Primary Aldosteronism
A 2017 Update for Nephrologists

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COI of F. Satoh

• Collaboration Study:
  Wako Pure Chemical Industries, Ltd.
Primary aldosteronism (PA) is a type of hormonal disorder that leads to high blood pressure. In primary aldosteronism, your adrenal glands produce too much aldosterone, causing you to lose potassium and retain sodium. The excess sodium in turn holds onto water, increasing your blood volume and blood pressure.

**Diffenition by Mayo Clinic**
The prevalence of PA among all hypertesives

<table>
<thead>
<tr>
<th>Authors</th>
<th>year</th>
<th>Screening</th>
<th>Confirmation test</th>
<th>No of patients</th>
<th>PA pts. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al.</td>
<td>1994</td>
<td>ARR &gt; 30</td>
<td>FST</td>
<td>199</td>
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</tr>
<tr>
<td>Lim et al.</td>
<td>2000</td>
<td>ARR &gt; 27</td>
<td>FST &amp; SLT</td>
<td>495</td>
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<td>Nishikawa et al.</td>
<td>2000</td>
<td>PAC &gt; 12 ng/dl &amp; PRA &lt; 1</td>
<td>ACTH-AVS</td>
<td>1020</td>
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<tr>
<td>Loh et al.</td>
<td>2000</td>
<td>ARR &gt; 20 &amp; PAC &gt; 15</td>
<td>SLT</td>
<td>350</td>
<td>4.6</td>
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<tr>
<td>Fardella et al.</td>
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<tr>
<td>Rossi et al.</td>
<td>2002</td>
<td>postcaptopril ARR &gt; 35</td>
<td>Saline LT</td>
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<td>6.3</td>
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<td>Mulatero et al.</td>
<td>2004</td>
<td>ARR &gt; 40 &amp; PAC &gt; 15</td>
<td>Saline LT</td>
<td>7,343</td>
<td>8</td>
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<tr>
<td>Mulatero et al.</td>
<td>2004</td>
<td>ARR &gt; 40 &amp; PAC &gt; 15</td>
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<tr>
<td>Youg et al.</td>
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<td>10.8</td>
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<tr>
<td>Stowesser et al.</td>
<td>2002</td>
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<td>FST</td>
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<td>21.7</td>
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<tr>
<td>Loh et al</td>
<td>2002</td>
<td>ARR &gt; 20</td>
<td>Saline LT</td>
<td>3,850</td>
<td>4.6</td>
</tr>
<tr>
<td>Fogari et al</td>
<td>2007</td>
<td>ARR &gt; 25</td>
<td>Saline LT</td>
<td>3,000</td>
<td>5.9</td>
</tr>
</tbody>
</table>
Prevalence of PA in different population

- Whole hypertensives: 6.1%
  Stage 1: SBP 140-159, DBP 90-99 mmHg: 2%
  Stage 2: SBP 160-179, DBP 100-109 mmHg: 8%
  Stage 3: SBP > 180, DBP > 110 mmH: 13%
- Resistant hypertension with DM: 14%  (Umpierrez 2007)
- Adrenal incidentaloma: 2%  (range, 1.1-10%)  
- Hypertensive with obstructive sleep apnea: 34%
Evidence for an Increased Rate of Cardiovascular Events in Patients With Primary Aldosteronism


OBJECTIVES: The aim of this report was to show that the rate of cardiovascular events is increased in patients with either subtype of primary aldosteronism (PA). BACKGROUND Primary aldosteronism involves hypertension (HTN), hypokalemia, and low plasma renin. The two major PA subtypes are unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia.

METHODS: During a three-year period, the diagnosis of PA was made in 124 of 5,500 patients referred for comprehensive evaluation and management. Adenomas were diagnosed in 65 patients and idiopathic hyperaldosteronism in 59 patients. During the same period, clinical characteristics and cardiovascular events of this group were compared with those of 465 patients with essential hypertension (EHT) randomly matched for age, gender, and systolic and diastolic blood pressure.

RESULTS: A history of stroke was found in 12.9% of patients with PA and 3.4% of patients with EHT (odds ratio [OR] 4.2; 95% confidence interval [CI] 2.0 to 8.6). Non-fatal myocardial infarction was diagnosed in 4.0% of patients with PA and in 0.6% of patients with EHT (OR = 6.5; 95% CI 1.5 to 27.4). A history of atrial fibrillation was diagnosed in 7.3% of patients with PA and 0.6% of patients with EHT (OR = 12.1; 95% CI 3.2 to 45.2). The occurrence of cardiovascular complications was comparable in both subtypes of PA.

CONCLUSIONS: Patients presenting with PA experienced more cardiovascular events than did EHT patients independent of blood pressure. The presence of PA should be detected, not only to determine the cause of HTN, but also to prevent such complications.
## Rate of Cardiovascular Events in Primary Aldosteronism Patients and Controls

<table>
<thead>
<tr>
<th>Event</th>
<th>Primary Aldosteronism (n = 124)</th>
<th>Essential Hypertension (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (%)</td>
<td>4.2 [2.0-8.6]</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>6.5 [1.5-27.4]</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>12.1 [3.2-45.2]</td>
<td>1</td>
</tr>
</tbody>
</table>

Milliez P et al. J Am Coll Cardiol 2005
Long-term cardio- and cerebrovascular events in patients with primary aldosteronism.

Abstract
BACKGROUND:
Aldosterone plays a detrimental role on the cardiovascular system and PA patients display a higher risk of events compared with EH.

OBJECTIVES:
The objectives of the study were to compare cardio- and cerebrovascular events in patients with primary aldosteronism (PA) and matched essential hypertension (EH).

METHODS:
We retrospectively compared the percentage of patients experiencing events at baseline and during a median follow-up of 12 years in 270 PA patients case-control matched 1:3 with EH patients and in PA subtypes [aldosterone-producing adenoma (n = 57); bilateral adrenal hyperplasia (n = 213)] vs matched EH.

RESULTS:
A significantly higher number of PA patients experienced cardiovascular events over the entire period of the study (22.6% vs 12.7%, P < .001). At the diagnosis of PA, a higher number of patients had experienced total events (14.1% vs 8.4% EH, P = .007); furthermore, during the follow-up period, PA patients had a higher rate of events (8.5% vs 4.3% EH, P = .008). In particular, stroke and arrhythmias were more frequent in PA patients. During the follow-up, a higher percentage of PA patients developed type 2 diabetes. Parameters that were independently associated with the occurrence of all events were age, duration of hypertension, systolic blood pressure, presence of diabetes mellitus, and PA diagnosis. After division into PA subtypes, patients with either aldosterone-producing adenoma or bilateral adrenal hyperplasia displayed a higher rate of events compared with the matched EH patients.

CONCLUSIONS:
This study demonstrates in a large population of patients the pathogenetic role of aldosterone excess in the cardiovascular system and thus the importance of early diagnosis and targeted PA treatment.
Increased Rate of Cardiovascular Events in PA patients vs EH

PA and EH matched 1:3 for sex, age, SBP and DBP, duration of hypertension, BMI, smoke and comorbidity for type 2 diabetes mellitus.

Events: MI, Stroke, Arrhythmias, HF

Mulatero P, Monticone S, Bertello C et al JCEM 2013
Increased Rate of Cardiovascular Events in PA Patients vs EH - Events Subtype

Mulatero P, Monticone S, Bertello C et al JCEM 2013
PA Patients Develop Diabetes more Frequently During Follow-Up Compared to EH

Prevalence of Diabetes

Diagnosis

End of Follow-Up

PA

EH

Mulatero P, Monticone S, Bertello C et al JCEM 2013

p=0.04
How about renal function?
Predictors of Decreasing Glomerular Filtration Rate and Prevalence of Chronic Kidney Disease After Treatment of Primary Aldosteronism: Renal Outcome of 213 Cases

Yoshitsugu Iwakura Ryo Morimoto Masataka Kudo Yoshikiyo Ono Kei Takase Kazumasa Seiji Yoichi Arai Yasuhiro Nakamura Hironobu Sasano Sadayoshi Ito Fumitoshi Satoh


CONTEXT:
In primary aldosteronism (PA), glomerular hyperfiltration due to excessive aldosterone is considered to underestimate actual renal damage.

OBJECTIVE:
Our objectives were to determine the prevalence of chronic kidney disease (CKD) in PA and identify the predictors of decreasing estimated glomerular filtration rate (eGFR) after treatment.

DESIGN AND SETTING:
This was a 12-month prospective study of patients with PA treated at Tohoku University Hospital.

PATIENTS AND INTERVENTIONS:
All patients were treated according to the results of adrenal venous sampling; 102 patients with aldosterone-producing adenoma underwent adrenalectomy, and 111 with bilateral hyperaldosteronism were treated with mineralocorticoid receptor antagonists.

MAIN OUTCOME MEASURES:
Electrolytes, blood pressure, and indicators of renal function were determined at 1 and 12 months after intervention.

RESULTS:
Blood pressure, urinary albumin excretion (UAE), and eGFR, which significantly decreased at 1 month after treatment of PA, did not further decrease at 12 months. Prevalence of CKD, which was 15.7% in aldosterone-producing adenoma and 8.1% in bilateral hyperaldosteronism at the first visit, increased to 37.1% and 28.3%, respectively, at the end of study (P < .0001). Multivariate regression analysis revealed that higher UAE and lower serum potassium levels were found to be independent predictors of decreasing eGFR after treatment.

CONCLUSIONS:
This large cohort study shows that the prevalence of CKD in PA was increased after treatment and that higher UAE and lower serum potassium levels at the first visit were predictors of decreasing eGFR after treatment of PA. To prevent a large decrease of eGFR after intervention, PA patients should be diagnosed before evolution to severe albuminuria and hypokalemia.
Prevalence of CKD and albuminuria in 213 PAs

Prevalence of CKD (%)

- APA
- BHA

First visit
End of study
Paired t-test

- p < 0.0001

Prevalence of albuminuria (%)

- APA
- BHA

First visit
End of study
Paired t-test

- p < 0.0001

Iwakura Y et al. J Clin Endo Metab. 2014
Decrement of eGFR after treatment; the predictors

Table 3. Potential predictors of the decrement of eGFR at 1 month after treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE (log_{10})</td>
<td>0.0029</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>0.0092</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.0144</td>
</tr>
</tbody>
</table>

Backward stepwise regression analysis was performed.
Adjusted $R^2 = 0.178, F = 12.13, P < 0.0001$
UAE, urinary albumin excretion; log, logarithm

Iwakura Y et al. J Clin Endo Metab. 2014
Changes of eGFR

Hyperfiltration

Nephrosclerosis

Masked CKD

CKD stage 3-5

HD

Time
Long-term Renal Outcomes in Patients With Primary Aldosteronism

Figure 2. Creatinine Clearance at Baseline and During Follow-up and Change From Baseline of Urinary Albumin Excretion in Patients With Primary Aldosteronism and Essential Hypertension

Creatinine Clearance

Change in Albuminuria

No. of Patients
Essential Hypertension 100 100 100 56 32
Primary Aldosteronism 50 50 50 28 16

Duplicate 24-hour urine collections were obtained for determination of creatinine clearance and urinary albumin excretion, and the mean was considered. Creatinine clearance was normalized to body surface area. Albuminuria was expressed as the log-transformed urine albumin to urine creatinine (UA/UCr) ratio. The mean follow-up time was 6.4 years. Decrease of creatinine clearance during the initial 6-month period was significantly greater ($P < .001$) in patients with primary aldosteronism (13.6 mL/min per 1.73 m$^2$) than in those with essential hypertension (2.1 mL/min per 1.73 m$^2$). Subsequent decline of creatinine clearance was comparable in the 2 groups ($P = .49$). Decrease of albuminuria during the initial 6-month period was significantly greater ($P < .001$) in patients with primary aldosteronism (34%) than essential hypertension (20%). The difference between the groups persisted in the remainder of the follow-up period with only minor further changes. To convert creatinine clearance to mL/s, multiply by 0.0167. Error bars indicate SE for creatinine clearance and 95% confidence interval for albuminuria.
Renal Doppler Ultrasonography

Renal Resistive Index (RRI)

Originally, a predictor of the effect of the angioplasty treatment for the renal artery stenosis (RRI >0.8: poor prognosis). RRI is also useful to predict a renal prognosis of nephrosclerosis or acute renal injury.

\[
RRI = \frac{PSV}{EDV}
\]

WNL: 0.55～0.65

( How is blood flow kept for a diastolic phase? )

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 be correlated 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 mmHg, 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;67:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05924.)
### Comparisons of Intrarenal Hemodynamic Indices between Control and APA Patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n = 100)</th>
<th>APA (n = 94)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta velocity (cm/s)</td>
<td>87.4 ± 2.7</td>
<td>83.2 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Resistive index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>0.67 ± 0.01</td>
<td>0.70 ± 0.01</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>0.64 ± 0.00</td>
<td>0.67 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interlobar arteries</td>
<td>0.60 ± 0.01</td>
<td>0.63 ± 0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak systolic velocity (cm/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>101.3 ± 2.8</td>
<td>100.4 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>64.1 ± 1.6</td>
<td>65.1 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Interlobar arteries</td>
<td>24.9 ± 0.6</td>
<td>24.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>End diastolic velocity (cm/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>33.0 ± 1.0</td>
<td>29.7 ± 1.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>23.0 ± 0.6</td>
<td>21.2 ± 0.6</td>
<td>&lt;0.05</td>
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<tr>
<td>Interlobar arteries</td>
<td>9.9 ± 0.2</td>
<td>8.9 ± 0.3</td>
<td>&lt;0.005</td>
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</table>
Comparisons of Parameters in APA Patients between Baseline and 1 and 12 Months after Adrenalectomy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>1 month</th>
<th>p</th>
<th>12 months</th>
<th>p*</th>
<th>p§</th>
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<tbody>
<tr>
<td>Sample size</td>
<td>94</td>
<td>93</td>
<td>-</td>
<td>80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>28.0 ± 1.6</td>
<td>8.8 ± 0.3</td>
<td>&lt;0.01</td>
<td>10.7 ± 0.5</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>0.8 ± 0.2</td>
<td>1.4 ± 0.1</td>
<td>NS</td>
<td>3.7 ± 0.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>ARR (ng/dL per ng/mL/h)</td>
<td>149.6 ± 16.6</td>
<td>17.4 ± 2.2</td>
<td>&lt;0.01</td>
<td>10.9 ± 1.6</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.4 ± 0.1</td>
<td>4.5 ± 0.0</td>
<td>&lt;0.01</td>
<td>4.4 ± 0.0</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>152 ± 2</td>
<td>136 ± 1</td>
<td>&lt;0.01</td>
<td>130 ± 2</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>94 ± 1</td>
<td>84 ± 1</td>
<td>&lt;0.01</td>
<td>82 ± 1</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse Pressure (mmHg)</td>
<td>59 ± 2</td>
<td>51 ± 1</td>
<td>&lt;0.01</td>
<td>48 ± 1</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Cre eGFR (mL/min/1.73 m²)</td>
<td>78 ± 2</td>
<td>67 ± 2</td>
<td>&lt;0.01</td>
<td>64 ± 2</td>
<td>&lt;0.01</td>
<td>NS</td>
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<tr>
<td>UACR (mg/g creatinine)</td>
<td>109 ± 30</td>
<td>36 ± 10</td>
<td>-</td>
<td>23 ± 5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Log transformed</td>
<td>1.6 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>&lt;0.01</td>
<td>1.0 ± 0.1</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Aorta velocity (cm/s)</td>
<td>83.2 ± 2.1</td>
<td>74.5 ± 2.1</td>
<td>&lt;0.01</td>
<td>72.6 ± 2.2</td>
<td>&lt;0.01</td>
<td>NS</td>
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<tr>
<td>Resistive index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>0.70 ± 0.01</td>
<td>0.67 ± 0.01</td>
<td>&lt;0.01</td>
<td>0.66 ± 0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>0.67 ± 0.01</td>
<td>0.63 ± 0.01</td>
<td>&lt;0.01</td>
<td>0.64 ± 0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Interlobar arteries</td>
<td>0.63 ± 0.01</td>
<td>0.60 ± 0.01</td>
<td>&lt;0.05</td>
<td>0.59 ± 0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Peak systolic velocity (cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>100.4 ± 3.1</td>
<td>91.6 ± 2.7</td>
<td>&lt;0.05</td>
<td>90.5 ± 3.1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>65.1 ± 1.5</td>
<td>61.3 ± 1.5</td>
<td>&lt;0.01</td>
<td>55.3 ± 1.7</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Interlobar arteries</td>
<td>24.3 ± 0.6</td>
<td>24.6 ± 0.6</td>
<td>NS</td>
<td>21.8 ± 0.6</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End diastolic velocity (cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main artery</td>
<td>29.7 ± 1.0</td>
<td>30.3 ± 1.0</td>
<td>NS</td>
<td>29.9 ± 1.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hilum arteries</td>
<td>21.2 ± 0.6</td>
<td>22.4 ± 0.7</td>
<td>NS</td>
<td>20.2 ± 0.7</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interlobar arteries</td>
<td>8.9 ± 0.3</td>
<td>9.9 ± 0.3</td>
<td>&lt;0.01</td>
<td>8.8 ± 0.2</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Analyses of variance followed by Tukey’s tests or Dunn’s tests were performed to compare the variables between the periods. UACR was logarithmically transformed. The values are expressed as mean ± standard error of the mean (SEM). APA, aldosterone-producing adenoma; NS, not significant; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone renin ratio; BP, blood pressure; Cre eGFR, estimated glomerular filtration rate based on serum creatinine; UACR, urinary albumin corrected by urinary creatinine; Log, logarithm; *, compared with baseline; §, compared with 1 month.

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>$\beta$</th>
<th>SE ($\beta$)</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)$\times100$</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)$\times100$</td>
<td>0.184</td>
<td>0.046</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.175</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>
</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 $\geq$140 mm Hg, increase in blood pressure, taking $\geq$3 antihypertensive agents, or increase in the number of agents at the end of study. $\beta$ indicates the standardized regression coefficient; AIC, Akaike information criterion; AUC, area under the curve; NS, not significant; and RI, resistive index.
RRI predicts the blood pressure outcomes

Significantly higher systolic blood pressure and more number of the antihypertensive agents at one year after surgery in the Highest RRI group in comparison with the Lowest RRI group.

Changes of eGFR

Hyperfiltration

Nephrosclerosis

Masked CKD

CKD stage 3-5

HD
【Case presentation】59-year-old man

Chief complaint; refractory hypertension (HTN), leg edema

Life history; no alcohol, past smoker (BI; 15x40)
Family history; His father, mother and sister had history of HTN.
Past history; nothing in particular

Present illness;

He was admitted to our hospital due to chronic renal failure (CRF) and hyperaldosteronism. He had not visited hospital in his 30s and 40s, although he had been pointed out HTN. When he was 51 years old, he started taking anti-hypertensive agents. At the age of 58, his family doctor pointed out elevated serum creatinine (2.53 mg/dL) and leg edema at regular check-up. Further examination revealed hypokalemia (2.7 mM), nephrotic-range proteinuria (5.3 g/gCr).
59-year-old man with resistant hypertension and CRF

Clinical parameters at admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>170.5 cm</td>
</tr>
<tr>
<td>Weight</td>
<td>84.0 kg</td>
</tr>
<tr>
<td>BMI</td>
<td>28.9</td>
</tr>
<tr>
<td>Blood pressure*</td>
<td>145/95 mmHg</td>
</tr>
<tr>
<td>Heart rate*</td>
<td>99 beats/min</td>
</tr>
</tbody>
</table>

*prescribing drugs (/day); nifedipine 80 mg, azelnidipine 16 mg, amlodipine 10 mg, doxazosin 4 mg

No murmurs, No rales, Bilateral tibial edema ++

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>143 mM</td>
</tr>
<tr>
<td>K</td>
<td>3.6 mM</td>
</tr>
<tr>
<td>Cl</td>
<td>109 mM</td>
</tr>
<tr>
<td>BUN</td>
<td>16 mg/dL</td>
</tr>
<tr>
<td>Cre</td>
<td>2.68 mg/dL</td>
</tr>
<tr>
<td>eGFR</td>
<td>20 mL/min/1.73m²</td>
</tr>
<tr>
<td>TP</td>
<td>4.8 g/dL</td>
</tr>
<tr>
<td>Alb</td>
<td>2.5 g/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>47.4 pg/mL</td>
</tr>
<tr>
<td>Cortisol</td>
<td>10.9 μg/dL</td>
</tr>
<tr>
<td>PAC</td>
<td>29.4 ng/dL</td>
</tr>
<tr>
<td>→ ARR</td>
<td>13.4</td>
</tr>
<tr>
<td>PRA</td>
<td>2.2 ng/mL/h</td>
</tr>
</tbody>
</table>

*K replacement; 94 mmol/day

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-Na</td>
<td>235 mmol/gCr</td>
</tr>
<tr>
<td>U-K</td>
<td>58 mmol/gCr</td>
</tr>
<tr>
<td>→ TTKG</td>
<td>6.57</td>
</tr>
<tr>
<td>U-Cl</td>
<td>233 mmol/gCr</td>
</tr>
<tr>
<td>U-Alb</td>
<td>3.48 g/gCr</td>
</tr>
<tr>
<td>U-TP</td>
<td>5.34 g/gCr</td>
</tr>
<tr>
<td>U-β2MG</td>
<td>30060 μg/L</td>
</tr>
<tr>
<td>U-Aldo</td>
<td>27.1 μg/day</td>
</tr>
<tr>
<td>UFC</td>
<td>41.2 μg/day</td>
</tr>
</tbody>
</table>

*PRA; plasma renin activity, PAC; plasma aldosterone conference, UFC; urinary free cortisol
###【Endocrinological evaluation】

####【Circadian rhythm】

<table>
<thead>
<tr>
<th>Time</th>
<th>ACTH</th>
<th>Cortisol</th>
<th>PAC</th>
<th>PRA</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:00</td>
<td>47.4</td>
<td>10.9</td>
<td>29.4</td>
<td>2.2</td>
<td>13.4</td>
</tr>
<tr>
<td>11:00</td>
<td>24.6</td>
<td>5.2</td>
<td>22.1</td>
<td>7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>17:00</td>
<td>8.3</td>
<td>6.9</td>
<td>21.7</td>
<td>8.5</td>
<td>2.6</td>
</tr>
<tr>
<td>23:00</td>
<td>14.3</td>
<td>4.4</td>
<td>32.4</td>
<td>3.8</td>
<td>8.5</td>
</tr>
</tbody>
</table>

####【Captopril challenge test (CCT)】

<table>
<thead>
<tr>
<th>Time</th>
<th>PAC</th>
<th>PRA</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0分</td>
<td>19.2</td>
<td>2.8</td>
<td>6.9</td>
</tr>
<tr>
<td>60分</td>
<td>31.3</td>
<td>7.6</td>
<td>4.1</td>
</tr>
<tr>
<td>90分</td>
<td>32.3</td>
<td>6.0</td>
<td>5.4</td>
</tr>
<tr>
<td>120分</td>
<td>29.1</td>
<td>6.6</td>
<td>4.4</td>
</tr>
</tbody>
</table>

ACTH; pg/mL, cortisol; μg/dL, PAC; ng/dL, PRA; ng/mL/hr

- **ARR was lower than “20” due to elevated PRA caused by CRF.**
- **However, PAC did not decrease and remained higher** in CCT.
• Computed tomography revealed a right adrenal tumor (φ 8 mm).
• The sizes of kidneys were kept (φ 10 cm).
【Cosyntropin-stimulated AVS】

Right adrenal vein (RAV)  Left adrenal vein (LAV)

<table>
<thead>
<tr>
<th></th>
<th>RAV</th>
<th>EIV</th>
<th>LAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA 9.3 ng/mL/hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>20378.5</td>
<td>34.1</td>
<td>1760.1</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>1191.9</td>
<td>13.2</td>
<td>1320.1</td>
</tr>
<tr>
<td>Aldosterone/cortisol</td>
<td>17.10</td>
<td>2.58</td>
<td>1.33</td>
</tr>
</tbody>
</table>

12.82 times

- We successfully performed AVS with only 8 mL of contrast media.
- AVS confirmed hyperaldosteronism from right adrenal gland.
He underwent laparoscopic right adrenalectomy.
The right adrenal tumor was diagnosed as aldosterone-producing adenoma.
<table>
<thead>
<tr>
<th></th>
<th>At AVS</th>
<th>At Surgery</th>
<th>POD 8</th>
<th>POD 26</th>
<th>POD 181</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>145/95</td>
<td>139/77</td>
<td>139/74</td>
<td>137/79</td>
<td>131/75</td>
</tr>
<tr>
<td>AZL/SPL (mg/day)</td>
<td></td>
<td>30/90</td>
<td></td>
<td></td>
<td>10/25</td>
</tr>
<tr>
<td>Other AHT (n)</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PRA (ng/mL/hr)</td>
<td>2.2</td>
<td>12.0</td>
<td>6.7</td>
<td></td>
<td>32.1</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>29.7</td>
<td>26.1</td>
<td>17.3</td>
<td></td>
<td>14.1</td>
</tr>
<tr>
<td>U-Aldo (µg/day)</td>
<td>29.0</td>
<td></td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum K (mM)</td>
<td>3.6</td>
<td>5.7</td>
<td>5.4</td>
<td>4.8</td>
<td>6.9</td>
</tr>
<tr>
<td>Cre (mg/dL)</td>
<td>2.68</td>
<td>2.97</td>
<td>3.27</td>
<td>2.69</td>
<td>2.92</td>
</tr>
<tr>
<td>U-Alb (g/gCr)</td>
<td>3.48</td>
<td>0.38</td>
<td>0.43</td>
<td>0.69</td>
<td>0.16</td>
</tr>
<tr>
<td>U-P (g/gCr)</td>
<td>5.34</td>
<td>0.54</td>
<td>0.60</td>
<td>1.12</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* AHT; anti-hypertensive agents, BP; blood pressure AZL; azilsartan, SPL; spironolactone

After surgery, the control of BP, hypokalemia and proteinuria improved without exacerbation of renal function.
Objective: To develop clinical practice guidelines for the management of patients with primary aldosteronism.

Participants: The Task Force included a chair, selected by the Clinical Guidelines Subcommittee of the Endocrine Society, six additional experts, a methodologist, and a medical writer. The guideline was co-sponsored by American Heart Association, American Association of Endocrine Surgeons, European Society of Endocrinology, European Society of Hypertension, International Association of Endocrine Surgeons, International Society of Endocrinology, International Society of Hypertension, Japan Endocrine Society, and The Japanese Society of Hypertension. The Task Force received no corporate funding or remuneration.

Evidence: We searched for systematic reviews and primary studies to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation group criteria to describe both the quality of evidence and the strength of recommendations. We used “recommend” for strong recommendations and “suggest” for weak recommendations.

Consensus Process: We achieved consensus by collecting the best available evidence and conducting one group meeting, several conference calls, and multiple e-mail communications. With the help of a medical writer, the Endocrine Society’s Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and Council successfully reviewed the drafts prepared by the Task Force. We placed the version approved by the Clinical Guidelines Subcommittee and Clinical Affairs Core Committee on the Endocrine Society’s website for comments by members. At each stage of review, the Task Force received written comments and incorporated necessary changes.

Conclusions: For high-risk groups of hypertensive patients and those with hypokalemia, we recommend case detection of primary aldosteronism by determining the aldosterone-renin ratio under standard conditions and recommend that a commonly used confirmatory test should confirm/exclude the condition. We recommend that all patients with primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adenocortical carcinoma. We recommend that an experienced radiologist should establish/exclude unilateral primary aldosteronism using bilateral adrenal venous sampling, and if confirmed, this should optimally be treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia or those unsuitable for surgery should be treated primarily with a mineralocorticoid receptor antagonist. (J Clin Endocrinol Metab 101: 1889–1916, 2016)
Algorithm for the detection, confirmation, subtype testing, and treatment of PA

Patients with Hypertension that are at Increased Risk for PA

PA Unlikely

ARR to Detect Cases (1|⊕⊕ΟΟ)

+ → Patient Unwilling/Unable to Proceed

↓ K⁺, renin ↓↓
PAC >20 ng/dL

PA Unlikely

Confirmatory Testing (1|⊕⊕ΟΟ)

+ → No Need for Confirmatory Testing

↓↓

(2|⊕ΟΟΟΟ) b

Treat with MR Antagonist

(2|⊕⊕ΟΟΟΟ) a

↓↓

Subtype Testing

If Surgery Desired

Adrenal CT (1|⊕⊕⊕Ο)

If Surgery Not Desired

AVS (1|⊕⊕⊕Ο)

Bilateral

Treat with MR Antagonist

(1|⊕⊕⊕Ο)

Unilateral

Marked PA, Young Age, and + CT (2|⊕ΟΟΟΟ) c

Treat with Laparoscopic Adrenalectomy (1|⊕⊕⊕Ο)

Rapid Screening of Primary Aldosteronism by a Novel Chemiluminescent Immunoassay

Ryo Morimoto,* Yoshikiyo Ono,* Yuta Tezuka, Masataka Kudo, Sachiko Yamamoto, Toshiaki Arai, Celso E. Gomez-Sanchez, Hironobu Sasano, Sadayoshi Ito, Fumitoshi Satoh

See Editorial Commentary,

Abstract—Measurement of plasma aldosterone and renin concentration, or activity, is useful for selecting antihypertensive agents and detecting hyperaldosteronism in hypertensive patients. However, it takes several days to get results when measured by radioimmunoassay and development of more rapid assays has been long expected. We have developed chemiluminescent enzyme immunoassays enabling the simultaneous measurement of both aldosterone and renin concentrations in 10 minutes by a fully automated assay using antibody-immobilized magnetic particles with quick aggregation and dispersion. We performed clinical validation of diagnostic ability of this newly developed assay-based screening of 125 patients with primary aldosteronism from 97 patients with essential hypertension. Results of this novel assay significantly correlated with the results of radioimmunoassay (aldosterone, active renin concentration, and renin activity) and liquid chromatography–tandem mass spectrometry (aldosterone). The analytic sensitivity of this particularly novel active renin assay was 0.1 pg/mL, which was better than that of radioimmunoassay (2.0 pg/mL). The ratio of aldosterone-to-renin concentrations of 6.0 (ng/dL per pg/mL) provided 92.0% sensitivity and 76.3% specificity as a cutoff for differentiating primary aldosteronism from essential hypertension. This novel measurement is expected to be a clinically reliable alternative for conventional radioimmunoassay and to provide better throughput and cost effectiveness in diagnosis of hyperaldosteronism from larger numbers of hypertensive patients in clinical settings. (Hypertension. 2017;70:334-341. DOI: 10.1161/HYPERTENSIONAHA.117.09078.)
Rapid Diagnosis of Primary Aldosteronism

by Morris J. Brown

Hypertension
Volume 70(2):247-249
July 12, 2017

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The Primary Aldosteronism hurdles: Ten large leaps to removing 1 small aldosterone-producing adenoma.

Withdrawal of interfering treatment
Screening for aldosterone and renin
Interpretation of aldosterone-renin ratio
Repeat measurement before and after saline
Computed tomography or magnetic resonance imaging
Withdrawal of treatment, again, for
Lateralization by adrenal vein sampling (AVS)
Repeat AVS if failure to cannulate both veins
Adrenalectomy – usually keyhole
50% cured of hypertension
The novel methods for diagnosis of primary aldosteronism
Backgrounds and Objects

- The measurement of plasma aldosterone concentration (PAC) and renin activity (PRA) or active renin concentration (ARC) is clinically important not only for detection of primary aldosteronism (PA) but also for the selection of antihypertensive agents to treat patients successfully.

- However, it has taken approximately 7 days for clinicians to get the results. Of late, we developed the novel rapid non-RIA assays of PAC and ARC, which can be measure in 10 minutes.

- This study is intended to investigate the utility and accuracy of the new measurements.
Methods and Patients

• Both PAC and ARC in 25 μL plasma sample were simultaneously measured by chemiluminescent enzyme immunoassay (CLEIA) system machine, “Accuraseed “with their specific monoclonal antibodies, using the automatically washable antibody immobilized magnetic particles with very quick aggregation and dispersion, “MAGRAPID”.

• We retrospectively compared PAC and ARC measured by Accuraseed with those by RIA and PAC by LC-MS/MS in 222 patients with aldosterone producing adenoma (APA, n=75), bilateral idiopathic hyperaldosteronism (IHA, n=50) and essential hypertension (EH, n=97).

• We examined the accuracy of Accuraseed by Bland-Altman plot analysis.
Specification

1. Measuring Principle : CLEIA
2. **Total Assay Time** : 10 min 20 sec
3. Throughput : 180 test/hour
4. **Number of different assays Simultaneously** (max.) 24 assays.
   Random access available.
5. **Sample volume** : 25μL (10-25uL)
6. Sampling method : disposable tip
7. Reagents and consumables are hot swappable.
8. STAT : available
9. Sample Track compatibility : available (optional)
10. **Dimensions** : (W)1325 × (H)1415 × (D)905
11. Power supply : 100VAC, 10A
Why is the rapid measurement possible?
Benefit of MAGRAPID (Quick aggregation & Quick dispersion)

**Aggregation**
- Conventional magnetic particle
- MAGRAPID
  - 0:00: Magnet
  - 0:02: Magnet
  - 0:11: Magnet

MAGRAPID aggregates faster (11sec.) than conventional magnetic particles (86sec.)

**Dispersion**
- Conventional magnetic particle
- MAGRAPID
  - 0:00: Magnet
  - 0:01: Magnet
  - 0:00: Remove magnet

MAGRAPID disperses faster than conventional magnetic particles.
Measuring principle of PAC

~ Total Assay Time 10min20sec, Competitive immunoassay ~

1st reaction:
- Anti-aldosterone monoclonal antibody (✓) binds to Aldosterone (●) and anti-mouse antibody immobilized MAGRAPID

2nd reaction:
- Enzyme labeled aldosterone (●) and aldosterone (●) react competitively to anti-aldosterone monoclonal antibody bounded MAGRAPID

Luminescence measurement
B/F separation 60sec
Add Substrate solutions
Magnet

Some of aldosterone (●) is replaced with Enzyme labeled aldosterone (●)

Substrate solutions:
- Add Enzyme labeled aldosterone
- Add Substrate solutions
- Magnetic separation
- Luminescence measurement

Total Assay Time: 10min20sec

Competitive reaction at 37°C for 180sec
**Measuring principle of PAC**

~ Total Assay Time 10min20sec ~ Competitive immunoassay ~

1st reaction:
- Anti-aldosterone monoclonal antibody (♀) binds to Aldosterone (♂) and anti-mouse antibody immobilized MAGRAPID

2nd reaction:
- **Enzyme labeled aldosterone** (♂) and aldosterone (♂) react competitively to anti-aldosterone monoclonal antibody bounded MAGRAPID

- 1st reaction:
  - Anti-aldosterone monoclonal antibody (♀) binds to Aldosterone (♂) and anti-mouse antibody immobilized MAGRAPID
  - 37°C 180sec

- 2nd reaction:
  - **Enzyme labeled aldosterone** (♂) and aldosterone (♂) react competitively to anti-aldosterone monoclonal antibody bounded MAGRAPID
  - 37°C 180sec

- MAGRAPID has shortened the aggregation time.

- Some of aldosterone (♂) is replaced with Enzyme labeled aldosterone (♂)

- B/F separation 60sec

- Luminescence measurement

- MAGRAPID has shortened the dispersion time
Measuring principle of Accuraseed ARC

1st reaction:
- Renin binds to anti-renin monoclonal antibody immobilized MAGRAPID.

2nd reaction:
- Enzyme labeled anti-renin monoclonal antibody binds to immunocomplex of Renin and anti-renin monoclonal antibody immobilized MAGRAPID.

Total Assay Time: 10min20sec

Sandwich immunoassay

B/F separation: 60sec

Magnet

Luminescence measurement

Add Substrate solutions.
Measuring principle of Accuraseed ARC

~ Total Assay Time 10min20sec ~ Sandwich immunoassay ~

1st reaction:
- Renin binds to anti-renin monoclonal antibody immobilized MAGRAPID

37°C 180sec

2nd reaction:
- Enzyme labeled anti-renin monoclonal antibody binds to immunocomplex of Renin and anti-renin monoclonal antibody immobilized MAGRAPID

MAGRAPID has shortened the aggregation time.

MAGRAPID has shortened the dispersion time.

B/F separation 60sec
Accuraseed v.s. MS-MS
N=120
(Spearman's r = 0.988, p< 0.0001)

SPAC v.s. MS-MS
N=120
(Spearman's r = 0.963, p< 0.0001)

Accuraseed v.s. SPAC
N=120
y = 1.097x + 3.263
Spearman’s ρ = 0.9523
P< 0.0001

Bland-Altman plot analysis

<table>
<thead>
<tr>
<th></th>
<th>Accuraseed v.s. MS-MS</th>
<th>SPAC v.s. MS-MS</th>
<th>Accuraseed v.s. SPAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td>13.7026</td>
<td>33.3718</td>
<td>8.80917</td>
</tr>
<tr>
<td>Std Dev</td>
<td>1.44374</td>
<td>9.18359</td>
<td>1.19985</td>
</tr>
<tr>
<td>Upper 95% Cl</td>
<td>16.5545</td>
<td>51.5129</td>
<td>11.185</td>
</tr>
<tr>
<td>Lower 95% Cl</td>
<td>10.8506</td>
<td>15.2307</td>
<td>6.43335</td>
</tr>
</tbody>
</table>
Distribution of CLEIA PAC measurements in APA, BHA and EH.

* $p < 0.05$

Morimoto R, Ono Y et al. *Hypertens* 2017
Accuraseed-ARC v.s. RIA-ARC

Bland-Altman plot analysis

N=222
Spearman's r = 0.930,
Y= 0.960 X + 1.128, p< 0.0001

<table>
<thead>
<tr>
<th>Bias</th>
<th>-0.977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std Dev</td>
<td>0.0558</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>-0.8671</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>-1.087</td>
</tr>
</tbody>
</table>
CLEIA ARC v.s. PRA

N=222
\[ y = 4.082x + 0.549 \]
Spearman’s \( \rho = 0.912 \)
P< 0.0001

Accuraseed ARC

- By Accuraseed ARC, we can get more precise ARC data with low concentrations in PA patients or low renin hypertensive patients in ten minutes 20 sec with compared to conventional ARC measurements.
Distribution of CLEIA ARC measurements In APA, BHA and EH

How about the diagnosis of PA?
Distribution of $\text{ARR}_{\text{ARC}}$ in PA, APA, BHA and EH.

Morimoto R, Ono Y et al. *Hypertens* 2017
Measurements of the ARC more strongly influence the diagnosis of the PA.
Conclusions

• This novel measurement is expected to be a clinically reliable alternative for conventional radioimmunoassay and to provide better throughput and cost-effectiveness in diagnosis of hyperaldosteronism from larger numbers of hypertensive patients in clinical settings.
Algorithm for the detection, confirmation, subtype testing, and treatment of PA

Patients with Hypertension that are at Increased Risk for PA

- PA Unlikely
  - ARR to Detect Cases (1|⊕⊕ΟΟ)
    - +
    -Confirmatory Testing (1|⊕⊕ΟΟ)
      - +
      - Adrenal CT (1|⊕⊕⊕Ο)
        - If Surgery Desired
          - AVS (1|⊕⊕⊕Ο)
            - Bilateral
              - Treat with MR Antagonist (1|⊕⊕⊕Ο)
            - Unilateral
              - Marked PA, Young Age, and + CT (2|⊕ΟΟΟΟ)
                - Treat with Laparoscopic Adrenalectomy (1|⊕⊕⊕Ο)
        - Subtype Testing
          - If Surgery Not Desired
            - Marked PA, Young Age, and + CT (2|⊕ΟΟΟΟ)
              - Treat with MR Antagonist (2|⊕ΟΟΟΟ)
AVS-CT concordance rate

Case 1
Right tumor n=43
- Ipsilateral: 65.1% (n=28)
- Bilateral: 34.9% (n=15)

Case 2
Left tumor n=72
- Ipsilateral: 56.9% (n=41)
- Bilateral: 37.5% (n=27)
- Contralateral: 5.6% (n=4)

Bilateral tumor n=22
- Bilateral: 50.0% (n=11)
- Lt. Unilateral: 31.8% (n=7)
- Rt. Unilateral: 18.2% (n=4)

No tumor n=102
- Bilateral: 80.0% (n=84)
- Unilateral: 20.0% (n=21)

➢ about 32% of PAs can’t be detected localization by CT scan!
## Successful rate of AVS

<table>
<thead>
<tr>
<th>References</th>
<th>Study Methods</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vonend O et al. <em>Hypertension</em>. 2011</td>
<td>Multi-centers</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Young WF Jr. <em>Endocrinology</em>. 2003</td>
<td>Metanalysis</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>Degenhart C et al. <em>Diagn Interv Radiol</em>. 2015</td>
<td>An expert radiologist In a single center</td>
<td>93%</td>
<td>99%</td>
</tr>
<tr>
<td>Trerotola SO et al. <em>J Vasc Interv Radiol</em>. 2014</td>
<td>An expert radiologist In a single center</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>
Why is the drawing blood from a right adrenal vein difficult?

The anatomy of the right adrenal vein.

• The right adrenal vein is thin and is also short.

• It flows into inferior vena cava directly.

• There are various anatomical variations
  It often forms a common trunk together with an accessory hepatic vein.
The anatomy of adrenal veins.

Adrenal venous sampling
By 6.5 Fr (5 Fr) catheters
Simultaneous sampling
Left adrenal vein
Right adrenal vein
A common trunk is formed by an accessory hepatic vein and right adrenal vein. How often does it happen?
Depiction of the right adrenal vein by CT

To evaluate the run of the right adrenal vein, height and the direction of the junction meeting inferior vena cava (IVC) using a rearrangement image of CT.
Depicting a right adrenal vein by CT

- General cases
- Cases with common trunk

Rt. Adrenal vein

IVC

Accessory hepatic vein

Rt. Adrenal vein
# Frequency of the common trunk

<table>
<thead>
<tr>
<th>References</th>
<th>Methods</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Matsuura T et al. <em>AJR.</em> 2008</td>
<td>Arterial phase by 8-channeled multidetector CT(MDCT)</td>
<td>7.6% (6/79)</td>
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<td>Miotto D et al. <em>Hypertension.</em> 2009</td>
<td>AVS</td>
<td>12.1% (8/66)</td>
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<td>Ota H et al. <em>Eur Radiol.</em> 2015</td>
<td>Late arterial phase by 64-channeled MDCT</td>
<td>16.1% (18/112)</td>
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<td>Morita S et al. Cardiovasc Intervent Radiol. 2016</td>
<td>Two venous phases (45, 55s) by 64-channeled MDCT</td>
<td>24.4% (22/90)</td>
</tr>
</tbody>
</table>
Problems

• How should we image it to depict an adrenal vein by CT?
• The frequency of the common trunk with the accessory hepatic vein was assumed around 10% conventionally, but actually?
• Does the right adrenal vein depicted by CT really match?
Adrenal Vein Sampling

Anatomical Variations of the Right Adrenal Vein
Concordance Between Multidetector Computed Tomography and Catheter Venography

Kensuke Omura, Hideki Ota, Yuuki Takahashi, Tomonori Matsuura, Kazumasa Seiji, Yoichi Arai, Ryo Morimoto, Fumitoshi Satoh, Kei Takase

Abstract—Adrenal venous sampling is the most reliable diagnostic procedure to determine surgical indications in primary aldosteronism. Because guidelines recommend multidetector computed tomography (CT) to evaluate the adrenal gland, some past reports used multidetector CT as a guide for adrenal venous sampling. However, the detailed anatomy of the right adrenal vein and its relationship with an accessory hepatic vein remains uncertain. The purpose of this study was to describe detailed anatomical variations of the right adrenal vein and to determine the concordance between CT and catheter venography in patients with primary aldosteronism. In total, 440 consecutive patients who underwent adrenal venous sampling were included. Four-phase dynamic CT was performed. Anatomical locations and variations of the right adrenal vein and its relationship with the accessory hepatic vein were compared with catheter venographic findings. Successful catheterization was achieved in 437 patients (99%). The right adrenal vein was visualized in the late arterial phase with CT in 420 patients (95%). The right adrenal vein formed a common trunk with the accessory hepatic vein in 87 patients (20%). CT identified the correct craniocaudal level of the orifice in 354 patients (84%). Anatomical variations, location, and angle of inflow of the right adrenal vein based on CT demonstrated high concordance with catheter venography. CT may provide useful information for preparation before adrenal venous sampling. (Hypertension. 2017;69:428-434. DOI: 10.1161/HYPERTENSIONAHA.116.08375.) • Online Data Supplement

Key Words: adenoma ■ adrenal gland ■ hyperaldosteronism ■ multidetector computed tomography ■ prevalence
Examination about the anatomical variations of the right adrenal vein based on contrasted dynamic CT and the adrenal vein sampling angiography in 440 consecutive patients.

and angle of inflow of the right adrenal vein based on CT demonstrated high concordance with catheter venography. CT may provide useful information for preparation before adrenal venous sampling. (Hypertension. 2017;69:428-434. DOI: 10.1161/HYPERTENSIONAHA.116.08375.) • Online Data Supplement

Key Words: adenoma ■ adrenal gland ■ hyperaldosteronism ■ multidetector computed tomography ■ prevalence
Objections

• To analyze the detailed right suprarenal vein dissection in patients with many primary aldosteronism

• To compare the angiography with CT and examine the validity of referring to anatomy by CT at AVS.
Patients

• Consecutive 440 cases of primary aldosteronism
• They underwent CT and AVS between January in 2008 and February in 2014.
• Male; 214 cases: Female; 226 cases: Averaged age: 53.
Imaging protocol
4 phases dynamic imaging CT

<table>
<thead>
<tr>
<th></th>
<th>Early arterial phase</th>
<th>Bolus tracking (+50 HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Late arterial phase</td>
<td>13s after 1st phase is finished</td>
</tr>
<tr>
<td>3rd</td>
<td>Venous phase</td>
<td>70s after contrast media infusion</td>
</tr>
<tr>
<td>4th</td>
<td>Late venous phase</td>
<td>180s after contrast media infusion</td>
</tr>
</tbody>
</table>

- **1st phase (Early arterial phase):** Bolus tracking (+50 HU)
- **2nd phase (Late arterial phase):** 13s after 1st phase is finished
- **3rd phase (Venous phase):** 70s after contrast media infusion
- **4th phase (Late venous phase):** 180s after contrast media infusion

Images show RT. Adrenal vein and Accessory hepatic vein in different phases.
Rt. Adrenal vein

Accessory hepatic vein

Late arterial phase

Venous phase
Image analysis of the anatomical variations

• Relationship with the accessory hepatic vein
• The height in the opening
• Position in the horizontal phase of the opening
• Direction of the run of the right adrenal vein
  - Angle on the horizontal cut
  - Angle on the perpendicular cut
• Accordant degree of CT and the angiography
The height in the opening

Dividing each body of vertebra into 3 parts in the beginning and end direction and adding the images of intervertebral disks

Rt. Adrenal vein

Adrenal gland
The height in the opening

Angiography

- T10: 2 (0.5%)
- T10/11: 8 (1.9%)
- T11: 16 (3.8%)
- T11/12: 27 (6.4%)
- T12: 47 (11.1%)
- T12/L1: 66 (15.6%)
- T12/L1: 84 (19.9%)
- T12/L1: 66 (15.6%)
- T12/L1: 51 (12.1%)
- T12/L1: 43 (10.2%)
- T12/L1: 28 (6.6%)
- T12/L1: 7 (1.7%)
- T12/L1: 3 (0.7%)
- T12/L1: 1 (0.2%)

MDCT

- T10: 1 (0.2%)
- T10/11: 6 (1.4%)
- T11: 9 (2.1%)
- T11/12: 55 (13.0%)
- T11/12: 67 (15.9%)
- T11/12: 78 (18.5%)
- T11/12: 61 (14.5%)
- T11/12: 52 (12.3%)
- T11/12: 33 (7.8%)
- T11/12: 17 (4.0%)
- T11/12: 12 (2.8%)
- T11/12: 4 (0.9%)
Image analysis of the anatomical variations

• Relationship with the accessory hepatic vein
• The height in the opening
• Position in the horizontal phase of the opening
• Direction of the run of the right adrenal vein
  - Angle on the horizontal cut
  - Angle on the perpendicular cut
• Accordant degree of CT and the angiography
Position & direction of the opening

Concordant degree of CT and the angiography

+/− (The right, left, up and down)
Accordant degree of CT and the angiography

Rate of agreement of the height:

<table>
<thead>
<tr>
<th>Accordant (≤±1)</th>
<th>354 pts (83.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost accordant (=±2)</td>
<td>57 pts (13.5%)</td>
</tr>
<tr>
<td>Uncertainty (=±3)</td>
<td>11 pts (2.6%)</td>
</tr>
<tr>
<td>Disagreement (≥±4)</td>
<td>0 pts (0.0%)</td>
</tr>
</tbody>
</table>

The difference of the height is within 1 body of vertebra in all cases.
Accordant degree of CT and the angiography

- Position of the opening agreement in all cases
  - Horizontal direction: 327例 (97.6%)
  - Direction of the beginning and end: 317例 (94.6%)

## Success rate of depicting Rt. AV

<table>
<thead>
<tr>
<th>CT</th>
<th>Methods</th>
<th>Depicting rate</th>
</tr>
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<tbody>
<tr>
<td>Matsuura et al.</td>
<td>8 Ch Early arterial phase</td>
<td>76%</td>
</tr>
<tr>
<td>Degenhart et al.</td>
<td>64 Ch 90 s</td>
<td>78%</td>
</tr>
<tr>
<td>Morita et al.</td>
<td>64 Ch 45, 55 s</td>
<td>91%, 92%</td>
</tr>
<tr>
<td>Higashide et al.</td>
<td>320Ch 30, 45, 60, 90 s</td>
<td>合わせて88%</td>
</tr>
<tr>
<td>The present study</td>
<td>16Ch Late arterial phase (other 3 phases)</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

Optimal for the depiction of the adrenal vein
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<tr>
<td>The present study</td>
<td>Late arterial phase (other 3 phases)</td>
<td>20.5% 87/425</td>
</tr>
</tbody>
</table>
Frequency of the common trunk

- The present study; **20%**
- Analysis of the previously reported imaging


We should grasp it beforehand, and then we should collect blood of a right adrenal vein.
Adrenal CT to lead adrenal vein sampling to the success

- The right suprarenal vein anatomy based on CT accords with angiography findings well

- It is useful in success rate improvement to grasp the anatomy of the right adrenal vein using CT before AVS.
An Expert Consensus Statement on Use of Adrenal Vein Sampling for the Subtyping of Primary Aldosteronism


Figure 2. A and B. The contrast-enhanced multidetector computed tomography (CT) images show right adrenal vein (white arrow) that drains to accessory hepatic vein (black arrows) before entering inferior vena cava (arrowheads). C, Digital subtraction angiography (DSA) image confirms the anatomy of these veins before the superselective adrenal venous sampling (white arrow) that meets accessory hepatic vein (black arrows). Black arrowheads indicate the position of inferior vena cava.

D, The contrast-enhanced MDCT images show right adrenal vein (white arrow) that directly drains into inferior vena cava.

E, The contrast-enhanced MDCT images show right adrenal vein (white arrow) that drains into accessory hepatic vein (black arrowhead).
Catheters for adrenal venous sampling

Adselect Type 1

Adselect Type 2

Adselect Type 3

Adselect Type 4

Adselect Type 5
Type 5: accessory hepatic-right adrenal catheter

Accessory hepatic vein

Place second curve at medial side of IVC

For right adrenal vein which joins the accessory hepatic vein making common trunk. (≒20%)
Acc. hepatic v.

Right adrenal v.
Team “Hypertension & Endocrinology”

Internists

Pathologists

Radiologists

International Collaborators

- William E. Rainey
- Celsov E. Gomez-Sanchez
- Paolo Mulatero
- Gian Paolo Rossi
- Vin-Cent Woo