Renal Involvement Follows Cardiac Enlargement in Essential Hypertension

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• **To assess the relationship between early clinically detectable involvement of hypertensive vascular disease in heart and kidneys, we obtained systemic and renal hemodynamic and M-mode echocardiographic measurements in 65 patients with essential hypertension. The results indicate that patients with and without left ventricular hypertrophy had similar renal hemodynamic findings. In contrast, patients with altered renal hemodynamic measurements (ie, reduced renal distribution of cardiac output and, therefore, absolute renal blood flow with increased renal vascular resistance) and increased serum uric acid levels also had increased left ventricular posterior and septal wall thicknesses and mass index. Moreover, these data also demonstrated that in patients with altered renal hemodynamics, the lower the renal distribution of cardiac output and the higher the serum uric acid levels, the greater were the indexes of cardiac enlargement. These results demonstrated that the pathophysiological and hemodynamic effects of essential hypertension in the heart precede those in the kidneys.**
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Both the heart and the kidneys are target organs of hypertension. Left ventricular hypertrophy (LVH) permits adaptation to the pressure overload; ultimately, if treatment is not provided, congestive heart failure results.[1-3] Renal hemodynamic changes[4-9] with a rising serum uric acid concentration[4] are among the most prominent early signs. Most studies concerned with the effects of hypertension on target organs have been epidemiologically oriented or have focused attention on either the heart or the kidneys; there is a paucity of information relating the simultaneous effects on both organs. The present study was designed to assess simultaneously the early pathophysiological evidence of the effects of hypertension on these two major target organs in the same patient with uncomplicated essential hypertension.

PATIENTS AND METHODS

Patients

Sixty-five patients (32 men and 33 women; 34 white and 31 black) were the subjects of this study. All had uncomplicated established essential hypertension; their outpatient systolic and diastolic blood pressures were persistently above 160 and 90 mm Hg, respectively. None of the patients had elevated serum creatinine or serum urea nitrogen concentrations, and none had electrocardiographic evidence of LVH. All patients either had never received antihypertensive therapy or had discontinued their medications at least four weeks previously. In all patients, a complete medical history and physical examination and appropriate clinical laboratory evaluation failed to reveal a secondary cause for the hypertension.[10] Each patient provided written informed consent to a protocol approved by our institution's review committee.

Hemodynamic Assessment

Systemic and regional hemodynamic measurements were determined by methods previously reported in detail.[10] In brief, using the modified Seldinger procedure, the brachial artery and median antecubital vein were cannulated with polyethylene tubing. Intra-arterial and venous pressures were monitored continuously. Supine cardiac output was determined in triplicate, using indocyanine green dye (5 mg), after an overnight fast. The rate of renal plasma flow was determined from the single injection clearance of *p*-aminohippurate sodium tagged with iodine 131.[10] Renal vascular resistance was calculated by dividing the mean arterial pressure by the renal blood flow. Plasma volume was determined from the decline in plasma radioactivity 15 and 30 minutes after injection of iodinated I 125 serum albumin.[10]

Echocardiography

M-mode echocardiograms were recorded in all patients. The techniques for visualization of the left ventricle were described previously.[11,12] Measurements were made of posterior and septal wall thicknesses and systolic and diastolic dimensions.[13] From these data, the left ventricular mass index was derived.[14] Cardiac dimensions were regarded as abnormal when posterior or septal wall thicknesses were 1.2 cm or more or when left ventricular mass index was greater than 135 g/sq m.[13]

Group Criteria

To assess early physiological evidence of cardiac and renal involvement and to relate cardiac with renal function, we categorized patients according to various criteria.

Cardiac Enlargement.—The entire study group was subdivided into those individuals with and without LVH, as defined by the echocardiographic criteria described above.

Reduced Renal Distribution of Cardiac Output.—The normal ratio of renal blood flow to cardiac output is approximately 20%.[15] Therefore, patients with ratios less than 16% were grouped as having reduced renal distribution of cardiac output; levels of 16% or more were considered to be normal. No patient demonstrated clinical evidence of impaired renal excretory function; all had serum creatinine levels less than 1.7 mg/dL.

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Table 1.—Findings in Essential Hypertensives With and Without LVH*

	Men		Women	
	No LVH	LVH	No LVH	LVH
Patients, No.	15	17	24	9
Age, yr	48.5±2.6	44.7±2.2	46.0±2.5	41.2±4.2
Race, white-black ratio	9:6	9:8	11:13	5:4
Body surface area, sq m	2.02±0.05	2.06±0.04	1.84±0.03	1.90±0.07
Arterial pressure, mm Hg				
Systolic	157±5	158±6	159±5	164±6
Diastolic	94±3	93±4	89±3	94±4
Mean	115±3	114±4	112±4	116±5
Cardiac output, L/m	5.9±0.5	6.2±0.4	5.3±0.3	5.5±0.6
Cardiac index, L/min/sq m	2.8±0.1	2.8±0.1	2.9±0.1	2.9±0.1
TPR, units	21.1±1.2	20.4±0.9	22.1±0.8	20.8±1.2
TPRI, units/sq m	42.7±2.3	42.1±1.8	40.8±1.0	39.6±1.9
PW thickness, cm	0.99±0.03	1.28±0.02†	0.98±0.02	1.24±0.03‡
SW thickness, cm	1.15±0.04	1.39±0.06‡	1.10±0.02	1.24±0.05†
LVMI, g/sq m	121.8±6.9	171.1±12.7‡	118.4±5.8	153.8±8.9
RBF, mL/min	940±56	937±62	968±48	1,023±86
RVR, units	0.128±0.008	0.133±0.012	0.127±0.005	0.122±0.018
Renal distribution of cardiac output, %	17.2±0.9	16.3±0.8	17.7±0.5	18±0.9
Serum uric acid, mg/dL	7.0±0.3	7.8±0.4	5.4±0.2	5.9±0.6
Plasma volume, mL/cm	17.61±0.65	18.52±0.55	16.1±0.40	17.1±0.68

*Left ventricular hypertrophy (LVH) was defined as posterior wall (PW) thickness of 1.2 cm or more. Values are given as means ± SEs. TPR indicates total peripheral resistance; TPRI, TPR index; SW, septal wall; LVMI, left ventricular mass index; RBF, renal blood flow; and RVR, renal vascular resistance.
†$P<.02$.
‡$P<.01$.

Serum Uric Acid Concentration.—Men and women were analyzed separately because of normal differences in serum uric acid levels with respect to sex. Thus, the entire study group was subdivided according to whether the serum uric acid concentration was greater or less than 7.5 mg/dL in men or 5.5 mg/dL in women.

Statistics

Statistical comparisons were made using Student's unpaired t test, linear regression analysis, and χ^2 analysis.[16] A probability of less than 5% was considered to be statistically significant. The unpaired t test was used when variables of two different subgroups were compared. Linear regression analysis was applied to the variables in the entire patient population as well as in each subgroup, and χ^2 analysis was used to assess the difference in prevalence of LVH between subgroups.

RESULTS

Cardiac Enlargement

No differences were found between patients with and without LVH (using each cardiac mensuration criterion) with respect to age, race, body surface area, or systemic and renal hemodynamic findings. The same number of patients in each subgroup had a family history of hypertension, and the average duration of the disease was similar. When the data were analyzed for possible differences between the groups with and without LVH with respect to each of the criteria for LVH (septal wall thickness, posterior wall thickness, left ventricular mass index), the results were confirmed. Thus, only the data obtained from the groups that were divided according to the posterior wall thickness are presented in Table 1. Serum uric acid concentrations were slightly higher in the men with LVH, but this difference was not significant for the entire group (Table 1).

Renal Distribution of Cardiac Output

When the patients were classified according to whether or not they had reduced renal distribution of cardiac output to the kidney, no differences were found with respect to age, sex, race, body weight, body surface area, or systemic hemodynamic findings (Table 2). Moreover, no differences were found with respect to smoking habits, history of alcohol consumption, severity of hypertensive retinopathy, electrocardiographic findings, or serum lipid, creatinine, and urea nitrogen concentrations. However, more patients with reduced renal distribution of cardiac output had a family history of hypertension (30 vs 20 patients [$\chi^2=7.38$, $P<.01$]) and duration of hypertension greater than five years (22 vs 13 patients [$\chi^2=4.43$, $P<.05$]).

By design, renal blood flow rates were lower and renal vascular resistance was higher in the patients with reduced renal distribution of cardiac output, even though the arterial pressures in the two groups were similar ($160\pm3/91\pm2$ vs $158\pm3/93\pm2$ mm Hg). The serum uric acid concentration, which reflects renal vascular involvement in hypertension,[4] was significantly higher in the patients with reduced fractions of renal blood flow. And most noteworthy were the findings that all three cardiac measurements (ie, posterior and septal wall thicknesses and left ventricular mass index) were significantly larger in patients with reduced renal blood flow (Table 2). Furthermore, the prevalence of LVH (ie, with respect to each of the three criteria) was significantly greater in patients with reduced renal blood flow (Table 3). Significant correlations were found between the percent distribution of cardiac output to the kidneys and the posterior wall thickness ($r=.423$, $P<.05$), septal wall thickness ($r=.448$, $P<.05$), and left ventricular mass index ($r=.415$, $P<.05$) in the patients with renal hemodynamic impairment and cardiac enlargement.

The plasma volumes in patients with reduced renal distribution of cardiac output were significantly greater than in patients with normal renal distribution of cardiac output. These results were further substantiated when the men were assessed separately; their mean plasma volumes

Table 2.—Findings in Essential Hypertensives With Normal and Impaired Renal Distribution of Cardiac Output*

	Distribution	
	Normal	Impaired
Patients, No.	32	33
Age, yr	44±2	47±2
Sex, male-female ratio	17:15	15:18
Race, white-black ratio	18:14	16:17
Height, cm	170.2±1.5	169.6±1.6
Weight, kg	79.4±3.0	86.6±2.9
Body surface area, sq mm	1.89±0.04	1.97±0.04
Arterial pressure, mm Hg		
Systolic	158±3	160±3
Diastolic	93±2	91±2
Mean	115±2	114±2
TPR, units	22.0±0.8	20.7±0.9
TPRI, units/sq m	41.9±1.5	41.3±1.3
Cardiac output, L/min	5.5±0.3	5.7±0.2
Stroke volume, mL/beat	82.6±3.7	84.2±2.6
Renal distribution of cardiac output, %	19.0±0.6†	14.0±0.5
RBF, mL/min	1,020±44†	796±28
RVR, units	0.119±0.005†	0.150±0.007
Serum uric acid, mg/dL	5.9±0.3‡	7.0±0.3
Serum creatinine, mg/dL	1.10±0.02	1.17±0.03
PW thickness, cm	1.05±0.02§	1.18±0.03
SW thickness, cm	1.1±0.02†	1.3±0.04
LVMI, g/sq m	126.3±4.9‖	150.4±8.9
Plasma volume, mL/cm	16.31±0.4‡	17.9±0.4
Δ Plasma volume, %	−6.16±2.8§	6.4±2.6

*Impairment was defined as distribution of less than 16%. Values are given as means ± SEs. TPR indicates total peripheral resistance; TPRI, TPR index; RBF, renal blood flow; RVR, renal vascular resistance; PW, posterior wall; SW, septal wall; LVMI, left ventricular mass index; and Δ plasma volume, the difference from the expected normal level (15.3 mL/cm in women and 18.7 mL/cm in men[17]).

†$P<.001$.
‡$P<.02$.
§$P<.01$.
‖$P<.05$.

were 19.1±0.5 and 16.9±0.5 mL/cm in patients with reduced and normal cardiac output distribution to the kidneys, respectively ($P<.02$). Because of greater variation of plasma volume (eg, during the menstrual cycle),[17,18] these data did not achieve statistical significance in women (16.9±0.5 and 15.4±0.6 mL/cm, respectively).

When the men and women were categorized according to whether their serum uric acid concentrations were greater or less than 7.5 or 5.5 mg/dL, respectively, significant differences were revealed (Table 4). Thus, patients of both sexes with higher uric acid concentrations had significantly greater cardiac enlargement. In addition, the women with higher uric acid levels also had significantly lower renal blood flow rates and higher renal vascular resistances (Table 4). This difference was not found in the men, although the data reflected lower renal blood flows in those patients with higher uric acid levels. Moreover, in both sexes, significant correlations were obtained between the serum uric acid concentration and cardiac dimensions: posterior wall thickness ($r=.415$, $P<.05$), septal wall thickness ($r=.420$, $P<.05$), and left ventricular mass index ($r=.438$, $P<.05$).

Table 3.—Cardiac Hypertrophy in Essential Hypertensives With Normal and Impaired Renal Distribution of Cardiac Output*

	Distribution			
	Normal	Impaired	χ^2	$P<$
Patients with PW thickness≥1.2 cm	8	18	5.9090	.025
Patients with SW thickness>1.2 cm	12	24	8.1590	.005
Patients with LVMI>135 g/sq m	11	21	5.3968	.025

*Impairment was defined as distribution of less than 16%. PW indicates posterior wall; SW, septal wall; and LVMI, left ventricular mass index.

COMMENT

The heart and the kidneys are two of the three major target organs affected by hypertension. With early organ involvement, patients usually are asymptomatic, and there is no clinical evidence of cardiac or renal functional impairment. However, during this asymptomatic phase, structural and physiological changes develop in these organs, and, therefore, it is important to identify the early clinical findings that can point toward early detection of target organ involvement.[3,4,12]

As hypertensive vascular disease progresses, total peripheral resistance increases, and with it left ventricular afterload.[1-3] The left ventricle adapts to this increasing afterload by concentric hypertrophy, the earliest clinical evidence of which is left atrial enlargement (disclosed by electrocardiography) and the atrial diastolic gallop rhythm (fourth heart sound).[1-3,11,12,19,20] The hemodynamic changes in the kidney include increased renal vascular resistance, decreased renal blood flow, and, ultimately, development of nephrosclerosis and renal failure.[4-9] An elevated serum uric acid concentration is found in uncomplicated essential hypertension and correlates with the two former hemodynamic indexes.[4]

Although these pathophysiological developments in the heart and kidneys are well established, there is a paucity of information about their coexistence and about whether one organ involvement may precede development of the other. The results of the present study indicate that these patients with uncomplicated essential hypertension, with or without echocardiographically demonstrable LVH, have similar renal hemodynamic findings. However, once renal hemodynamic function is altered (ie, once renal blood flow is slightly reduced and renal vascular resistance is increased), the left ventricular mass and wall thickness are already demonstrably greater than in patients with the same arterial pressure but with normal renal hemodynamic findings.

Some of the patients with uncomplicated essential hypertension reported herein had been treated in the past with antihypertensive agents that may have reduced their cardiac mass. This possibility only serves to reinforce the foregoing observation, since the renal hemodynamic findings were similar in the groups with and without cardiac enlargement and the degree of cardiac enlargement would only have been greater without antihypertensive therapy.

Reduced renal blood flow in hypertensive patients is among the earliest renal hemodynamic changes.[4-9] The absolute rate of renal blood flow associated with these changes depends on a variety of factors, including the age, race, and sex of the patient as well as renal mass and systemic hemodynamics. As a result, serial measurements in the same individual are necessary in order to assess

Table 4.—Findings in Essential Hypertensives With Normal and Elevated Levels of Serum Uric Acid*

	Men		Women	
	<7.5	≥7.5	<5.5	≥5.5
Patients, No.	17	15	17	16
Age, yr	45.9±2.6	47.7±2.3	43.5±2.6	49.8±2.6
Race, white-black ratio	10:7	9:6	7:10	8:8
Weight, kg	85.6±2.8	90.7±3.1	77.0±3.2	83.4±3.5
Body surface area, sq m	1.99±0.03	1.95±0.03	1.80±0.03	1.89±0.03
Arterial pressure, mm Hg				
Systolic	160±6	156±5	158±4	162±5
Diastolic	95±4	92±4	92±9	89±3
Mean	117±4	114±4	114±2	113±3
Cardiac output, L/min	5.6±0.2	5.1±0.2	5.8±0.2†	5.0±0.2
Cardiac index, L/min/sq m	2.80±0.12	2.63±0.09	3.2±0.2‡	2.6±0.1
TPR, units	22.0±0.9	21.5±1.0	21.6±1.0	22.3±1.1
TPRI, units/sq m	43.8±2.0	42.0±1.8	38.8±2.2	42.2±1.2
RBF, mL/min	970±71	844±36	1,000±61‡	780±51
RVR, units	0.141±0.012	0.125±0.009	0.119±0.007‡	0.154±0.01
Renal distribution of cardiac output, %	17.6±1.1	15.6±0.8	17.4±1.1§	14.9±0.7
Serum uric acid, mg/dL	6.4±0.16‖	8.7±0.22	4.4±0.18‖	6.8±0.13
PW thickness, cm	1.08±0.04§	1.22±0.04	0.98±0.03†	1.10±0.03
SW thickness, cm	1.17±0.05†	1.39±0.07	1.05±0.03‡	1.23±0.05
LVMI, g/sq m	131.8±7.6§	168.5±15.9	122.2±7.0	134.2±7.0

*Elevation was defined as levels of at least 7.5 mg/dL in men and 5.5 mg/dL in women. Values are given as means±SEs. TPR indicates total peripheral resistance; TPRI, TPR index; RBF, renal blood flow; RVR, renal vascular resistance; PW, posterior wall; SW, septal wall; and LVMI, left ventricular mass index.
†$P<.02$.
‡$P<.01$.
§$P<.05$.
‖$P<.001$.

changes in renal blood flow as disease progresses. However, this is neither feasible nor ethical. For this reason, we chose to classify our patients on the basis of renal distribution of cardiac output.

As might be expected, those patients with reduced renal distribution of cardiac output had significantly lesser renal blood flow and higher renal vascular resistances. Furthermore, they also had significantly larger and thicker left ventricular chambers than those with no renal hemodynamic impairment. Thus, even though both groups of patients with uncomplicated essential hypertension had similar levels of arterial pressure and total peripheral resistance, their target organ involvement was different. One explanation might be differences with respect to family history and duration of hypertension. Indeed, this seemed to hold true; more patients in the subgroup with lower renal blood flow rates and LVH had family histories and relatively long personal histories of hypertension, lending further credence to the notion that the duration of hypertension and genetic predisposition are important factors.

Reduced distribution of cardiac output to the kidneys was associated with greater circulating plasma volumes and higher serum uric acid concentrations. Previous studies from our laboratory have shown that increased arterial pressure was associated with contracted plasma volume in men with essential hypertension and normal renal hemodynamic findings.[18,21,22] In contrast, patients with parenchymal disease and hypertension, primary aldosteronism, or with low-renin essential hypertension may have volume-dependent hypertension.[23,24] The present study suggests that patients with uncomplicated essential hypertension but with reduced renal distribution of cardiac output may have a more volume-dependent form of hypertension.

Hyperuricemia has long been known to be a frequent finding in untreated patients with uncomplicated essential hypertension unassociated with a personal or family history of gout.[25-29] As indicated above, we recently reported that serum uric acid concentration increases in patients with uncomplicated essential hypertension and is associated with early renal hemodynamic involvement from hypertensive vascular disease.[4] Thus, the higher the serum uric acid levels in these patients with essential hypertension and normal renal excretory function (and normal-size hearts), the lower the renal blood flow rate and the renal vascular resistance. These findings relating serum uric acid levels to intrarenal hemodynamic alterations supported earlier observations of rises in serum uric acid concentration in normotensive subjects during infusions of pressor doses of norepinephrine or angiotensin II.[30] In these normal volunteer subjects, as arterial pressure and the uric acid level rose, glomerular filtration rates remained unchanged as renal plasma flow and urate excretion declined. Then, with cessation of these pressor infusions, as arterial pressure and renal plasma flow returned to normal levels, so did urate excretion and the serum uric acid concentration. The data from these two studies[4,30] strongly suggest that the serum uric acid level reflects not only alterations in purine metabolism or in renal parenchymal functions mediating tubular urate excretion but also intrarenal hemodynamic function.

The present data further strengthen that concept: reduced renal fractions of cardiac output were associated with higher concentrations of uric acid. Moreover, when our patients were classified according to their uric acid levels, regardless of renal hemodynamic values, those with higher serum uric acid concentrations had larger left ventricles. These findings add further support to the concept that the first evidence of renal involvement is an increasing serum

uric acid concentration and that the renal distribution of cardiac output falls as renal hemodynamic involvement progresses.

We therefore conclude that renal involvement in essential hypertension is usually preceded by cardiac enlargement and that an increasing serum uric acid level may be an early sign of renal involvement in patients with essential hypertension, which is later followed by a reduction in the renal distribution of cardiac output.

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CORRECTION

Incorrect Data.—In an article titled "Time and Financial Analysis of an Academic General Internal Medicine Unit," published in the November 1985 ARCHIVES (1985;145:2093-2097), errors appeared in the key to Fig 2. "Inpatient: Consults (Direct Care)" should have been indicated by the top dotted bar, and "Inpatient: Medical Service (Direct Care)" should have been indicated by the solid dark bar.