Assessment of Renal Artery Stenosis Severity by Pressure Gradient Measurements

Bernard De Bruyne, MD, PhD,* Ganesh Manoharan, MD,* Nico H. J. Pijls, MD, PhD,† Katia Verhamme, MD, PhD,‡ Juraj Madaric, MD,* Jozef Bartunek, MD, PhD,* Marc Vanderheyden, MD,* Guy R. Heyndrickx, MD, PhD*

Aalst, Belgium; and Eindhoven and Rotterdam, the Netherlands

Methods

The purpose of this study was to define “significant” renal artery stenosis (i.e., a stenosis able to induce arterial hypertension).

The degree of renal artery stenosis that justifies an attempt at revascularization is unknown.

In 15 patients, transtestinal pressure measurements were obtained before and after unilateral stenting. After stenting, graded stenoses were created in the stented segment by progressive inflation of a balloon catheter. Stenosis severity was expressed as the ratio of distal pressure ($P_d$) corrected for aortic pressure ($P_a$). Balloon inflation pressure was adjusted to create 6° of stenosis ($P_d/P_a$ from 1.0 to 0.5, each step during 10 min). Plasma renin concentration was measured at the end of each step in the aorta and in both renal veins.

For a $P_d/P_a$ ratio $>0.90$, no significant change in plasma renin concentration was observed. However, when $P_d/P_a$ became $<0.90$, a significant increase in renin was observed in the renal vein of the stenotic kidney, finally reaching a maximal increase of 346 ± 145% for $P_d/P_a$ of 0.50 ($p = 0.006$). These values returned to baseline when the stenosis was relieved. In addition, plasma renin concentration increased significantly in the vein from the non-stenotic kidney ($p = 0.02$).

In renal artery stenoses, a $P_d/P_a$ ratio of 0.90 can be considered a threshold value below which the stenosis is likely responsible for an up-regulation of renin production and, thus, for renovascular hypertension. These findings might contribute to better patient selection for renal angioplasty. (J Am Coll Cardiol 2006;48:1851–5) © 2006 by the American College of Cardiology Foundation

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A unilateral renal artery stenosis induces a decrease in renal perfusion pressure that, in turn, drives the production of renin by the juxtaglomerular apparatus. The subsequent increase in angiotensin II causes vasoconstriction and stimulates aldosterone secretion and distal sodium reabsorption but also causes renal vasoconstriction that reduces plasma flow and enhances sodium reabsorption. The non-stenotic kidney responds with “pressure natriuresis” that lowers the blood pressure by excreting sodium. Yet, this decrease in systemic blood pressure further reduces the perfusion pressure of the stenotic kidney. Thus, in this model of unilateral renovascular hypertension, the renin-angiotensin-aldosterone system plays a central pathophysiological role.

Because a decrease in renal pressure distal to the stenosis (and its subsequent release of renin) is the fundamental trigger of renovascular hypertension, measurement of transstenotic pressure gradient with pressure wires (9) provides the most accurate means of hemodynamic assessment. Yet, what constitutes a significant pressure gradient remains largely unknown.

Accordingly, the goal of the present study was to define a hemodynamically significant renal artery stenosis. Therefore, we induced a unilateral, controlled, graded renal artery stenosis and correlated the magnitude of the pressure gradients with the production of renin by the kidneys.

Methods

Patient population. The patient population consisted of 15 patients (9 men and 6 women) scheduled for percutaneous transluminal renal angioplasty because of suspected renovascular hypertension. All patients had normal creati-
nine clearance (10), arterial hypertension, and a unilateral renal stenosis with a diameter stenosis of more than 50% at selective quantitative angiography. One patient received 4 antihypertensive drugs, 8 patients received 3 antihypertensive drugs, 4 patients received 2 antihypertensive drugs, and 2 received 1 antihypertensive drug. In all patients, diuretics were stopped for at least 48 h before catheterization.

The study protocol was approved by the medical ethics committee of the Onze-Lieve-Vrouw Clinic in Aalst, Belgium, and all patients gave informed consent.

**Catheterization.** A 6-F arterial introducer was inserted in the femoral artery. A 6-F renal guiding catheter was advanced in the ostium of the stenosed renal artery, and a control angiogram was performed for quantitative angiography. Two 6-F introducers were inserted in the femoral vein. Two 6-F left Amplatz catheters were advanced and deeply seated in the right and left renal veins. Their proper position was checked by angiography as well as by oximetry. After proper calibration, a 0.014-inch pressure monitoring guide wire (PressureWire, RadiMedical, Uppsala, Sweden) was then advanced through the guiding catheter across the stenosis. The sensor was positioned in one of the large branches of bifurcations of the main renal artery. Phasic and mean aortic pressures recorded by the guiding catheter and phasic and mean pressures recorded by the pressure monitoring guide wire distal to the renal artery stenosis were continuously recorded and digitally stored. Once the catheters were in place, direct stenting of the renal artery stenosis was performed. The occlusion of the renal artery for stent deployment was kept as short as possible (<15 s). The result was accepted when the residual diameter stenosis was <10% by quantitative angiography and no pressure gradient persisted. Stenting was successful and uncomplicated in all patients. A 15-min period allowed all parameters to come back to baseline. Thereafter, a compliant angioplasty balloon catheter 1 mm smaller in diameter than the final diameter of the stent was advanced in the stented segment and kept deflated for 10 min. Then the balloon was inflated to create a controlled pressure gradient between the aorta ($P_a$) and the distal part of the renal artery ($P_d$). To correct for the actual level of aortic pressure, the magnitude of the pressure gradient was not expressed in absolute terms but as the ratio of distal renal pressure to aortic pressure ($P_d/P_a$, dimensionless value). The following levels of $P_d/P_a$ ratio were achieved successively by balloon inflation: 1.0 (when the balloon was deflated), 0.9, 0.8, 0.7, 0.6, 0.5, and 1.0. Each step was maintained in steady state for 10 min. An example of pressure tracing is given in Figure 1.

**Quantitative angiography.** Before renal stenting, a high-quality angiogram was obtained. With the guiding catheter as scaling device, reference diameter, minimal luminal diameter, and percent diameter stenosis were determined.

**Color duplex ultrasound.** With a sector transducer with a 2.5-MHz pulsed Doppler frequency (Siemens-Acuson; Siemens, Malvern, Pennsylvania), flow velocity was measured in the segmental arteries. From peak and end-diastolic velocities the renal resistance index was obtained as previously described (11).

**Renin sampling and assessment.** Blood samples were obtained in the central aorta and in both renal veins before angioplasty, 10 min after stenting at the end of each 10-min interval during which stenoses of increasing severities were applied, as well as 10 min after relieving the stenosis. Before angioplasty and after 10 min of $P_d/P_a$ of 1.00, the blood samples were taken in duplicate to test the reproducibility of the renin measurements. The timing of blood samplings is depicted in Figure 1. The blood samples were immediately

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**Abbreviations and Acronyms**

- $P_a$ = mean aortic pressure
- $P_d$ = mean pressure distal to the renal artery stenosis

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![Figure 1](image-url)  
*Figure 1.* Example of mean pressure tracings obtained simultaneously in the aorta and distal to the artificial renal stenoses induced by incremental balloon inflations. Each degree of stenosis severity was maintained for 10 min. The arrows indicate the timing of sampling in the aorta and in both renal veins.
stored at −20° for further analysis. The determination of plasma renin concentration (expressed in pg/ml) was performed with a commercially available assay.

**Statistical analysis.** Data are presented as mean values ± SD. Spearman’s rho (non-parametric correlation) was used to study correlation between hemodynamic parameters and the percent diameter stenosis of the renal artery. The Wilcoxon signed rank test was used for comparison of plasma renin concentration before and after stenting. A repeated measures analysis of variance was used to study the effects of different balloon dilatation on plasma renin concentration. The Huynh-Feldt correction was used if the sphericity assumption was not met. Bonferroni adjustment for pairwise comparisons of the renin concentrations for the different \( P_d/P_a \) ratios was used. A \( p \) value of <0.05 (2-tailed) was considered to indicate statistical significance. All analyses were performed with the software package SPSS 11.5 (SPSS, Chicago, Illinois).

**RESULTS**

The demographic, clinical, angiographic, and hemodynamic characteristics of the patients are outlined in Table 1. All renal stenoses were atherosclerotic in nature. Renal size and function was normal in all patients. The severity of the renal artery stenoses was moderate as assessed both by angiography (diameter stenosis ranging from 51% to 74%) and pressure measurements (\( P_d/P_a \) ranging from 0.72 to 1.00). Percent diameter stenosis correlated moderately with \( P_d/P_a \) (\( r = -0.60, p < 0.02 \)) and with systolic pressure gradient (\( r = 0.58, p < 0.024 \)). On the blood samples taken in duplicate (\( n = 84 \)), a very close correlation was found between the first and the second measurement of plasma renin concentration (\( r = 0.95, p < 0.001 \)). The variation coefficient between the 2 measurements of renin was 13.1%.

The \( P_d/P_a \) ratio correlated with both systolic and mean pressure gradient. However, for each level of \( P_d/P_a \) ratio, very large variations in absolute value of systolic and mean pressure gradients were observed (Fig. 2).

Before renal stenting, there was no relationship between the \( P_d/P_a \) ratio and the level of plasma renin concentration. Plasma renin concentrations before and after stenting were compared for the aorta, the renal vein of the stenotic kidney, and the renal vein of the non-stenotic kidney. There was no significant difference in plasma renin concentration for any of the vessels.

The effects of a unilateral, controlled, graded trans-stenotic pressure gradient on plasma renin concentration in the aorta, in the vein of the stenotic kidney, and in the vein of the non-stenotic kidney are shown in Figure 3. Because of the large interindividual variations in the absolute levels of renin, changes in plasma renin concentration are expressed in percent of the baseline values obtained after stenting (when the balloon is deflated and \( P_d/P_a \) is 1). After a 10-min period of balloon inflation to induce a \( P_d/P_a \) ratio of 0.90, no significant changes in plasma renin concentration were observed. However, when a progressively increasing degree of stenosis was applied, a progressive and significant increase in renin was observed in the renal vein of the stenotic kidney, finally reaching a maximal increase of 346 ± 145% for \( P_d/P_a \) of 0.50 (F[1.51,21.2] = 7.38; \( p = 0.006 \)). These values came back to baseline when the balloon was deflated to induce again a \( P_d/P_a \) ratio of 1.00. Changes in plasma renin concentration observed in the aorta were nonsignificant (F[1.44,14.13] = 3.77; \( p = 0.06 \)). However, the large increase in plasma renin concentration in the renal vein of the stenotic kidney was paralleled by a smaller albeit significant transient increase in plasma renin concentration.

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 ± 10</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.06</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Concomitant CAD</td>
<td>12 (75%)</td>
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<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dl</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Familial history of CAD</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>No. of antihypertensive drugs taken</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.83 ± 0.15</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>72 ± 20</td>
</tr>
<tr>
<td>Size of the kidney with the stenotic renal artery (cm)</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td>2.22 ± 0.58</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>Renal resistance index (dimensionless)</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>Systolic pressure gradient (mm Hg)</td>
<td>21 ± 22</td>
</tr>
<tr>
<td>Diastolic pressure gradient (mm Hg)</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>Mean pressure gradient (mm Hg)</td>
<td>9 ± 10</td>
</tr>
<tr>
<td>( P_d/P_a )</td>
<td>0.92 ± 0.08</td>
</tr>
</tbody>
</table>

**Figure 2. Relationship between the individual values of mean aortic pressure (\( P_a \)) / mean pressure distal to the renal artery stenosis (\( P_d \)) ratios and the corresponding systolic pressure gradients (open circles) and mean pressure gradients across the stenosis (closed circles).**

**Figure 3.**
in the renal vein of the non-stenotic kidney (maximal increase of 139 ± 207% for P$_a$/P$_d$ ratio of 0.50 [F1.57,21.98] = 5.21; p = 0.02), suggesting a production of renin also by the non-stenotic kidney.

**DISCUSSION**

There is little controversy regarding the potential benefit of renal artery stenting in hemodynamically significant renal artery stenosis. However, the definition of a hemodynamically significant stenosis (i.e., able to induce renin-mediated hypertension) remains unknown. The present data obtained in patients with renal artery stenosis but no indication of parenchymal disease indicate that stenoses with a P$_d$/P$_a$ ratio smaller than 0.90 are able to induce a significant rise in renin production and should therefore be considered hemodynamically significant. Conversely, renal artery stenoses with a P$_d$/P$_a$ ratio larger than 0.90 are not hemodynamically significant, and stenting these lesions is unlikely to be useful for treating suspected renovascular hypertension.

**Diagnostic difficulties of renal artery stenosis.** The accurate diagnosis and appropriate treatment of renovascular hypertension is complex for several reasons.

First, renal artery stenosis is often an incidental finding in patients with arterial hypertension and atherosclerosis in other locations (5–8). A renal artery stenosis of at least 50% was present in 16% of patients with severe coronary artery disease, 27% of patients with carotid disease, and in 31% of patients with aortic or lower extremity disease. In addition, aided by technical advancement in vascular imaging (e.g., digital computer tomography, magnetic resonance reconstruction, color flow duplex imaging, “drive-by” renal angiography during catheterization), the “fortuitous diagnosis” of renal artery stenoses has become commonplace (12). Therefore, the finding of a renal artery stenosis in patients with arterial hypertension is frequent but often leaves the physician with the question of whether the renal artery stenosis is the cause of the arterial hypertension or whether the arterial hypertension is one of the risk factors that contributed to the development of atherosclerotic lesions, among which are renal artery stenoses.

Second, the definition of a hemodynamically severe stenosis is lacking. Catheter angiography remains the “gold standard” for the evaluation of renal artery stenosis (12), and interventionalists generally define the minimal threshold for an angiographically significant stenosis to be a >50% luminal diameter reduction (13). However, angiography is at best only an estimate of the hemodynamic effect of a stenosis. To cause hypertension, a renal artery stenosis should produce a significant pressure gradient between the aorta and glomerular afferent arterioles. Direct measurement of this pressure gradient is therefore an intuitively more logical means of assessing the potential consequences of a renal artery stenosis. These gradients are often measured by placing a 4-F catheter distal to the lesion while simultaneously measuring the pressure in the aorta (14,15). However, the catheter itself partially obstructs flow and thereby artifactually increases the transstenotic pressure gradient. This problem has been circumvented by the use of 0.014-inch pressure wires (9,16). A peak systolic pressure gradient larger than 20 mm Hg has been proposed to define a significant renal artery stenosis, but this value has no physiologic foundation and has not been validated clinically. As a consequence, the definition of “significant” renal artery stenosis remains an open question. Unlike the situation in the coronary circulation where, in case of epicardial stenosis, myocardial flow is preserved at the expense of perfusion pressure, a stenosis in the renal artery induces vasoconstriction of the efferent arteriole in an attempt by the kidney to keep glomerular filtration pressure normal, although at the expense of flow. This might explain, at least partially, why a rather modest pressure gradient across a renal artery (10% of aortic pressure) represents a hemodynamically significant stenosis with increase of renin production, as observed in this study.

Third, the randomized studies comparing renal angioplasty with medical treatment in hypertensive patients who had renal artery stenosis were too small to be definitive and were, at best, slightly in favor of angioplasty (2–4). The inclusion of patients with irreversible structural changes in the intrarenal vasculature and an elevated renal resistance might be a reason for these mitigated results of renal angioplasty (11).
diameter stenosis is weak, it is likely that patients without significant pressure gradient were included in these trials. In these patients, no clinical benefit could be expected from renal angioplasty, because it will not improve renal hemodynamics.

**Human model of “2-kidney-1-clip” hypertension.** In the present study we used a human model of controlled, graded stenosis by progressive inflation of a compliant angioplasty balloon after renal stenting. The hemodynamic impact was not expressed merely by the pressure gradient, because the latter depends on the level of aortic pressure. Instead, we used the \( P_{a}/P_{d} \) ratio, which corrects the pressure distal to the renal stenosis (measured with a high-fidelity pressure sensor-tipped guide wire) for the prevailing aortic pressure. The \( P_{a}/P_{d} \) ratio actually expresses the renal pressure as a fraction of what it should be without the stenosis. On average, a \( P_{a}/P_{d} \) ratio of 0.90 corresponds approximately to a systolic gradient of 25 mm Hg. Yet, a large range of values of systolic pressure gradient for a narrow range of \( P_{a}/P_{d} \) values was observed, making the systolic pressure gradient alone little useful for individual clinical decision making.

Under the effect of decreasing renal perfusion pressure, a significant release of renin was noticed not only by stenotic kidney but also—albeit modestly—by the contralateral, non-stenotic kidney. The present data do not reveal any insights into the potential mechanisms of this finding. It might be speculated that the production of a mediator by the stenotic kidney or a neurohumoral reflex up-regulates the gene coding for renin also in the non-stenotic kidney. **Study limitations.** The vast majority of patients had only mild renal stenosis. Actually, only 4 patients had a \( P_{a}/P_{d} \) ratio <0.90 before the intervention. This was done on purpose to investigate patients that were as close to normal as possible. This also largely explains why there was no correlation between the ratio of \( P_{a}/P_{d} \) and the plasma renin concentration and why the venous renin plasma concentration from the stenotic kidney was not significantly larger than the arterial renin plasma concentration.

**Clinical implications.** Renal artery stenoses with a \( P_{a}/P_{d} \) ratio larger than 0.90 can be considered hemodynamically not significant, and it is unlikely that renal angioplasty would be useful in these patients even though percent diameter stenosis is larger than 50%. Conversely, renal artery stenoses with a \( P_{a}/P_{d} \) ratio <0.90 should be considered hemodynamically significant regardless of their angiographic severity. These pressure measurements, which should be performed with pressure measuring wires, only take a few minutes, do not need any vasodilatory stimulus, and can be performed during diagnostic catheterization. This index needs to be validated in larger populations before recommending renal revascularization in all patients on the basis of this index. Therefore, larger randomized studies assessing the potential benefit of renal angioplasty should include patients on the basis of these cut-off pressure measurements rather than on merely the angiographic appearance of the stenosis.

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**Reprint requests and correspondence:** Dr. Bernard De Bruyne, Cardiovascular Center, Aalst Onze-Lieve-Vrouw Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E-mail: bernard.de.bruyne@olvz-aalst.be.

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