Translesional Pressure Gradients to Predict Blood Pressure Response After Renal Artery Stenting in Patients With Renovascular Hypertension

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Background—In previous studies on the effect of renal stenting on arterial hypertension, patients were selected mainly on the basis of angiographic parameters of the renal artery stenosis. The aim of the present study was to evaluate whether translesional pressure gradients could identify the patients with renal artery stenosis who might benefit from stenting.

Methods and Results—A total of 53 consecutive hypertensive patients with unilateral RAS scheduled for renal artery intervention were recruited. Transstenotic pressure gradients were measured at baseline and during maximal hyperemia, before renal artery stenting. Twenty-four-hour ambulatory blood pressure measurements were performed in all patients before and 3 months after the intervention. Average reductions in systolic blood pressure and diastolic blood pressure at follow-up were −20±30 mm Hg and −2±12 mm Hg, respectively. At multivariate analysis, dopamine-induced mean gradient was the only independent predictor of the variations of both systolic blood pressure (regression coefficient = −4.03, standard error = 1.11; P<0.001) and diastolic blood pressure (regression coefficient = −3.11, standard error = 1.20; P = 0.009). Patients who showed a decline in systolic blood pressure from the baseline value >20 mm Hg were considered as “responders.” The optimal cutoff for identification of “responders” was a dopamine-induced mean gradient ≥20 mm Hg (area under the curve, 0.77; 95% confidence interval, 0.64 to 0.90; P = 0.001).

Conclusions—A dopamine-induced mean pressure gradient of ≥20 mm Hg is highly predictive of arterial hypertension improvement after renal stenting, and therefore this measurement is useful for appropriate selection of patients with arterial hypertension. (Circ Cardiovasc Interv. 2010;3:00-00.)

Key Words: renal hypertension □ renal artery stenosis □ renal artery stent □ renal pressure gradients

The clinical evidence to show that renal artery stenting is effective in improving blood pressure and renal function is weak.1–3 In these studies, patients were selected on the basis of angiographic parameters. The lack of a functional evaluation to ascertain the hemodynamic significance of the renal artery stenosis might account, at least in part, for the lack of improvement after stenting. Recent studies have indicated that translesional pressure gradient measurement might help to identify those patients with renal artery stenosis (RAS) in whom renal artery stenting would be beneficial in terms of hypertension improvement.4,5 However, the definition of improvement in hypertension used in these studies, as suggested by guidelines,6 is based on definite threshold values and therefore may not be able to reflect the actual variations in blood pressure after treatment.

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Table 1. Baseline Clinical and Procedural Characteristics (n=53)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>24-Hour ABPM</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>162±24</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81±12</td>
</tr>
<tr>
<td>Antihypertensive medications, n</td>
<td>3.2±1.2</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2±0.5</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>61±23</td>
</tr>
<tr>
<td>Preintervention arterial blood pressure measurements</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>162±24</td>
</tr>
<tr>
<td>DBP</td>
<td>81±12</td>
</tr>
</tbody>
</table>

Table 2. Translesional Pressure Gradients

<table>
<thead>
<tr>
<th>Gradient</th>
<th>Baseline</th>
<th>Papaverine</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic gradient</td>
<td>31±27</td>
<td>49±31*</td>
<td>49±31*</td>
</tr>
<tr>
<td>Diastolic gradient</td>
<td>4±6</td>
<td>7±9*</td>
<td>10±10†</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>12±12</td>
<td>21±15*</td>
<td>23±16†</td>
</tr>
</tbody>
</table>

*P<0.001 versus baseline; †P value <0.05 versus after papaverine.

Invasive Renal Pressure Gradient Measurement

After quantitative renal angiography (CAAS II; Pie Medical Imaging, Maastricht, The Netherlands) was obtained, a 0.014-inch pressure wire (PressureWire Certus, RADI, St Jude Medical, Upplala, Sweden) was advanced at least 4 cm distal to the renal stenosis for the assessment of distal renal pressure (Pd). Aortic pressure (Pa) was measured through the guiding catheter. Hyperemia was then induced first with papaverine (intrarenal bolus injection of 30 mg) and, after restoration of basal conditions, with dopamine (intrarenal bolus injection of 50 μg/kg)8. Systolic, diastolic, and mean pressure gradients as well as the Pd/Pa ratio were measured under resting conditions and after hyperemic stimuli. Renal artery stenting was then performed according to the standard technique. Procedural success was defined as a residual stenosis <30% in the target vessel.

Quantitative Renal Angiography

Percent DS was derived from quantitative renal angiography performed off-line and using the guide catheter as a scaling device by means of the QuantCor.QCA system (ACOM,PC 5.01, Siemens Medical Systems Inc, Malvern, Pa), based on the CAAS II system (Pie Medical Imaging, Maastricht, The Netherlands).

Statistics

Statistical analysis was carried out using SPSS 15.0 software (SPSS Inc, Chicago, Ill) and significance was defined as a probability value <0.05. Continuous variables are expressed as mean±SD. Categor-
Procedural and angiographic success was achieved in all patients with a reduction of the DS from 58±16% to 8±7%.

Both papaverine and dopamine induced an increase in transstenotic pressure gradient (Table 2), but dopamine-induced hyperemia resulted in significantly higher diastolic gradient (DG) and mean gradient (MG), than papaverine-induced hyperemia (P<0.05 for both comparisons). No significant difference was observed in systolic gradient (SG) and in Pd/Pa.

Clinical follow-up was obtained in all patients. Three months after renal artery stenting, 24-hour mean blood pressure values were significantly lower compared with those recorded preintervention (SBP: 143±32 mm Hg, P<0.001 versus baseline; DBP: 78±13 mm Hg, P=0.039 versus baseline; Figure 1). Average variations (difference between follow-up value and baseline value) in SBP and DBP were −20±30 mm Hg and −2±12 mm Hg, respectively (Figure 2). Univariate analysis showed that transstenotic pressure gradients and Pd/Pa ratios, as well as DS, significantly correlated to blood pressure changes at follow-up. At multivariable linear regression analysis, dopamine-induced MG was the only independent predictor of the variations of both SBP (regression coefficient=−4.03, standard error=1.11; P<0.001) and DBP (regression coefficient=−3.11, standard error=1.20; P=0.009). The number of antihypertensive medications decreased significantly after renal artery stenting (3.2±1.2 versus 2.8±1.4; P=0.005), whereas serum creatinine remained unchanged (1.25±0.53 mg/dL versus 1.21±0.51 mg/dL, P=0.206) as well as creatinine clearance (61±23 mL/min versus 62±23 mL/min; P=0.454).

Responders Versus Nonresponders
At follow-up, 25 patients (47%) showed a decline in SBP from the baseline value >20 mm Hg (the average value in the overall population) with the same or reduced number of antihypertensive medicines. These patients were considered as “responders.” Receiver-operating characteristic curve analysis demonstrated that percent DS, SG, MG, and Pd/Pa, both at baseline and during hyperemia could significantly discriminate between responders and nonresponders (Table 3). Dopamine-induced MG had the highest value of area under the curve (AUC: 0.77; 95% confidence interval, 0.64 to 0.90; P=0.001). A dopamine-induced MG ≥20 mm Hg was the optimal cutoff point to predict a favorable response of hypertension after renal stenting (sensitivity of 72% and specificity of 82%). A dopamine-induced MG ≥32 mm Hg was 95% predictive of a favorable response after renal stenting (Figure 3).

Quantitative Angiography Versus Pressure Gradients
A moderate correlation was found between baseline MG and percent DS (r=0.34, P=0.013; Figure 4A), and between dopamine-induced MG and percent DS (r=0.36, P=0.009;

Table 3. Receiver Operating Characteristic Analyses for the Identification of Responders to Treatment

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>P Value</th>
<th>Optimal Cutoff</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic gradient</td>
<td>0.68</td>
<td>0.53–0.82</td>
<td>0.029</td>
<td>33 mm Hg</td>
<td>52</td>
<td>79</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>Diastolic gradient</td>
<td>0.62</td>
<td>0.46–0.77</td>
<td>0.146</td>
<td>6 mm Hg</td>
<td>32</td>
<td>89</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>0.71</td>
<td>0.57–0.86</td>
<td>0.008</td>
<td>9 mm Hg</td>
<td>64</td>
<td>79</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>Pd/Pa</td>
<td>0.69</td>
<td>0.54–0.83</td>
<td>0.020</td>
<td>0.86</td>
<td>48</td>
<td>79</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td><strong>After papaverine</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic gradient</td>
<td>0.69</td>
<td>0.54–0.83</td>
<td>0.021</td>
<td>34 mm Hg</td>
<td>80</td>
<td>50</td>
<td>59</td>
<td>74</td>
</tr>
<tr>
<td>Diastolic gradient</td>
<td>0.64</td>
<td>0.48–0.79</td>
<td>0.089</td>
<td>11 mm Hg</td>
<td>48</td>
<td>86</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>0.74</td>
<td>0.60–0.87</td>
<td>0.003</td>
<td>23 mm Hg</td>
<td>56</td>
<td>86</td>
<td>78</td>
<td>69</td>
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<tr>
<td>Pd/Pa</td>
<td>0.70</td>
<td>0.56–0.85</td>
<td>0.011</td>
<td>0.75</td>
<td>56</td>
<td>86</td>
<td>79</td>
<td>69</td>
</tr>
<tr>
<td><strong>After dopamine</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic gradient</td>
<td>0.75</td>
<td>0.61–0.88</td>
<td>0.002</td>
<td>48 mm Hg</td>
<td>68</td>
<td>82</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Diastolic gradient</td>
<td>0.63</td>
<td>0.48–0.78</td>
<td>0.099</td>
<td>15 mm Hg</td>
<td>32</td>
<td>93</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>0.77</td>
<td>0.64–0.90</td>
<td>0.001</td>
<td>20 mm Hg</td>
<td>72</td>
<td>82</td>
<td>78</td>
<td>77</td>
</tr>
<tr>
<td>Pd/Pa</td>
<td>0.74</td>
<td>0.60–0.89</td>
<td>0.003</td>
<td>0.79</td>
<td>86</td>
<td>68</td>
<td>74</td>
<td>73</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CI, confidence interval; PPV, positive predictive value; and NPV, negative predictive value.
Of note, among the whole population 31 (58%) patients presented a baseline mean gradient \( <9 \text{ mm Hg} \) and 28 (53%) patients presented a dopamine-induced MG \( <20 \text{ mm Hg} \).

Discussion

Summary of the Present Findings

The present data indicate that patients in whom a substantial decrease in SBP will occur after renal artery stenting for RAS can be reliably identified on the basis of the mean gradient after an intrarenal bolus injection of dopamine. In contrast, the mere angiographic DS is a poor predictor of treatment success.

Previous Studies

The debate around clinical usefulness of renal artery stenting on top of optimal medical treatment is ongoing.\(^9\)\(^{–}\)\(^11\) Only a limited number of randomized studies have directly compared renal artery stenting with intensive medical treatment alone in patients with RAS, and none of these has shown a clear benefit in terms of cardiovascular and renal outcomes in favor of renal revascularization.\(^1\)\(^{–}\)\(^3\) The main reasons for these results are related to the heterogeneity of the outcome measures of these studies and—even more so—to the heterogeneity of patients included in these studies. The definition for success has been widely variable ranging from blood pressure at 6 months\(^1\) to changes in renal function\(^3\) or event-free survival from cardiovascular and renal adverse events.\(^12\) In agreement with guidelines,\(^6\) some authors defined an improvement in arterial hypertension when DBP was \( \leq 90 \text{ mm Hg} \) and/or SBP was \( \leq 140 \text{ mm Hg} \) or in the presence of a reduction in DBP by at least 15 mm Hg with the same or reduced number of antihypertensive medications.\(^4\)\(^\text{,}^5\) However, in these studies, DBP was already around 90 mm Hg to start with in half of the patients; this precludes...
the evaluation of the actual efficacy of the treatment. In the present study, we evaluated blood pressure variations using 24-hour ambulatory blood pressure monitoring, the results of which are known to be markedly lower than those obtained from casual blood pressure measurements. Accordingly, in our patient population, only 25% of patients had an average DBP on 24-hour monitoring >90 mm Hg. This is the main reason why we elected to use criteria for improvement in hypertension, based on actual variations in blood pressure we identified in our population rather than those described by Rundback et al. The renal function was not considered as an end point because the follow-up was very short.

In most studies, comparing medical treatment with renal stenting, patients with refractory hypertension were included mainly on the basis of an RAS at angiography. Arterial narrowings are frequent in patients with hypertension so that it is often difficult to determine whether the RAS is the cause of the hypertension. Moreover, the actual severity of the RAS is often grossly overestimated by angiography. Therefore, it is likely that in previous randomized studies, many patients have been included in whom no improvement could be expected from renal stenting. The present data indicate that in more than half of patients selected for renal stenting on the basis of a RAS of >50% by subjective evaluation of the angiogram, dopamine-induced pressure gradient was <20 mm Hg.

Function Versus Morphology of the RAS
Measuring a pressure difference across the renal artery refers to the very mechanisms by which RAS is supposed to induce hypertension: A decrease in perfusion pressure of the juxtaglomerular apparatus induces a local release of rennin, which in turn triggers the renin-angiotensin system. In addition, a pressure gradient is proportional to the flow across the stenosis and thus provides indirect information about the renal parenchymal resistances. It might be speculated that—for a given degree of stenosis—when parenchymal resistance is high, hyperemic flow will be low. In turn, hyperemic gradient will be small, suggesting that little effect can be expected from renal stenting. In contrast, in the case of moderate stenosis with a normal renal parenchyma, a high hyperemic flow will elicit a large gradient, indicating that renal stenting might be clinically useful. Nevertheless, it should be noted that Zeller et al have reported that patients with more severe resistance indices actually benefit more from revascularization.

Resting Versus Hyperemic Pressure Measurements
Previous studies investigated pharmacologically induced renal hyperemia. In these studies, hyperemia has been proposed as a way to increase the accuracy of the pressure measurements, as is the case in the coronary arteries. The hyperemic stimulus used in previous studies was papaverine. Yet, Manoharan et al have shown that the most powerful renal vasodilator was dopamine (50 μg/kg as an intrarenal bolus). In line with these findings, dopamine appeared to induce significantly higher mean transstenotic gradients in the present study. These larger gradients translated in a slightly better predictive value for dopamine than for papaverine. Nevertheless, it should be observed that renal hyperemia is modest (flow reserve of 1.8) as compared with the myocardium (flow reserve of 5 to 6) and with the peripheral muscles (flow reserve of 8 to 10). Teleologically, this makes sense as the kidney “aims” at maintaining filtration pressure constant (be it at the cost of renal blood flow), whereas the heart “aims” at maintaining blood flow constant (be it at the cost of perfusion pressure). The limited renal hyperemia also explains why the predictive value of mean resting gradient is almost as good as that of mean dopamine-induced gradient.

In conclusion, these data suggest that renal stenting is an effective means of treating hypertension in patients with unilateral RAS selected on the basis of renal artery hemodynamics. The present study indicates that a dopamine-induced mean pressure gradient of ≥20 mm Hg is highly predictive of a marked improvement of the arterial hypertension after renal stenting and therefore that this measurement is useful for appropriate individual decision-making in patients with arterial hypertension.

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Disclosures
None.

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CLINICAL PERSPECTIVE

The clinical usefulness of renal artery stenting in improving blood pressure control in patients with hypertension and a renal
artery stenosis has been questioned by recent studies. We evaluated whether translesional pressure gradients using a
0.014-inch pressure guide wire, both at rest and during hyperemia, could help in selecting patients who will benefit from
renal artery stenting. Dopamine-induced mean gradient was found to be the strongest predictor of the actual blood
pressure improvement at follow-up. Moreover, whereas angiographic parameters of stenosis severity were poor predictors
of treatment success, a dopamine-induced mean gradient ≥20 mm Hg reliably predicted a favorable reduction in
hypertension after stenting. Interestingly, in our study, more than half of the patients selected for renal stenting on
the basis of a subjective angiographic evaluation had a hyperemic translesional gradient below the threshold we found to
be predictive of hypertension improvement. Thus, a dopamine-induced mean pressure gradient of ≥20 mm Hg is highly
predictive of arterial hypertension improvement after renal stenting, and therefore this measurement is useful for
appropriate selection of patients with arterial hypertension.
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