Hemodynamic Index of Atheromatous Renal Artery Stenosis for Angioplasty

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Background and objectives: Trans-stenotic pressure gradient across the constriction (PG), a hemodynamic variable of atheromatous renal artery stenosis (ARAS), is a widely used indicator for angioplasty, but its association with the outcome of angioplasty has not been fully investigated.

Design, setting, participants & measurements: In 34 hypertensive cases with unilateral ARAS, we evaluated hemodynamic variables of ARAS with reference to the systemic BP reduction after angioplasty as the outcome.

Results: In each phase, PG divided by its corresponding prestenotic arterial BP (PG/preBP) had better association with the outcome than PG. The mean phase PG/preBP had the largest area under the curve in the receiver operating characteristic analysis (0.794) with the sensitivity/specificity of 0.957/0.545 for its cut-off >0.15. Although the plasma renin activity, which reflects the perfusion to renal parenchyma, was higher in the angioplasty-efficacious cases than in the angioplasty-inefficacious cases before angioplasty (7.8 ± 6.6 versus 3.4 ± 3.8 ng/ml/h, P = 0.049), it was not generally reduced by angioplasty independent of the outcome.

Conclusions: As the index to select ARAS for angioplasty, PG/preBP was better than PG and the mean phase PG/preBP could be the best. However, other factors such as the microvascular kidney disease, which affect the perfusion to renal parenchyma, would influence the outcome.


Materials and Methods

Patients Selection

All of the patients who were referred to our department for suspicion of renovascular hypertension between January 1999 and December 2007 (n = 808) were enrolled in this study. Patients with at least one risk factor of atheroma (smoking, dyslipidemia, or DM) in addition to hypertension were evaluated by computed tomographic arteriography (CTA) or magnetic resonance arteriography (MRA), if they had relatively preserved renal function (serum creatinine concentration (sCr) <176.8 mmol/L). Patients suspected of having ARAS based on the results of CTA and MRA were further evaluated by selective renal arteriography, and 34 patients with unilateral ARAS on one of the main trunks were included in the study. In all 34 patients, ARAS was treated by percutaneous transluminal renal angioplasty with the insertion of a stainless steel endoprosthesis (Palmaz stent with a diameter of 5 to 7 mm). Informed consent was obtained from all of the patients.

Data Collection

Baseline and postangioplasty information were recorded before the angioplasty and at 1 to 3 mo after the angioplasty, respectively. All blood samples were collected under fasting conditions in the morning. The sCr and the plasma renin activity (PRA) were enzymatically measured. The glomerular filtration ratio (GFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) study equation modified for Japanese (7).

Therapeutic Outcome of Angioplasty

As the therapeutic outcome of angioplasty, we used the systemic BP reduction after angioplasty, which was defined as reduction in the total score of the administered antihypertensive agents with no increase in the office BP after angioplasty. For each patient, the total score was

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calculated before and after angioplasty as follows. Each antihypertensive agent was standardized by dividing the administered dose by its corresponding maximum approved daily dose. The sum of all of the standardized doses was used as the total score. The office BP reading was performed before and after angioplasty according to the guideline (6). The self-monitoring of the pre- and postangioplastic BP was also performed in all of the patients (8,9), and no increase in self-monitored BP was confirmed in the patients with no increase in the office BP.

Evaluation of the Arteriography
We evaluated the angiography of ARAS as described previously (10). In brief, the width of the renal artery was measured by a computer-based method on the arteriography with the narrowest image of ARAS. The width of the narrowest part was taken as the minimal lumen diameter, and the mean width of the first normal segments proximal and distal to ARAS was taken as the reference width. The % diameter reduction was calculated as “100 (1 − width of narrowest part/the reference width).”

Measurement of PG
We measured PG in each ARAS lesion using an end-hole 3-French catheter. The catheter was placed distal to the lesion, and the pressure measured there was recorded as the prestenotic arterial BP. Then the catheter was pulled back over the lesion and placed proximal to the lesion. The pressure measured there was recorded as the poststenotic arterial BP. PG was calculated by subtracting the poststenotic arterial BP from the prestenotic arterial BP in each phase. In all of the ARAS lesions, the systolic phase PG was decreased to <10 mmHg after angioplasty.

Statistical Analysis
Continuous variables were expressed as the mean ± SD (SD) and compared by using t test. Discrete variables were expressed as counts and compared by using χ² test. Statistical analysis was performed by using the Dr. SPSS II software package (SPSS, Chicago, IL). Probability values of P < 0.05 were considered statistically significant.

Results
Baseline Characteristics of the Patients
The baseline characteristics of the 34 cases examined in this study are summarized in Table 1. Angioplasty decreased the total score of antihypertensive agents in 23 cases (angioplasty-efficacious cases), but it did not decrease the score in the other 11 cases (angioplasty-inefficacious cases). The baseline systemic BP was lower and the baseline PRA was higher in the angioplasty-efficacious cases than in the angioplasty-inefficacious cases, while both had nearly the same estimated GFR and used nearly the same doses of antihypertensive agents. The angioplasty-inefficacious cases were younger than the angioplasty-inefficacious cases, whereas the difference was not statistically significant.

The total score of the antihypertensive agents was generally high in the cases with low baseline systemic BP and high baseline PRA. However, the correlation of the score with either the systemic BP in each phase or the PRA was NS; the correlations with the systolic BP, the diastolic BP, and the PRA were −0.097 (P = 0.584), −0.212 (P = 0.229), and 0.269 (P = 0.123), respectively.

Hemodynamic Variables and the Angioplasty Outcome
Hemodynamic variables of ARAS are summarized in Table 2. We introduced PG divided by its corresponding prestenotic arterial BP (PG/preBP) as the variables. In each phase of BP, preangioplasty PG was higher in the angioplasty-inefficacious cases than in the angioplasty-efficacious cases. Preangioplas-

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<th>Table 1. Baseline characteristics of patientsa</th>
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<td>Age (years)</td>
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<td>Gender (% female)</td>
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<td>Systemic BP (mmHg)</td>
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<td>Systolic</td>
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<td>Diastolic</td>
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<tr>
<td>sCr (μmol/L)</td>
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<tr>
<td>GFR (ml/min/1.73 m²)</td>
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<td>PRA (ng/ml/h)</td>
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<td>Antihypertensive, n (%)</td>
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<td>Total score</td>
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<td>CCB</td>
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<td>ACEI</td>
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<td>ACEI or ARB</td>
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<tr>
<td>β-blocker</td>
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<td>α-blocker</td>
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<td>diuretic</td>
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aData are presented as the mean ± SD when appropriate. BP, blood pressure; sCr, serum creatinine; GFR, estimated glomerular filtration ratio; PRA, plasma renin activity; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
tic PG/preBP was also higher in the former than in the latter, and its difference was more significant than that of PG in each phase. In all of the cases, angioplasty was successful; sufficient stent-deployment and no residual stenosis were confirmed by postangioplastic renal arteriography. Although postangioplastic PG was slightly lower in the angioplasty-inefficacious cases than the angioplasty-efficacious cases, the difference was NS in each phase.

In both the systolic and mean phases, PG/preBP had larger area under the curve (AUC) in the receiver operating characteristic (ROC) analysis for the systemic BP reduction after angioplasty than PG (Figure 1). The mean phase PG/preBP had the largest AUC of 0.794; the other variables, the mean phase PG, the systolic phase PG/preBP, and the systolic phase PG, had AUC of 0.775, 0.764, and 0.749, respectively. The mean phase PG/preBP had also higher combination of sensitivity and specificity than the other variables. At a cut-off >0.15, the sensitivity/specificity for the mean phase PG/preBP was 0.957/0.545. In comparison, the systolic phase PG had the sensitivity/specificity of 0.957/0.273 at a cut-off >20 mmHg, one of the widely used threshold values for it to perform angioplasty.

The total score of the antihypertensive agents was generally high in the cases with high preangioplastic PG. However, its correlation with each variable of preangioplastic PG was NS, and even the correlation with the mean phase PG/preBP, which had the largest AUC for the outcome, was 0.218 (P = 0.216).

Angiographic Indices and PG/prePG

We further compared the mean phase PG/preBP with the angiographic indices (Figure 2). The cases with the mean phase PG/preBP >0.15 had the minimal lumen diameter <3 mm in 18/20 cases, and the % diameter reduction >50% in 17/20 cases.

![Figure 1. ROC for the angioplastic outcome. Variables in the systolic (left panel) and mean phases (right panel) are analyzed by ROC curve for the systemic BP reduction after angioplasty. Black and gray lines show analysis of PG and PG/preBP, respectively. PG, trans-stenotic pressure gradient; preBP, prestenotic arterial BP.](image1)

![Figure 2. Correlation of hemodynamic index with angiographic indices. Angiographic indices, minimal lumen diameter (left panel) and % diameter reduction (right panel), were plotted against the mean phase PG/preBP. Vertical lines indicate PG/preBP of 0.15. Horizontal lines in the left and right panels indicate the diameter of 3 mm and the reduction of 50%, respectively. PG/preBP, trans-stenotic pressure gradient/prestenotic arterial BP in the mean phase.](image2)
cases. Conversely, the cases with the minimal lumen diameter <3 mm had the mean phase PG/preBP >0.15 in 18/24 cases, and the cases with the % diameter reduction >50% had the mean phase PG/preBP >0.15 in 17/25 cases.

Association of PRA and the Angioplastic Outcome

As a variable that reflects the renal perfusion, we compared the baseline and postangioplastic PRA in the angioplasty-efficacious and the angioplasty-inefficacious cases (Table 3). PRA was generally not reduced after angioplasty, and it rather increased after angioplasty in many cases independent of the outcome. The postangioplastic PRA was still higher in the angioplasty-efficacious cases than in the angioplasty-inefficacious cases, and the mean ratio of the postangioplastic PRA to baseline PRA was same in both.

Discussion

The results of this study showed that the mean phase PG/preBP, a hemodynamic variable of ARAS introduced in this study, was the best index to select ARAS for angioplasty among hemodynamic variables examined. The angioplastic parameters such as residual stenosis could affect the angioplastic outcome. However, the difference of angioplastic parameters would not have affected the outcome in this study, because postangioplastic PG was not different independent of the outcome. In this study, we used a micro-catheter as a device to measure PG, and the PG in “high-grade” stenosis could have been overestimated. However, “high-grade” stenosis would have high PG without overestimation, and the ARAS that has PG around the cut-offs for angioplasty would be “low-grade” stenosis. In these “low-grade” ARAS, a micro-catheter and PressureWire, one of the thinnest devices, is reported to give nearly same PG (11). Therefore, the obstructive effect by the device would not have affected the cut-offs of hemodynamic variables for angioplasty in this study.

The systolic phase PG is a generally used variable to indicate the “hemodynamic significance” of ARAS, although it has not been validated sufficiently with regard to the therapeutic outcome (6). The systolic phase PG ≥15 or >20 mmHg is widely considered to be “clinically significant” (2,4,6), but it was also reported that no cases with the systolic phase PG <40 mmHg benefited by angioplasty (12). However, because the systemic BP before angioplasty was >190/120 mmHg in the cases without benefit from angioplasty, the high prestenotic arterial BP is thought to have increased the PG in these cases.

Hydrodynamically, the prestenotic arterial BP affects PG; PG increases accordingly as the prestenotic arterial BP increases (13,14). Therefore, owing to the fluctuation of the prestenotic arterial BP, PG would be inconsistent (4). PG/preBP, which has linear relation to PG (15), is thought to cancel out the effect of the prestenotic BP on PG and to be a better index for the “hemodynamic significance” of ARAS than PG. Supporting this notion, it is reported that renin in the renal vein of the kidney with stenosis increases when poststenotic arterial BP/prestenotic arterial BP is <0.90 (PG/preBP >0.10) (15).

The mean phase PG/preBP had larger AUC in the ROC analysis than the systolic phase PG/preBP. The systolic and mean phases of BP correspond to the peak and mean of the ejected bolus volume of cardiac contraction, respectively (16), and the latter reflects more closely the total amount of blood supply to the organs. Therefore, the poststenotic arterial BP in the mean phase is thought to reflect the total blood supply to the kidney. The PG, the poststenotic arterial BP subtracted from the prestenotic arterial BP, in the mean phase is thought to reflect the reduction of the total blood supply to the kidney, and it would be suitable to indicate “hemodynamic significance” of ARAS.

Previously, we showed that the minimal lumen diameter <3 mm could be a good angiographic index to select ARAS for angioplasty; it could select the angioplasty-efficacious ARAS more adequately than % diameter reduction ≥50% and ≥75%, widely used angiographic indices for ARAS (10). Supporting this notion, most of ARAS with the mean phase PG/preBP >0.15 could be selected by the minimal lumen diameter <3 mm. These results indicate that ARAS could be selected for PG-measurement by the angiographic index of the minimal lumen diameter <3 mm, and then selected for angioplasty by the hemodynamic index of the mean phase PG/preBP >0.15.

The AUC was only 0.794 even for the mean phase PG/preBP. This indicates that the systemic BP reduction after angioplasty cannot be predicted only by “hemodynamic significance” of the stenosis. Because ARAS is frequently accompanied with atheromatous lesions in the intrarenal arteries (2,17), the microvascular kidney disease is thought to have affected the outcome in ARAS. PRA is known to increase accordingly as perfusion to the viable renal parenchyma decreases (18,19), and PRA in the cases of ARAS would reflect the ischemia caused by not only ARAS lesions but also the microvascular kidney disease. The baseline PRA in this study, which was higher in the angioplasty-efficacious cases than in the angioplasty-inefficacious cases, indicated that more amount of viable renal parenchyma was ischemic in the former than in the latter. No reduction of

Table 3. PRA with reference to the angioplastic outcomea

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<th>All (n = 34)</th>
<th>Angioplasty</th>
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<tr>
<td></td>
<td>Efficacious (n = 23)</td>
<td>Inefficacious (n = 11)</td>
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<tr>
<td>Pre-angioplastic PRA (ng/ml/h)</td>
<td>6.4 ± 6.1</td>
<td>7.8 ± 6.6</td>
<td>3.4 ± 3.8</td>
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<tr>
<td>Post-angioplastic PRA (ng/ml/h)</td>
<td>6.0 ± 9.2</td>
<td>8.0 ± 10.7</td>
<td>1.8 ± 1.6</td>
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<tr>
<td>Post/Pre ratio</td>
<td>1.3 ± 1.5</td>
<td>1.3 ± 1.5</td>
<td>1.3 ± 1.6</td>
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aData are presented as the mean ± SD. PRA, plasma renin activity.
postangioplasty PRA not only in the latter but also in the
former indicated persistence of the ischemia even after angi-
plasty in both. The ischemia would have been caused mostly by
the microvascular kidney disease in many cases independent of
the outcome. The usage of the variables that could reflect the
microvascular kidney disease might improve prediction of the
outcome in ARAS (1,2,17).

The angioplasty-efficacious cases had lower baseline sys-
temic BP than the angioplasty-in efficacious cases. This would
indicate that the angioplasty-efficacious cases had more medi-
cation-controllable hypertension, whereas angioplasty is gener-
ally recommended for the cases with medication-uncontrolla-
hypertension (3,20,21). However, the angioplasty-efficacious cases used the antihypertensive agents that can
inhibit the renin-angiotensin cascade at higher prevalence than
the angioplasty-in efficacious cases, although the baseline total
antihypertensive score was the same in both. The usage of these
agents might have effectively reduced the systemic BP in the
angioplasty-efficacious cases. The effectiveness of these agents
and younger age in these cases might have indicated that a larger
amount of viable renal parenchyma was preserved in them.

Conclusion

The mean phase PG/preBP would be a better index to select
ARAS for angioplasty than the systolic phase PG, a widely used
indicator. However, the efficacy of angioplasty could be influ-
enced by the factors that affect the intrarenal perfusion, such as
the microvascular kidney disease. To predict the efficacy of
angioplasty, appropriate evaluation of these factors would be
necessary. The analysis in future studies with the variables that
reflect these factors could afford more information to select
treatment for ARAS.

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Disclosures

None.

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