INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Plasma Renin Activity Predicts the Improvement in Resistant Hypertension after Percutaneous Transluminal Renal Artery Angioplasty

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Abstract

Objective Percutaneous transluminal renal artery angioplasty (PTRA) has been recommended for the treatment of renovascular resistant hypertension. However, large randomized trials have reported that PTRA did not improve the outcomes compared with optimal medical therapy in patients with renal artery stenosis (RAS). It is important to identify patients with renovascular hypertension who are likely to respond to PTRA. We herein examined whether or not the plasma renin activity (PRA) could predict the improvement in resistant hypertension after PTRA for RAS.

Methods and Results A total of 40 patients (mean age: 63±15 years) with unilateral RAS who received PTRA for resistant hypertension were enrolled in this study. Twenty-two (55%) patients experienced a significant reduction in their blood pressure while using few antihypertensive agents at the 3-month follow up. The median PRA was significantly higher in patients using few antihypertensive agents than in those using more [4.2 ng/mL/hr, interquartile range (IQR) 2.6-8.0 vs. 0.8 ng/mL/hr, IQR 0.4-1.7, $p<0.001$]. To predict the improvement in hypertension after PTRA, a receiver operating characteristic analysis determined the optimal cut-off value of PRA to be 2.4 ng/mL/hr. A multivariate logistic regression analysis showed that higher PRA (>2.4 ng/mL/hr) was an independent predictor of the improvement in hypertension after PTRA (odds ratio: 22.3, 95% confidence interval: 2.17 to 65.6, $p<0.01$).

Conclusion These findings suggest that the evaluation of preoperative PRA may be a useful tool for predicting the improvement in resistant hypertension after PTRA for patients with RAS.

Key words: percutaneous renal artery angioplasty, renal artery stenosis, plasma renin activity

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Introduction

Atherosclerotic renal artery stenosis (RAS) and fibromuscular dysplasia are the common causes of secondary hypertension (1, 2). A previous study reported that atherosclerotic RAS was present in approximately 7% of persons over 65 years of age, according to a population-based estimation (1). RAS is closely associated with resistant hypertension, chronic kidney disease, and acute pulmonary edema (3). Percutaneous transluminal renal artery angioplasty (PTRA) has been demonstrated to be effective in improving the blood pressure in hypertensive patients with RAS (4). However, large randomized trials have shown that PTRA does not improve outcomes compared with optimal medical therapy in patients with RAS (5, 6). Conversely, a recent study showed that the appropriate selection of patients with RAS resulted in improved blood pressure control after renal artery revascularization (7). However, while the accurate selection of suitable patients is important, few predictors of favorable

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clinical outcomes after PTRA in patients with RAS have been identified.

The activation of the renin-angiotensin system results in a series of enzymatic reactions and subsequently leads to hypertension, heart failure, renal dysfunction, and atherosclerosis (7, 8). The plasma renin activity (PRA) has been demonstrated to be a biomarker which reflects the activation of the renin-angiotensin system (9). In addition, higher PRA levels were associated with an increased risk of cardiovascular events and mortality in patients with chronic vascular disease or chronic heart failure (10, 11). However the association between the PRA and the effectiveness of renal artery revascularization in patients with RAS remains unclear. The aim of this study was to evaluate whether or not the PRA could identify patients with RAS who might benefit from PTRA.

Materials and Methods

Study population

Between March 2010 and June 2015, PTRA was successfully performed in 53 patients with RAS in Yamagata Prefectural Center Hospital. PTRA was performed in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (12). RAS was defined as a percentage diameter stenosis ≥60% by angiography or a pressure gradient >15 mmHg, or both (13). Among these patients, eight patients who underwent PTRA for renal dysfunction, congestive heart failure, and bilateral RAS were excluded. The PRA was not measured in five patients. The remaining 40 patients who underwent PTRA for resistant hypertension were included in this study. Resistant hypertension was diagnosed based on either or both a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in patients on at least two antihypertensive agents. Informed consent was obtained from all patients before participation in the study, and the study protocol was approved by the Human Investigations Committee at our institution.

Percutaneous renal artery angioplasty

All of the patients were treated with double anti-platelet agents. We started the administration of aspirin (100-200 mg/day) and clopidogrel (75 mg/day) at least 3 days before PTRA. Aspirin was administered indefinitely after the procedure, and clopidogrel was required for at least 1 month after the procedure. After the intravenous administration of 5,000 U of heparin, PTRA was performed. All procedures were performed using six French guiding catheters and 0.014-inch guidewire systems through either the radial, brachial, or femoral artery approach. The operator decided whether or not a distal protection device should be used, and the position and length of the stent was determined based on gray-scale intravascular ultrasound findings. Stents (Palmaz Genesis; Johnson & Johnson, Cordis Co., Bridgewater, NJ, USA) ranging between 4.0 and 6.0 mm in diameter were implanted in the patients in this study. Successful PTRA was defined as a percentage diameter stenosis <30%, a pressure gradient <15 mmHg, or both (13).

Measurement of the blood pressure and plasma renin activity

The blood pressure was measured in both arms after the patient had been resting for 10-15 minutes for patients that were either hospitalized or were treated on an out-patient basis. We used the average of these two measurements in this study. The PRA was obtained from a blood sample collected from the peripheral vein after a 10- to 15-minute rest in the sitting position and after at least a 30-minute rest in the supine position (14). The blood sample was collected in EDTA tubes and rapidly frozen at -20℃ after centrifugation. The PRA was measured using a radioimmunoassay kit (PRA [SRL]; Special Reference Laboratory Co., Tokyo, Japan) at the laboratory of the manufacturer.

Clinical outcomes

All of the patients were followed-up in our hospital for three months after PTRA. In the present study, clinical responders to PTRA were defined as subjects who had a systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg and who were using few antihypertensive agents at the 3-month follow up. A board-certified member of the Japanese Society Hypertension or the Japanese Circulation Society determined whether or not to reduce the use of antihypertensive agents in a given patient at our hospital (15).

Statistical analysis

The continuous variables are expressed as the mean value ± standard deviation. Skewed variables are presented as the median and interquartile range. Student's *t*-test and the chi-square test were used to compare continuous and categorical variables, respectively. When the data were not normally distributed, the Mann-Whitney test was used. A receiver operating characteristic curve analysis was performed to determine the cut-off values of the PRA. Areas under the curves were calculated using the trapezoidal rule. Univariate and multivariate analyses with the Cox proportional hazard regression model were used to determine significant predictors for clinical responders after PTRA. Age, sex, and other variables that were significant according to the univariate analyses were entered into the multivariate Cox proportional hazard analysis. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using the SAS statistical software package (version 9.0 SAS Institute Inc., Cary, NC, USA).

Table 1. Patient Baseline Clinical Characteristics.

	All patients n=40	Responder n=22	Non-responder n=18	p value
Age, years	63 ± 15	59 ± 17	68 ± 8	0.03
Male gender, (%)	23 (58%)	12 (55%)	11 (61%)	0.68
BMI, kg/m^2	24 ± 4	24 ± 5	23 ± 4	0.85
Use of stent, (%)	36 (90%)	19 (86%)	17(94%)	0.38
Etiology				0.15
Arteriosclerosis, (%)	35 (87%)	18 (82%)	17 (94%)	
Fibromuscular dysplasia, (%)	5 (13%)	4 (18%)	1 (6%)	
Risk factors				
Smoking, (%)	23 (58%)	14 (63%)	9 (50%)	0.39
Diabetes mellitus, (%)	12 (30%)	7 (32%)	5 (28%)	0.78
Dyslipidemia, (%)	15 (38%)	9 (41%)	6 (33%)	0.62
Blood examination				
Plasma renin activity, ng/mL/hr	2.55 (0.70-4.65)	4.15 (2.58-8.01)	0.75 (0.40-1.70)	< 0.001
eGFR, mL/min/1.73m^2	58 ± 22	61 ± 23	54 ± 21	0.31
Medication				
ACE inhibitor or ARB, (%)	34 (85%)	19 (86%)	15 (83%)	0.79
Calcium channel blocker, (%)	38 (95%)	21 (95%)	17 (94%)	0.88
β-blocker, (%)	12 (30%)	6 (27%)	6 (33%)	0.68
Diuretics, (%)	16 (40%)	10 (45%)	6 (33%)	0.43
α-blocker, (%)	12 (30%)	7 (32%)	5 (28%)	0.78
Renin inhibitor, (%)	5 (13%)	2 (9%)	3 (17%)	0.47
Statin, (%)	14 (35%)	9 (41%)	5 (28%)	0.39
Echographic examination				
Peak systolic velocity, cm/sec	318 ± 77	306 ± 76	332 ± 78	0.30
Acceleration time, msec	82 ± 32	93 ± 35	67 ± 19	0.02

Data are presented as the mean ± SD, number (%) of patients, or median (interquartile range), BMI: body mass index, eGFR: estimated glomerular filtration rate, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker

Results

Baseline patient characteristics

The baseline patient characteristics are summarized in Table 1. A total of 40 consecutive patients (23 men and 17 women, mean age 63±15 years), who received PTRA for resistant hypertension were enrolled in this study. The etiologies were arteriosclerosis in 35 (87%) patients and fibromuscular dysplasia in the remaining 5 (13%) patients. All patients with arteriosclerosis and 1 patient with fibromuscular dysplasia underwent stent implantation (n=36, 90%). Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (85%), Ca-channel blockers (95%), β-blockers (30%), diuretics (40%), α-channel blockers (30%), renin inhibitors (13%), and statins (35%) were administered before renal artery intervention. A total of 22 (55%) patients had a significant reduction in their blood pressure using few antihypertensive agents. The responder group tended to be younger than the non-responder group (59±17 vs. 68±8 years, p=0.03). The PRA was significantly higher in the responder group than in the non-responder group (4.2 ng/mL/hr, interquartile range [IQR]: 2.6-8.0 vs. 0.8 ng/mL/hr, IQR: 0.4-1.7, p<0.001). In addition, the acceleration time measured through renal echography was significantly longer in the responder group than in the non-responder group (93±35 vs. 67±19 msec, p=0.02). No significant differences were noted between the two groups in gender, body mass index, etiology of RAS, risk factors for arteriosclerosis, estimated glomerular filtration rate, medication before procedure, or peak systolic velocity as measured via renal echography.

Blood pressure after renal artery intervention

The mean systolic blood pressure decreased from 152±12 mmHg before intervention to 134±14 mmHg at the 3-month follow-up, and the mean diastolic blood pressure decreased from 85±13 to 77±10 mmHg. The mean number of antihypertensive agents used decreased from 3.4±1.5 before procedure to 2.7±1.7 at the 3-month follow-up. No significant differences were noted between the two groups in the systolic blood pressure or the number of antihypertensive agents used before the procedure. The diastolic blood pressure before the procedure was significantly higher in the responder group after PTRA than in the non-responder group (89±12 vs. 80±13 mmHg, p=0.03). The systolic blood pressure, the diastolic blood pressure, and the number of antihypertensive agents used at the 3-month follow-up were significantly lower in the responder group than in the non-responder group (129±10 vs. 141±15 mmHg, p=0.008; 73±9 vs. 81±9 mmHg, p=0.005; 1.9±1.5 vs. 3.6±1.5, p=0.001, respectively) (Table 2).

Predictors of the improvement in hypertension after PTRA

A receiver operating characteristic curve analysis showed that a PRA of 2.4 ng/mL (sensitivity, 86%; specificity, 83%; area under the curve, 0.89) was the threshold value for predicting an improvement in the blood pressure using fewer

Table 2. Changes in the Blood Pressure and Number of Antihypertensive Medications after PTRA.

	All patients n=40	Responder n=22	Non-responder n=18	p value
Systolic blood pressure, mmHg				
Preprocedure	152 ± 12	152 ± 11	151 ± 14	0.84
Follow-up at 3-months	134 ± 14	129 ± 10	141 ± 15	0.008
Mean difference	-17 ± 13	-22 ± 11	-11 ± 11	0.002
Diastolic blood pressure, mmHg				
Preprocedure	85 ± 13	89 ± 12	80 ± 13	0.03
Follow-up at 3-months	77 ± 10	73 ± 9	81 ± 9	0.005
Mean difference	-8 ± 12	-16 ± 10	1 ± 7	<0.001
Antihypertensive agent, No.				
Preprocedure	3.4 ± 1.5	3.4 ± 1.6	3.3 ± 1.5	0.79
Follow-up at 3-months	2.7 ± 1.7	1.9 ± 1.5	3.6 ± 1.5	0.001
Mean difference	-0.7 ± 1.1	-1.45 ± 0.73	0.33 ± 0.69	<0.001

Data are presented as the mean ± SD.

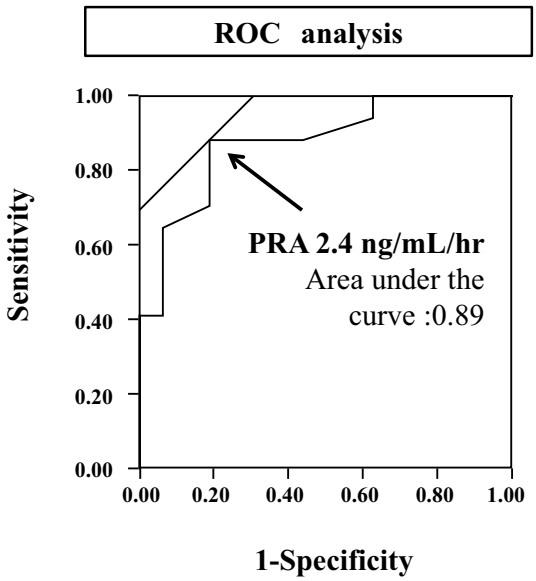

Figure. A receiver operating characteristic curve analysis for predicting the reduction in number of antihypertensive agents used after PTRA. This analysis showed the optimal cut-off PRA value to be 2.4 ng/mL (sensitivity, 86%; specificity, 83%; area under the curve, 0.89).

antihypertensive agents (Figure). A univariate Cox analysis showed that age, diastolic blood pressure, PRA, and acceleration time were significantly associated with the improvement in the blood pressure while using few antihypertensive agents (Table 3). A multivariate Cox analysis revealed that only the PRA was an independent predictor for the improvement in hypertension after PTRA (odds ratio: 22.3, 95% confidence interval: 2.17 to 65.6, p<0.01) (Table 4).

Discussion

Our results demonstrated that an elevated PRA was an independent predictor of the improvement in hypertension in patients with RAS after PTRA. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial demonstrated that, compared with optimal medical therapy, renal intervention did not improve the outcomes of renal artery revascularization in patients with RAS (4). Furthermore, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial showed that PTRA does not improve the outcomes of patients with advanced or symptomatic RAS (5). In light of findings from these two large randomized trials and interventional complications, physicians increasingly often choose medical therapy over renal artery intervention. However, although demonstrating the benefits of renal artery intervention has proven difficult in large groups, some patients do indeed experience remarkable improvements in the blood pressure, kidney function, and cardiovascular stability after PTRA (7, 8). Therefore, there is a need to identify the optimal timing and the subpopulation of patients who are likely to benefit from PTRA.

Lim et al. previously demonstrated that dynamic contrast-enhanced magnetic resonance imaging may be useful for predicting the outcome of revascularization in patients with RAS (16). However, the use of contrast-enhanced magnetic resonance imaging may carry a risk of nephrogenic systemic fibrosis. Staub et al. reported that B-type natriuretic peptide may be a useful marker for predicting an improvement in blood pressure after PTRA for RAS (8). However, B-type natriuretic peptide has been shown to be elevated in patients with congestive heart failure and has a low specificity (approximately 50%); therefore, this biomarker has not been routinely used as marker for predicting the outcome of renal artery revascularization. In the present study, we focused on another blood biomarker: the PRA.

The renin-angiotensin system plays an important role in the process of hypertension among patients with RAS. Decreased renal perfusion activates the release of renin in renovascular hypertension. These elevated plasma renin levels then lead to increased concentrations of angiotensin II, which subsequently cause systemic hypertension due to vasoconstriction, renal sodium retention, aldosterone secretion, and sympathetic nerve system activation (17). Of note, the activation of the renin-angiotensin system in renovascular hypertension is not a transient phenomenon. The PRA returns to normal levels after leaving the renal artery. Other

Table 3. A Univariate Analysis for Predicting the Improvement in Hypertension after PTRA.

Variables	Odds ratio	95% CI	p value
Age, per 1-year increase	0.94	0.88 – 0.99	0.02
Male gender	0.76	0.21 – 2.70	0.67
BMI, per SD increase	1.33	0.07 – 27.2	0.85
Fibromuscular dysplasia	4.23	0.56 – 87.3	0.17
Systolic blood pressure	1.00	0.95 – 1.06	0.83
Diastolic blood pressure	1.06	1.00 – 1.13	0.02
Risk factor			
History of smoking	1.75	0.49 – 6.39	0.38
Diabetes mellitus	1.21	0.31 – 4.98	0.78
Dyslipidemia	1.38	0.38 – 5.23	0.62
Blood tests			
Plasma renin activity >2.4ng/mL/hr	31.6	6.44 – 222	<0.01
eGFR, per SD increase	1.02	0.98 – 1.05	0.29
Echocardiography			
Peak systolic velocity, per SD increase	0.99	0.98 – 1.00	0.28
Acceleration time, per SD increase	1.04	1.00 – 1.10	0.01
Use of			
ACE inhibitors and/or ARBs	1.27	0.21 – 7.72	0.79
Ca channel blockers	1.23	0.05 – 32.8	0.88
β-blocker	0.75	0.19 – 2.96	0.67
Diuretics	1.67	0.46 – 6.31	0.43
α-blocker	1.21	0.31 – 4.98	0.78
Renin inhibitor	0.50	0.06 – 3.37	0.47
Statin	1.80	0.48 – 7.26	0.38

CI: confidence interval, SD: standard deviation, BMI: body mass index, eGFR: estimated glomerular filtration rate, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker

Table 4. A Multivariate Analysis for Predicting the Improvement in Hypertension after PTRA.

Variables	Odds ratio	95% CI	p value
Age, per 1-year increase	0.96	0.83 – 1.08	0.53
Male gender	0.29	0.01 – 3.20	0.33
Diastolic blood pressure	1.02	0.93 – 1.13	0.60
Plasma renin activity >2.4ng/mL/hr	22.3	2.17 – 65.6	<0.01
Acceleration time, per SD increase	1.02	0.95 – 1.10	0.61

CI: confidence interval, SD: standard deviation

mechanisms can perpetuate hypertension, such as vascular remodeling and kidney injury, which may not be dependent on RAS (17). A previous study reported that approximately 20% of patients with renovascular hypertension have normal PRA levels (18). Renovascular hypertension may often be superimposed on essential hypertension. Mahmud et al. showed that renal artery stenting was effective in treating impaired renal perfusion measured using the renal frame count and renal blush grade, in patients with RAS (19). In the present study, the PRA was significantly higher among patients who had successfully achieved improved blood pressure after PTRA than in those who had not. Renal artery revascularization may be more effective at higher PRA levels during decreased renal perfusion, meaning the phase before the complete shift to essential hypertension.

Additionally, the suppression of the renin-angiotensin system is important among both patients with RAS as well as in those with essential hypertension. A previous study reported that a high PRA level was a risk factor for cardiovascular disease in hypertensive patients (10). However, achieving optimized suppression of the renin-angiotensin system is difficult using currently available antihypertensive agents. ACE inhibitors and angiotensin II receptor blockers are conventionally used to treat the patients with renovascular hypertension. Indeed, although ACE inhibitors and angiotensin II receptor blockers can activate the compensatory feedback cascade and increases renin release, these drugs often improve the blood pressure (20). Similarly, a β-blocker and immediate renin inhibitor can suppress the PRA and subsequently reduce the blood pressure. Lowering the PRA levels with a combination of select antihypertensive agents is important for patients with renovascular hypertension (21).

However, Fang et al. reported a case of renovascular hypertension in which both the blood pressure and PRA were normalized using PTRA (22). In the present study, although antihypertensive agents used varied among individuals, no significant differences were noted in the specific medications used in the responder group versus the non-responder group. PTRA was more effective in patients with higher PRA levels than in those with lower levels, despite the administration of select antihypertensive agents. While an improvement in the blood pressure in patients with higher PRA can be achieved by lowering the PRA levels using renal artery intervention, no marker has yet been established for the prediction of responses to renal artery revascularization. Thus, the measurement of the PRA levels may be a useful tool for identifying the patients who are likely to benefit from PTRA.

Study limitations

Several limitations associated with the present study warrant mention. First, this was a single-center study conducted in a relatively small population. Future investigations that include a greater accumulation of patients and outcome events are necessary to better delineate the prognostic value of the PRA as a biomarker. Second, the PRA levels were only measured on one occasion before PTRA. The PRA should be compared before and after renal artery intervention. Furthermore, the PRA should be measured before the administration of antihypertensive agents. Third, the mean blood pressure should be measured via 24 hours ambulatory blood pressure monitoring before and after renal artery revascularization. Finally, we did not evaluate the long-term outcomes after PTRA.

Conclusion

In the present study, the PRA levels were closely associated with an improved blood pressure after PTRA. These optimal cut-off values for PRA may be useful as a reliable predictor for the improvement in resistant hypertension after PTRA for RAS.

The authors state that they have no Conflict of Interest (COI).

Ethics: Informed consent was obtained from all of the patients before participation in the study, and the study protocol was approved by the Human Investigations Committee at our institution.

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