Splanchnic Blood Flow in Essential Hypertension and in Hypertensive Patients with Renal Artery Stenosis

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SUMMARY

Splanchnic blood flow (SBF) was measured simultaneously with cardiac output (dye dilution) and intraarterial blood pressure by constant infusion of indocyanine green in 11 control subjects, 13 patients with essential hypertension (EH) and seven hypertensive patients with renal artery stenosis (RAS). The cardiac index (CI) was lower (P < 0.05) in patients with EH (3.17 ± 0.07 L/min/m²) (mean ± SEM) than in control subjects (3.43 ± 0.09). Associated with the lower CI was a significantly (P < 0.01) lower SBF (0.797 ± 0.02 L/min/m² vs 0.859 ± 0.04). Patients with RAS presented with higher (P < 0.01 vs EH, nonsignificant vs control subjects) cardiac index (3.66 ± 0.17) and even lower SBF (0.749 ± 0.02). Furthermore, there was a negative correlation (r = −0.652) between the mean arterial pressure and the SBF when results for all patients were considered. The correlation remained (r = −0.568) in the EH group and the slope of regression line was not different from that for all subjects. The CI and SBF were weakly correlated (r = 0.423) in control subjects and patients with EH, whereas in patients with RAS, a negative correlation was found (r = −0.778).

This study indicates that the SBF, although significantly decreased in patients with EH, remains proportional to the CI in control subjects and in essential hypertensive patients. No redistribution of CI in regard to the splanchnic circulation occurs in EH. In contrast, in patients with RAS a dissociation of CI and SBF occurs and the fraction of the CI which passes through the splanchnic vascular bed is markedly reduced. The close correlation between mean arterial pressure and SBF suggests that both parameters are influenced by a common pathophysiological factor.

Additional Indexing Words
Hepatic blood flow Cardiac output Renovascular hypertension
Plasma renin activity

DATA on splanchnic blood flow (SBF) in essential hypertension (EH) are still fragmentary and inconclusive and no data exist in hypertensive patients with renal artery stenosis (RAS). In 1951, Culbertson et al., measuring SBF by a constant infusion of bromsulphalein in 12 hypertensive patients and eight normal subjects, found no significant difference between the two groups during recumbency and after passive tilting. In a subsequent study, the same group reported a mean SBF of 755 ml/min/m² in 41 hypertensive subjects and 798 ml/min/m² in their 21 normal controls. In contrast, Pippig and Schmitt, using colloidal chronic-³¹ phosphate and an external counting system, reported a 20% lower value in 45 essential hypertensive subjects than in 40 normal controls. Other than these contradictory reports, no conclusive data on this subject have been presented. In addition, no data were provided about the type and stage of hypertension studied and obstructive lesions of the renal arteries were not eliminated in patients with EH.

The above fact is of considerable importance because a reduction in SBF could be expected to slow down the metabolism of physiological and pharmacological substances by the liver. This in turn might cause an increased plasma level of these agents. We have measured SBF in well-defined hypertensive patients and control subjects according to the principle of Bradley et al. by a constant infusion of indocyanine green (ICG). Cardio output and intra-
arterial blood pressure were simultaneously determined.

Materials and Methods

Thirty-one subjects were investigated, 13 patients with stable EH, seven hypertensive patients with RAS and 11 control subjects. The control group consisted of two healthy volunteers and nine patients with atypical chest pain, in whom a diagnostic study was being carried out to exclude coronary heart disease. All of these subjects had normal coronary angiograms and normal hemodynamic findings on subsequent study. Blood pressure was repeatedly below 140/90 in the controls and none of them had a family history of high blood pressure or other cardiovascular diseases. Tests of liver function (SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, BSP) were within normal limits in all subjects.

The hypertensive patients presented no or only slight symptoms and underwent a complete evaluation which included urine analysis and culture, electrocardiography, radiography of the chest, rapid sequence intravenous pyelography, determinations of plasma electrolytes and creatinine clearance and renal arteriography. No patient presented with advanced retinopathy (grade III or IV, Keith-Wagener-Barker classification) and no signs of atheroma of the splanchic arteries were seen on the arteriographic pictures. Blood for determinations of plasma renin activity (PRA) was obtained after the patients with EH had been kept on a sodium intake of 135 mEq/24 hr for at least three days, during recumbency and after stimulation by 4 hr of upright posture. The main clinical and laboratory findings in patients with EH and RAS are shown in table 1. No one presented with symptoms or signs of left ventricular failure or of atherosclerosis of large vessels. Five patients out of 13 in the EH group and three out of seven in the RAS group showed ECG signs of left ventricular hypertrophy. In six patients signs of borderline left ventricular hypertrophy were also present on cardiopulmonary reoentgenography. Only patients with stable hypertension were included in the study.

In the seven patients with renal arterial disease abdominal aortography depicted stenosis of more than 50% of the main renal artery or of one or more of its branches on one side. In three out of the seven patients RS was associated with fibromuscular dysplasia, in the remainder with atheroma of the renal artery. Blood for measurement of PRA was obtained four to six days after the hemodynamic study by selective catheterization of both renal veins and simultaneous puncture of the femoral artery in all seven patients (table 1). In order to achieve a marked stimulation of renin secretion the patients were kept on a sodium restricted diet (10 mEq/24 hr) three days prior to the catheterization of the renal veins. In addition, they received 40 mg of oral furosemide 12 hours and 4 hours prior to the study.

The subjects were thoroughly acquainted with all experimental procedures and their informed consent was obtained. All antihypertensive medication including diuretics had been discontinued at least two weeks prior to the study.

Methods

Hemodynamic studies were performed 4 to 6 hr after a light, fat-free breakfast (fruit juice or black coffee). All subjects were premedicated approximately one hour prior to the hemodynamic study with diazepam given intramuscularly in a dose ranging from 5 to 15 mg. They had been recumbent since 11 o'clock the preceding evening and remained supine throughout the procedure. A catheter was introduced into the right femoral vein by the Seldinger technique and was advanced under fluoroscopic guidance into the right atrium. In hypertensive subjects, an arterial catheter was inserted by the same technique and advanced to the level of the renal arteries so that aortic angiography could be performed after the hemodynamic study. In control subjects, a Cournand needle was placed in the left brachial artery. Patency of the catheter was maintained by slow saline drip. The subjects remained at rest for at least 30 min after the insertion of the catheters before any measurements were performed. Cardiac output was determined by the dye dilution technique described by Stewart and Hamilton et al. After the injection of 6.2 mg of indocyanine green (ICG) into the right atrium, at least two indicator dilution curves were obtained by means of a Waters cuvette and a Waters densitometer. Arterial blood was drawn by means of a Harvard pump and the curves were recorded on a Hewlett-Packard multichannel recorder, which also continuously registered the electrocardiogram. The curves were replotted semilogarithmically for the calculation of cardiac output. Arterial and venous pressures were measured by means of Statham P23Db strain gauges attached to the multichannel recorder. The mean arterial pressure was obtained by electrical integration during infusion of ICG and remained constant throughout the procedure.

Table 1

Clinical and Laboratory Findings in Essential Hypertension and in Hypertensive Patients with Renal Artery Stenosis*

<table>
<thead>
<tr>
<th>Known duration of HBP (yr)</th>
<th>BP on day of admission</th>
<th>ECG signs of LVH</th>
<th>Sodium (mEq/L)</th>
<th>Potassium (mEq/L)</th>
<th>Creatinine (mg/100 ml)</th>
<th>Clearance of creatinine (ml/min/1.73 m²)</th>
<th>Plasma renin activity† (ng/ml/hr)</th>
<th>Patients with essential hypertension (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>6.61</td>
<td>173.5/115.0</td>
<td>5/13</td>
<td>141.4</td>
<td>4.08</td>
<td>1.05</td>
<td>98.0</td>
<td>0.680</td>
</tr>
<tr>
<td>± SEM</td>
<td>1.47</td>
<td>5.3/1.7</td>
<td>0.72</td>
<td>0.10</td>
<td>0.07</td>
<td>6.5</td>
<td>0.188</td>
<td>0.29</td>
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</table>

<table>
<thead>
<tr>
<th>Patients with renal artery stenosis (N = 7)</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>8.71</td>
</tr>
<tr>
<td>± SEM</td>
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<tr>
<td>1.17</td>
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<tr>
<td>6.4/3.05</td>
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<tr>
<td>0.70</td>
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<td>0.25</td>
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<tr>
<td>0.08</td>
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<tr>
<td>11.2</td>
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<td>0.85 (0.17)†</td>
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*Plasma renin activity on a sodium intake of 135 mEq/24 hrs in patients with EH and 10 mEq/24 hrs in patients with RAS.
†Renal venous PRA ratio (affected divided by nonaffected side).
‡Plasma renin activity was measured according to the method of Boucher et al.

Abbreviations: HBP = high blood pressure; LVH = left ventricular hypertrophy.

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After determination of the cardiac output, the venous catheter was placed into the major right hepatic vein. The position of the catheter was verified by rapidly injecting 2 ml of saline in a nearby wedged position. This procedure caused slight upper right quadrant discomfort in all patients. Thereafter, the catheter was retracted sufficiently to allow free withdrawal of blood and yet remain well in the hepatic vein. Immediately thereafter, a constant infusion of the dye was started at a rate of 0.64 mg/min. Thirty minutes were allowed for equilibration. During this time, constancy of arterial blood levels of ICG was monitored by means of a Waters cuvette and a Waters densitometer. Usually, a plateau was seen after 15 to 20 min. Three paired arterial and hepatic venous samples were withdrawn at intervals of 5 min. The ICG solution was freshly prepared for each subject and stabilized by the addition of human albumin up to a concentration of 0.5%. Hepatic extraction of ICG varied between 62% and 93% with a mean value of 84.3 ± 4.5% (SEM). The infusion pump (Harvard) and the syringe were calibrated after each procedure. ICG concentrations were estimated with a Beckman DU-2 spectrophotometer at a wavelength of 805 nm. Concentrations were read off a standard calibration curve prepared with solutions of known concentrations of the dye made up in pooled human serum. The same serum was also used to dilute aliquots of the infusion solution for determination of the concentration of ICG in the infusion mixture.

Cardiac index (CI) was expressed as liters per minute per square meter of body surface. Splanchnic blood flow was calculated according to the formula of Bradley4:

$$SBF = \frac{SR}{(A-V) \times (1-HCT)}$$

where SR means splanchnic removal rate of ICG (= infusion rate), A equals arterial concentration and V equals venous concentration of the dye and HCT is hepatic venous hematocrit. The value of SBF was calculated for body surface. Total peripheral resistance and hepatic resistance were calculated by dividing the mean arterial pressure by CI and SBF, respectively.

Statistical comparisons were made by Student's t-test. For the values of SBF and mean arterial pressure and of SBF and CI a linear regression analysis was performed.

### Results

The CI was lower (P < 0.05) in EH (3.17 ± 0.07 L/min/m²) than in control subjects (3.43 ± 0.09) (table 2). Associated with the lower cardiac output was a significantly (P < 0.01) diminished SBF (0.797 ± 0.017 L/min/m² vs 0.889 ± 0.04). Patients with RAS presented with higher (P < 0.01 vs EH, nonsignificant vs control subjects) CI (3.66 ± 0.17) and even lower (P < 0.01 vs controls) SBF (0.749 ± 0.02). The difference between normotensives and patients with EH was 10%, between control subjects and patients with RAS 16%. The mean SBF in women with EH was 0.772 ± 0.023, in hypertensive men 0.826 ± 0.012. Female and male control subjects showed values of 0.894 ± 0.068 and 0.885 ± 0.036, respectively. The ratio between SBF and CI which gives the fraction of CI which passes through the splanchnic vascular bed did not differ between control subjects (26.5 ± 0.98) and patients with EH (25.2 ± 0.58), whereas in patients with RAS, the fraction was markedly reduced (21.0 ± 1.6; P < 0.01). Furthermore, there was a strong (P < 0.001) negative correlation between the mean arterial blood pressure and the SBF when results for all patients were considered together (fig. 1). When only the group with EH was considered (dotted line, fig. 1), the correlation still existed (r = −0.575) and the slope of the regression line was not significantly different from that for all subjects.

The CI and SBF were weakly (r = 0.423) correlated in control subjects and in patients with EH (fig. 2). In the seven patients with RAS, however, a negative correlation (r = −0.778) between the two parameters was found (dotted line). As expected, the total

### Table 2

Hemodynamic Data in Control Subjects, in Patients with Essential Hypertension and in Hypertensive Patients with Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex ratio m:f</th>
<th>Body surface m²</th>
<th>MAP (mm Hg)</th>
<th>Pulse rate (beats/min)</th>
<th>CI (L/min/m²)</th>
<th>SBF (L/min/m²)</th>
<th>SBF/CI (L/min/m²)</th>
<th>Total peripheral resistance (units)</th>
<th>Splanchnic resistance (units)</th>
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<td>Control subjects (N = 11)</td>
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<tr>
<td>Mean</td>
<td>41.7 ± 0.5</td>
<td>6.5 ± 0.4</td>
<td>81.8 ± 2.1</td>
<td>75.5 ± 2.8</td>
<td>3.43 ± 0.09</td>
<td>0.889 ± 0.04</td>
<td>26.5 ± 1.4</td>
<td>24.1 ± 0.8</td>
<td>91.1 ± 4.3</td>
</tr>
<tr>
<td>SEM</td>
<td>4.6 ± 0.4</td>
<td>0.04 ± 0.01</td>
<td>2.11 ± 0.1</td>
<td>2.8 ± 0.1</td>
<td>0.09 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.98 ± 0.01</td>
<td>1.02 ± 0.05</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>Patients with essential hypertension (N = 13)</td>
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<tr>
<td>Mean</td>
<td>45.4 ± 0.4</td>
<td>6.7 ± 0.4</td>
<td>130.8 ± 1.8</td>
<td>75.9 ± 1.8</td>
<td>3.17 ± 0.07</td>
<td>0.797 ± 0.04</td>
<td>25.2 ± 1.6</td>
<td>41.7 ± 1.1</td>
<td>165 ± 2.2</td>
</tr>
<tr>
<td>SEM</td>
<td>3.1 ± 0.4</td>
<td>0.039 ± 0.01</td>
<td>5.0 ± 0.1</td>
<td>4.4 ± 0.1</td>
<td>0.07 ± 0.01</td>
<td>0.017 ± 0.01</td>
<td>0.58 ± 0.01</td>
<td>1.9 ± 0.05</td>
<td>9.2 ± 0.5</td>
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<tr>
<td>Patients with renal artery stenosis (N = 7)</td>
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<tr>
<td>Mean</td>
<td>43.4 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>147.7 ± 1.6</td>
<td>86.9 ± 1.6</td>
<td>3.66 ± 0.17</td>
<td>0.749 ± 0.04</td>
<td>21.0 ± 1.6</td>
<td>40.5 ± 1.6</td>
<td>199 ± 2.6</td>
</tr>
<tr>
<td>SEM</td>
<td>2.9 ± 0.4</td>
<td>0.064 ± 0.01</td>
<td>6.5 ± 0.1</td>
<td>6.0 ± 0.1</td>
<td>0.17 ± 0.01</td>
<td>0.023 ± 0.01</td>
<td>1.6 ± 0.1</td>
<td>1.63 ± 0.05</td>
<td>13.4 ± 0.5</td>
</tr>
</tbody>
</table>

*P < 0.05.
†P < 0.01 difference vs control subjects.
‡P < 0.01 difference vs patients with essential hypertension.

Abbreviations: MAP = mean arterial pressure as obtained by electrical integration; CI = cardiac index; SBF = splanchnic blood flow.

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Correlation between mean arterial pressure and SBF in all subjects and in patients with EH only (dotted line). ○ = control subjects; • = patients with EH; Δ = patients with RAS.

Peripheral resistance and the splanchnic resistance were much higher in patients with EH (41.7 ± 1.9 and 165 ± 9.2 resistance units, respectively) and in patients with RAS (40.5 ± 1.63 and 199 ± 13.4 respectively) than in normotensive controls (24.1 ± 1.02 and 91.1 ± 6.2, respectively) (table 2).

No significant correlation was found between PRA values and SBF or between PRA values and other hemodynamic parameters in patients with EH and RAS. However, a negative correlation was seen between the age of the patients with EH and the PRA values during recumbency (r = -0.650) and after stimulation by upright posture (r = -0.870).

Discussion

The splanchnic vascular system is unusual in having two capillary systems, the intestinal and the hepatic. The liver possesses a double blood supply from the portal vein under low peripheral pressure and from the hepatic artery in which the perfusion pressure equals systemic arterial pressure. This anatomic situation explains the fact that SBF is equal to hepatic blood flow if no significant collateral circulation exists. In subjects with normal liver function collaterals are usually absent or meaningless and the two terms hepatic and splanchnic blood flow can be used interchangeably.

The major finding of our study is that patients with EH showed a lower SBF and a lower CI than control subjects. In contrast, hypertensive patients with RAS had a normal or slightly elevated CI and an even lower SBF. In addition, we found a strong negative correlation between the mean arterial blood pressure and the SBF in all subjects. If one assumes that this is not due to chance, then either hepatic blood flow and arterial blood pressure are being influenced by some common pathophysiological factor or there exists a more direct interaction between them. This finding could at least partially be explained in hypertensive patients with RAS, where circulating pressor substances might produce vasoconstriction in the splanchnic vascular bed, thereby diminishing hepatic blood flow. This possibility is suggested by the disproportionally reduced fraction of the CI which passes through the splanchnic vascular bed in patients with RAS and is further supported by the decrease in SBF which has been produced by angiotensin II infusion in animals and in normotensive men with or without liver disease. A decrease in SBF was also found in experimental renal hypertension in the rat. It remains doubtful, however, whether our findings in EH could be explained by the same pathophysiological mechanism. Nevertheless, it is well known that the splanchnic vessels are more sensitive to the vasoconstrictor effect of angiotensin than the remainder of the circulation.

In hypertensive patients with RAS, cardiac output has been previously reported to be normal or slightly elevated and this is consistent with the present data. These findings in humans are also in agreement with the results obtained by Bianchi et al. and Ferrario in experimental renovascular hypertension in dogs. In contrast, CI tends to be normal or slightly lower than normal in patients with stable EH. It is, however, important to distinguish clearly between hypertensive patients with normal heart size and those with marked cardiac enlargement, left ventricular failure, or severe hypertensive cardiovascular disease in whom, for obvious reasons, cardiac output may be markedly reduced.

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The fact that the fraction of cardiac output which passes through the splanchnic vascular bed is the same in normal subjects and EH patients may be partially due to a decreased cardiac output in stable EH. A significant positive correlation between the CI and the SBF was demonstrated in control subjects and those with EH — a correlation almost identical with that found in patients with different degrees of cardiac failure in whom obviously the variation in cardiac output is more pronounced. It seems therefore, that the SBF decreases proportionally with the CI in patients with EH. These findings argue against an eventual redistribution of cardiac output in regard to the splanchnic circulation in EH. Our data thus disagree with those of a previous study, in which, in resting hypertensives, a blood shift from the viscera and skin to muscle was demonstrated.

In contrast to those with EH, in patients with RAS a dissociation of CI and SBF occurs: a negative correlation between the CI and the SBF was found.

A decrease in hepatic blood flow could slow down the inactivation of physiological and pharmacological agents by the liver. These substances are cleared from the circulation according to the formula HC = SBF × E, in which HC denotes hepatic clearance and E, hepatic extraction (arteriovenous difference in concentration divided by arterial concentration of the substance). Provided that the hepatic extraction remains constant or is nearly complete (E = 1), the hepatic clearance depends entirely on SBF. The finding of a lower SBF in EH and in patients with RAS could be especially important in the metabolism of aldosterone and other steroids, which are inactivated to a high degree by the liver. Previous investigations by our group showed that the mean metabolic clearance rate of aldosterone, measured by a constant infusion technique, was 46% lower (P < 0.001) in patients with EH than in healthy subjects. In addition, Kaufmann et al. also reported a marked decrease in the metabolic clearance rate of aldosterone in patients with RAS, which partially normalized after corrective surgery. However, the decrease in SBF was only 10% in EH and could thereby account for only a part of the observed 46% decrease in metabolic clearance in EH.

It has to be remembered that the blood flow to the adrenal glands might well be reduced by the same decrement in cardiac output in EH. This in turn might reduce the secretory rates by some proportion. This potential complexity may help to explain the various contradictory reports on aldosterone secretion and excretion rates in EH.

The present finding of a negative correlation between PRA and age in patients with EH is consistent with previous reports of ours as well as those of other laboratories. It remains unknown whether the low PRA values in the older patients are caused by the spontaneous course of the disease or represent an effect of treatment.

In conclusion, we have shown that SBF is significantly decreased in EH and in hypertensive patients with RAS. Whereas in EH this decrease is accompanied by a diminished cardiac output, in patients with RAS a dissociation between SBF and cardiac output occurs. The close correlation between the mean arterial pressure and the SBF in all subjects suggests that both hemodynamic parameters are influenced by some common pathophysiological factor(s).

Acknowledgment

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