Renal and Systemic Hemodynamics in Sustained Essential Hypertension

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SUMMARY Cardiac output (CO), renal blood flow (RBF), calf blood flow (CBF), and hepatic blood flow (HBF), glomerular filtration rate (GFR), and dopamine beta hydroxylase (DβH) activity were studied in 198 men (67 normotensive controls and 131 hypertensive patients) of the same age with sustained uncomplicated essential hypertension. In the hypertensive men, the RBF and the RBF/CO ratio were significantly decreased (p < 0.001). The RBF and RBF/CO ratio were negatively correlated with age (p < 0.01), blood pressure (p < 0.01), and DβH activity (p < 0.01). None of these relationships were observed with CBF and HBF. The observed decreases in RBF and the RBF/CO ratio in hypertensive men were reversed after administration of clonidine and alpha-methyldopa (p < 0.01), but not after administration of propranolol. The study provides evidence that the reduction of renal perfusion in essential hypertension is partly reversible and related to an abnormality in the adrenergic system control. (Hypertension 6: 743-754, 1984)

KEY WORDS • renal perfusion • dopamine beta-hydroxylase • renal blood flow • renal plasma flow • glomerular filtration rate • cardiac output • adrenergic system

The most characteristic pattern of renal dysfunction reported in essential hypertension consists of reduced renal plasma flow (RPF). The glomerular filtration rate (GFR) is reported to be normal or decreased proportionately less than RPF, which results in an increase in filtration fraction (FF). In malignant hypertension, GFR and RPF are seriously impaired, while in mild-to-benign hypertension, GFR is usually normal. Renal blood flow (RBF) and RPF are reported to vary from decreased flow to normal flow and even to increased flow, according to the definition of the severity of the essential hypertension. There is disagreement regarding a possible correlation between the severity of hypertension as shown by the level of arterial blood pressure and RBF. Some authors report an inverse relationship between blood pressure level and RBF in both benign and malignant hypertension. Others claim no correlation between arterial pressure and kidney hemodynamics.

Discrepancies also exist concerning the influence of aging on renal function both in normal subjects and in hypertensive patients.

Most investigations of renal hemodynamics have been cross-sectional studies. These studies require stable, homogeneous populations with precisely defined clinical and experimental conditions in order to compare two or more populations with respect to the function studied. The difficulty in comparing results and the discrepancies that often exist have probably been due to differences among the various populations. Some populations have not been matched for size or age nor have they been representative of the age distribution of the particular society; some had more or fewer young or elderly subjects than the population as a whole.

Kidney function is closely related to sodium and water balance, and any study of renal hemodynamics should be determined under conditions of precisely defined sodium balance and extracellular fluid volume. This point is of importance in populations of both sexes since women experience cyclic changes of hormonal function that influence sodium and fluid volume regulation. Finally, several hypertension studies have included some subjects with various degrees of renal insufficiency. In these cases it is questionable to use clearance of substances that depend on tubular function as an index of RBF in the absence of determining the renal extraction of these substances. Furthermore, in the analysis of human renal hemodynamics, three important considerations are frequently
neglected. First, it is necessary to distinguish between RPF and RBF, since different results are achieved according to variations in hematocrit and the relationship between hematocrit and age. Second, it is necessary to use an adequate frame of reference for the normalization of RBF. Use of body surface area (BSA) interferes greatly in the estimation of RPF and GFR as a function of sex, race, and body weight. Third, it is necessary to interpret renal hemodynamic functions with regard to the central hemodynamic status, especially cardiac output (CO).

The purpose of this study was to: 1) analyze characteristics of the renal circulation in a homogeneous male population with sustained essential hypertension and to compare these characteristics with those of a normotensive population of the same age; 2) analyze the renal hemodynamic parameters as functions of CO; 3) compare renal hemodynamics in the two populations with those of other regional circulations; and 4) study the relationship between renal hemodynamics and some neurohumoral parameters such as plasma renin activity (PRA) and dopamine β-hydroxylase (D/βH) activity.

Methods

Subjects

The study group was composed of 198 white men, 67 normotensive controls, and 131 patients with sustained essential hypertension of similar age (36.5 ± 1 years vs 38.9 ± 1 years) (mean values ± SEM). Hypertensive patients were heavier (76.5 ± 1 kg than normotensive controls (71 ± 1 kg) (p < 0.01). All patients were untreated or had discontinued their treatments at least 4 weeks prior to the study. They were hospitalized for 6 days and placed on a 100 mEq/day sodium diet. From Days 3 to 6 it was verified, on the basis of weight, sodium intake, and urinary output, that steady state sodium balance was achieved.

For inclusion into the study the following criteria were defined: absence of a past history of renal disease, absence of proteinuria determined by a 24-hour urine sample, normal Addis count, normal timed intra-

venous pyelography, and a plasma creatinine level lower than 140 /umol/liter (1.6 mg/dl). Patients were classified on the basis of outpatient blood pressure determinations. The subjects were considered normotensive if their blood pressure levels (measured with a mercury sphygmomanometer of an adapted cuff size) were constantly lower than 140 mm Hg systolic and 90 mm Hg diastolic and if the reason for their admission was not because of a cardiovascular disease. Clinical and extensive laboratory investigations had to show strictly normal results.

Systemic hypertension was documented in all patients by an average of three successive measurements of supine diastolic blood pressure equal to or above 100 mm Hg (measured with a mercury sphygmonanometer and according to disappearance of Korotkoff Phase V sounds) on at least two separate outpatient visits. All patients in this study had sustained essential hypertension, with a diastolic pressure constantly equal to or above 100 mm Hg on the 3rd day of hospitalization. Extensive investigations included the determinations of blood and urinary electrolytes, blood sugar, urinary catecholamines level, endogenous creatinine clearance, timed intravenous pyelography, chest rentgenogram, electrocardiogram, and optic fundus evaluation. In all cases, the known duration of hypertension was less than 5 years. Mean creatinine clearance was (71.3 ± 1.1 ml/min/m²) in hypertensive patients and (70.7 ± 1.0 ml/min/m²) in the control group. Fundoscopy showed neither hemorrhages, exudates, nor papilledema. No patient had clinical cardiac or neurological involvement. Moderate left ventricular hypertrophy, assessed by standard criteria, was present in 34 hypertensive patients.

Protocol

The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM). Consent was obtained from all patients after a detailed description of the procedure. The study was carried out on 4th day of hospitalization with the patients off all medication. The patients fasted overnight and at 8 a.m. received 10 ml of water per kg of body weight for hydration. An antecubital vein of each arm was catheterized for blood sampling and injection. All studies were performed on subjects in the supine position. Blood samples for sodium, potassium, plasma creatinine, plasma protein concentration, and hematocrit were taken at 10 a.m. together with blood samples for hormonal studies. Analyses were done by an automatic system of chemical analysis.

All 67 normal control subjects and 131 hypertensive patients underwent a central hemodynamic study and a measure of RBF; 50 normal controls and 100 hypertensives also had tests to determine inulin clearance for estimation of GFR. In these patients, the study started with the determination of CO, followed by the measurement of inulin clearance. The RBF was estimated between the 75th and 105th minute of the inulin clearance measurement. The 18 normal control subjects and 20 hypertensive patients had, simultaneously with CO measurements at least 4 weeks prior to the study. They were untreated or had discontinued their treatments also had tests to determine inulin clearance for estimation of GFR. In these patients, the study started with the determination of CO, followed by the measurement of inulin clearance. The RBF was estimated between the 75th and 105th minute of the inulin clearance measurement.
and RBF measurements, an estimation of hepatic blood flow. In these 38 subjects, the GFR was not measured. Venous occlusion plethysmography for calf-blood flow (CBF) estimation was done in 36 normotensive subjects and 59 hypertensive patients after the CO determination.

Hemodynamic Studies

The CO was measured three times by dye dilution technique with the use of indocyanine green dye.22 The results were expressed in ml/min or in ml/min/m² (cardiac index) after correction for BSA. Dye-dilution curves were measured planimetrically. Arterial pressure was recorded with a Siemens apparatus (Oscillog-mink).

Renal Hemodynamic Indices

Glomerular Filtration Rate. The GFR was estimated from the total inulin clearance determined simultaneously with the inulin space26 as described previously.23 The inulin space method was derived from the theory of Meier and Zierler28 for flow and volume estimations with the use of tracer injection techniques. Inulin was measured by the method of Roe et al.24 Inulin clearance was corrected for the plasma water content10 and expressed in ml/min.

Renal Blood Flow: The RPF was measured by 112 Hippuran clearance (20/15Ci) by means of a single injection.11 Calculations were made by using the one-compartment model.12 As previously shown, the bolus infusion technique resulted in a slight overestimation of the standard clearance, which requires blood and urinary collections.11 The RBF was estimated from RPF and systemic hematocrit. The FF was expressed as the GFR/RPF ratio.

Hepatic Blood Flow

Hepatic blood flow (HBF) was determined in 18 normal subjects and 20 hypertensive patients. In a previous study in which we catheterized hepatic veins in men,13 we showed that the hepatic extraction of D-propranolol, a substance without pharmacological effects, was 79% ± 2%. In the same investigation the D-propranolol clearance was demonstrated to be equal to the HBF measured by the indocyanine green technique. In the present investigation, D-propranolol clearance was used to estimate HBF. A bolus dose of D-propranolol (0.2 mg/kg) was administered intravenously in 30 seconds. Blood samples were taken before and 5, 10, 15, 20, 30, 60, 120 and 180 minutes after propranolol administration. Propranolol was measured fluorimetrically as described by Shand et al.15 The D-propranolol clearance was calculated from the disappearance curve of D-propranolol by using a one-compartment model. The HBF was expressed in ml/min and normalized to BSA.

Calf Blood Flow

In 36 normotensive control subjects and 59 hypertensive patients, the CBF was measured three times at 5-minute intervals by venous occlusion plethysmography with a strain gauge plethysmography, as previously described.16,17 and expressed as ml/min/100 g of tissue.

Hormone Study

Hormone study was performed at 10 a.m. after the subjects had rested supine for 120 minutes. Blood for renin and aldosterone determinations was drawn into chilled tubes of ethylenediaminetetraacetic acid (EDTA) which were kept on ice until the samples could be centrifuged and the plasma frozen at —30° C. The PRA was determined by radioimmunoassay (RIA),19 with the results expressed in nanograms of angiotensin I (ANG I) generated per liter of plasma per minute (ng/liter/min). Plasma aldosterone concentration was determined by RIA,18 and the results were expressed as picograms per ml of plasma (pg/ml). Blood for plasma D8H determinations was drawn into chilled heparin tubes and kept on ice until the samples were centrifuged and the plasma frozen at -30° C for assay. Enzymatic activity was determined spectrophotometrically,19 with the results expressed as international units (IU)/liter of plasma (IU/liter), where 1 IU was equal to 1 ixmo® of octopamine formed from tyramine per minute at 37° C.

Effects of Adrenergic Blocking Drugs on Renal and Central Hemodynamics

A second series of central and renal hemodynamic tests was carried out in 37 patients after 7 days of treatment with one of the following drugs, given orally in monotherapy: 10 patients received clonidine (7.65 ± 0.7/Mg/kg/day); 15 patients received alpha-methyl-dopa(12.1 ± 1 mg/kg/day); and 12 patients received propranolol (1.15 ± 1.5 mg/kg/day). Treatments were started on Day 5 of hospitalization while the patients continued to receive 100 mEq/day of a sodium diet. The drugs were given orally and were progressively increased to obtain a decrease in arterial pressure of 25 mm Hg or more for systolic and 15 mm Hg or more for diastolic. Propranolol was adjusted to maintain a supine heart rate of between 55 and 60 bpm.

Statistics

Results are expressed as means ± SEM. Student’s t test determined the significance of differences between normotensive controls and hypertensive patients. Correlations were performed by linear least-squares regression analysis. Partial correlations coefficients were calculated according to standard statistical methods.20 For therapeutic trial, the Wilcoxon’s rank sum test for paired data was used; p values of less than 0.05 were accepted as being significant.

Results

Mean Values Study

Patient Characteristics

The age of the hypertensive subjects was similar to that of the control subjects: 36.5 ± 1 vs 38.9 ± 1 years (Table I). The weight and BSA of the hyperten-
Subjects and Patients with Sustained Essential Hypertension

TABLE 1. Clinical and Humoral Parameters of Normotensive Subjects and Patients with Sustained Essential Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensives</th>
<th>Hypertensives</th>
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<tbody>
<tr>
<td>Number</td>
<td>67</td>
<td>131</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>36.5±1</td>
<td>38 ±4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71±1</td>
<td>76.5±1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 1</td>
<td>171 ± 1</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.83±0.02</td>
<td>1.89 ±0.01</td>
</tr>
<tr>
<td>Plasma creatinine* (½mol/liter)</td>
<td>92.1 ±2</td>
<td>94.3±2</td>
</tr>
<tr>
<td>Plasma sodium (½mol/liter)</td>
<td>141 ±0.3</td>
<td>141 ±0.2</td>
</tr>
<tr>
<td>Plasma potassium (½mol/liter)</td>
<td>4.2±0.04</td>
<td>4.1±0.05</td>
</tr>
<tr>
<td>Plasma proteins (g/liter)</td>
<td>70±1</td>
<td>71±1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43 ±1</td>
<td>44 ±1</td>
</tr>
<tr>
<td>Urinary sodium output (mmol/day)</td>
<td>87±3</td>
<td>84±2</td>
</tr>
<tr>
<td>Urinary potassium output (mmol/day)</td>
<td>53±3</td>
<td>57±3</td>
</tr>
</tbody>
</table>

Dopamine β-hydroxylase (IU/liter) 15.3±4.1 19±1.25
Plasma renin activity: (ng/liter/min) 85.1±7.6 70.8±6
Plasma aldosterone (pg/ml) 97.9±1.16 116±13

Values are means ± SEM. * p < 0.05.

The number of subjects for dopamine β-hydroxylase = 38 normotensives, 131 hypertensives, for plasma renin activity = 46 normotensives, 76 hypertensives; and for plasma aldosterone = 34 normotensives, 58 hypertensives.

TABLE 2. Central Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensives</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>131±1</td>
<td>192±2</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>76±4</td>
<td>110±1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94±1</td>
<td>138±1</td>
</tr>
<tr>
<td>CI (ml/min/m²)</td>
<td>3670±62</td>
<td>3450±58*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>74±1</td>
<td>76±1</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>50±1</td>
<td>46±1</td>
</tr>
<tr>
<td>TPR (dyne/sec/cm²/m²)</td>
<td>2150±44</td>
<td>3370±71</td>
</tr>
</tbody>
</table>

Values are means ± SEM. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure, CI = cardiac index, HR = heart rate; SI = stroke index; TPR = total peripheral resistance; TBV = total blood volume.

Central Hemodynamic Determinations

Systolic, diastolic, and mean arterial blood pressures were significantly increased in the hypertensive patients (p < 0.001), but the CO was similar in both groups (normotensive group, 6689 ± 128 ml/min; hypertensive group, 6542 ± 104 ml/min). Cardiac index of normotensive patients was slightly higher (3650 ± 62 ml/min/m²) than the mean value observed in hypertensive patients (3450 ± 58 ml/min/m²) (p < 0.05) (Table 2). The heart rate was similar in the two groups, as was stroke volume (SV): (SV in normotensive group, 91.6 ± 2 ml; in hypertensive group, 87.1 ± 1.8 ml). The stroke index of the normotensive subjects was significantly higher than the value observed in the hypertensive patients (50 ± 1 ml/m² vs 46 ± 1 ml/m²; p < 0.01). In hypertensive patients, the total peripheral resistance (TPR) was significantly increased (p < 0.001).

Regional Hemodynamic Determinations

Renal Blood Flow. The RBF and RPF differed significantly in the two groups. The RBF in normotensive subjects was 1626 ± 43 ml/min compared to 1411 ± 39 ml/min in hypertensive patients (p < 0.001). Similar differences were observed for RPF: 927 ± 24 ml/min in normotensive controls vs 795 ± 20 ml/min in hypertensive patients (p < 0.001). A positive correlation existed between the RBF and BSA (Figure 1). Renal vascular resistances (RVR) were significantly reduced in hypertensive patients. Distribution of the RBF was unimodal in normotensive as well as hypertensive subjects (Figure 2). Renal vascular resistances (RVR) was significantly increased in hypertensive patients (8401 ± 95 vs 14907 ± 229 dynes-sec-cm²/m²; p < 0.001).

The renal fraction of the CO (RBF/CO) was significantly lower in hypertensive patients (21.7 ± 0.5%) than in normal controls (24.5% ± 0.6%; p < 0.001) (Table 3).

Glomerular Filtration Rate. The GFR (ml/min) was similar in normotensive subjects (143 ± 3 ml/min) and hypertensive subjects (138 ± 3 ml/min). When re-
FIGURE 1. Relationship between body surface area and renal blood flow: Left: Normotensive subjects. Right: Hypertensive patients: the dotted line represents the mean regression line of the normotensive population.

FIGURE 2. Distribution frequency of the renal blood flow in normotensive and hypertensive subjects.
ferred to the BSA, the GFR of the control subjects was slightly higher than that of the hypertensive patients (77 ± 2 ml/min/m² vs 73 ± 2 ml/min/m²; p < 0.05). The FF was increased in hypertensive patients (18% ± 0.4%) as compared to the control subjects (15.5 ± 0.4; p < 0.001).

Hepatic Blood Flow and Calf Blood Flow. In contrast with RBF, the HBF was similar in hypertensive patients and normotensive subjects. Also, the hepatic fraction of the CO (HBF/CO), the CBF, and CBF/CO were identical in the two groups.

Effects of Adrenergic Blocking Drugs on Central and Renal Hemodynamics. In the three subgroups of patients, a similar significant (p < 0.01) decrease in blood pressure was observed. The CO was unchanged with clonidine, but RBF (p < 0.05) and RBF/CO (p < 0.01) increased. Endogenous creatinine clearance did not change, and the FF fell significantly (p < 0.01). The TPR fell by 12.9% ± 5.3%, and RVR fell by 32.1% ± 4%. Alpha-methyldopa did not produce any change in CO, but it increased significantly both the RBF (p < 0.05) and RBF/CO (p < 0.02). Creatinine clearance did not change, and FF decreased (p < 0.05). The TPR fell by 16.1% ± 4.1%, and RVR fell by 28.7% ± 6.3%. Propranolol did not produce any significant change in the central or renal hemodynamic parameters (Table 4).

Correlation Study
Normotensive Subjects

In normotensive subjects, the RBF and the RPF were negatively correlated with age (Figure 3) (p < 0.001). The correlation of RPF with age was weaker (r = -0.25; p < 0.05) than that of RBF (r = -0.40; p < 0.001). A negative correlation between age and hematocrit (r = -0.28; p < 0.02) was observed in normal patients. Age and CO were negatively correlated in normotensive patients (r = -0.38; p < 0.01).

No significant correlation was observed between RBF/CO and age (Figure 4). The RBF was significantly and positively correlated with CO (r = 0.40; p < 0.001) (Figure 5). The RBF and RBF/CO in normotensive controls did not correlate with either systolic or diastolic pressure. Also, the RBF, RPF, and RBF/CO did not correlate with PRA (r = -0.10; NS). The RBF correlated negatively with D/3H activity (β = -0.32; p < 0.05), but D/3H activity was also positively correlated with age (r = 0.50; p < 0.01). Studied for a constant age (partial coefficient study), the correlation between RBF and D/3H activity was not significant (r = -0.24; NS).

In normotensive subjects, the GFR was positively and strongly correlated with RPF (r = 0.68; p < 0.001) (Figure 6) and significantly correlated with age and CO, but these two correlations disappeared when RPF was constant. The FF increased with age in normal controls (r = 0.25; p < 0.05).

Hypertensive Patients

In patients with essential hypertension, the RBF was negatively correlated with age (r = -0.40; p < 0.001) (Figure 3). The slope of the regression was significantly steeper than in normal controls (p < 0.001). The RPF was negatively correlated with age (r = -0.32; p < 0.001). The correlation coefficient of the age/RPF relationship was weaker than the coefficient of the age/RBF relationship. There was a negative correlation between age and hematocrit in hypertensive patients (r = -0.23; p < 0.02). For a constant blood pressure (partial correlation coefficients), there was a negative relationship between age and RBF (r = -0.28; p < 0.01). The RBF was positively correlated with CO (Figure 5) (p < 0.001). Comparison of hypertensive patients with normotensive subjects showed that the relationship between RBF and CO was significantly reset (p < 0.001). For any level of CO, the RBF

<table>
<thead>
<tr>
<th>MAP (mm-Hg)</th>
<th>CO (ml/min/m²)</th>
<th>TPR (dynes sec-cm⁻²)</th>
<th>RBF (ml/min/m²)</th>
<th>RVR (dynes sec cm⁻²)</th>
<th>RBF/CO (%)</th>
<th>GFR (ml/min/m²)</th>
<th>FF (%)</th>
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<tbody>
<tr>
<td>Clonidine (n = 10)</td>
<td></td>
<td></td>
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<tr>
<td>Before</td>
<td>134±3.4</td>
<td>6443±300</td>
<td>1643±131</td>
<td>1415±79</td>
<td>7593±597</td>
<td>22.2±14</td>
<td>105.7±2.6</td>
</tr>
<tr>
<td>After</td>
<td>104±5.3</td>
<td>5816±481</td>
<td>1421±92</td>
<td>1619±121</td>
<td>5127±402</td>
<td>28.3±1.7</td>
<td>102.1±2.1</td>
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<tr>
<td>p</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
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<tr>
<td>Alpha methyldopa (n = 15)</td>
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<tr>
<td>Before</td>
<td>137±4.9</td>
<td>6410±337</td>
<td>1712±124</td>
<td>1317±82</td>
<td>8317±667</td>
<td>20±7</td>
<td>105±5.4</td>
</tr>
<tr>
<td>After</td>
<td>110±3.3</td>
<td>6109±237</td>
<td>1436±79</td>
<td>1477±96</td>
<td>5944±437</td>
<td>24.6±1.7</td>
<td>103.5±5.4</td>
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<tr>
<td>p</td>
<td>&lt;0.01</td>
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<td>Propranolol (n = 12)</td>
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<tr>
<td>Before</td>
<td>140±5.4</td>
<td>6222±406</td>
<td>1788±142</td>
<td>1481±120</td>
<td>7579±681</td>
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<td>107.2±5.8</td>
</tr>
<tr>
<td>After</td>
<td>128±6.9</td>
<td>5528±374</td>
<td>1857±151</td>
<td>1313±110</td>
<td>7805±700</td>
<td>24.1±1.4</td>
<td>102.2±5.3</td>
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<tr>
<td>p</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

GFR = endogenous creatinine clearance; MAP = mean arterial pressure; CO = cardiac output; TPR = total peripheral resistances; RBF = renal blood flow; RVR = renal vascular resistances; GFR = glomerular filtration rate; FF = filtration fraction; NS = nonsignificant.
FIGURE 3. Relationship between renal blood flow and age. Left: Normotensive subjects. Right: Hypertensive patients: the dotted line represents the mean regression line of the normotensive population.

FIGURE 5. Relationship between cardiac index and renal blood flow. Left: Normotensive subjects. Right: Hypertensive patients; the dotted line represents the mean regression line of the normotensive group.

FIGURE 6. Relationships between renal plasma flow and glomerular filtration rate. Left: Normotensive subjects. Right: Hypertensive patients; the dotted line represents the mean regression line of the normotensive group.
Discussion

Since many metabolic functions have a close correlation with body weight or BSA, it has become customary to relate hemodynamic functions to BSA.\textsuperscript{21} This relationship was verified in our present study and was the reason for referring renal hemodynamic indices to square meter surface area (Figure 1). But this procedure of normalization is not free from criticism. The relationships of indices such as BSF and RBF are not necessarily the same in every population. The slope or the intercept of this function can be different between normotensive and hypertensive subjects, as illustrated in Figure 1. In normal subjects, the relationship also differs between men and women. In women, RBF is lower than in men, even when normalized to BSA.\textsuperscript{21, 41, 42} Moreover, a reference to body size can be used easily in normal men, but can be confusing in certain pathological states. For instance, in patients with sustained essential hypertension, body weight and consequently the BSA are frequently increased,\textsuperscript{43} which contributes possibly to the development and maintenance of hypertension and associated hemodynamic disorders.\textsuperscript{44-46} In such cases, the reference of RBF to body weight or BSA must be questioned. For these reasons, it is necessary to introduce another reference constant for RBF normalization. In the present study, in both normotensive subjects and hypertensive patients, the RBF was positively correlated to CO, and the ratio between RBF and CO could be used as an adequate index of renal perfusion.

From analysis of the values of RBF normalized to BSA, it is obvious that a large proportion of hypertensive patients have a normal RBF value (Figure 2), especially younger patients (Figure 3). It should be concluded, therefore, that hypertension is not associated with a reduction in RBF in many hypertensive patients.\textsuperscript{2, 7} Figure 5 shows that such an interpretation is questionable, since a significant reset existed in the relationship between CO and RBF in the hypertensive patients; for a given CO the RBF flow was lower. In particular, normal RBF was related to elevated values of CO. The reduction of the RBF/CO ratio in the overall hypertensive population indicates clearly that essential hypertension is associated with renal "ischemia." This fact is also emphasized by the study of blood flow in other vascular beds (Table 3). The HBF and CBF were similar in the normotensive subjects. The hepatic fraction of the CO and the ratio between CBF and CO were also similar.

The reset of the RBF/CO relationship means that intrarenal vascular resistance is increased. Since the GFR was strongly correlated with RBF and since no differences existed between the GFR and RPF relationship in the normal and hypertensive subjects (Figure 6), we can conclude that the increased intrarenal resistance in essential hypertension was preglobular in origin, as observed in animal models.\textsuperscript{46, 47}

In agreement with many authors,\textsuperscript{5, 10, 49, 51} our results confirm the participation of kidneys in the aging process, both in normal subjects and in hypertensive patients (Figure 3). The age-related decline in RBF was lower in hypertensive patients. The effect of CO on RBF was maintained independently of age and blood pressure (p < 0.001). Age and CO were negatively correlated in hypertensive patients (r = -0.38; p < 0.001). Also in hypertensive patients, the RBF was negatively correlated with age in hypertensive patients (r = -0.41; p < 0.01) and with diastolic pressure (r = -0.20; p < 0.02). The relationship between systolic blood pressure and RBF existed even for a constant age (partial correlation coefficient) (r = -0.32; p < 0.001).

From the humoral factors studied, RBF was negatively correlated to the plasma D\textsubscript{3}H activity (Figure 7) (r = -0.38; p < 0.001). The D\textsubscript{3}H activity was positively correlated with age in hypertensive patients (r = 0.28; p < 0.01). Correlation between RBF and D\textsubscript{3}H activity persisted even for a constant age (r = -0.26; p < 0.01). The renal fraction of CO was negatively correlated with age (p < 0.001) (Figure 4), systolic pressure (r = -0.37; p < 0.001), diastolic pressure (r = -0.20; p < 0.02), and D\textsubscript{3}H activity (r = -0.33; p < 0.001). In hypertensive patients, the GFR was strongly correlated with RPF (r = 0.71; p < 0.0001). Neither the slope nor the intercept of the RPF/GFR correlation differed between hypertensive and normotensive subjects (Figure 6).

The FF was positively correlated with age (r = 0.38; p < 0.01) and with blood pressure in hypertensive patients (r = 0.57 for systolic pressure and r = 0.45 for diastolic). The significance of these correlations disappeared for a constant RPF (partial correlation coefficient study). In hypertensive patients, CBF and HBF were not correlated with age and blood pressure. The D\textsubscript{3}H activity was not related to CBF or HBF in hypertensive patients. The HBF/CO and the CBF/CO were independent from the hemodynamic parameters studied from D\textsubscript{3}H activity.
accelerated in hypertensive patients and confirms the findings of previous reports.\(^{5,6}\) Nevertheless, a closer analysis indicates that the negative relationship between RBF and age did not have the same meaning in the normotensive and hypertensive patients. In the normotensive subjects, a negative correlation existed between age and RBF and between age and CO. The decline of RBF was proportional to the decrease in CO, and the renal fraction of CO remained unchanged during aging (Figure 4). In the hypertensive patients, age was also negatively correlated with CO, but the age-related decline in RBF was more pronounced than the decrease of CO and resulted in a negative correlation between age and the renal fraction of CO (Figure 4).

The role of the sympathetic nervous system and catecholamines in causing renal vasoconstriction in essential hypertensive patients has been emphasized.\(^{12,13,54,55}\) The negative correlations between renal perfusion indices and plasma D/3H activity in our present study are in agreement with this viewpoint, but deserve several comments. The D/3H activity is not considered a precise index of sympathetic activity for at least two reasons: 1) D/3H activity in the plasma also depends on genetic factors;\(^{54,55}\) and 2) the range of normal D/3H levels is extremely wide and overlaps in various populations.\(^{56}\) This latter restriction can nevertheless be overcome when a very large population, as in our present study, is investigated. In both the normotensive and hypertensive subjects, the plasma D/3H activity was negatively correlated with RBF (Figure 7). Differences appeared when the effect of age on RBF and D/3H activity were taken into consideration together. In normotensive and hypertensive subjects, the D/3H activity increased with age.\(^{34}\) and there was also a significant decrease in RBF with age. When analyzed for a constant age, there was a negative correlation between D/3H activity and RBF and the RBF/CO ratio in hypertensive patients but not in normotensive subjects. In agreement with other reports,\(^ {35,57}\) our study showed that the D/3H activity was not correlated with arterial pressure and that the D/3H/RBF correlation was independent of blood pressure level. The importance of the relationship between sympathetic activity and renal vessels was emphasized by the effects of antihypertensive drugs on renal hemodynamics (Table 4). Clonidine and methyldopa are known to maintain RBF despite a fall in blood pressure, presumably by reduction in renovascular resistance.\(^ {36}\) Such a favorable effect was also observed in our study, since RBF but principally RBF/CO reductions were reversed with treatment. The specific importance of renal vasoconstriction was documented by the observation that these two drugs induced a decrease in RVR, which was much more pronounced than the decrease in TPR. Renal hemodynamic changes were observed with clonidine and methyldopa but not with propranolol, which suggests a predominant role of alpha vasoconstriction, as previously observed with phentolamine.\(^ {58}\) The lack of a relationship between D/3H activity and HBF or CBF indicates that autonomic activation was regional, rather than generalized.\(^ {12}\) The nature of the relationship between renal hemodynamics and sympathetic activity could be interpreted on the basis of an increased sympathetic tone or an increase in the reactivity or sensitivity of renal vessels to sympathetic stimulation.\(^ {13,15}\) The fact that the plasma level of the D/3H activity was identical in normal and hypertensive subjects favors the latter hypothesis. An increase in the renal vascular response to various stimuli\(^ {13,15,52,53}\) was documented in hypertension. This potentiated response could be due either to enhanced mechanical advantage\(^ {12,61}\) or an increase in the intrinsic responsiveness of the vascular smooth muscle.\(^ {12}\)

The activity of the renin-angiotensin system is increasing in many pathological conditions, accompanied by consistent alterations in the RBF.\(^ {5,6}\) Almost all these conditions are characterized by their acuteness, absence of a steady state, and decrease in the perfusion pressure of the kidney associated with a decrease in RBF. These conditions are very different from those observed in our study in which, in agreement with other authors,\(^ {7,58,59}\) we found that the resting PRA was not correlated with the RBF or RBF/CO ratio. The lack of correlation between RBF and PRA does not exclude a mutual interrelationship, since it seems that the common denominator between renin secretion and RBF may be the intrarenal distribution of blood rather than the total flow.\(^ {60}\)

Many other factors could be involved in RBF control, especially the role of the prostaglandins PGE, and PGF,\(_2\) in the regulation of renal hemodynamics, which was demonstrated in patients with sustained and with borderline essential hypertension,\(^ {61}\) but which was not studied in the present populations.

Whatever the cause of decreased renal perfusion, this abnormality is present early in the development of hypertension and is already evident for the youngest hypertensives when compared to their age-matched normotensive counterparts (Figure 3). This is consistent with previous reports concerning the role of the renal vasculature in early essential hypertension.\(^ {12}\) The question is: What is the pathogenetic significance of the blood flow reduction? Is the reduction in RBF the cause or consequence of the hypertension? We cannot answer these questions from our present study since the changes in renal hemodynamics and the blood pressure increase were already present together. Perhaps the most consistent observations suggesting that renal vascular abnormalities are not a consequence but rather a cause of long-standing hypertension were made by Hollenberg et al.\(^ {51}\) and Bianchi et al.\(^ {71}\) who observed that abnormalities in the renal circulation and its control were present in some normotensive subjects whose parents were hypertensive.

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