Asymmetry of Renal Blood Flow in Patients With Moderate to Severe Hypertension


Abstract—It is generally assumed that renal blood flow is symmetric in the absence of renal artery stenosis. The aim of the present study was to evaluate whether this is really the case. From a group of consecutive hypertensive patients who had undergone renal angiography, we selected those with patent renal arteries. In all of them selective renal blood flow (RBF) measurements (133Xenon washout technique) had been performed with blood sampling from aorta and both renal veins (n=148). Asymmetry of RBF, defined as ≥25% difference in RBF between left and right kidney, was present in 51% of the patients. Subjects with and without asymmetry did not differ in age, body mass index, blood pressure, creatinine clearance, renal volume, or activity of the renin-angiotensin system. The presence of asymmetry coincided with an increased rate of false-positive results on renal scintigraphy. Preliminary data suggest that there may be a relation between asymmetry and renal sympathetic nerve activity. This study demonstrates that asymmetry of RBF is a frequent finding in essential hypertension, which may confound the results of diagnostic tests for renal artery stenosis. Furthermore, the present results underscore the importance of studying the function of both kidneys separately, because it cannot be assumed that they are functionally equal. (Hypertension. 2003;41:108-113.)

Key Words: renal circulation ■ kidney ■ hypertension, essential ■ norepinephrine ■ renin-angiotensin system

E valuation of split renal function in patients with elevated blood pressure may be useful as a screening procedure to detect (unilateral) renal artery stenosis. Renal scintigraphy and, more recently, Doppler ultrasonography are among the tests that have been developed for this purpose. The implicit assumption underlying these diagnostic tests is that, in the absence of a hemodynamically significant renal artery stenosis, blood flow through the kidneys will be roughly symmetrical. Whether this is truly the case, however, has not been proven.

In our clinic, we routinely perform selective renal blood flow (RBF) studies in all patients in whom renal angiography is performed on the suspicion of renovascular hypertension. During these investigations we frequently noted differences in RBF between the left and the right kidney in patients without angiographic abnormalities. Whereas asymmetry of RBF is the hallmark of (unilateral) renal artery stenosis, inequality in RBF between 2 kidneys in patients with patent renal arteries is a more elusive phenomenon.

To assess how often asymmetry of RBF exists in patients without renal artery stenosis and to search for possible determinants of this asymmetry, we have re-evaluated the blood flow data that were obtained in a large group of patients, all of whom had undergone the same study protocol.

Methods

Study Protocol
Since February 1994, all patients who are referred to our clinic for evaluation of their hypertension (ie, diastolic blood pressure above 90 mm Hg on at least 3 occasions) are subjected to a standard diagnostic protocol. This includes renal angiography with selective RBF measurements and arterial and renal venous blood sampling when patients fulfill one or more of the following criteria: hypertension despite 2 or more antihypertensive drugs, accelerated hypertension, documented atherosclerotic vascular disease in 2 or more vascular beds, the presence of an abdominal bruit, or unexplained impairment of renal function in response to antihypertensive treatment.

For reasons of standardization, all antihypertensive medication is discontinued for 3 weeks, and patients are requested to use a sodium-restricted diet (55 mmol/24 h) during the week preceding the study. Compliance with the diet is estimated from a 24-hour collection of urine. After an overnight fast, the aorta and both renal veins are cannulated via the femoral route, and blood samples are drawn simultaneously from the aorta and renal veins for determination of active plasma renin concentration (APRC) in all patients and angiotensin II, aldosterone, and norepinephrine in subgroups as part of other study protocols. Subsequently, we measure selective mean renal blood flow (MRBF) by means of the 133Xenon washout technique as described previously. As a matter of routine, we start 133Xenon washout studies in the left kidney, and the whole Xenon-wash-out procedure for both kidneys is completed within approximately 10 minutes. Blood pressure and heart rate are monitored during the MRBF measurements, and no contrast material is...
administered before the flow studies have been completed. Thereafter, intra-arterial renal angiography is performed with a commercially available digital subtraction system (Integris 5000, Philips Medical Systems). A radiologist who is unaware of the results from the RBF studies evaluates the angiographic films.

The 133Xenon washout curves are analyzed off-line using a 2-phase exponential model after subtraction of background radiation2,3 (GraphPad Software, Inc). In our hands, the 95th percentile of differences between 2 repeated flow measurements in the same kidney is 25% (mean variability of 2 measurements plus 2×SD), with no systematic left-right differences between the first and the second measurements.

All patients gave written informed consent and the Maastricht University Hospital Medical Ethics Committee approved the study.

Renal Scintigraphy
In the early phase of the study period, renal scintigraphy was still used as a screening test for renal artery stenosis. Renography was always performed with Technetium-99 m labeled mercaptoacetyltriglycine (99mTc-MAG3), initially under baseline conditions, later on also after the ingestion of 50 mg of captopril. Because a recent meta-analysis did not demonstrate that performing both a baseline and a post-captopril study was superior to a post-captopril study alone,6 results from all renographic observations were pooled for analysis.

Kidney Volume Measurements
As of January 1999, all patients clinically suspected of having a renal artery stenosis underwent computed tomography angiography (CTA) of the renal arteries on the day before intra-arterial angiography. Spiral CT examinations were performed with a CT Twin RTS (Elsctis) during inspiratory breath-hold with the administration of 140 mL iohexol (Omnipaque 300, Nycomed) and a scan delay time of 18 seconds. The contrast-enhanced scans were obtained using a 2.7 mm collimation slice thickness and a pitch of 0.7. A 430-mm field of view and a 512×512 matrix with a reconstruction interval of 1.3 mm were used. CT-imaging series were only used to calculate kidney volume when both kidneys were depicted completely and the subject had been able to hold his/her breath sufficiently long to allow acceptable imaging. The original images were reconstructed in a coronal plane with a 5-mm slice thickness without an intersection gap. On each created image the boundaries of both kidneys were traced manually. In cases of partial voluming, ie, a voxel containing both kidney and surroundings, the segmentation line was drawn halfway. The renal volume was then calculated automatically by adding all voxel volumes lying within the borders of the kidney.

Assay Methods
APRC was measured using a 2-side immunoradiometric assay method.7 Angiotensin II and aldosterone were determined after extraction from plasma by radio-immunoassay using highly specific antibodies.8,9 A sensitive high-performance liquid chromatography (HPLC) method with fluorometric detection was used to determine norepinephrine concentrations.10

Calculations and Statistics
Creatinine clearance was estimated from the Cockcroft formula.11 MRBF ratio was calculated by dividing the flow in the kidney with the highest MRBF by that in the kidney with the lowest MRBF. In absence of asymmetry in MRBF, we expected a maximum difference between left and right kidney MRBF of approximately 25% (mean variability of 2 measurements in the same kidney plus 2×SD). We therefore defined symmetry of MRBF as <25% difference between left and right MRBF and asymmetry of MRBF as ≥25% difference. According to this definition, we divided the study participants into 2 groups. Differences between the symmetry and the asymmetry groups in patient characteristics and MRBF were analyzed using unpaired t tests and the Pearson χ2 test. The Friedman test was applied for analysis of repeated measurements of blood pressure and heart rate. Because the distributions of MRBF ratio, kidney volume, and neurohormones were not normal, nonparametric tests, including the Mann-Whitney U test, the Wilcoxon signed rank test, and the Spearman analysis for correlations, were applied to test differences in these variables. The nonparametric χ2 test was used to assess differences in the rate of false-positive results on scintigraphy. For statistical analyses, SPSS 10.0 was used. A probability value of <0.05 was considered statistically significant. Data with a normal distribution are presented as mean±SD; otherwise medians and interquartile ranges are given.

Results
Between February 1994 and February 2001, combined angiography and selective renal blood flow studies were successfully performed in 233 patients who were without treatment at that time. Of these, 85 patients were excluded from analysis. Reasons for exclusion are listed in Table 1. The study group consisted of 90 males and 58 females with a mean age of 51±13 years. None had angiographic, biochemical, or other abnormalities suggestive of secondary hypertension, and they were all diagnosed as having essential hypertension. Before the study, patients were taking medication of 2±1 (range 0 to 5) classes of antihypertensive drugs. The withdrawal of treatment was tolerated well by all patients and none of the patients was endangered. Systolic blood pressure at admission averaged 175±28 mm Hg and diastolic blood pressure, 105±15 mm Hg. One patient was normotensive at the time of study, but on other occasions consistently had blood pressures >140/90 mm Hg. The average blood pressures during the 133Xenon washout studies (178±30/101±17 mm Hg) were similar to the average blood pressures at admission. During the measurements, mean arterial pressure and heart rate did not change (data not shown). The average amount of sodium in the 24-hour urine collections was 82 (53 to 125) mmol. Average creatinine clearance was 93±34 mL/min; in 23 patients (16%) creatinine clearance was lower than 60 mL/min.

Renal Blood Flow
Mean values for left and right MRBF in the entire group were not different (183±68 versus 193±78 mL/100g/min, NS). Asymmetry of MRBF was found in 75 patients (51%). Clinical characteristics of the symmetry and asymmetry groups are shown in Table 2. Groups did not differ with regard to age, gender, body mass index, blood pressure, heart rate, 24-hour sodium excretion, and renal function.

In patients with an asymmetric MRBF, median ratio was 1.52 (1.34 to 1.88), and in 11 (15%) cases, MRBF ratio exceeded 2.00 (Figure 1). In subjects with symmetric MRBF,
median flow ratio was 1.09 (1.05 to 1.15). In patients with asymmetric perfusion, left MRBF was on average lower than the right MRBF (163 ± 68 versus 187 ± 90 mL/100 g/min, \( P = 0.008 \)). When patients with asymmetric flow were compared with those with symmetric flow, left MRBF was again lower in the former (163 ± 68 versus 204 ± 62 mL/100 g/min, \( P = 0.001 \)), whereas right MRBF was similar (187 ± 90 versus 200 ± 64 mL/100 g/min, NS). Although this suggests that asymmetry is predominantly caused by a reduction of left MRBF, right MRBF was lower than left MRBF in 31 of the 75 subjects (41%) with an asymmetric flow pattern. The MRBF ratio, or in other words the degree of asymmetry, was similar in those with dominance of left and those with dominance of right MRBF (1.57 [1.35 to 1.87] versus 1.39 [1.31 to 1.88], NS). The percentage distribution of renal blood flow to the cortex (fast component of the \(^{133}\)Xenon washout curve) was similar between the symmetry and the asymmetry group. When patients with reduced kidney function (creatinine clearance ≤ 60 mL/min) were left out of the analysis, similar findings were obtained with respect to asymmetry and left-right differences.

**Renal Scintigraphy**

Renal scintigraphy had been performed in 12 subjects from the symmetry group and 16 patients of the asymmetry group. In 7 of the patients with asymmetry of MRBF (44%), renal scintigraphy suggested renal artery stenosis, whereas this was the case in only 1 of the subjects with symmetry of MRBF (9%). This difference was statistically significant (\( P = 0.02 \)). As judged by renal angiography, all of these subjects had patent renal arteries, indicating that renal scintigraphy results that suggested renal artery stenosis must be false-positive.

### Figure 1

**Figure 1.** Frequency distribution of mean renal blood flow (MRBF) ratio in 148 patients with essential hypertension

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Symmetry</th>
<th>Asymmetry</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50 ± 13</td>
<td>51 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>45 (62)</td>
<td>45 (60)</td>
<td>NS</td>
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<tr>
<td>BMI, kg/m(^2)</td>
<td>28 ± 5</td>
<td>28 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>No. of classes of antihypertensive drugs before study</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>44 (60)</td>
<td>32 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>( \beta ) blockers</td>
<td>41 (56)</td>
<td>39 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>27 (37)</td>
<td>19 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>25 (34)</td>
<td>25 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin type 1 receptor antagonists</td>
<td>14 (19)</td>
<td>14 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Other: ( \alpha ) blockers, centrally acting agents, direct vasodilators</td>
<td>9 (12)</td>
<td>11 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, * mm Hg</td>
<td>180 ± 31</td>
<td>177 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, * mm Hg</td>
<td>101 ± 17</td>
<td>100 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>HR, * beats per minute</td>
<td>71 ± 15</td>
<td>73 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 hour</td>
<td>83 (52–121)</td>
<td>79 (56–127)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>94 ± 36</td>
<td>91 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>No. of persons with &gt;2 renal arteries</td>
<td>23</td>
<td>24</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD or median (interquartile range) or number (%). BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

*Blood pressure and heart rate were measured during \(^{133}\)Xenon washout.

### Table 2

**TABLE 2. Clinical Characteristics of Hypertensive Subjects With Symmetric and Asymmetric RBF**

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BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

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**Figure 2.** Scatterplot of MRBF (Y-axis) and kidney volume (X-axis). There is no correlation between left MRBF and left kidney volume (Spearman \( r = -0.03 \), NS) nor between right MRBF and right kidney volume (Spearman \( r = -0.14 \), NS).
Kidney Volume

Adequate kidney volume measurements could be obtained in 14 patients with symmetric renal blood flow and 9 patients with asymmetric perfusion. Renal volume did not differ between left and right kidneys, either in the symmetry group (187 mL [158 to 205] versus 185 mL [166 to 203], NS) or in the asymmetry group (154 mL [122 to 179] versus 151 mL [130 to 217], NS). When all volumes of the kidneys with the lowest flow were compared with those of kidneys with the highest flow, regardless of side, no differences were found either. This was true for patients with symmetry (184 mL [166 to 214] versus 187 [153 to 196], NS) as well as for those with asymmetry of MRBF (151 [128 to 217] versus 154 [130 to 178], NS). Although kidney volumes tended to be a bit lower in the asymmetry group compared with the symmetry group, differences were not statistically significant. Moreover, MRBF, which is expressed per 100 g of kidney mass, did not correlate with kidney volume (Figure 2).

Creatinine clearance was comparable between subjects with positive and negative results on scintigraphy.

Neurohormones

Arterial and selective renal venous concentrations of renin, angiotensin II, and aldosterone in hypertensive subjects (Table 3) and veno-arterial differences of renin and angiotensin II did not differ between the 2 groups. In the asymmetry group, no differences in these hormones were found between the kidneys with the highest and the lowest MRBF. Because the left adrenal vein drains into the left renal vein, we used norepinephrine values from the left renal vein only when mixing with blood from the adrenal gland could virtually be excluded on the basis of concurrent aldosterone measurements. In each patient the difference between the arterial and the venous concentration of norepinephrine was calculated for the kidney with the lowest flow. The same was done for the kidney with the highest MRBF. Although numbers were low, there tended to be a relation between the veno-arterial differences of norepinephrine and MRBF ratio in patients with a ratio up to 2.00. This was of borderline significance when the norepinephrine gradient across the kidneys with the lowest MRBF was taken as independent variable ($r=0.61, P=0.06$) (Figure 3).

Discussion

This study shows that substantial differences between left and right renal blood flow may be present in up to 51% of hypertensive patients with angiographically proven patent renal arteries. Inequality in perfusion between kidneys has been observed in only a few studies. Kioschos et al determined selective renal blood flow by means of the dye dilution technique in 5 normotensive controls and 15 essential hypertensives, including 8 subjects who were suspected of having nephrosclerosis. In 6 of the 15 essential hypertensives, differences in flow between kidneys exceeded 25%, whereas asymmetry was not found in the normotensives. In a study performed by Baldwin et al, selective clearances of inulin and p-aminohippurate were used to investigate subjects who were judged to be in the early stage of essential hypertension. They defined disparity of effective renal plasma flow (ERPF) as being abnormal when it exceeded the 90th percentile of differences between two kidneys in subjects with normotension and found this to be present in 19 out of 36 patients.

Figure 3. Scatterplot of MRBF ratio (Y-axis) and the veno-arterial differences for norepinephrine in kidneys with the lowest MRBF (X-axis). The correlation between the MRBF ratio and the veno-arterial difference for norepinephrine in the kidney with the lowest MRBF was borderline significant in subjects with MRBF ratio $\leq 2.00$ (Spearman $r=0.61$, $P=0.06$). $\bullet$ indicates left kidney; $\bullet$ indicates right kidney. Numbers in parentheses correspond to the actual ratio of outlying values.
Interestingly, in 16 of these patients, this was accompanied by a concordant disparity of the glomerular filtration rate (GFR). In a more recent study, Van Jaarsveld et al. evaluated in a large group of hypertensive patients Technetium-99 labeled diethylenetriamine pentaacetic acid (99mTc-DTPA) scintigraphy. They noticed that, without captopril challenge, the single kidney fractional uptake was statistically significantly lower on the left side than on the right side (46% versus 54%). Unfortunately, dye dilution and clearance techniques generate absolute flow values per kidney, whereas scintigraphy results are presented as a percentage contribution of each kidney. So, differences in kidney volume may have confounded these data. On the other hand, the 133Xenon washout technique, which we applied in the present study, measures flow per unit of kidney mass. Therefore, our data on differences in flow between the left and right kidney cannot be explained by differences in kidney mass. To strengthen this point, we have determined kidney volumes in a subset of our patients who underwent CT angiography, and these data do not point to any association between kidney volume and asymmetry of renal blood flow in our study population either.

From sequential renal blood flow measurements in the same kidney in patients with essential hypertension, Hollenberg et al. observed differences in flow that were comparable to those between the 2 kidneys as found by Baldwin et al. Compared with normotensive controls, renal blood flow in patients with essential hypertension exhibited a 2.2-fold greater variability, which the authors attributed to sinusoidal-like oscillations in renal blood flow with a similar cycle length (about 40 sec), but increased maximal amplitude. It can be concluded from their experiments that the total variability of blood flow in each kidney will randomly result in significant flow differences between both kidneys. Although this phenomenon may have contributed to our results, in our opinion it is not sufficient to explain our observations. After all, we measured 133Xenon washout for 3 minutes, which is almost 5 times the duration of the oscillatory cycle length, thereby outweighing the effect of oscillations by far.

Inequality of renal blood flow between the kidneys, therefore, is likely to originate from structural or functional differences, or both. The degree of structural abnormalities at the level of interlobar and arcuate arteries has been shown to correlate with renal blood flow and renal vein renin levels. Regarding the symmetry of peripheral abnormalities on renal angiography, data from the literature are inconclusive. Arlart et al. found approximately symmetric peripheral involvement, whereas Carlals et al. demonstrated asymmetric alterations of the interlobar and arcuate arteries in 11 of 25 patients. Interestingly, the latter investigators reported in 10 of the 11 asymmetry cases that the left kidney was more affected than the right one. The smallest renal vessels have been studied in 2 large histopathologic studies using bilateral kidney biopsies of hypertensive subjects. The severity of arteriosclerotic changes differed between the kidneys in 25% to 39% of all cases. However, these numbers are difficult to interpret in the light of inter- and intraobserver disagreement rates of 13% and 20%, respectively. Additionally, it has been observed that there is also intrarenal heterogeneity of arteriosclerotic changes in the renal cortex. Apart from structural abnormalities, asymmetry in renal perfusion could also be caused by functional differences between kidneys. However, in our population, renin levels did not differ between subjects with symmetry and those with asymmetry. Although not identical to norepinephrine release rates and available only in a small subgroup, veno-arterial differences of norepinephrine were not symmetric in our study and tended to be the highest in patients with more pronounced grades of asymmetry. In patients with differences in MRBF exceeding 200%, this relation is absent, which may indicate that with severe asymmetry different pathophysiological processes are involved. Interestingly, recent data suggest that in isolated renal arteries from WKY rats the vasoconstrictor responses to electric field stimulation are enhanced on the left side, which may be explained by a more dense sympathetic nerve innervation of the left kidney.

Whatever the nature of the (patho-)physiological processes leading to asymmetry of renal blood flow, our study shows that the asymmetric phenotype coincides, at least in the subgroup that we were able to study, with an increased rate of false-positive results on renal scintigraphy. This provides evidence that the presence or absence of asymmetry is a consistent characteristic, which may interfere with the accuracy of diagnostic tests that depend on renal blood flow.

An obvious limitation of our study is that we measured MRBF only once in every kidney on one occasion. Therefore, we do not know whether asymmetry is really a consistent trait in a particular person. Secondly, our data were obtained in a selected population of patients who were suspected of renal vascular disease. To what extent our data can be extrapolated to the entire hypertensive population remains elusive. Thirdly, we performed blood flow studies in a fixed order: first left, then right. One may argue that our findings are biased by order effect, especially because we found asymmetry to occur more often at the expense of the left kidney. However, in 31 of the 75 subjects (41%) with an asymmetric flow pattern, right RBF was lower than left RBF. In case of a strong and predominant order effect, we would have expected this fraction to be much less. A reason for an order effect may be that the stress related to the measurements would lower the first measurement. However, the fact that heart rate and blood pressure remained constant during the measurements indicates that the level of arousal did not change during the washout studies. Moreover, we did not detect systematic differences between repeated measurements in the same kidney in reproducibility studies. In this context we also like to stress that all measurements are completed within 10 minutes, thereby reducing time-dependent variation in RBF as found by Persson at al. in conscious dogs. Finally, our data leave the question unanswered whether asymmetry is an inborn phenomenon or a consequence of (longstanding) hypertension.

Perspectives

Although asymmetric renal perfusion had already been described over 40 years ago, these studies were small and hampered by imperfect methodology. We have revisited this subject and demonstrated that considerable left-to-right differences in RBF exist in a substantial number of subjects with...
moderate-to-severe essential hypertension. More studies are necessary to define the underlying mechanism(s) and to assess whether such differences are mainly related to structural or functional abnormalities. Also, the exact clinical importance of this characteristic needs to be sorted out. In this respect, one would like to know whether asymmetry is a constant feature that interferes with the results of screening tests for renovascular disease. Furthermore, studies need to be undertaken to determine whether asymmetric perfusion in itself could be responsible for a rise in blood pressure. Finally, we have to better understand the potential differential effects of antihypertensive drugs on both kidneys. For the present, we think that our results underscore the importance of studying the function of both kidneys separately, because it cannot be assumed a priori that they are functionally equal.

Acknowledgments
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References
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