Development of a method to discriminate salt sensitivity in hypertension by single-nephron blood flow (SNBF) index and new insights into the relationship between SNBF and hypertension.

Motoei Kunimi (kunimi1999@gmail.com)
Shinkawabashi Hospital  https://orcid.org/0000-0003-4042-9082
Toshikazu Takizawa
Hadano Red Cross Hospital
Koichi Tamura
Yokohama City University Hospital

Article

Keywords: Hypertension, Salt resistant hypertension (SRH), Salt sensitive hypertension (SSH), Renal blood flow (RBF), Whole renal blood flow (WRBF), Single-nephron blood flow (SNBF)

Posted Date: April 24th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2811071/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

More than 95% of hypertensive patients have essential hypertension, which can be divided into salt-resistant hypertension (SRH) and salt-sensitive hypertension (SSH). They differ in several aspects. If they can be easily diagnosed, treatment, complications and prognosis can be improved. But there is no easy way to differentiate them. We focused on renal salt excretion process and renal blood flow (RBF). RBF of SRH decreases by increasing renal vascular resistance, and RBF of SSH increases by fluid accumulation for decreasing salt excretion efficiency. Since both can be distinguished by measuring RBF, we created a renal blood flow index using uric acid. Then, we divided RBF into 2 categories: whole renal blood flow (WRBF) and single-nephron blood flow (SNBF). We studied in 26 SRH and 16 SSH patients from 3/1/ to 30/11, 2018. SSH was higher than SRH in WRBF and SNBF, with no significant difference in WRBF (81.3±29.8 vs 73.3±32.4, p=0.43), but significant difference in SNBF (1.94±0.75 vs 1.04±0.39, P<0.01), suggesting that SNBF can distinguish SSH and SRH. Therefore, SNBF allows differentiation between SRH and SSH, and this study showed that essential hypertension is an abnormal condition in which SNBF is increased or decreased from the physiological range of SNBF.

Background

Hypertension is the leading cause of cerebral disease, heart disease, and end-stage renal disease, affecting more than 1.3 billion people worldwide. More than 95% of hypertensive patients have essential hypertension (EH). Several studies have suggested that EH is caused by impaired salt excretion. Based on salt sensitivity, EH can be divided into salt-resistant hypertension (SRH) and salt-sensitive hypertension (SSH). Salt sensitivity is classified according to the degree of blood pressure increase with salt intake in hypertensive patients. SRH and SSH have some differences in cardiovascular and renal complications and life expectancy. Differentiating between SRH and SSH at the time of diagnosis facilitates better treatment and life expectancy, but there is no simple method. The process of salt excretion in the kidney occurs in three stages as follows: (I) movement of blood flow to the glomerulus; (II) glomerular filtration; and (III) tubular Na excretion and reabsorption. Abnormalities in any stage of salt excretion can result in salt excretion disorders. Impairment of the first stage leads to the development of SRH. SRH occurs due to decreased blood flow to the glomerulus by an increase in arterial blood flow resistance, resulting in a decrease in Na filtration and excretion. A representative disease in SRH is nephrosclerosis. Next, impairment of the second and third stages leads to the development of SSH. SSH is the result of decreased efficiency of Na excretion due to decreased glomerular Na filtration capacity or increased Na reabsorption in the renal tubules. Increased salt intake increases Na concentration, resulting in increased blood volume. Chronic kidney disease (CKD) is a second stage disease, diabetes mellitus (DM) is a third stage disease. Therefore, the renal blood flow (RBF) would be expected to decrease in SRH and increase in SSH. Measuring RBF can distinguish SRH and SSH, but it is difficult to measure RBF directly. We tried to create an index of RBF by using uric acid (UA) levels. The reason for using uric acid is that it is freely filtered in the glomerulus and then almost completely reabsorbed in the early proximal tubule. It is then secreted in the later proximal tubule, so urinary UA
excretion may be a good indicator of RBF. In contrast, urinary UA concentration (U-UA) is partially influenced by serum UA concentration (S-U). Therefore, we hypothesized that the total amount of U-UA divided by S-UA would represent the total blood flow of the kidney. The blood flow of the kidney mentioned above refers to the blood flow in the whole kidney. However, the actual salt filtration is performed by the individual glomerular blood flow in the nephron. To distinguish between the two, we have divided the RBF index into whole renal blood flow (WRBF) and single-nephron blood flow (SNBF). We determined the formula for renal blood flow index as follows: WRBF = [total U-UA /gram creatinine (g Cre)]/[S-UA]. We used g Cre as a surrogate for the urine collection test to account for the difficulty of collecting urine from ambulatory patients throughout the day. Next, we looked at the method of calculating SNBF. Since SNBF is the average blood flow in each nephron, it can be calculated by dividing the WRBF by the number of nephrons. However, it is difficult to calculate the number of nephrons. Therefore, we developed a calculation method using the estimated glomerular filtration rate (eGFR).

Because eGFR can be expressed as the glomerular filtration capacity, which consists of the single glomerular filtration capacity and the number of nephrons (NN). The eGFR would be a value that reflects to some extent the number of nephrons. We postulated that WRBF divided by eGFR would give some indication of SNBF and expressed it as SNBF = WRBF / eGFR.

We investigated whether these newly developed indices could be used to differentiate SRH from SSH and present the results and discussion below.

**Method**

**Patient grouping**

We used the classification method proposed by Kimura to classify the EH patients into SRH and SSH. According to the characteristics of DM and CKD, SSH subjects have the characteristics of decreased eGFR, positive urine protein, and worsened HbA1c. We established the criteria according to the guidelines of the Japanese Society of Nephrology and the Japanese Diabetes Society that patients with eGFR $\geq 60\text{ml} / \text{min} / 1.72\text{m}^2$ or $\geq 45\text{ml} / \text{min}$ (age: $\geq 40$), HbA1c < 6.0 and urine protein creatinine ratio (U-PCR) $< 0.15 \text{g} / \text{g Cre}$ were in SRH, and patients with eGFR < 60ml / min or < 45ml / min (age: $\geq 40$) were in SSH. HbA1c $\geq 6.5$ or U-PCR $\geq 0.15 \text{g} / \text{g Cre}$ were in SSH. We selected 91 outpatients with hypertension who were admitted to Hadano Red Cross Hospital (HRCH) in Hadano-city, Kanagawa Prefecture, Japan from March 1, 2018 to November 30, 2018. Of the 91 patients, 41 were receiving hyperuricemic or immunosuppressive medications and were excluded from the study. Of the 50, 8 were not classified as SRH or SSH and were referred to as the intermediate group. The remaining 42 patients were included in the analysis.

**Clinical and laboratory measures**
We retrospectively collected and analyzed data from the electronic medical records of enrolled outpatients. Laboratory tests were performed at each hospital visit. Blood chemistry and urinalysis were performed in a central laboratory (Laboratory Division, HRCH) using the BioMajesty Throughput Clinical Chemistry Analyzer (BM6050, JEOL, Tokyo). Glycated HbA1c was measured by an automated glycated hemoglobin analyzer HLC-723 G8 (Tosho, Tokyo). Each of the above parameters was measured in at least two tests per patient and averaged.

Ethical review

This study was reviewed and approved by HRCH Ethic Commission (application number 30-03). All patients were informed about the investigation by the hospital information board and the hospital website, and had the opportunity to refuse participation in this study.

Statistics

All results are expressed as mean ± SD. Chi-squared test, Student's t-test, Welch's t-test, and Mann-Whitney U-test were performed. Student's t-test, Welch's t-test, and Mann-Whitney U-test were used to test for differences in means between the two groups. We performed the Student's t-test when the data followed a normal distribution and both groups had equal variance. In contrast, the Mann-Whitney U test was performed when the data did not follow a normal distribution, and the Welch's t-test was performed when the requirement for equal variance was not met. P values < 0.05 were considered statistically significant. The chi-squared test was used for differences in proportions between the two groups. All analyses were performed using Microsoft Excel.

Results

Patient's background

Table 1 displays the patient characteristics of SSH and SRH: 16 patients in SSH, 9 males and 7 females, and 26 patients in SRH, 21 males and 5 females, with a mean age of 64.8±10.1 in SRH and 73.2±12.1 in SSH, with significantly older in SSH (P=0.025). Besides hypertension, the patient complications were 1 DM in SRH, 9 DM, 8 CKD, and 4 DM + CKD complications in SSH in Table 2. All patients with DM had type II diabetes. Major hypertensive medications for those with SSH and SRH, renin-angiotensin system (RAS) inhibitor including angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI), calcium antagonists (CA), diuretics (DU), and other medicines are shown in Table 2. Patients medicated with RAS were higher in the SSH group, compared to the SRH group. On the contrary, a higher number of patients with SRH were medicated with CA, compared to those with SSH. Similarly, patients with DM were administered sodium-glucose cotransporter-2 inhibitors (SGLT2I) and other medications. A higher percentage of patients with SSH and DM were administered other drugs. However,
a higher percentage of those with SRH used SGLT2I. Table 2 also summarizes the biochemical data of all patients. The levels of serum albumin, liver function indicator enzymes, such as aspartate transaminase (AST) and alanine transaminase (ALT), triglycerides (TG), and hemoglobin (Hb) were higher in patients with SRH, compared to those with SSH. In contrast, the HbA1c levels were higher in patients with SSH, compared to those with SRH in Table 2. Table 3 shows the results of U-UA, S-UA, eGFR, U-PCR. There was no significant difference in urinary uric acid level and serum uric acid level. The level of eGFR and U-PCR showed a significant difference between SSH and SRH. There was no hyponatremia or hypernatremia among the patients in this study. (Data is not shown.)

WRBF and SNBF

We showed the frequency distribution table of SRH and SSH for WRBF and SNBF in figure 1-4.

As shown in 4-segment distribution table of WRBF and SNBF for SRH and SSH in Table 4, most SRH were in the 40-80 range in WRBF and most in the 1.5 or less range in SNBF, while most SSH were in the 40-120 range in WBRF and most in the 1.5 or more range in SNBF. The data of WRBF was higher in SSH (81.3±29.8), compared to in SRH (73.3±32.4). However, the difference was not significant. In SNBF, it was significantly higher in SSH (1.94±0.75), compared to in SRH (1.04±0.39) (P <0.01). Hence it was possible to distinguish between SRH and SSH on SNBF in this study. (Table 5)

Pearson's correlation coefficient test

To investigate the relationship between WRBF, SNBF, U-PCR, and eGFR in SRH and SSH, we measured the correlation coefficients and found the following significant correlations. (Table 6)

In SRH: WRBF & eGFR (r=0.4741, p=0.0144), WRF & SNBF (r=0.8521, p=1.60E-07), eGFR & U-PCR (r=0.5257, p=0.0058), WRBF &U-PCR (r=0.4761, p=0.0139)

In SSH: WRBF & eGFR (r=0.6115, p=0.0118), SNBF & eGFR (r=-0.5827, p=0.0178,) SNBF & U-PCR (r=0.5766, p=0.0194)

Comparison of various data between subjects with diabetes mellitus (DM) and chronic kidney diseases (CKD) in SSH.

We compared WRBF, SNBF, eGFR, and U-PCR in subjects with DM (n=5, age71.4, M=1, F=4) and CKD (n=4, age 78.5, M=4) in SSH subjects. When comparing the data from DM and CKD patients, we found that WRBF was 112.83 for DM and 66.37 for CKD, and eGFR was 60.27 for DM and 35.97 for CKD, both of
which were significant differences. On the other hand, SGBF showed 1.9145 for DM and 2.0 for CKD, while U-PCR showed 0.412 for DM and 0.404 for CKD, with no significant differences observed. (Table 7)

**Discussion**

Blood pressure is determined by the sum of cardiac output and peripheral vascular resistance. Hypertension can be caused by an increase in cardiac output, peripheral vascular resistance, or both. SRH is caused by increased peripheral vascular resistance, whereas SSH is caused by fluid retention, i.e., increased cardiac output. Thus, SRH and SSH are two causes of hypertension, each with a different etiology, and they also differ in salt sensitivity. Dahl et al. conducted experiments in which SSH rat kidneys transplanted into SRH rats resulted in SSH salt sensitivity and vice versa, indicating the existence of salt sensitivity in the kidney. Subsequently, studies by Kawasaki and Fujita confirmed the existence of SSH and SRH in humans and noted that SSH is a risk factor for cardiovascular and renal disease. Since SRH and SSH differ in salt sensitivity, it is important to accurately diagnose them for better treatment, complication management, and prognosis. However, there is no simple discriminative method available. To address this issue, we developed a new RBF index, WRBF and SNBF, and measured them in SRH and SSH. We found no significant difference between SRH and SSH in WRBF, but SNBF was significantly different. For reference, the WRBF and SNBF values for 8 intermediate subjects (M4, F4 mean age 74.125 ± 12.01 with 2 CKD and 4 DM patients, eGFR was 61.2 ± 10.0, U-PCR was 0.06 ± 0.03), were 100.3 ± 60.2 and 1.62 ± 0.95, respectively. Next, we examined the correlation between WRBF and SNBF with eGFR, U-PCR in SRH and SSH. In SRH, a significant positive correlations were observed between WRBF and SNBF, WRF and eGFR, U-PCR and eGFR, and U-PCR and WRBF. A significant negative correlation was found between eGFR and SNBF in SSH. This result may indicate a state of glomerular hypertension in SSH, where eGFR reflects the number of glomeruli, and nephron loss may lead to a compensatory increase in SNBF. These results suggest that SNBF is an accurate index of renal blood flow. We further compared DM and CKD patients in SSH with our generated indices to confirm their accuracy. Based on the disease characteristics, we expected that eGFR would be significantly lower in CKD than in DM and that U-PCR would not show a significant difference. The results were as expected: eGFR was significantly lower in CKD than in DM, and U-PCR was similar. The correlation coefficients between eGFR and WRBF and between U-PCR and SNBF were 0.6115 and 0.5766, respectively, indicating a more than moderate correlation, and the WRBF/eGFR and SNBF/U-PCR values were very similar at DM and CKD patients in SSH respectively, suggesting that WRBF and SNBF strongly reflect eGFR and U-PCR. These results also indicate the accuracy of WRBF and SNBF as indicators of RBF. In this study, we present the results of the association between SNBF and hypertension. The results confirmed that SNBF decreased in SRH and increased in SSH, with an approximately 2-fold difference in mean values between the two. This SNBF gap was estimated to represent the innate physiological range in normotensive individuals, which we referred to as the physiological SNBF range in this study. The physiological SNBF range allows for adequate salt excretion without an increase in blood pressure. When SNBF is displaced from the physiological SNBF range, blood pressure rises, with a decrease indicating SSH and an increase indicating SRH. Hypertension is caused by impaired salt excretion, and expressing impaired salt excretion
as a change in SNBF, hypertension is a phenomenon caused by impaired salt excretion due to a change in SNBF from the physiological SNBF range. Impaired salt excretion is divided into two categories: SRH and SSH. In SRH, the decrease in SNBF from the physiological SNBF range due to increased blood flow resistance results in a decrease in the amount of salt excretion, leading to salt accumulation, then an increase in fluid volume, resulting in an increase in blood pressure. Increased blood flow resistance may be caused by intimal thickening of the arcuate arteries and interlobular arterioles located anterior to the glomerulus, therefore SNBF does not increase after fluid retention in SRH. In contrast, in SSH, salt excretion efficiency is reduced, resulting in salt accumulation during salt intake, increased body fluid, and increased SNBF from the physiological SNBF range, ultimately leading to hypertension. SRH and SSH differ in salt sensitivity because the direction of change from the physiological SNBF range is opposite. Therefore, salt sensitivity is determined by the direction of change from the physiological SNBF range. A decrease in SNBF from the physiological SNBF range results in SRH and salt sensitivity is resistant, while an increase in SNBF from the physiological SNBF range results in SSH and salt sensitivity is sensitive. Weinberg et al. demonstrated salt sensitivity and resistance in normotensive and hypertensive subjects, respectively. The reason can be explained by the relationship between salt sensitivity and SNBF. Estimating the relationship between SNBF and blood pressure, as SNBF increases from below the physiological SNBF range to that range and then beyond, the characteristics of blood pressure changes from salt-resistant hypertension to salt-resistant normotension and further changes to salt-sensitive normotension and then to salt-sensitive hypertension. Thus, hypertension is a condition in which SNBF is altered from the normal range, and salt sensitivity can be differentiated by an increase or decrease in SGBF. Finally, regarding Dahl's experiment, the reason salt sensitivity exists in the kidney is that the kidney SNBF determines salt sensitivity. Therefore, the SNBF in the recipient's kidney is lost and the SNBF in the donor determines the new salt sensitivity. In conclusion, we created a new index, WRBF and SNBF, to differentiate SRH and SSH, with a significant difference in SNBF. Our results provided that hypertension is a condition in which SNBF is altered from the physiological range. And salt sensitivity is a phenomenon determined by the direction of SNBF abnormality. The measurement of WRBF and SNBF is a novel and simple method to distinguish between SRH and SSH. We were also able to explain the mechanism of the Dahl experiment. This index could be used to differentiate SRH from SSH at diagnosis, and thus improving treatment, complications, and prognosis. Therefore, treatment of hypertension will require normalization of SNBF in addition to current treatments such as blood pressure lowering and salt restriction. Of course, further studies are needed to elucidate the mechanism of onset and progression of hypertension in more detail, including the determination of SRH and SSH categories and the establishment of normal ranges.

Study limitation

Our study had several limitations, including a limited cohort of only 42 patients.

We did not directly measure the relationship between RBF and salt sensitivity of the subjects.
The older age of patients with SSH compared with those with SRH may have lowered the P value used for statistical evaluation. Patients with hypertension were administered RASI or diuretics and those with DM were treated with SGLT2I, which may have interfered with RBF. We should determine the cutoff for SNBF between SRH and SSH to clarify the ranges of SRH and SSH and the two should be divided, but the SNBF range for normotensives between SRH and SSH has not been measured, the range for normotensives is unknown and the cutoff has not been determined.

The existence of intermediate types between SRH and SSH obscures their classification of them. Extending the analysis to large and more diverse patient cohorts and correlating the direct measure of the RBF with WRBF and SNBF are essential to validate the predictive power of these indices.

**Declarations**

**Conflicts of interest**

The authors have declared no conflict of interest.

**References**


32. Jami m, Alun H. Cardiac and vascular pathophysiology in hypertension. *Heart*. 2003 Sep; 89(9): 1104-1109


**Tables**

Table 1: Demographic and clinical data of patients

<table>
<thead>
<tr>
<th></th>
<th>SSH</th>
<th>SRH</th>
<th>P-value</th>
<th>Test name*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (men/women)</td>
<td>16 (9/7)</td>
<td>26 (21/5)</td>
<td>0.09</td>
<td>C</td>
</tr>
<tr>
<td>Age (y/o)</td>
<td>73.2±10.0</td>
<td>64.8±12.1</td>
<td>0.025</td>
<td>S</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SD. SSH, salt-sensitive hypertension; SRH-salt-resistant hypertension.

*S, Student’s t-test; C, chi-squared test for independence.; N=16 in SSH and 26 in SRH.

Table 2: Medical complications and laboratory data of patients with salt-sensitive hypertension and salt-resistant hypertension
<table>
<thead>
<tr>
<th>Complications</th>
<th>SSH (n=16)</th>
<th>SRH (n=26)</th>
<th>P-value</th>
<th>Test name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>9</td>
<td>1</td>
<td>0.000181</td>
<td>C</td>
</tr>
<tr>
<td>CKD</td>
<td>8</td>
<td>0</td>
<td>6.2E-05</td>
<td>C</td>
</tr>
<tr>
<td>DM+CKD</td>
<td>4</td>
<td>0</td>
<td>0.00724</td>
<td>C</td>
</tr>
<tr>
<td>HT medication (number/%)</td>
<td>16</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS (ARB+ACEI)</td>
<td>12/75%</td>
<td>17/65.4%</td>
<td>0.513</td>
<td>C</td>
</tr>
<tr>
<td>CA</td>
<td>10/62.5%</td>
<td>21/80.8%</td>
<td>0.191</td>
<td>C</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2/12.5%</td>
<td>5/19.2%</td>
<td>0.323</td>
<td>C</td>
</tr>
<tr>
<td>Others</td>
<td>5/31.3%</td>
<td>3/11.5%</td>
<td>0.114</td>
<td>C</td>
</tr>
<tr>
<td>DM medication</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2I</td>
<td>8/88.9%</td>
<td>1/100%</td>
<td>0.0004</td>
<td>C</td>
</tr>
<tr>
<td>Others</td>
<td>9/100%</td>
<td>0/0%</td>
<td>1.6E-05</td>
<td>C</td>
</tr>
<tr>
<td>Lab data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alb g/dl (n=15/25)</td>
<td>4.2±0.3</td>
<td>4.4±0.3</td>
<td>0.02</td>
<td>S</td>
</tr>
<tr>
<td>AST U/L (n=16/25)</td>
<td>25.3±9.9</td>
<td>28.5±9.4</td>
<td>0.089</td>
<td>M</td>
</tr>
<tr>
<td>ALT U/L (n=16/25)</td>
<td>21.0±12.4</td>
<td>29.8±15.7</td>
<td>0.028</td>
<td>M</td>
</tr>
<tr>
<td>TG mg/dl (n=16/24)</td>
<td>132.4±40.3</td>
<td>145.9±67.5</td>
<td>0.61</td>
<td>W</td>
</tr>
<tr>
<td>Hb g/dl (n=16/25)</td>
<td>13.4±1.6</td>
<td>14.3±1.7</td>
<td>0.098</td>
<td>S</td>
</tr>
<tr>
<td>HbA1c (n=9/1)</td>
<td>6.27±0.41</td>
<td>5.9±0.4</td>
<td>0.22</td>
<td>M</td>
</tr>
</tbody>
</table>

All data are within the normal range. SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; *S, Student’s t-test; M, Mann-Whitney U test; and W, Welch’s t-test. C, chi-squared test for independence DM, diabetes mellitus; HL, hyperlipidemia; ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CA, calcium antagonists; DU, diuretics; SGLT2I, sodium-glucose cotransporter-2 inhibitors; albumin (Alb), 4.1–5.1 g/dl; aspartate transaminase (AST), 13–30 U/L; alanine transaminase (ALT), 7–23 U/L; triglyceride (TG), 30–117 mg/dl; Hemoglobin (Hb), 11.4–14.8 g/dl (women) and 13.7–16.8 g/dl (men); and HbA1c (NGSP 4.9-6.0%). N=16 in SSH and 26 in SRH.

Table 3: Metabolite levels and renal blood flow rates in patients with salt-sensitive hypertension and salt-resistant hypertension
<table>
<thead>
<tr>
<th>Test name*</th>
<th>SSH</th>
<th>SRH</th>
<th>P-value</th>
<th>Test name*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine, uric acid (mg/dl)</td>
<td>483.8±136.2</td>
<td>407.8±107.8</td>
<td>0.052</td>
<td>S</td>
</tr>
<tr>
<td>Serum, uric acid (mg/dl)</td>
<td>6.2±1.2</td>
<td>5.9±1.1</td>
<td>0.546</td>
<td>S</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>45.7±18.4</td>
<td>70.7±16.2</td>
<td>0.0002</td>
<td>M</td>
</tr>
<tr>
<td>U-PCR (mg/gCre)</td>
<td>0.34±0.36</td>
<td>0.05±0.03</td>
<td>0.0004</td>
<td>M</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SD. SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; eGFR, estimated glomerular filtration rate, U-PCR, urine protein creatinine ratio. *S, Student’s t-test; M, Mann-Whitney U test. N=16 in SSH and 26 in SRH.

Table 4: 4-segment distribution table of WRBF and SNBF for SRH and SSH.

<table>
<thead>
<tr>
<th>SRH</th>
<th>WRBF N</th>
<th>SSH</th>
<th>WRBF N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>2</td>
<td></td>
<td>&lt;40</td>
</tr>
<tr>
<td>40-80</td>
<td>18</td>
<td>40-80</td>
<td>7</td>
</tr>
<tr>
<td>80-120</td>
<td>3</td>
<td>80-120</td>
<td>7</td>
</tr>
<tr>
<td>&gt;120</td>
<td>3</td>
<td></td>
<td>&gt;120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SRH</th>
<th>SNBF N</th>
<th>SSH</th>
<th>SNBF N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>14</td>
<td>&lt;1.0</td>
<td>1</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>10</td>
<td>1.0-1.5</td>
<td>3</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>1</td>
<td>1.5-2.0</td>
<td>6</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>1</td>
<td></td>
<td>&gt;2.0</td>
</tr>
</tbody>
</table>

SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; WRBF, whole renal blood flow; and SNBF, single nephron blood flow; N=26 in SRH and 16 in SSH.

Table 5: WRBF and SNBF in patients with SRH and SSH

<table>
<thead>
<tr>
<th></th>
<th>SRH</th>
<th>SSH</th>
<th>P-Value</th>
<th>Test Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRBF</td>
<td>73.3 ± 32.4</td>
<td>81.3 ± 29.8</td>
<td>0.42957</td>
<td>S</td>
</tr>
<tr>
<td>SNBF</td>
<td>1.04 ± 0.39</td>
<td>1.94 ± 0.75</td>
<td>0.000249</td>
<td>W</td>
</tr>
</tbody>
</table>

SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; WRBF, whole renal blood flow; and SNBF, single nephron blood flow. N=16 in SSH and 26 in SRH. *S, Student’s t-test; W, Welch t-test.

Table 6: Peason’s correlation coefficient test
SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; WRBF, whole renal blood flow; SNBF, single nephron blood flow. eGFR, estimated glomerular filtration rate. U-PCR: Urine protein creatinine ratio. N=16 in SSH and 26 in SRH.

Table 7 Comparison subject’s data between DM and CKD in SSH

**Figures**
Figure 1

The frequency distribution table of SRH for SNBF
Figure 2

The frequency distribution table of SSH for SNBF

Figure 3

The frequency distribution table of SRH for WRBF
Figure 4

The frequency distribution table of SSH for WRBF

SSH, salt-sensitive hypertension; SRH, salt-resistant hypertension; WRBF, whole renal blood flow; and SNBF, single nephron blood flow; N=26 in SRH and 16 in SSH.