Suppression of Aldosterone Secretion After Recumbent Saline Infusion Does Not Exclude Lateralized Primary Aldosteronism

Erika Cornu, Olivier Steichen, Luis Nogueira-Silva, Elselien Küpers, Jean-Yves Pagny, Christine Grataloup, Stéphanie Baron, Franck Zinzindohoue, Pierre-François Plouin, Laurence Amar

See Editorial Commentary, pp 857–858

Abstract—Guidelines recommend suppression tests such as the saline infusion test (SIT) to ascertain the diagnosis of primary aldosteronism (PA) in patients with a high aldosterone:renin ratio. However, suppression tests have only been evaluated in small retrospective series, and some experts consider that they are not helpful for the diagnosis of PA. In this study, we evaluated whether low post-SIT aldosterone concentrations do exclude lateralized PA. Between February 2009 and December 2013, 199 patients diagnosed with PA on the basis of 2 elevated aldosterone:renin ratio results and a high basal plasma or urinary aldosterone level or high post-SIT aldosterone level had a selective adrenal venous sampling. We used a selectivity index of 2 and a lateralization index of 4 to interpret the adrenal venous sampling results. Baseline characteristics of the patients were the following (percent or median): men 63%, 48 years old, office blood pressure 142/88 mm Hg, serum potassium 3.4 mmol/L, aldosterone:renin ratio 113 pmol/mU, plasma aldosterone concentration 588 pmol/L. The proportion of patients with lateralized adrenal venous sampling was 12 of 41 (29%) among those with post-SIT aldosterone <139 pmol/L (5 ng/dL) and 38 of 104 (37%) among those with post-SIT aldosterone <277 pmol/L (10 ng/dL). Post-SIT aldosterone levels were not associated with the blood pressure outcome of adrenalectomy. A low post-SIT aldosterone level cannot rule out lateralized PA, even with a low threshold (139 pmol/L). Adrenal venous sampling should be considered for patients who are eligible for surgery with elevated basal aldosterone levels even if they have low aldosterone concentrations after recumbent saline suppression testing. (Hypertension. 2016;68:989-994. DOI: 10.1161/HYPERTENSIONAHA.116.07214.) • Online Data Supplement

Key Words: adrenal glands ■ adrenalectomy ■ blood pressure ■ catheterization ■ hyperaldosteronism

Primary aldosteronism (PA) is defined as an overproduction of aldosterone, relatively autonomous from the renin–angiotensin system.1 Its prevalence ranges from 5% to 10% among hypertensive patients.2 It can be caused by unilateral or bilateral disease.3 Unilateral PA can be treated by adrenalectomy.

Clinical practice guidelines recommend using the plasma aldosterone:renin ratio (ARR) to screen for PA in selected patients. It is recommended that a suppression test then be performed to confirm or exclude the diagnosis of PA. Four suppression tests are suggested: the oral sodium loading test, the saline infusion test (SIT), the fludrocortisone suppression test, and the captopril challenge test.1 Suppression tests should be highly sensitive—to avoid missing good candidates for surgery—and highly specific—to avoid useless, costly, and invasive lateralization procedures.

Suppression tests have been mostly evaluated in relatively small retrospective series of patients selected with a high probability of having PA.4,5 Most of the studies compare one test with another and not to a gold standard or to the outcome after surgery. The cut-offs differ according to the centers where they were performed and these tests can be dangerous for some patients (risk of fluid overload or severe hypokalemia). Several patients who had suppressed post-SIT aldosterone levels, still had their lateralized PA cured after adrenalectomy.6 It has been proposed that confirmation tests do not aid the diagnosis of PA in the majority of cases.7

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The objective of the study was to evaluate the proportion of patients with suppressed aldosterone levels after the SIT who nonetheless exhibited unilateral hypersecretion of aldosterone on adrenal venous sampling (AVS). The secondary objective was to evaluate whether post-SIT aldosterone predicts the outcome of adrenalectomy for patients with a lateralized AVS.

Materials and Methods

Patients
This retrospective study concerned all PA patients who were eligible for surgery and whose cases were discussed in multidisciplinary meetings of our hypertension center from February 2009 to December 2013. Patients were initially referred for exploration of resistant hypertension, hypertension with hypokalemia, hypertension with adrenal incidentaloma, or for AVS when PA had already been suspected elsewhere.

All patient signed an informed consent to have their data collected 4 routine clinical care reused for research purposes. Baseline clinical, biochemical, hormonal, and radiological data were extracted from the electronic health record database.

Diagnostic Criteria
Our methods for diagnosing PA rely on repeatedly elevated ARR and high basal plasma or urinary aldosterone measurements. Following guideline recommendations, we have systematically performed an SIT in patients who are eligible for surgery since 2009. We measured the plasma aldosterone concentration (PAC), active renin concentration (ARC), and urinary aldosterone concentration under standard conditions: blood was collected in the morning, after the patients had remained in a recumbent or seated position for 30 to 45 minutes. Interfering antihypertensive drugs were discontinued at least 2 weeks before blood collection, whenever possible (6 weeks for mineralocorticoid receptor and renin antagonists). Nondihydropyridine calcium-antagonists, α-blockers, and centrally acting antihypertensive drugs were prescribed for patients with severe hypertension if necessary. Unrestricted dietary sodium intake was recommended, and patients with persistent hypokalemia were given potassium supplements. The diagnosis of PA was based on the combination of (1) an ARR >64 pmol/mUI on at least 2 occasions plus (2) a pre-SIT PAC >500 pmol/L, post-SIT PAC >139 pmol/L, a basal standing PAC >550 pmol/L, or a urinary aldosterone concentration >63 nmol/24 h. The ARC threshold was set to a minimum of 5 mUI/L for the ARR calculation to avoid overestimation of the ARR in subjects with an undetectable ARC (Figure S1 in the online-only Data Supplement).

SIT was not performed in patients with severe symptomatic hypertension, hypokalemia, or congestive heart failure. For the SIT, the PAC was measured in the recumbent position before and after the infusion of 2 L of saline >4 hours (from 08:00 AM to 12:00 noon). Aldosterone hypersecretion was considered to be nonsuppressible if the post-SIT PAC was >139 pmol/L (5 ng/dL). A cutoff of 277 pmol/L (10 ng/dL) was also evaluated, according to guidelines.

All patients underwent an abdominal computed tomographic scan or magnetic resonance imaging to assess adrenal morphology. Typical unilateral adenoma was defined as a unilateral nodule with a diameter of at least 8 mm, a density below 10 HU on a noncontrast computed tomographic scan, and the remaining ipsilateral and contralateral glands smooth and not enlarged.

AVS Protocol
Bilateral simultaneous AVS without ACTH stimulation was performed in the morning by 2 experienced vascular radiologists following a standardized protocol. Two catheters were inserted via the femoral vein, and their placement was verified before sampling by injection of a small amount of contrast agent. Blood samples were then collected simultaneously from each adrenal vein and the inferior vena cava, for the measurement of cortisol and aldosterone concentrations.

We considered the AVS to be successful if the selectivity index, defined as the ratio of the cortisol concentration in the adrenal vein:the inferior vena cava, exceeded 2 on both sides. The ratios of aldosterone:cortisol concentration were then calculated for each adrenal vein. The lateralization ratio was defined as the highest adrenal aldosterone:cortisol ratio divided by the lowest one. We used a cutoff value of 4 to categorize the patients as lateralized or not for statistical analyses, as recommended.

Measurements
Blood pressure (BP) was measured by trained nurses using a validated semiautomated manometer (Omron 705 CP). The office BP was determined by calculating the average from 3 measurements in the semirecumbent position after a 5-minute rest period.

The sodium and potassium levels were measured using standard methods. The glomerular filtration rate was estimated by the CKD-EPI (Chronic Kidney Disease–Epidemiology Collaboration) formula. The ARC was determined by chemiluminescent immunoassay (Liaison; Diasorin) and aldosterone concentration by radioimmunoassay (Coat-A-Count; Siemens Healthcare Diagnostics). Urinary excretion of aldosterone was determined as the sum of free aldosterone and aldosterone 18-glucuronide after hydrolysis at pH 1.

Outcome Definition
There is no consensus classification of postoperative outcomes in patients with unilateral PA. In this study, we used the classification of the German Conn’s Registry:

1. Cure was defined as plasma potassium >3.4 mmol/L and BP <140/90 mm Hg without treatment. Significant improvement was defined as normokalemia associated with a decrease of ≥10 mm Hg of systolic BP and a decrease of antihypertensive drugs of at least 1 class.
2. Slight improvement was defined as normokalemia associated with a decrease of ≥10 mm Hg of systolic BP or a decrease of antihypertensive drugs of at least 1 class.
3. No improvement was defined as the persistence of hypokalemia or no BP improvement according to the above criteria.

Statistical Analysis
Quantitative variables are given as medians (interquartile range) and categorical data as numbers (percentage). We used Cuzick test for quantitative variables and the Cochrane–Armitage test for categorical variables to identify trends across the 3 groups with increasing post-SIT PAC. We computed the odds ratio of the proportion of lateralized AVS with increasing post-SIT PAC to quantify the observed trends. For all tests, P<0.05 were considered to be statistically significant. All analyses were performed using Stata 9.2 (StataCorp, College Station, TX) software.

Results
We excluded patients who could not undergo the SIT or whose AVS was not selective, leaving 199 patients with PA, an SIT and a valid AVS for analysis (Figure 1).
Patient Characteristics

Relevant clinical, biochemical, hormonal, and radiological features of the patients are reported in Table 1. Patients with increasing post-SIT PAC values had lower plasma potassium and ARC, higher PAC and ARR, and a higher proportion of unilateral adenoma on computed tomographic scan than those with a post-SIT PAC <139 pmol/L. However, they did not have significantly higher BP levels.

Association Between the Post-SIT PAC and AVS Result

There was an increase of lateralized AVS with high post-SIT PAC (P<0.001; Table 2). Compared with patients with a post-SIT PAC <139 pmol/L, the odds ratio for a lateralized AVS was 1.7 (95% confidence interval, 0.7–3.9; P=0.23) in patients with a post-SIT PAC between 139 and 277 pmol/L (5–10 ng/dL) and 5.0 (95% confidence interval, 2.2–11.1; P<0.001) in those with a post-SIT PAC exceeding 277 pmol/L (10 ng/dL).

A clinically relevant proportion of patients with suppressible aldosterone hypersecretion had a lateralized AVS: 12 of 41 patients (29%) with a post-SIT PAC <139 pmol/L and 38 of 104 patients (37%) with post-SIT PAC >277 pmol/L (Table 2). Conversely, 7 (44%) of the 16 patients with PA diagnosed by unsuppressed post-SIT PAC without elevated basal aldosterone had a lateralized PA.

Among the 102 patients with a lateralized PA, 12 (12%) had a post-SIT PAC <139 pmol/L and 38 (37%) <277 pmol/L (Table S2).

Prognostic Value of the SIT

Among the 102 patients with lateralized PA, 20 did not undergo surgery in our center: 6 patients were sent from other centers and were not followed up after the AVS; 7 patients refused surgery; 5 patients had a lateralization index between 4 and 5 but were not sent to the surgeon according to our practice; 1 patient had an acute coronary syndrome, and 1 had a stroke before surgery and were not operated on. Moreover, 10 patients were lost to follow-up after surgery in our center. Finally, 72 patients underwent adrenalectomy and had a measurement of BP and potassium after surgery. Among these patients, there was a higher rate of hypertension cure among patients with a post-SIT aldosterone higher than 277 pmol/L; however, it did not reach statistical significance (P=0.16; Figure 2).

Discussion

Summary of Findings

Our results confirm that nonsuppressible aldosterone hypersecretion is associated with lateralization by AVS. Patients with a post-SIT PAC >139 or 277 pmol/L have an odds ratio of, respectively, 1.7 and 5 to have a lateralized PA compared with those with a post-SIT PAC <139 pmol/L. However, 12 of 41 (29%) patients with a post-SIT PAC <139 pmol/L (5 ng/dL) had a lateralized PA and 38 of 104 (37%) of those with a post-SIT PAC >277 pmol/L (10 ng/dL). A low post-SIT PAC would have discarded 12% to 37% of patients with a lateralized PA.

Table 1. Baseline Characteristic (at Primary Aldosteronism Diagnosis) of Included Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Population (n=199)</th>
<th>Post-SIT Aldosterone &lt;139 pmol/L (n=41)</th>
<th>Post-SIT Aldosterone 139–277 pmol/L (n=63)</th>
<th>Post-SIT Aldosterone &gt;277 pmol/L (n=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male patients</td>
<td>199 (63%)</td>
<td>41 (22 [54%])</td>
<td>63 (47 [75%])</td>
<td>95 (56 [59%])</td>
<td>0.99</td>
</tr>
<tr>
<td>Age, y</td>
<td>199</td>
<td>48 [41, 55]</td>
<td>50 [43, 57]</td>
<td>48 [43, 53]</td>
<td>0.20</td>
</tr>
<tr>
<td>Familial hypertensive</td>
<td>190 (63%)</td>
<td>39 (28 [72%])</td>
<td>60 (39 [65%])</td>
<td>91 (52 [57%])</td>
<td>0.10</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>199</td>
<td>6 [2, 12]</td>
<td>3 [1, 13]</td>
<td>6 [3, 14]</td>
<td>0.64</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>195</td>
<td>142 [130, 156]</td>
<td>143 [130, 158]</td>
<td>143 [133, 156]</td>
<td>0.23</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>195</td>
<td>88 [81, 95]</td>
<td>88 [81, 93]</td>
<td>88.5 [81, 97.5]</td>
<td>0.51</td>
</tr>
<tr>
<td>Antihypertensive drug classes</td>
<td>194</td>
<td>2 [2, 3]</td>
<td>2 [1, 3]</td>
<td>91 [3, 2]</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>199</td>
<td>3.6 [3.4, 3.8]</td>
<td>3.4 [3.2, 3.6]</td>
<td>3.2 [2.9, 3.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>199</td>
<td>12 [29%]</td>
<td>12 [32%]</td>
<td>68 [72%]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>199</td>
<td>97 [80, 109]</td>
<td>94 [74, 104]</td>
<td>95 [76, 111]</td>
<td>0.96</td>
</tr>
<tr>
<td>Basal ARC, mU/L</td>
<td>199</td>
<td>1.5 [0.5, 3.5]</td>
<td>2.5 [1.2, 4.8]</td>
<td>1.9 [1.4]</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal PAC, pmol/L</td>
<td>199</td>
<td>447 [366, 620]</td>
<td>501 [349, 663]</td>
<td>823 [575, 1142]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Basal ARR, pmol/mU</td>
<td>199</td>
<td>85 [56, 124]</td>
<td>99 [61, 112]</td>
<td>160 [111, 223]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary aldosterone, nmol/d</td>
<td>184</td>
<td>60 [41, 100]</td>
<td>78 [45, 101]</td>
<td>92 [63, 142]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-SIT PAC, pmol/L</td>
<td>199</td>
<td>88 [73, 115]</td>
<td>192 [164, 212]</td>
<td>484 [372, 683]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unilateral adenoma</td>
<td>197</td>
<td>98 (48%)</td>
<td>9 (23%)</td>
<td>62 (25%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Reported values are the number of patients with available data and then number (percentages) or median [first quartile, third quartile]. ARC indicates active renin concentration; ARR, aldosterone:renin ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; and SIT, sodium infusion test.
who could benefit from surgery. A higher post-SIT PAC was not associated with a significantly better BP outcome after surgery, in our patients.

Strengths and Limitations
This was a retrospective study, but clinical and biochemical data were prospectively collected in an electronic form.

Some patients with PA were not included in this study: 52 of 279 patients (19%) did not undergo an SIT mainly because of safety reasons; 28 of 227 (12%) patients had a nonselective AVS, which is in the range of the other studies from 5% to 20%.13,14

The ARR was used as a screening test for the diagnosis of PA, despite its limitations,15 as recommended by guidelines.16 Among the 4 suppression tests recommended by the guidelines, only the SIT was evaluated in this study. But, with a specificity of 84% and a sensitivity of 88%, SIT is a reasonable alternative to the fludrocortisone suppression test, considered by some to be the gold standard suppression test.17 It is widely used because it is easy to perform, cost effective compared with the other tests, and the intravenous administration avoids interpatient variations of sodium intake or bioavailability.

SIT was performed in the recumbent position in this study. It has been suggested that seated SIT might be superior to recumbent SIT using the fludrocortisone test as a gold standard. These preliminary results still need to be confirmed in a validation cohort with an adequate diagnostic gold standard.13

The gold standard used in this study was the AVS. Even if it is a surrogate marker, it is essential in the management of PA as it determines surgical treatment.4 The interpretation of AVS differs among centers.19 We used the selectivity and lateralization indices advocated by the guidelines.14 Use of the AVS prevented the circular reasoning associated with the use of another nonvalidated suppression test as gold standard.

The definitions we used to study the postoperative outcome were arbitrary, and other definitions have been proposed in other studies.20,21

Comparison With Other Studies
To our knowledge, no other study has evaluated the prevalence of a lateralized PA in patients with a post-SIT PAC <139 pmol/L. Weigel et al12 studied the correlation between post-SIT PAC and the severity and outcome of PA. Among 256 patients included in the German Conn’s Registry who underwent a recumbent SIT, patients with a post-SIT PAC >277 pmol/L displayed a higher prevalence of unilateral disease and a significantly better outcome after specific treatment.12 The patients with a post-SIT PAC <139 pmol/L were not described in this study as they were considered to be patients with essential hypertension and were not followed up further. It has also been shown that the post-SIT PAC is associated with the left ventricular mass, independent of age, body mass index, and BP.22 It is possible that patients with suppressible aldosterone secretion have a milder phenotype and would not benefit from surgery. However, the post-SIT PAC was not associated with the outcome of adrenalectomy in our study. From a clinical point of view, the preoperative phenotype does not accurately predict the cure of hypertension or its persistence in individual patients.21

A confirmatory test should be highly sensitive and highly specific: for example, confirmatory testing for HIV has a sensitivity >98% and a specificity >>99%.23 In the PAPy study (PA Prevalence in Hypertensives), using a cutoff of 188 pmol/L (6.8 ng/dL), the sensitivity and specificity of the SIT were 83% and 75%, respectively, resulting in an overlap of patients with and without PA.5,17 Mulatero et al17 showed that when using a threshold of 139 pmol/L, the sensitivity and the specificity of SIT were 88%. These studies show that the SIT misses 12% to 17% of the patients with PA.5,17,23 We show that close to 30% of them (12/41) have a lateralized PA.

Perspectives
These results suggest that the lack of suppression of aldosterone after recumbent SIT should not be mandatory for the diagnosis of PA. Patients with elevated ARR and basal aldosterone concentrations could undergo an AVS without a suppression test because some patients with suppressed aldosterone may have a lateralized PA. This strategy may increase the number of AVS. Therefore, its cost–benefit ratio needs to be evaluated. This strategy is also proposed in the recently published guidelines for patients with hypokalemia.16

SIT remains important for the diagnosis of PA: in this study, 44% of the 16 patients with normal basal but nonsuppressible aldosterone levels had lateralized PA. The proportion of these patients is underestimated in our center.

Table 2. Distribution of Aldosterone Concentrations After Saline Infusion and Lateralization of Aldosterone Secretion on Adrenal Vein Sampling

<table>
<thead>
<tr>
<th>Aldosterone Concentration, pmol/L</th>
<th>Nonlateralized (Ratio &lt;4)</th>
<th>Lateralized (Ratio ≥4)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone &lt;139</td>
<td>29 (71%)</td>
<td>12 (29%)</td>
<td>41</td>
</tr>
<tr>
<td>139 ≤ aldosterone &lt; 277</td>
<td>37 (59%)</td>
<td>26 (41%)</td>
<td>63</td>
</tr>
<tr>
<td>Aldosterone ≥ 277</td>
<td>31 (33%)</td>
<td>64 (67%)</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>102</td>
<td>199</td>
</tr>
</tbody>
</table>

Figure 2. Outcome after adrenalectomy in 72 patients, based on the aldosterone concentration after saline infusion before surgery. SIT indicates saline infusion test.
because patients with elevated ARR, but normal basal aldosterone levels, do not routinely undergo the SIT. Stowasser and Gordon reported basal PAC levels of <416 pmol/L in 4 of 21 (19%) patients with unilateral, surgically correctable PA.

The 277 pmol/L cutoff should be revisited as it misses a large number of patients with lateralized PA (37% in this study). This cutoff was established in the first studies on SIT but has never been validated. Mulatero et al showed that a post-SIT PAC >208 pmol/L resulted in an increase in the false-negative diagnosis of PA to >30.17

The ARR is used to screen patients for the diagnosis of PA. A confirmatory test is needed to overcome its low specificity. The guidelines recommend the use of suppression tests, such as the SIT, for this purpose. This study confirms that recumbent SIT has a good positive predictive value for lateralized PA even in patients with normal basal aldosterone levels. However, it cannot be used to make a go/no-go decision because 30% of the patients with elevated basal aldosterone levels, but a post-SIT PAC <139 pmol/L, had lateralized secretion of aldosterone by AVS.

In conclusion, AVS should be considered for all patients with an elevated ARR, who are eligible for surgery, with either elevated basal aldosterone levels or a post-SIT PAC >139 pmol/L. This strategy should be assessed in a prospective study.

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Disclosures None.

References


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**Novelty and Significance**

**What Is New?**

- Aldosterone is suppressed by a saline infusion test in 12% to 37% of patients with PA and lateralized secretion.
- The majority of these patients (58%–71%) are cured or significantly improved by unilateral adrenalectomy.

**What Is Relevant?**

- The lack of aldosterone suppression after saline infusion should not be a mandatory confirmation criterion for the diagnosis of PA.
- Patients with PA and a high basal aldosterone concentration could therefore be sent for AVS without first undergoing a suppression test.

**Summary**

We analyzed the results of saline infusion tests of 199 patients with primary aldosteronism who underwent adrenal venous sampling. Aldosterone was suppressed by saline infusion in 12% to 37% of patients with unilateral aldosterone hypersecretion. These patients were cured or significantly improved after adrenalectomy in 58% to 71% of cases.
Suppression of Aldosterone Secretion After Recumbent Saline Infusion Does Not Exclude Lateralized Primary Aldosteronism

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ONLINE SUPPLEMENT

Suppression of aldosterone secretion after recumbent saline infusion does not exclude lateralized primary aldosteronism

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Short title : saline infusion test and lateralized PA

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Figure S1: Algorithm for the diagnosis of primary aldosteronism, with numbers of patients at each step in this study (included only if they had both a SIT and a successful AVS)

ARR: Aldosterone to Renin Ratio, SIT: Saline infusion test, PAC: Plasma Aldosterone concentration, N: number of patients, AVS: adrenal vein sampling
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Lowest serum potassium mmol/L</th>
<th>Basal ARR, pmol/mU</th>
<th>Basal PAC, pmol/L</th>
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