Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements

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Received 14 March 2007; revised 7 December 2007; accepted 20 December 2007

Aims
A ratio of distal renal pressure to aortic pressure ($P_d/P_a$) <0.90 can be considered a threshold for defining a significant renal artery stenosis (RAS). The aim of this study was to compare renal angiography (QRA) and colour duplex ultrasound (CDUS) to pressure measurements in assessing RAS.

Methods and results
In 56 RAS, percent diameter stenosis (DSangio), minimal luminal diameter (MLD), Doppler-derived peak systolic velocity (PSV), end-diastolic velocity (EDV), and renal-to-aortic ratio (RAR) were obtained and compared with the $P_d/P_a$ measured with a 0.014” pressure wire. $P_d/P_a$ correlated with angiography- and CDUS-derived parameters. The best correlation was observed with EDV ($R = 0.61$). To identify stenosis associated with a $P_d/P_a < 0.90$, the diagnostic accuracy of DS angio was $50\%$, MLD $2 \text{ mm}$, PSV $180 \text{ cm/s}$, EDV $> 90 \text{ cm/s}$ and RAR $> 3.5$ were, respectively, $60\%$, $77\%$, $45\%$, $77\%$ and $79\%$, yet, with a high proportion of false positives ($38\%$, $15\%$, $55\%$, $11\%$ and $15\%$, respectively) indicating an overestimation of the severity of the RAS by both QRA and CDUS. New cut-off values for QRA- and CDUS-derived indices were proposed.

Conclusion
Generally accepted QRA and CDUS-derived indices of RAS severity overestimate the actual severity of RAS. This ‘overdiagnosis’ is likely the main cause of the disappointing results of renal angioplasty for renovascular hypertension.

Keywords
Angioplasty • Renal hypertension • Pressure • Stenosis

Introduction
Treatment of renal artery stenosis (RAS) by percutaneous angioplasty achieved a widespread use although there is no consensus about the degree of renal artery narrowing which justifies revascularization. Several methods have been proposed to identify a ‘significant’ RAS.

Angiography remains the gold standard. Its invasive nature renders it unsuitable for screening purposes. Lesions $> 50\%$ are considered to be significant and amenable to percutaneous treatment. Colour duplex ultrasound (CDUS) is frequently used as a screening tool, but it remains highly operator-dependent. Criteria describing a $60\%$ stenosis have been published. Computed tomography (CT) and magnetic resonance imaging (MRI) angiography are promising alternatives to intra-arterial angiography, the latest evolutions in these techniques allowing for functional characterization of renal tissue. An important limitation of angiography (be it conventional CT or MRI) is that it only provides anatomical information about RAS. The functional implication of a given stenosis remains unclear as these techniques cannot document whether a stenosis is severe enough to cause a pressure gradient, trigger renin release and subsequent renovascular hypertension.

We have shown recently that direct pressure measurement could identify stenoses severe enough to be the cause of renovascular hypertension. Instead of using the trans-stenotic pressure gradient that varies with the level of aortic pressure, the ratio between distal renal pressure ($P_d$) to proximal renal pressure (or aortic pressure, $P_a$) was used. It was shown that $P_d/P_a$ ratio $< 0.90$ was associated with a release of renin in humans, thus providing, for the first time, a functional definition of a ‘significant’ RAS.

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In the present study, we compared the diagnostic accuracy of renal angiography and of CDUS in identifying an RAS associated with a $P_d/P_a$ ratio < 0.90.

**Methods**

In 47 consecutive patients (age 72 ± 7 years) scheduled for renal artery intervention, we evaluated the severity of 56 RAS by CDUS, quantitative renal angiography and pressure measurements. The majority of patients were recruited after screening for aortography, performed after coronary angiography if the following criteria were met: insufficiently controlled arterial hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg) under three or more anti-hypertensive drugs; unexplained renal dysfunction (serum creatinine > 177 µmol/L). Other patients were referred from the outpatient clinic (cardiology, nephrology, endocrinology) with a high suspicion of significant RAS based on screening CDUS1 (peak systolic velocity (PSV) > 180 cm/s, renal-to-aortic ratio (RAR) > 3.5) or after MRA angiography. Patients with creatinine > 300 µmol/L were not included in this study. All patients were recruited between January 2004 and April 2006. The study was approved by the local medical ethics committee. Informed consent was obtained from all patients.

**Quantitative renal angiography**

Quantitative renal angiography (QRA) was obtained by selective injection of 5–10 mL of contrast medium through a 6 or 7F guiding catheter. Using the guiding catheter as scaling device, reference diameter, minimal luminal diameter (MLD, mm), and percent diameter stenosis (DS$_{angiography}$ %) were computed (CAAS II; Pie Medical Imaging, Maastricht, the Netherlands).

**Colour duplex ultrasound**

The CDUS was performed prior to angiography using a commercially available echocardiography unit (Acuson Sequoia C512 imaging system) equipped with the 2.5 MHz sector transducer. Images were acquired in supine and lateral positions. After Doppler angle correction (60°), PSV (cm/s), and end-diastolic velocity (EDV, cm/s) were measured in the aorta and at the site of the stenosis to calculate of RAR (ratio of PSV in aorta and PSV at the site of the stenosis).

**Invasive pressure gradient**

Aortic pressure ($P_a$) was measured through a guiding catheter, while distal renal pressure ($P_d$) was assessed using a 0.014" pressure wire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden) advanced at least 4 cm distal to the renal stenosis. Systolic, diastolic, and mean pressure gradients as well as the $P_d/P_a$ ratio were computed. All measurements were obtained under resting conditions.

Only patients in whom all three techniques (CDUS, angiography, invasive pressure gradient measurement) could be successfully performed were considered for further analysis. Ten patients were not included in this study: in eight patients it was impossible to perform conclusive CDUS measurements, while in two patients, a critical stenosis could not be crossed with a pressure wire, hence translesional pressure gradient measurement could not be performed.

Operators performing the QRA and CDUS measurements were blinded to the invasive pressure assessments.

**Statistical analysis**

All data are expressed as mean ± 1 SD. Gaussian distribution of all parameters was confirmed by Kolmogorov-Smirnov test. In patients with bilateral RAS ($n=9$), we randomly omitted data from one side and considered the data from the contralateral RAS for further analysis, to avoid statistical interdependency. To compare the haemodynamic measurements with angiography- and CDUS-derived data, Pearson correlation coefficient was computed. With a $P_d/P_a$ ratio < 0.90 as cut-off value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were computed for different values of angiography- and CDUS-derived indices. Receiver-operating characteristics (ROC) curves were obtained for the abovementioned parameters and overall sensitivity, specificity, and area under curve were calculated, as well as optimal cut-off values. Optimal cut-off values correspond with the maximum sum of sensitivity and specificity.

Confidence intervals for the optimal cut-off values for the different angiography- and Doppler-derived parameters of RAS were obtained by a bootstrap procedure based on $n=1000$ random samples. Confidence limits reflect the fifth and 95th percentiles of the bootstrap-generated distributions of optimal cut-off values.

It is known that the values for sensitivity and specificity as obtained from our study might be slightly overoptimistic when applied to other patient samples. Unfortunately, the size of our study population did not allow a proper internal cross-validation analysis.

A $P$-value lower than 0.05 was considered to be statistically significant for correlation analysis. Statistical analysis was performed with commercially available software (SPSS Inc., Chicago, IL, USA).

**Results**

Baseline characteristics and cardiovascular risk factors of the study population are depicted in Table 1. Angiographic, Doppler and haemodynamic characteristics of the stenoses are given in Table 2. Figures 1 and 2 show representative examples of the angiographic, Doppler and haemodynamic measurements.

**Angiographic parameters vs. $P_d/P_a$**

$P_d/P_a$ ratio correlated significantly with both percent diameter stenosis ($R = -0.43, P < 0.001$) and with MLD ($R = 0.47, P < 0.001$). The sensitivity, specificity, PPV, NPV, and the diagnostic accuracy of DS$_{angiography}$ % > 50% and an MLD < 2 mm for identifying a haemodynamically significant stenosis ($P_d/P_a < 0.90$) are summarized in Table 3. The corresponding values for a DS$_{angiography}$ % > 60% were 80%, 69%, 55%, 88%, and 72%, respectively. The corresponding values for a DS$_{angiography}$ % > 70% were 40%, 94%, 75%, 77%, and 77%, respectively. MLD in patients with haemodynamically significant RAS ($P_d/P_a < 0.90$) was not statistically different from those patients with $P_d/P_a > 0.90$ (Figure 3).

**Doppler parameters vs. $P_d/P_a$**

$P_d/P_a$ ratio correlated significantly with peak systolic velocity ($R = -0.41, P = 0.001$), with EDV ($R = -0.61, P < 0.001$) and with RAR ($R = -0.59, P < 0.001$) (Figure 4). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of peak systolic velocity > 180 cm/s, EDV > 90 cm/s, and RAR > 3.5 for identifying a haemodynamically significant stenosis ($P_d/P_a < 0.90$) are summarized in Table 3. The corresponding values for a peak systolic velocity > 200 cm/s were 100%, 31%, 41%, 100%, and 53%, respectively.
Pressure gradients vs. $P_d/P_a$

The $P_d/P_a$ ratio correlated with both systolic and mean pressure gradient. However, for each level of $P_d/P_a$ ratio, large variations in absolute value of systolic pressure gradients were observed (Figure 5).

Comparison of techniques

Diagnostic performance of all angiography- and Doppler-derived parameters, for identifying a significant RAS ($P_d/P_a$, 0.90) was assessed using ROC curves.

From ROC analysis, optimal cut-off values as well as sensitivity and specificity were derived.

The data are reported in Table 4. The optimal cut-off value for each index was markedly different than the corresponding, commonly accepted, cut-off values. In addition, RAR had a better diagnostic performance than other indices (highest area-under curve).

Confidence intervals (obtained by bootstrap procedure) for the optimal cut-off values for each parameter are depicted in Table 5. These confidence intervals do not contain the classical cut-off values for DSangio and PSV, illustrating the inferior ability of the classical cut-off values to identify a significant RAS (corresponding to $P_d/P_a < 0.90$).

Pathophysiology of renovascular hypertension

Renovascular hypertension is defined as a syndrome of arterial hypertension induced by stenosis in the renal artery that is severe enough to induce an upregulation of the production
of renin. A decrease in pressure in the afferent arteriole is the major stimulus for renin release from the juxtaglomerular renin-secreting granular cells. The pressure drop changes the degree of stretch of these cells, which leads to baroreceptor-mediated renin release which, in turn, triggers the renin angiotensin system. Since a decrease in renal perfusion pressure is the ‘primum movens’ for renovascular hypertension, it is obvious that when no (or a minimal) pressure gradient is present, the stenosis observed at angiography cannot be held responsible for the systemic hypertension.

### Means of assessing renal artery stenosis

Because of the technical advancement in vascular imaging (e.g., digital computer tomography, MRI reconstruction, colour flow duplex imaging, ‘drive-by’ renal angiography during catheterization), the fortuitous finding of a stenosis of the renal artery has become common place. This is further stimulated by the appealing possibility of ‘curing’ arterial hypertension by a technically easy technique as renal angioplasty.

The ideal test to diagnose RAS should have a high sensitivity, because of its long-term prognostic implications. In the presence

### Table 3

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS&lt;sub&gt;sangio&lt;/sub&gt; &gt;50%</td>
<td>93</td>
<td>44</td>
<td>44</td>
<td>93</td>
<td>60</td>
</tr>
<tr>
<td>MLD &lt; 2 mm</td>
<td>73</td>
<td>78</td>
<td>61</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>PSV &gt; 180 cm/s</td>
<td>100</td>
<td>19</td>
<td>37</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>EDV &gt; 90 cm/s</td>
<td>60</td>
<td>84</td>
<td>64</td>
<td>82</td>
<td>77</td>
</tr>
<tr>
<td>RAR &gt; 3.5</td>
<td>80</td>
<td>78</td>
<td>63</td>
<td>89</td>
<td>79</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; DS<sub>sangio</sub>, percentage diameter stenosis derived from quantitative renal angiography; MLD, minimal luminal diameter; PSV, peak systolic velocity; EDV, end-diastolic velocity; RAR, renal-to-aortic ratio.
Figure 3 Plot of the individual values of $P_d/P_a$ ratio vs. percent diameter stenosis (left panel) and minimal luminal diameter (MLD) (right panel). The vertical line indicates the cut-off value for haemodynamic significance based on invasive pressure gradient measurement. The horizontal line corresponds with the cut-off values based on renal angiography, respectively, 50% diameter stenosis (left) and an MLD of 2 mm (right).

Figure 4 Plot of the individual values of $P_d/P_a$ ratio vs. peak systolic velocity (upper left panel), end-diastolic velocity (EDV) (lower panel), and renal-to-aortic ratio (RAR) (upper right panel). The vertical line indicates the cut-off value for haemodynamic significance based on invasive pressure gradient measurement. The horizontal line corresponds with the cut-off values based on peak systolic velocity (180 cm/s, upper left panel), RAR (>3.5, upper right panel), and EDV (>90 cm/s, lower panel).
of RAS, overall cardiovascular survival is significantly impaired—especially, if bilateral RAS is documented. However, if that same test does not possess adequate specificity, the issue of falsely positive test will become significant.

The diagnostic performance of all current imaging modalities (CDUS, MRI, CT) is always compared with intra-arterial angiography, which is far from ideal, taking into account the often irregular eccentric plaques and substantial interobserver variability.7 Furthermore, the documentation of a ‘significant’ (>50%) stenosis on angiogram does not automatically mean that this stenosis is functionally significant (i.e. there is a trans-stenotic pressure gradient). This is clearly illustrated by our data.

Gross et al.8 showed that systolic and mean arterial pressure gradients highly correlated with stenosis severity, systolic blood pressure, and serum creatinine. At 50% stenosis severity, the systolic pressure gradient was 22 mmHg. Colyer et al.9 showed that ΔP obtained by pressure-sensing guidewire correlated more strongly with angiographic MLD than those obtained by the 4F catheter. The different means of assessing RAS can be subdivided into morphological (angiography) and functional types (Doppler ultrasound, scintigraphy, etc.).3

The main limitation of angiography (be it conventional CT or MRA) is that it is a two dimensional lumenogram. It neither provides any information on the renal flow on driving pressure in the distal part of the renal artery nor on renal tissue resistance. In addition, percent diameter stenosis takes into account a ‘normal’ reference segment, while these atherosclerotic arteries barely show any segment devoid of atherosclerosis. This phenomenon will tend to lead to an underestimation of the actual normal lumen size and, thus, to an underestimation of percent diameter stenosis. In contrast, positive remodelling and post-stenotic dilatation will tend to overestimate the original diameter of the artery and thus to an overestimation of percent diameter stenosis. Both limitations should theoretically be avoided by measuring the absolute MLD. This is, however, contradicted by our findings, as we could not demonstrate any difference in MLD between the subgroup with haemodynamically significant stenosis as compared with patients having $P_d/P_s$ ratio higher than 0.90. The present data suggest that 65% and 1.74 mm are more appropriate cut-off values for $D_{\text{Angio}}$% and MLD, respectively, as they correspond with a stenosis with a $P_d/P_s$ ratio <0.90.

Measuring renal flow velocity by CDUS has the advantage of providing information on the functional significance of the stenosis, i.e. its impact on renal perfusion. It is generally admitted that a PSV larger than 200 cm/s indicates a significant RAS.10,11 Renal blood flow velocity is influenced by both the dimensions of the stenosis and by the renal parenchymal resistance, which explains why EDV can be low in the presence of a haemodynamically significant stenosis.2 Radermacher et al.12 have proposed the renal resistance index [RI, computed as $100*(1-\text{EDV}/\text{PSV})$] as a marker for distal parenchymal resistance. In addition, these authors have shown that patients with a renal stenosis associated with RI lower than 0.8 did significantly better after angioplasty than those in whom the RI was larger than 0.8: stenting renal arteries supplying renal tissue with high resistance does indeed make little sense as nephro-angiosclerosis will not be alleviated by treating the RAS. Therefore, CDUS provides the clinician with information on both the stenosis and the renal tissue. Zeller et al.13,14 however, contradict these findings, as they described an improvement in renal function and blood pressure control irrespective of diabetes mellitus, nephrosclerosis, and unilateral involvement. In the present study, we chose not to include RI as a study parameter, since we aimed to compare only ‘direct’ parameters (at the site of the stenosis).

![Plot of the individual values of $P_d/P_s$ ratio vs. peak systolic trans-stenotic gradient (dots) and mean trans-stenotic gradient (circles)](image)

**Figure 5**

### Table 4 Receiver-operating characteristic curves of different parameters compared with $P_d/P_s$ ratio

<table>
<thead>
<tr>
<th></th>
<th>Optimal cut-off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{\text{Angio}}$</td>
<td>&gt;65%</td>
<td>63 (49–75)</td>
<td>90 (78–96)</td>
<td>77</td>
<td>86</td>
<td>83</td>
<td>0.82 ± 0.072 (0.67–0.91)</td>
</tr>
<tr>
<td>MLD</td>
<td>&lt;1.74 mm</td>
<td>63 (49–75)</td>
<td>94 (83–98)</td>
<td>91</td>
<td>83</td>
<td>85</td>
<td>0.81 ± 0.062 (0.67–0.91)</td>
</tr>
<tr>
<td>PSV</td>
<td>&gt;318 cm/s</td>
<td>88 (76–95)</td>
<td>77 (63–87)</td>
<td>57</td>
<td>88</td>
<td>74</td>
<td>0.88 ± 0.060 (0.75–0.96)</td>
</tr>
<tr>
<td>EDV</td>
<td>&gt;70 cm/s</td>
<td>88 (76–95)</td>
<td>77 (63–87)</td>
<td>62</td>
<td>92</td>
<td>79</td>
<td>0.85 ± 0.066 (0.71–0.94)</td>
</tr>
<tr>
<td>RAR</td>
<td>&gt;3.74</td>
<td>75 (61–85)</td>
<td>97 (88–99)</td>
<td>92</td>
<td>89</td>
<td>89</td>
<td>0.94 ± 0.043 (0.83–0.99)</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; $D_{\text{Angio}}$, percentage stenosis derived from quantitative renal angiography; MLD, minimal luminal diameter; PSV, peak systolic velocity; EDV, end-diastolic velocity; RAR, renal-to-aortic ratio; values in brackets represent 95% confidence intervals.
Ultrasound remains, however, highly operator-dependent and cannot be obtained in all patients. In the present series, it has been impossible to obtain adequate signals in eight patients (not included in the present study). In large series, failure rates as high as 20% are reported. Multiple cut-off values for PSV have been reported in the literature. The present data suggest that the commonly accepted cut-off values provide a too high rate of false positive and that 318 cm/s, 73 cm/s, and 3.74 are more appropriate cut-off values for PSV, EDV, and RAR, respectively, as these values correspond to a stenosis with a significant translesional gradient (Pd/Pa < 0.90). In addition, the RAR was found to have a best diagnostic accuracy with the highest area-under curve.

Newer MRI techniques (such as arterial spin labelling techniques, semi-quantitative perfusion measurements with extracellular gadolinium chelates, and quantitative assessment of renal perfusion with intravascular contrast agents with absolute parameters of regional renal perfusion) are available; they also provide a good estimation of renal perfusion. In an animal model, normal kidney perfusion was 500 mL/100 g/min, which decreased to 150 mL/100 g/min in a 90% stenosis. In patients with pre-existing parenchymal disease, a similar decrease in renal function was observed. A decrease in renal perfusion will therefore be observed in very severe RAS and/or parenchymal disease, but it is unclear whether these techniques will adequately demonstrate a moderate stenosis (e.g. 50–70%). Currently, there are no unequivocal vascular data available describing the renal pressure–flow relationship in humans (it is unknown below which perfusion pressure a decrease in renal perfusion is observed).

In order to be the cause of arterial hypertension, an RAS 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 to assess the potential consequences of an RAS. These gradients are often measured by placing a 4F catheter distal to the lesion, while simultaneously measuring the pressure in the aorta. However, the catheter itself partially obstructs flow and thereby artificially increases trans-stenotic pressure gradient. This problem has been circumvented by the use of 0.014" pressure wires. A peak systolic pressure gradient larger than 20 mmHg has been proposed to define a significant RAS, but this value has no physiological foundation and has not been validated clinically.

The documentation of a trans-stenotic pressure gradient in RAS does not necessarily mean that a given stenosis is the cause of the hypertension in a given patient, as it can be an atherosclerotic consequence of longstanding essential hypertension. None of the presently applied techniques can unequivocally distinguish this entity from ‘true’ renovascular hypertension (which is ‘cured’ by stent-based angioplasty).

Limitations

It is well recognized that the presence of polar renal arteries cannot be adequately assessed by ultrasound. Leung described that ultrasound can only identify 5% of accessory arteries. Hansen et al. reported that the sensitivity of ultrasound to diagnose RAS was only 67% in the presence of polar arteries.

In this study, 0.90 was used as the cut-off value for Pd/Pa, ratio to distinguish between haemodynamically significant and non-significant stenoses. We based this on the observation that renin production increased in a model of unilateral graded artificially induced stenosis. We do not know whether this pressure gradient actually suffices to cause clinical renovascular hypertension.

Conclusion

CDUS as well as quantitative renal angiography-derived percentage of RAS correlate with invasively measured renal trans-stenotic haemodynamics. However, both approaches tend to overestimate the RAS severity when compared with the trans-stenotic pressure measurements. This may negatively influence our expectations of the clinical outcome after percutaneous renal interventions. Further studies describing the clinical outcome of renal interventions based on trans-stenotic pressure measurements are required.

Acknowledgements

The authors would like to thank Prof. Dirk De Bacquer (Department of Public Health, Ghent University, Belgium) for professional statistical advice. Dr Madaric was the recipient of a Slovak Cardiology Society Training Scholarship.

Conflict of interest: none declared.

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