renin activity of renal venous blood (as angiotensin II) measured in the patients on the low salt diet was 385 ng/100 ml ± 91 (SE).

Four of the twelve patients in whom arterial samples were obtained had a negative arteriovenous difference in renin activity (Table I). Two of these patients were receiving a high salt intake, one was on a normal diet, and the fourth was on a low salt diet but had the greatest fractional value of component I in the low salt group. A highly significant inverse relationship was noted between the renin secretion rate and the fraction of the total renal blood flow represented by component I \((r = 0.763, P < 0.01)\) (Fig. 1). The mean renin secretion rate in the patients with greater than 85% of the total renal blood flow to component I was -35 ng angiotensin II \(\cdot\) min\(^{-1}\)-100 g\(^{-1}\) ±57 (SE) and in the patients with less than 85% to component I the

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**Footnote:** Xenon supplied through courtesy of Nissler Laboratories.
secretion rate was 120 ng angiotensin II min⁻¹ 100 g⁻¹ ± 50 (SE) (P < 0.05). The mean secretion rate on the high salt diet was 11.2 ng angiotensin II min⁻¹ 100 g⁻¹ ± 44.7 (SE) and on the low salt diet, 91.2 ng angiotensin II min⁻¹ 100 g⁻¹ ± 68.8 (SE). Component I represented 88.5% ± 1.7 (SE) in individuals whose secretion rate was less than zero, and 74.5% ± 4.7 (SE) in those whose secretion rate was greater than 100 ng angiotensin II min⁻¹ 100 g⁻¹ (P < 0.025).

Mean renal blood flow for the entire group of patients was 230 ml min⁻¹ 100 g⁻¹ ± 12 (SE) on the low salt diet and 268 ml min⁻¹ 100 g⁻¹ ± 34 (SE) on the high salt diet.

There was a significant inverse linear correlation between the fraction of the renal blood flow to component I (cortical perfusion) and the ipsilateral renin activity of renal venous blood for the entire group of 16 patients (r = 0.64, P < 0.02) (Fig. 2). The fraction of blood flow to component II (corticomedullary) correlated directly and linearly with renin activity of renal venous blood (r = 0.58, P < 0.05) (Fig. 3). The fraction of flow to component I also correlated with the logarithm of urinary sodium excretion for the 24-hour period immediately preceding the blood flow study (r = 0.54, P < 0.05) (Fig. 4). There was also a significant correlation between the renin activity of renal venous blood and renin secretion (r = 0.813, P < 0.01).

Discussion

An increasing amount of evidence in the dog and in man suggests that component I of the xenon washout curve may be used as a reliable measure of the cortical renal blood flow and that component II may be taken as...
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\[ Y = 89.2 - 0.020X \]
\[ n = 16, r = -0.64, p = <0.02 \]

The data presented here suggest that as dietary sodium intake is increasingly limited, there occurs a progressive reduction in the fraction of the total renal blood flow perfusing the outer cortical nephrons with a concomitant increase in the fractional flow to the corticomedullary nephrons. The changes in blood flow per gram of kidney tissue calculated from the slopes of components I and II of the gas washout curve as well as the mean renal blood flow are in the expected direction with a reduction in cortical flow and an increase in corticomedullary flow after restriction of sodium intake. These changes, although suggestive, are not statistically significant. Increases in renal renin secretion and in renin activity of renal venous blood occurring in response to sodium deprivation and reduction in plasma volume are proportional to the degree of reduction in fractional cortical perfusion. Renin activity of renal venous blood may also be correlated with urinary sodium as has been shown in numerous other studies (3). The intrarenal distribution of blood flow appears to have a significant relationship to the logarithm of urinary sodium excretion which further supports the relationship of the intrarenal distribution of flow to sodium intake. Changes in the

\[ Y = 7.66 + 0.014X \]
\[ n = 16, r = 0.58, p = <0.05 \]
intrarenal distribution in blood flow in relation to sodium load in normal man have been noted previously by Hollenberg et al. (14), although they do not comment on renin secretion or urinary sodium. These authors noted that on a diet of less than 10 mEq/day, the cortical blood flow was 63.2 ± 4.6 (se) % of the total renal blood flow and on 200 mEq/day, it was 84.1 ± 1.6%. They could not reverse these changes by acute infusion of dextran in three of the salt-depleted subjects. The present study demonstrates that these alterations occur also in patients with essential hypertension and further that relationships to renin secretion and urinary sodium exist.

Recently Horster and Thurau (16) and Stein et al. (17) have reported changes in cortical and corticomedullary glomerular filtration rate and in the distribution of blood flow within the kidney in relation to sodium load. Horster and Thurau (16) report that superficial single nephron glomerular filtration rate is 23.5 ± 6.4 (se) × 10^-6 ml/min per gram kidney weight in rats on a low sodium intake. This is increased to 38.1 ± 11.3 on a high salt diet. The changes observed by micropuncture studies showed corticomedullary glomerular filtration rate to vary inversely with superficial glomerular filtration rate. These data suggest that sodium conservation may be a function of deep cortical or corticomedullary nephrons. The authors suggest that these changes may be mediated by the renal nerves or a local action of renin in the superficial cortex. The data of Stein et al. (17) were obtained in the dog during acute salt loading. They demonstrated an increase in superficial renal blood flow (hydrogen washout) as well as in glomerular filtration rate during acute volume expansion.

These recent data in the experimental animal and in man and the current study support the hypothesis that the conservation of salt by the kidney may be mediated by alterations in renal blood flow as well as alterations in glomerular filtration rate and...
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...renin secretion. However, the possibility still exists that the changes in blood flow distribution in man occur in response to changes in plasma volume and do not play a primary role in homeostasis.

Carriere et al. (18) have demonstrated a reduction in fractional cortical flow in dogs in response to volume depletion caused by hemorrhagic hypotension. Hollenberg et al. (19) have reported marked cortical ischemia in man in acute renal failure a condition in which plasma volume is frequently increased. Although plasma volume may still be a major determinant of the intrarenal distribution of blood flow an alternate and perhaps more potent stimulus must also exist.

Recent work by Martino and Earley (20) demonstrates vasodilatation and increased intrarenal venous pressure during natriuresis. The finding of increased intrarenal venous pressure was constant during plasma loading and variable with sodium load. They noted no change in renal blood flow in relation to these changes as calculated from clearances and extraction ratios of p-aminohippurate but they did not measure distribution. Their data are compatible with mediation of natriuresis by redistribution of blood flow. Since the major portion of the renal blood flow supplies the cortex and changes in intrarenal resistance would be largely a result of changes in that area, a reduction in cortical vascular resistance (vasodilatation) could result in an increase in cortical perfusion and would be in agreement with the data presented here.

Those pathophysiologic states in which the intrarenal distribution of blood flow has been studied adequately include hemorrhagic hypotension (18), renal transplantation (21), acute renal failure (19), hepatorenal syndrome, and malignant hypertension (22). In each of these conditions, there has also been ample documentation that there is increased renin activity as well as cortical ischemia. The observation of a relationship between increased renin activity and reduced fractional renal cortical blood flow appears to be well established. It is impossible at the present time to determine which exists as cause and effect, or if both changes in renin secretion and the distribution of renal blood flow are mediated by a single common stimulus.

Thurau's hypothesis (8) suggests that the sodium concentration as sensed by the macula densa may regulate renin release. He postulates an action of renin locally causing afferent

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**FIGURE 5**

Renin blood flow and renin secretion. The diagram here represents possible relationships in the regulation of urinary sodium. A reduction in dietary sodium results in reduced plasma volume and reduced glomerular filtration rate. These changes are accompanied by a reduction in cortical renal perfusion, increase in corticomedullary perfusion, and an increase in renin activity of renal-venous blood. The renin activity of the renal venous blood and changes in the distribution of the renal blood flow vary together and appear to be interdependent. The actual mediator of these changes is not yet clearly defined.

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arteriolar constriction. Since renin is predominantly located in superficial cortical glomeruli, this could result in redistribution of blood flow mediated by renin release which is itself mediated by urinary sodium. It seems equally plausible to postulate that a reduction in plasma volume results in a reduction in glomerular filtration rate and sodium load to the macula densa as well as a redistribution of the renal flow (Fig. 5). The increase in renin activity observed in these patients may show a significant inverse relationship to the intrarenal distribution of blood flow and renin release are dependent upon a still undefined control mechanism.

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References

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