Stepwise increase in the prevalence of isolated systolic hypertension with the stages of chronic kidney disease

Li-Tao Cheng¹, Yan-Li Gao¹,², Yue Gu¹, Li Zhang¹, Shu-Hong Bi¹, Wen Tang¹ and Tao Wang¹

¹Division of Nephrology, Peking University Third Hospital, Beijing and ²Division of Cardiology, the Second Clinical College of Guangzhou University of Traditional Chinese Medicine, Guangzhou, China

Abstract

Background. Hypertension is common in patients with chronic kidney disease (CKD), and isolated systolic hypertension (ISH) accounts for most patients with inadequate blood pressure (BP) control. However, it remains unclear whether the prevalence of ISH would increase with the advancement of CKD.

Methods. CKD patients of stages 3, 4 and 5 were recruited (n = 324). Based on office systolic BP (SBP) and diastolic BP (DBP), they were classified into any of the four hypertensive subtypes: normotension (SBP/DBP < 140/90 mmHg), isolated diastolic hypertension (IDH, SBP < 140 mmHg and DBP ≥ 90 mmHg), ISH (SBP ≥ 140 mmHg and DBP < 90 mmHg) and systolic–diastolic hypertension (SDH, SBP/DBP ≥ 140/90 mmHg).

Results. The control rate was 45.7% at stage 3, which decreased with the advancement of CKD (control rate was 51.9%, 40.4% and 38.6% in stage 3, 4 and 5, respectively; P < 0.05). The prevalence of IDH changed from 5.0% to 5.3% and 0% from stage 3 to 4 and 5; while there was no significant change in the prevalence of SDH (15.0%, 14.9% and 15.7% at stage 3, 4 and 5, respectively). There was a stepwise increase in the prevalence of ISH with the stages of CKD (it was 28.1%, 39.4% and 45.7% in stage 3, 4 and 5, respectively). Logistic regression showed that age and CKD stages [compared with stage 3, stage 4 and 5 had 2.57 (95% CI 1.04–6.33) and 3.68 (95% CI 1.09–12.47) folds higher risk to develop ISH, respectively] were independent predictors of ISH.

Conclusion. The prevalence of ISH increased correspondingly with advanced stages of CKD, which may partially contribute to the increased cardiovascular mortality during the progress of CKD.

Keywords: chronic kidney disease; hypertension; isolated diastolic hypertension; isolated systolic hypertension; systolic–diastolic hypertension

Introduction

Hypertension is not only very common but also far from reaching its optimal control in patients with chronic kidney disease (CKD). The subanalysis of the data from the Fourth National Health and Nutrition Examination Survey (NHANES IV) revealed that only 37% of CKD patients had blood pressure (BP) controlled to <130/80 mmHg [1], a goal that National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommended to achieve in CKD patients [2]. Interestingly, the above subanalysis also showed that isolated systolic hypertension (ISH), a type of hypertension reflecting increased arterial stiffness and related to higher risk of stroke, other cardiovascular disease and death [3–5], accounted for most of the CKD patients with inadequate BP control [1].

Although there is no big controversy that ISH dominates in CKD patients with poor BP control, it remains unclear whether there is any relationship between the prevalence of ISH and the stratifications of CKD stages, namely, whether the prevalence of ISH would increase with advanced stages of CKD. On the other hand, recent studies performed in CKD patients observed a stepwise increase in arterial stiffness corresponding to the stages of CKD [6,7], indicating that there might also be a similar relationship between the prevalence of ISH and the stages of CKD, because ISH was usually considered as a reflection of increased arterial stiffness [8,9].

Theoretically, the exploration of their relationship would help us to understand the pathogenesis of ISH and even new inspiration in treatment strategy in CKD patients with hypertension. Therefore, the aim of the present study is to investigate the prevalence of ISH relative to the stages of CKD.

Patients and methods

Study population

Consecutive patients were recruited from the Division of Nephrology, Peking University Third Hospital from 1 May 2006 to 30 September 2007. Patients were excluded...
for acute renal failure, dialysis or kidney transplantation, or changes in their antihypertensive regimens within 2 weeks of study enrolment. The study protocol was approved by the ethic committee of Peking University and all patients gave written informed consent.

**Definition of CKD and its stages**

CKD was defined as an estimated glomerular filtration (GFR) rate < 60 ml/min, as recommended by KDOQI guidelines [10]. Because the creatinine/protein ratio in spot urine examination was not available in our hospital, estimated GFR was used as the exclusive criterion to define CKD. GFR was estimated by a modified formula for Chinese [11], which was based on an abbreviated formula from the Modification of Diet in Renal Disease (MDRD) [12] and validated in Chinese population. According to the estimated GFR, these patients’ CKD stages were established: stage 3 with the GFR of 30–59 ml/min, stage 4 with the GFR of 15–29 ml/min and stage 5 with the GFR of <15 ml/min [10].

**BP measurement**

A dedicated renal nurse was in charge of all BP measurements, who used appropriate cuff sizes under strict instruction but was not aware of the study protocol and objective. The mercury sphygmomanometer used was calibrated regularly. All measurements were performed in a quiet room. Brachial BP was measured twice in both arms in sitting position after patients had rested for >10 min. Phases I and V of the Korotkoff sounds were taken as systolic BP (SBP) and diastolic BP (DBP), respectively. SBP and DBP were averaged from two averages from each arm was defined as the patient’s systolic BP (SBP), respectively. SBP and DBP were averaged if equal variance was assumed and Tamhane’s T2 test was performed if equal variance was not assumed, and the comparison of ratio or percentage among groups was performed by the chi-square test. To identify the predictor of ISH, a logistic regression was performed, which included age, gender (male = 0, female = 1), diabetic status (No = 0, Yes = 1), body mass index, hypertension as the aetiology of CKD (No = 0, Yes = 1), CKD stages, antihypertensive medication (No = 0, Yes = 1), smoking status (No = 0, Yes = 1), dislipidaemia (defined as raised low-density lipoprotein cholesterol or decreased high-density lipoprotein cholesterol; No = 0, Yes = 1) and statin therapy (No = 0, Yes = 1) as independent variables. In this model, continuous variables, such as age and body mass index, were treated as categorical variables by the quartile method. All tests were two sided. The P-value < 0.05 was considered statistically significant. All analyses were performed with SPSS software (SPSS Inc., version 11.0, Chicago, IL, USA).

**Results**

**Demographic characteristic of the study population**

During the study period, data of 406 patients were successfully collected. According to the prespecified definition of CKD (estimated GFR < 60 ml/min), 324 (79.8%) patients were eventually included, while 82 patients were excluded from the present study because they did not meet the standard of CKD in this study. There was no significant difference in demographic characteristic between the remained patients and the whole 406 patients. The demographic characteristic of the 324 patients is shown in Table 1. Among them, 182 were males and 142 were females, with a mean age of 64 years. The average height and weight of these patients were 161 cm and 63 kg, respectively. The pathologies of kidney disease were glomerulonephritis (22.2%), hypertension (21.3%), type 2 diabetes (11.1%), interstitial nephritis (12.3%), miscellaneous (19.5%) and unknown (13.6%). About 30% of patients were diagnosed based on renal biopsy, while the rest of the patients were diagnosed types: (1) normotension [15]: SBP < 140 mmHg and DBP < 90 mmHg; (2) ISH [15]: SBP ≥ 140 mmHg and DBP < 90 mmHg; (3) isolated diastolic hypertension (IDH) [16]: SBP < 140 mmHg and DBP ≥ 90 mmHg and (4) systolic–diastolic hypertension (SDH) [15]: SBP ≥ 140 mmHg and DBP ≥ 90 mmHg. Because these patients were all diagnosed as CKD, a more stringent target of BP control (<130/80 mmHg) was also used to define hypertension [2]. For example, SBP ≥ 130 mmHg and DBP < 80 mmHg would be considered as ISH by this stringent standard.

**Statistical analysis**

Continuous variables were expressed as mean ± SD or median and interquartile range, while categorical variables were expressed as ratio or percentage with 95% confidence interval (CI). The comparison of continuous variables among groups with different CKD stages was performed with ANOVA (for post hoc analysis, SNK was performed if equal variance was assumed and Tamhane’s T2 test was performed if equal variance was not assumed), and the comparison of ratio or percentage among groups was performed by the chi-square test. To identify the predictor of ISH, a logistic regression was performed, which included age, gender (male = 0, female = 1), diabetic status (No = 0, Yes = 1), body mass index, hypertension as the aetiology of CKD (No = 0, Yes = 1), CKD stages, antihypertensive medication (No = 0, Yes = 1), smoking status (No = 0, Yes = 1), dislipidaemia (defined as raised low-density lipoprotein cholesterol or decreased high-density lipoprotein cholesterol; No = 0, Yes = 1) and statin therapy (No = 0, Yes = 1) as independent variables. In this model, continuous variables, such as age and body mass index, were treated as categorical variables by the quartile method. All tests were two sided. The P-value < 0.05 was considered statistically significant. All analyses were performed with SPSS software (SPSS Inc., version 11.0, Chicago, IL, USA).
Table 1. Demographic characteristics of the study population (mean ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>Male (%)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>324</td>
<td>182 (56%)</td>
<td>161 ± 8</td>
<td>63 ± 11</td>
<td>24.3 ± 3.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The comparison of various parameters among the different stages of CKD 3, 4 and 5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of patients</th>
<th>Male (%)</th>
<th>Age (year)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
<th>GFR (mL/min)</th>
<th>Smoking (%)</th>
<th>TCHO (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
<th>LDL-C (mmol/L)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>160</td>
<td>59%</td>
<td>63 ± 13</td>
<td>162 ± 8</td>
<td>65 ± 11</td>
<td>25 ± 3</td>
<td>0.73 ± 2.61</td>
<td>13%</td>
<td>2.0 ± 1.3</td>
<td>1.4 ± 0.4</td>
<td>3.1 ± 0.9</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>Stage 4</td>
<td>94</td>
<td>52%</td>
<td>66 ± 14</td>
<td>161 ± 9</td>
<td>63 ± 11</td>
<td>24 ± 4</td>
<td>0.28 ± 0.11</td>
<td>11%</td>
<td>2.0 ± 0.9</td>
<td>1.5 ± 0.7</td>
<td>3.9 ± 1.6</td>
<td>59 ± 11</td>
</tr>
<tr>
<td>Stage 5</td>
<td>70</td>
<td>54%</td>
<td>64 ± 14</td>
<td>159 ± 8</td>
<td>59 ± 11</td>
<td>23 ± 4</td>
<td>0.13 ± 0.12</td>
<td>10%</td>
<td>1.6 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>3.0 ± 0.8</td>
<td>67 ± 23</td>
</tr>
</tbody>
</table>

Fig. 1. Prevalence of different hypertensive phenotypes in various stages of CKD (according to a modified MDRD formula). Blank represents controlled hypertension; grey represents SDH and black represents ISH. Panel A: hypertension was defined by SBP/DBP ≥140/90 mmHg; panel B: hypertension was defined by SBP/DBP ≥130/80 mmHg.

Prevalence of hypertensive subtypes with stages of CKD

The prevalence of hypertensive subtypes with stages of CKD is shown in Figure 1: panel A plotted according to conventional definition of hypertension (SBP/DBP ≥140/90 mmHg), and panel B plotted according to the target of BP control in CKD patients (<130/80 mmHg). Overall control rate of hypertension was 45.7% according to the conventional definition of hypertension, with decreased control rate relative to advanced CKD stages (control rate was 51.9%, 40.4% and 38.6% in stage 3, 4 and 5, respectively; \( P < 0.05 \) by the chi-square test). If the more stringent target of <130/80 mmHg was used, only 17.9% of these patients had optimal BP control. Based on the conventional definition of hypertension (panel A), the prevalence of IDH changed from 5.0% to 5.3% and from stage 3 to 4 and 5, while no significant change in the prevalence of SDH was observed (it was 15.0%, 14.9% and 15.7% in stage 3, 4 and 5, respectively). There was a stepwise increase in the prevalence of ISH with the stages of CKD (it was 28.1%, 39.4% and 45.7% in stage 3, 4 and 5, respectively). Based on the target of BP control in CKD patients (panel B), the prevalence of IDH decreased from 12.5% to 11.7% and 2.9% from stage 3 to 4 and 5, but no significant change in the prevalence of SDH was observed (it was 46.9%, 44.7% and 48.6% in stage 3, 4 and 5, respectively). Similar to the trend in panel A, the prevalence of ISH in panel B also increased stepwise with the stages of CKD (it was 15.0%, 26.6% and 37.1% in stage 3, 4 and 5, respectively). When patients were split into the non-antihypertensive medication group (ISH were 33.6% to 41.7% and 47.4% from stage 3 to 4 and 5, respectively), a similar trend in the prevalence of ISH (conventional definition) with the advancement of CKD stages could be observed in the non-antihypertensive medication group (ISH were 10.5% to 31.8% and 38.5% from stage 3, 4 and 5, respectively; \( P < 0.05 \) as compared with stage 3; \( P < 0.01 \) as compared with stage 4; \( P < 0.001 \) as compared with stage 3; \( P < 0.05 \) as compared with stage 4).

Comparison of clinical profile among different stages of CKD

The comparison of clinical profile among different stages of CKD is shown in Table 2. There were no significant differences in gender distribution, diabetic status and age among the three groups. The height, weight and body mass index in the stage 5 group were significantly lower than those in the stage 3 and 4 groups (\( P < 0.05 \)). As expected, the
serum creatinine concentration increased correspondingly with the advancement of CKD stages, and GFR showed a reverse trend. The smoking status, lipid profile, proportion of patients on statin treatment and heart rates were not significantly different among the three stage groups. The SBP and PP in the stage 5 group were significantly higher than those in stages 3 and 4 groups, but DBP was comparable among the three groups. The proportion of patients on antihypertensive medication and the total DDD were very similar among the three groups. However, the DDD for ACEI and ARB tended to decrease and the DDD for β-blocker and CCB tended to increase with the advancement of CKD stages.

Predicators of ISH in CKD patients

The predictors of ISH were identified by running logistic regression model (Table 3). In this model, the ISH status was treated as a dichotomic variable (No = 0, Yes = 1), while gender, diabetic status, age, body mass index, hypertension as aetiology of CKD, antihypertensive medication, smoking status, dislipidaemia and statin therapy were treated as independent variables. The output showed that only age and CKD stages were significant predictors of ISH. Compared with stage 3, stages 4 and 5 were associated with 2.57- (95% CI 1.04–6.33) and 3.68-fold (95% CI 1.09–12.47) increases in development of ISH (P < 0.05).

Discussion

The major finding of the present study was that BP control rate decreased while the prevalence of ISH increased along with the advanced stages of CKD, whatever definition of hypertension was used. Although previous studies showed that ISH dominated in both CKD and haemodialysis patients with poorly controlled BP, it remained unclear whether CKD stages had any effect on the prevalence of ISH. To our knowledge, this is the first study to show such a stepwise increase in the prevalence of ISH with the advanced stages of CKD.

ISH is mainly a reflection of increased arterial stiffness [8,9]. The Framingham study showed that the prevalence of ISH increased with ageing and became the dominant form of hypertension in the elderly [17]. Therefore, ISH could be used as a simple and easily performed maker to detect arterial stiffness. The results from the present study demonstrated a stepwise increase in the prevalence of ISH corresponding to the advanced stages of CKD. For example, the prevalence of ISH increased from 28.1% to 45.7% from stages 3 to 5 according to the conventional definition of hypertension (Figure 1A). The association between CKD stages and ISH was further demonstrated in logistic regression analysis; compared with stage 3, stages 4 and 5 were associated with 2.57- (95% CI 1.04–6.33) and 3.68-fold (95% CI 1.09–12.47) increases in development of ISH (P < 0.05 and P < 0.001, respectively). However, the contribution of CKD stages on the increased prevalence of ISH was independent of age in the present study. First, age was not significantly different among the three CKD stages (Table 2). Second, age was treated as one of the independent variables in logistical regression analysis, which showed that both CKD stages and age were independent determinants of ISH in CKD patients (Table 3). Therefore, the stepwise increase in the prevalence of ISH with advanced stages of CKD could be interpreted as the progress of CKD that might lead to increased arterial stiffness. This speculation was additionally supported by the observation that PP in the stage 5 group was significantly higher than that in the stage 3 and 4 groups (Table 2), because PP was usually considered as another surrogate of arterial stiffness [18]. Our results were also consistent with previous studies. Indeed, studies in literatures have shown that pulse wave velocity, the so-called true marker of arterial stiffness, increases correspondingly with the advanced stages of CKD [6,7]. Although increased sympathetic activity is a common finding in CKD patients [19,20], we could not observe any difference in heart rates among different CKD stages in this study (Table 2). Given the lower sensitivity of heart rate as a reflector of sympathetic tone, further study employing more sensitive index, such as muscle sympathetic nerve activity [21], is warranted to explore its influence on the relationship between ISH and CKD stages. Nevertheless, it should also be noted that because no patient in the present study has been followed longitudinally and the ISH has not been prospectively monitored, the above speculation should be tested in the future.

The increased prevalence of ISH with the advanced stages of CKD contributed dramatically to the gradually decreased BP control rate in these patients. For example, normotension (controlled hypertension) still dominated at stage 3, but its predominance shrunk gradually from stage 4 and gave way to ISH (45.7%) completely at stage 5. We think that the gradually decreased BP control rate and increased hypertensive prevalence, particularly the predominance of ISH, may contribute to the increased cardiovascular mortality during the progression of CKD. It is increasingly recognized that decreased GFR is a predictor of cardiovascular events [22]. For example, the Hoorn study showed that renal function estimated by the Cockcroft-Gault formula was inversely associated with cardiovascular mortality, and the relative risk was 1.15 for each decrease of 5 ml/min/1.73 m² in GFR [23]. Although the mechanism for this close link remains uncertain, a series of factors,

### Table 3. Predictors of isolated systolic hypertension in chronic kidney disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;56</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>56–68</td>
<td>3.90</td>
<td>1.08–14.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>68–75</td>
<td>4.62</td>
<td>1.22–17.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&gt;75</td>
<td>8.17</td>
<td>2.24–29.88</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>2.57</td>
<td>1.04–6.33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stage 5</td>
<td>3.68</td>
<td>1.09–12.47</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Adjusted for gender, diabetes, body mass index, hypertension as the aetiology of CKD, antihypertensive medication, smoking, dislipidaemia, and statin therapy.
including traditional and non-traditional CVD factors, have been proposed. Among them, the specific contribution of ISH is less emphasized. However, given the more potent power of ISH in predicting cardiovascular morbidity and mortality [24,25], it is attractive to speculate that the increased prevalence of ISH may partially contribute to this inverse relationship between GFR and cardiovascular mortality. Meanwhile, both population study [26] and clinical trials in elderly [27,28] have documented the beneficial effect of treating ISH in preventing coronary heart disease or stroke; therefore, ISH should also be treated aggressively to lower the occurrence of cardiovascular events in CKD patients.

We also found that the prevalence of SDH did not show any significant evolution from stages 3 to 5. In contrast, the prevalence of IDH also decreased correspondingly with the progression of CKD (from 5% at stage 3 to 0% at stage 5). Consequently, our results tended to indicate that the increased prevalence of ISH might evolve from normotension or IDH at early stages of CKD, a result which to some extent echoed the Framingham report that IDH was a risk factor for the development of ISH in the general population [29]. However, it should be noted that the cross-sectional design in the present study prevented us from drawing any definite conclusion unless a prospective follow-up study is performed. In addition, the decreased prevalence of IDH could not be interpreted as good news because some studies suggested that this kind of hypertension was related to lower mortality [30,31].

A potential confounding factor in this study was the administration of antihypertensive agents. Although the total DDDs and proportion of patients on antihypertensive medication were comparable among the three CKD stage groups, there were significant differences in the DDDs for ACEI, ARB and CCB agents (Table 2), with less use of ACEI/ARB and heavier use of CCB in stage 5 compared with stages 3 and 4. This trend may reflect the increased consideration of ACEI/ARB-related side effects (i.e. hyperkalaemia and worsened renal function) or increased difficulty in BP control in patients with more advanced CKD stages. However, when the use of ACEI/ARB or CCB was treated as an independent variable in logistic regression model, the result turned out that neither of them was a significant predictor of ISH in these patients (data not shown). In addition, when these patients were split into the non-antihypertensive medication group and antihypertensive medication group, a similar trend in the prevalence of ISH with the advancement of CKD stages could be observed in the non-antihypertensive medication group (P < 0.05), which further indicated that the relationship between the prevalence of ISH and CKD stages was independent of antihypertensive medication. Nevertheless, it should be pointed out that the stepwise correlation between CKD stages and the prevalence of ISH apparently indicated in this study should be further validated in longitudinal research, because the cause and consequence relationship could not be actually examined in any cross-sectional study.

In conclusion, we found in this cross-sectional study that the BP control rate decreased while the prevalence of ISH increased with the advanced stages of CKD whatever the definition of hypertension was used, which may indicate that increased vascular ageing accompanied the progression of CKD.

Acknowledgement. This study was partly supported by a Clinical Evidence Council (CEC) funding (07CEC2AP011) from Baxter Healthcare Corporation (awarded to Dr L.-T. Cheng).

Conflict of interest statement. None declared.

References


*Received for publication: 27.3.08
Accepted in revised form: 16.6.08*