Primary Aldosteronism

Renal Resistive Index Predicts Postoperative Blood Pressure Outcome in Primary Aldosteronism

Yoshitsugu Iwakura, Sadayoshi Ito, Ryo Morimoto, Masataka Kudo, Yoshikiyo Ono, Masahiro Nezu, Kei Takase, Kazumasa Seiji, Shigeto Ishidoya, Yoichi Arai, Yasuharu Funamizu, Takashi Miki, Yasuhiro Nakamura, Hironobu Sasano, Fumitoshi Satoh

Abstract—The renal resistive index (RI) calculated by Doppler ultrasonography has been reported to correlate with renal structural changes and outcomes in patients with essential hypertension or renal disease. However, little is known about this index in primary aldosteronism. In this prospective study, we examined the utility of this index to predict blood pressure (BP) outcome after adrenalectomy in patients with primary aldosteronism. We studied 94 patients with histopathologically proven aldosteronoma who underwent surgery. Parameters on renal function, including renal flow indices, were examined and followed up for 12 months postoperatively. The renal RI of the main, hilum, and interlobar arteries was significantly higher in patients with aldosteronoma compared with 100 control patients. BP, estimated glomerular filtration rate, and urinary albumin excretion significantly decreased after adrenalectomy. The resistive indices of all compartment arteries were significantly reduced 1 month after adrenalectomy and remained stable for 12 months. Patients whose interlobar RI was in the highest tertile at baseline had higher systolic BP after adrenalectomy than those whose RI was in the lowest tertile. Logistic regression analysis demonstrated that the RI of the interlobar and hilum arteries could be an independent predictive marker for intractable hypertension (systolic BP ≥ 140 mm Hg, increased BP, taking ≥ 3 antihypertensive agents, or increased number of agents) even after adrenalectomy. Therefore, in patients with aldosteronoma, the renal RI indicates partially reversible renal hemodynamics and renal structural damages that would influence postoperative BP outcome. (Hypertension. 2016;67:654-660. DOI: 10.1161/HYPERTENSIONAHA.115.05924.)

Key Words: adrenalectomy ■ blood pressure ■ hyperaldosteronism ■ hypertension ■ ultrasonography, Doppler

Patients with primary aldosteronism (PA) are known to have a higher incidence of cardiovascular and renal complications than patients with essential hypertension. About renal complications, both relative glomerular hyperfiltration and albuminuria have been reported. In addition, in those with aldosterone-producing adenoma (APA), intrarenal hemodynamics is altered by specific treatments, as reported in 2 previous studies in which the resistive index (RI) was measured using renal Doppler ultrasonography; yet, the specific changes remained to be determined because the results differed markedly between these 2 studies. Sechi et al reported that in patients with PA, this index was lower before treatment, suggesting relative vasodilatation of renal arteries leading to glomerular hyperfiltration. In contrast, Wu et al demonstrated that the initial RI in APA was higher than that in essential hypertension, and RI significantly decreased after adrenalectomy. The disparity may be because of differences in the study designs, including the diagnosis of laterality and treatment of APA, baseline renal function, or racial differences. Of particular importance may be baseline renal function because the estimated glomerular filtration rate (eGFR) in the study by Wu et al was substantially lower than that in the study by Sechi et al.

The RI, which is calculated based on systolic and diastolic flow velocity, has been shown to correlate significantly with histological findings, such as arteriosclerosis and tubulointerstitial changes. In addition, increased renal RI was reported to be significantly associated with the incidence of cardiovascular and renal organ damage and to serve as a predictor of worsening renal function in patients with chronic kidney disease. In patients with APA, plasma aldosterone levels decrease drastically after adrenalectomy. Postoperative residual hypertension, however, was observed in 55 of 150 patients...
with PA after adrenalectomy in the TAIPAI (Taiwan Primary Aldosteronism Investigation) study, and residual hypertension was thought to be a result of renal parenchymal injury.\textsuperscript{16}

We hypothesized that renal RI might be a predictor of blood pressure (BP) outcome in patients with APA after adrenalectomy. Thus, in this prospective study, we measured the RI before and after adrenalectomy in patients with APA and investigated whether preoperative renal RI was independently associated with the postoperative BP level.

Methods

Diagnosis of PA and clinical biochemical data are presented in the online-only Data Supplement.

Patients

Between January 2009 and December 2012, 94 consecutive patients who underwent adrenalectomy because of APA at Tohoku University Hospital participated in this study. Patients with other concurrent endocrine diseases were excluded, even those with APA and autonomous cortisol secretion, which was confirmed by cortisol concentrations >3.0 μg/dL after an overnight 1-mg dexmethasone suppression test. Exclusion criteria also included renal diseases, such as primary glomerular disease, nephrotic syndrome, renal cell carcinoma, renal artery stenosis, solitary kidney, or other diseases associated with a urinary tract disorder. Control patients were those with essential hypertension diagnosed by excluding any form of secondary hypertension. The ethics committee of Tohoku University School of Medicine approved this protocol, which was consistent with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects. In addition, informed consent was obtained from all patients.

Renal Doppler Ultrasonography

The utility of renal Doppler ultrasonography findings as indices of renal damage and predictors of renal outcome in patients with kidney diseases has been previously demonstrated.\textsuperscript{9–15} Color Doppler ultrasonography was performed by 2 well-trained ultrasonographers who were not informed of the details of the study to avoid any potential bias. The tracing findings were examined by an experienced reader who was blinded to the patients’ clinical information. A Philips iU22 device (Philips, Bothell, WA) and a 3.5-MHz convex probe were used. The Doppler angles measuring renal artery and aorta were maintained at ≤60° and as close to 0 as possible. If not, a sector probe was used to maintain the angle. After an approximate 6-hour fast, patients underwent ultrasonography in the dorsal position or the lateral recumbent position. The lateral recumbent position was used when the target was not visible in the dorsal position. The measurement of aortic flow velocity was performed at the level of the renal arteries. Renal flow velocity was measured in the artery of each compartment, including the main tract artery, hilum arteries, and interlobar arteries. The pulsatory velocity indices, including peak systolic velocity (PSV) and end-diastolic velocity (EDV), were measured, and values from both kidneys were averaged. Renal RI was calculated using Pourcelot formula: RI = PSV−EDV/PSV. The interobserver and intraobserver variations for the RI measurements between the 2 sonographers were 6.27% and 6.34%, respectively.

Prospective Protocol and Follow-Up

All of the patients with APA were treated with calcium-channel blockers or α\textsubscript{1}-adrenergic blockers to control BP during baseline examination of the Doppler ultrasonograms, BP, and biochemical sampling. In patients with APA, follow-up examinations were conducted at 1 and 12 months after adrenalectomy. BP was stringently controlled according to the guidelines of the Japanese Society of Hypertension.\textsuperscript{17} Renin–angiotensin system (RAS) inhibitors were used during the postoperative period if they were to prevent organ damage; however, they were substituted with calcium-channel blockers or α\textsubscript{1}-adrenergic blockers 1 month before the follow-up examination. Neither mineralocorticoid receptor antagonists nor diuretics were administered during this study.

Statistical Analysis

Data are expressed as mean±SEM of the mean (SEM). Independent \( t \) tests, Mann–Whitney \( U \) tests, or Fisher exact tests were performed, as appropriate, for comparison of parameters between patients with APA and control patients at baseline. ANOVA followed by Tukey tests or Dunn tests was performed for comparisons between measurements at baseline, 1 month, and 12 months postoperatively in the APA group. Urinary albumin corrected by urinary creatinine concentration (UACR) was logarithmically transformed to approximate a normal distribution. To examine the utility of RI, we divided patients with APA into 3 groups based on RI value tertiles (lowest RI group: RI≤0.60, n=32; middle RI group: 0.60<RI<0.65, n=32; and highest RI group: RI≥0.65, n=30) and compared the BP outcome and the number of antihypertensive agents used after adrenalectomy among these groups. To assess the predictors of intractable hypertension (systolic BP ≥140 mmHg, increment in BP, taking ≥3 antihypertensive agents, or an increase in the number of agents; n=39) at 12 months postoperatively, multivariate logistic regression analysis using a stepwise procedure was performed. The covariates included in this model were age and sex. All analyses were performed using Stat Flex version 6.0 (Artech Co Ltd, Osaka, Japan). Statistical significance was set at \( P<0.05 \).

Results

Patients

Ninety-four patients with APA (53 men and 41 women) aged 52±1.2 years and 100 control patients (53 men and 47 women) aged 49±1.3 years were evaluated (Table 1). Patients with APA were excluded for the following reasons: autonomous cortisol secretion (n=5), renal cell carcinoma (n=2), renal artery stenosis (n=1), and solitary kidney (n=1). The distributions of age and sex were similar in the 2 groups. In the APA group, the ages of the men and women were similar (53±1 versus 50±2 years; \( P=0.2094 \)). At the end of the study, 14 patients with APA were lost to clinical follow-up at 12 months postoperatively for the ultrasonographic examination because of various nonmedical reasons (eg, social issues, economical issues, or pregnancy). Still, BP measurements and the number of antihypertensive agents were recorded for all of the patients during the follow-up period.

Comparison of Clinical Characteristics and Intrarenal Index

At baseline, patients with APA had significantly higher plasma aldosterone concentration (PAC), aldosterone/renin ratio (ARR), serum sodium concentrations, and random spot urine potassium/sodium ratio; significantly longer duration of hypertension; and significantly lower plasma renin activity and serum potassium concentrations than the control patients (Table 1). There were no significant differences in body mass index, BP, eGFR, hemoglobin A1c, and prevalence of diabetes mellitus between the 2 groups. UACR was significantly higher in patients with APA than in control patients.

RI was significantly higher in the patients with APA than in the control patients in all compartments (Table 2). In the patients with APA, EDV in every compartment was significantly lower than in the control patients, although PSV was similar in every compartment in both groups.
Table 1. Clinical Characteristics and Biomedical Parameters of Patients at Baseline

<table>
<thead>
<tr>
<th>Parameters/Patients</th>
<th>Control (n=100)</th>
<th>APA (n=94)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±1.3</td>
<td>52±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (men, women)</td>
<td>53, 47</td>
<td>53, 41</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7±0.4</td>
<td>25.1±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>6.8±0.8</td>
<td>6.9±0.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>151±2</td>
<td>152±2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>94±2</td>
<td>94±1</td>
<td>NS</td>
</tr>
<tr>
<td>Cre eGFR, mL/min per 1.73 m²</td>
<td>83±2</td>
<td>78±2</td>
<td>NS</td>
</tr>
<tr>
<td>UACR, mg/g creatinine</td>
<td>44±10</td>
<td>109±30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum Na, mmol/L</td>
<td>141±0.2</td>
<td>143±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>4.1±0.0</td>
<td>3.4±0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary K/Urinary Na ratio</td>
<td>0.49±0.0</td>
<td>0.70±0.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>16.2±0.8</td>
<td>28.0±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARR, ng/dL per ng mL⁻¹ h⁻¹</td>
<td>3.0±0.5</td>
<td>0.8±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (NGSP), %</td>
<td>6.0±0.1</td>
<td>5.8±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (7)</td>
<td>14 (14.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Changes in Parameters During the Follow-Up Period

In the patients with APA, PAC, ARR, BP, eGFR, and UACR were significantly lower at 1 month after adrenalectomy compared with the values at 1 month postoperatively. Plasma renin activity and serum potassium concentrations (mmol/L) were significantly increased from 1.0 and 3.5 at baseline to 1.5 and 4.5 at 1 month after adrenalectomy (P<0.01), respectively, and were also increased significantly at 2 months. Plasma renin activity values (ng mL⁻¹ h⁻¹) and serum potassium concentrations (mmol/L) were significantly increased from 1.0 and 3.5 at baseline to 1.5 and 4.5 at 1 month after adrenalectomy (P<0.01), respectively, and were also increased significantly at 2 months (P<0.01) postoperatively. Multivariate logistic regression analysis was performed, using a stepwise procedure, to detect predictors of postoperative intractable hypertension. In each model, including RIs of the interlobar and hilum arteries (Table 4, models 1 and 2), RIs were the strongest predictors of postoperative intractable hypertension; age and duration of hypertension, on the other hand, were not significantly correlated in these models. In the model, including RI at the main renal artery and covariates (Table 4, model 3), age, but not RI, was a significant predictor of intractable hypertension. In this analysis, duration of hypertension was a significant predictor of intractable hypertension.
not correlated either. Male sex was a predictor of intractable hypertension in all models (Table 4, models 1–3).

**Discussion**

This study provides novel information on the utility of renal RI for the prediction of persistent postoperative hypertension in patients with APA subjected to adrenalectomy. In addition, this is the first study to report specific changes in hemodynamics during the very early phase (1 month) after surgery and in the arteries of multiple renal compartments. The initial RI in all compartment arteries was significantly higher in the patients with APA than in the control patients. In addition, the RI decreased in all compartments after adrenalectomy in the patients with APA, and the initial RI was significantly associated with long-term postoperative BP. These findings indicate that in patients with APA, renal RI could indicate not only irreversible renal damage like arteriosclerotic changes and structural damage of the tubulointerstitium but also reversible functional changes of the renal circulation because of hyperaldosteronism.

In this study, marked decreases in renal RIs were observed in patients with APA at 1 month postoperatively, and those changes persisted until the final measurement at 12 months; at the same time, eGFR and UACR decreased significantly and then remained stable at the lower level. Of particular interest, the hemodynamic changes differed among the renal arteries, with 2 different patterns being identified at 1 month after surgery; EDV increased in the interlobar artery, whereas PSV decreased in the renal main and hilum arteries near the aorta. The precise mechanisms for these changes remain to be clarified. PSV is considered to be determined by multiple factors, such as blood flow from the aorta and diameter of the artery. In this study, the change of the PSV was solely associated with a significant decrease in aortic velocity after adrenalectomy. Thus, the decreases in PSV in the main and hilum arteries may reflect direct influences of aortic hemodynamics. Because aldosterone promotes sodium retention, the higher initial PSV in the main renal artery may be because of expanded extracellular fluid volume in the preoperative state. On the other hand, major determinants of EDV might be stiffness of vasculature upstream (such as renal main artery and even aorta) of the site of measurement and resistance of the downstream vasculature (such as interlobular arteries and afferent and efferent...
arterioles in our study). One reason for the lower EDV levels in the interlobar artery before surgery might be heightened vascular stiffness because of high levels of aldosterone. It has been shown that adrenalectomy improves arterial stiffness in patients with PA.18 In addition, because aldosterone constricts distal small arteries, such as glomerular afferent and efferent arterioles,19,20 the lower EDV in the interlobar artery might be because of heightened downstream vascular resistance. We also observed that EDV decreased in the interlobar artery from 1 month to 12 months postoperatively, returning to the baseline level. This might reflect increased downstream vascular resistance because of the recovery of the RAS and tubuloglomerular feedback (TGF). It should be mentioned that TGF in hyperaldosteronism (before surgery) can be attenuated by direct action of aldosterone on the macula densa and by suppression of RAS.21 Thus, full recovery of TGF would have been achieved only when the RAS recovered at 12 months after surgery.

The significant decrease in eGFR observed after surgery would reflect the correction of glomerular hyperfiltration.1–6 Thus, our study may indicate that glomerular hyperfiltration can occur in the presence of a high RI in hyperaldosteronism. It may be mentioned that renal RI does not necessarily reflect renal vascular resistance. We and others have demonstrated that renal RI is greatly influenced by arterial stiffness.22–21 In vitro experiments have shown that renal RI is determined by interactions between aortic stiffness and renal vascular resistance and that in the case of zero vascular compliance, renal RI is independent of renal vascular resistance.24–22 On the basis of these observations, some researchers have pointed out that the term renal RI is misleading.23,24 Basic studies have demonstrated diverse renal actions of aldosterone, including enhanced sodium reabsorption, constriction of glomerular afferent and efferent arterioles, inhibition of TGF (because of direct action of aldosterone on the macula densa and inhibition of the RAS), and enhanced tubular glomerular feedback.19–21,26 Taking all of these data together, we may speculate that a high renal RI may reflect increased stiffness of preglomerular arteries and increased intrarenal vascular resistance, including postglomerular circulation. The increased stiffness would facilitate the transmission of systemic BP to the glomeruli, causing glomerular hypertension. This may be particularly evident in the presence of a high level of aldosterone that causes strong constriction of efferent arterioles versus the afferent arterioles and inhibition of TGF (Figure S2 in the online-only Data Supplement). In particular, inhibition of TGF would be pertinent because rhythmic oscillation of glomerular capillary pressure would be lost in hyperaldosteronism.

This prospective study provides new evidence that the initial RI in interlobar and hilum arteries could predict the development of intractable hypertension after adrenalectomy in patients with APA (Table 4). In additional analyses, the initial RIs of the patients with postoperative intractable hypertension

Table 4. Predictors of Intractable Hypertension at 12 Months After Adrenalectomy in Patients With Aldosterone-Producing Adenoma

<table>
<thead>
<tr>
<th>Variables in Each Model</th>
<th>β</th>
<th>SE (β)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) RI in the interlobar arteries and covariates (AIC=109 and AUC=0.78)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI (interlobar)×100</td>
<td>0.159</td>
<td>0.044</td>
<td>0.0003</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.085</td>
<td>0.492</td>
<td>0.0274</td>
</tr>
<tr>
<td>Age</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>(2) RI in the hilum arteries and covariates (AIC=105 and AUC=0.82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI (hilum)×100</td>
<td>0.184</td>
<td>0.046</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.75</td>
<td>0.509</td>
<td>0.0209</td>
</tr>
<tr>
<td>Age</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>(3) RI in the main artery and covariates (AIC=114 and AUC=0.76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.076</td>
<td>0.024</td>
<td>0.0012</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.083</td>
<td>0.484</td>
<td>0.0145</td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis using a stepwise procedure was performed for each model (1–3). Covariates included in each model (1–3) were age, sex, blood pressure, duration of hypertension, urinary albumin, estimated glomerular filtration rate (calculated using serum creatinine), and plasma aldosterone concentration at baseline. Intractable hypertension was defined as systolic blood pressure ≥140 mmHg, increase in blood pressure, taking ≥3 antihypertensive agents, or increase in the number of agents at the end of study.

Figure. Initial resistive index (RI) in the interlobar artery, expressed in tertiles; blood pressure (A and B) and the number of antihypertensive agents (C) at 12 months postoperative were compared using ANOVA or Kruskal–Wallis test in patients with aldosterone-producing adenoma who underwent adrenalectomy. The white columns indicate the first tertile (RI<0.60; n=32), the gray columns indicate the second tertile (0.60<RI<0.65; n=32), and the black columns indicate the third tertile (RI≥0.65; n=30). Data are expressed as mean±SE. NS indicates not significant.
were significantly higher than those of the patients in the remission and responded-residual hypertension groups (Figure S1). Thus, high RI may indicate the presence of established renal parenchymal damage or arteriosclerotic changes that would contribute to intractable or residual hypertension after adrenalectomy. Indeed, it was reported that in patients with untreated PA, the kidneys presented histopathologic changes, such as sclerosis of glomeruli, atrophy of the tubules, and interstitial fibrosis. In particular, tubulo-interstitial injuries are generally considered to lead to microvascular damage and renal ischemia, resulting in resistant hypertension. Male sex was an independent variable for postoperative hypertension. Compared with premenopausal women, male sex is known as a risk factor of arteriosclerosis and hypertension. We could not predict BP after surgery based on the initial values of either eGFR or UACR because these values might vary because of the presence of hyperfiltration and irreversible renal damage as consequences of hyperaldosteronism before treatment. Duration of hypertension and family history of hypertension were not predictors of intractable hypertension, and they were not even correlated with initial RI. Because the information was obtained based on self-report by the patient, there were limitations to analyze whether residual hypertension was caused by coexisting primary hypertension. Age was not a significant predictor of intractable hypertension in the multivariate regression analysis models, including RIs of interlobar and hilum arteries, although it was a predictor only in the analysis model, including RI of renal main artery. However, age was a strong correlation factor for initial RIs in interlobar and hilum arteries (Table S1). These results might indicate that progression of intrarenal arteriosclerosis caused by aging itself could partially cause postoperative intractable hypertension even in patients with APA. In addition, primary hypertension that might potentially coexist in patients with APA should be considered for understanding these results. Thus, these results indicate that the combination of RI (as a marker of PA associated arterial blood flow changes) and age (as a marker of atherosclerosis) would serve as a predictor of adverse postoperative BP outcomes.

This study has some limitations. First, some of the patients had diabetes mellitus, which could have partially affected the renal hemodynamic indices (Table S1). Second, the effect of antihypertensive agents on RI might have remained, to some extent, despite the systematic protocol for medication throughout the follow-up study (Table S2).

Perspectives

In this study, ≈40% of the patients with APA had intractable hypertension predicted by renal Doppler ultrasonography, indicating that patients with PA should be diagnosed as early as possible to prevent progressive or irreversible renal injury and resistant hypertension. Although this noninvasive device can provide significant information for clinicians and patients, still, this is a sophisticated technique, and therefore, sonographers must be knowledgeable and skillful. In addition, this was a prospective but monocentric study conducted in the Japanese population. Prospective, multicenter studies involving patients of different ethnicities may be needed to increase our understanding in this field.

Acknowledgments

We thank Junko Fujiwara and Masumi Koizumi for their experienced technical support on ultrasonography and Yasuko Tsukada and Akane Sugawara for secretarial assistance.

Disclosures

None.

References


What Is New?
- This study is the first to demonstrate the utility of renal Doppler ultrasound to predict postoperative blood pressure outcomes in patients with aldosterone-producing adenoma. New insights were provided on aldosterone-induced changes in renal resistive index and their interpretations.

What Is Relevant?
- Resistive index is a noninvasive and useful marker for predicting intractable hypertension after adrenalectomy in patients with aldosterone-producing adenoma.

Summary
Removal of aldosterone-producing adenoma reduces renal resistive index. Preoperative resistive index may predict blood pressure outcome after surgery. Early detection of primary aldosteronism is important for preventing organ damage.
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Short title: Renal resistive index in hyperaldosteronism

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Methods

Diagnosis of primary aldosteronism
Primary aldosteronism (PA) was diagnosed, as previously reported,\textsuperscript{1,2,3} when the patient had a plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio (ARR) of >20 (ng/dL per ng/mL/h) after loading with 50 mg captopril.\textsuperscript{4} During the diagnostic process, all of the patients were treated with antihypertensive agents that do not influence the renin-angiotensin-aldosterone system (i.e., calcium channel blockers and/or \(\alpha_1\)-adrenergic blockers) in order to control blood pressure. Laterality of aldosterone hypersecretion was clinically determined using adrenal vein sampling (AVS) with cosyntropin stimulation, as previously reported.\textsuperscript{2,5} Laparoscopic adrenalectomy was performed in patients diagnosed with unilateral disease based on the results of AVS. The diagnosis of aldosterone producing adenoma (APA) was confirmed by histopathological evaluation using steroidogenic enzyme staining\textsuperscript{3, 6, 7} and postoperative clinical data.

Clinical and biochemical data
All samples, laboratory data, and clinical personal information were collected, and the database was archived in a registry center. Blood pressure was measured using an Omron Hem-907 digital blood pressure monitor (Omron Healthcare Co. Ltd., Kyoto, Japan) with the patient in the sitting position, and the average of three consecutive values was recorded.\textsuperscript{8} PAC and PRA were measured as previously reported.\textsuperscript{3,6} The estimated glomerular filtration rate (eGFR) was calculated using the equation developed for the Japanese: $\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{women})$.\textsuperscript{9} Urinary creatinine concentration corrected values (mg/g creatinine) were used for urinary albumin (UACR).

Expanded analyses

Correlations with initial resistive index
Additionally, we determined the correlations with initial resistive indices (RIs) in all of the compartment arteries in the patients with APA. The covariates included in each model were age, sex, duration of hypertension, pulse pressure, and the diagnosis of diabetes mellitus. Neither systolic blood pressure (SBP) nor diastolic blood pressure (DBP) was included because of multi-collinearity. Pulse pressure was calculated as the difference between SBP and DBP. Diabetes mellitus was defined as HbA1c (NGSP)
≥6.5% and/or being under medical therapy.

Comparison of the initial resistive index
The patients were classified in 3 groups according to the outcome of blood pressure at the end of the study. The ‘remission hypertension’ group was defined as SBP <140 mmHg and requiring no antihypertensive agents. The ‘responded hypertension’ group was defined as SBP <140 mmHg, decreased blood pressure, or decreased number of antihypertensive agents to <3. The ‘intractable hypertension’ group was defined as SBP/DBP ≥140/90 mmHg, increasing blood pressure, taking ≥3 antihypertensive agents, or an increased number of antihypertensive agents. Then, we analyzed and compared the initial RIs among these 3 groups to confirm the utility of RI for predicting blood pressure as another form of evaluation.

Statistical analysis
To determine the covariates for initial RI in each artery, multivariate logistic regression analysis using a stepwise procedure with backward elimination was performed. For comparisons among the 3 groups, analysis of variance followed by Bonferroni’s correction was performed. RI is reported as mean ± standard error of the mean (SEM) for each group. All statistical analyses were performed with Stat Flex version 6.0 (Artech Co. Ltd., Osaka, Japan). Statistical significance was set at p < 0.05.

Results

Determinant of initial resistive index
In the multivariate analysis including duration of hypertension, PAC, eGFR, and UACR as covariates, age showed the strongest correlation with initial RI in interlobar and hilum arteries (interlobar, t = 4.246, p = 0.0001; hilum, t = 4.437, p < 0.0001) (Table S1).

Comparison of initial resistive index among the three groups
The initial RI of the interlobar artery in the intractable hypertension group (n=39) was the highest and also significantly higher than that in the other two groups (0.66 ± 0.01 vs 0.62 ± 0.01 in the responded group (n=29), p=0.0007; 0.66 ± 0.01 vs 0.59 ± 0.01 in the remission group (n=26), p < 0.0001) (Figure S1).

Number of the APA patients taking antihypertensive agents during the study
Biochemical tests and ultrasonographic studies were performed at baseline and 12 months postoperatively, while the patients were using the antihypertensive agents shown in Table S2. All of the antihypertensive agents that could influence the renin angiotensin system (RAS) were withdrawn at the first visit and exchanged with calcium (Ca) channel blockers and/or $\alpha_1$-blockers. In addition, only Ca channel blockers and/or $\alpha_1$-blockers were used for ≥1 month before the final exam. Actually, in 37 patients, agents that influenced the RAS were taken during the postoperative period and then substituted. In some of these patients, Ca channel blockers and $\alpha_1$-blockers were used together (e.g., amlodipine and nifedipine in 1 patient; diltiazem, doxazosin, and bunazosin in 2 patients). The number of patients using 2 or ≥3 agents is shown in Table S2.

References


### Table S1. Factors Correlating with Renal Resistive Index in Each Artery at Baseline in APA Patients

<table>
<thead>
<tr>
<th>Variables in each model</th>
<th>β</th>
<th>t</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>#1: RI in the interlobar artery</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.220</td>
<td>4.246</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.068</td>
<td>2.042</td>
<td>0.0440</td>
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<tr>
<td>(AIC = 595, R = 0.497)</td>
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<td></td>
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<tr>
<td>#2: RI in the hilum artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.229</td>
<td>4.437</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.701</td>
<td>2.202</td>
<td>0.0302</td>
</tr>
<tr>
<td>(AIC = 594, R = 0.516)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#3: RI in the main artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>0.239</td>
<td>1.960</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary albumin</td>
<td>0.005</td>
<td>1.636</td>
<td>NS</td>
</tr>
<tr>
<td>(AIC = 688, R = 0.252)</td>
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</table>

Multivariate logistic regression analysis using a stepwise procedure was performed for each model (#13). Covariates included in each model (#1-3) were age, duration and family history of hypertension, plasma aldosterone concentration, plasma renin activity, and estimated GFR at baseline. Diabetes mellitus was defined as HbA1c (NGSP) ≥6.5% and/or being under medical therapy. β indicates the standardized regression coefficient; t calculated by β over β (standard error); APA, aldosterone-producing adenoma; RI, resistive index; AIC, Akaike’s information criterion; R indicates the multivariate regression coefficient; GFR, glomerular filtration rate; NGSP, national glycohemoglobin standardization program.
Table S2. Number of APA Patients Using Each Antihypertensive Agent at each Time Point

<table>
<thead>
<tr>
<th>Number of Agents</th>
<th>First Visit</th>
<th>Baseline</th>
<th>Postoperative Period</th>
<th>Final</th>
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<tbody>
<tr>
<td>None</td>
<td>13</td>
<td>0</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Single agent</td>
<td>19</td>
<td>12</td>
<td>25</td>
<td>25</td>
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<tr>
<td>2 agents</td>
<td>22</td>
<td>24</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>≥3 agents</td>
<td>40</td>
<td>60</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Agent

- Ca channel blockers: 75, 92, 61, 63
- α1 blockers: 21, 81, 8, 26
- β blockers: 29, 0, 10, 0
- ACE inhibitors: 11, 0, 1, 0
- ARBs: 49, 0, 29, 0
- Renin inhibitors: 0, 0, 7, 0
- MRAs: 17, 0, 0, 0
- Diuretics: 17, 0, 0, 0

Ca, calcium; ACE, angiotensin converting enzyme; ARBs, angiotensin 2 type 1 receptor blockers; MRAs, mineralocorticoid receptor antagonists

Figure S1. Resistive index at baseline in patients distributed according to their long term blood pressure after adrenalectomy. The patients were classified into 3 groups based on changes in hypertension at the end of the study: remission, SBP 140 mmHg and no antihypertensive agents; responded, SBP <140 mmHg, decreased blood pressure, or decrease in number of antihypertensive agents to <3; intractable hypertension, SBP ≥140/90 mmHg, increase in blood pressure, taking ≥3 antihypertensive agents, or increase in the number of antihypertensive agents. APA, aldosterone-producing
adenoma; NS, not significant.

Figure S2. Schematic illustration of possible mechanisms for glomerular hyperfiltration and high resistive index (RI) in hyperaldosteronism. A (normal): Because of good compliance of preglomerular arteries, diastolic blood flow to the glomerulus is maintained. In addition, macula densa-mediated tubuloglomerular feedback (TGF) will make glomerular capillary pressure (GCP) oscillate very smoothly (about 2 times/minute) independent of systemic blood pressure. Note that TGF regulates the amplitude of the oscillation, and the area under the curve represents the driving force for single nephron glomerular filtration rate. RI, resistive index; GCP, glomerular capillary pressure; areas with oblique lines indicate expansion of arterial trees during systole that return to original states during diastole (complaint arteries)

B (hyperaldosteronism): Because of increased stiffness of the preglomerular arteries and attenuated TGF, systemic blood pressure would be effectively transmitted to the glomerulus. Thus, GCP would become higher and it would be affected by beat-by-beat systolic and diastolic blood pressures. In addition, because TGF is inhibited, normal oscillation would be lost. All these factors together with high blood pressure and
increased fluid volume would cause glomerular hyperfiltration (increased area under the curve) in hyperaldosteronism.