Pulse pressure and inhibition of renin–angiotensin system in chronic kidney disease

Debasish Banerjee1, Stephan Brincat1, Helen Gregson1, Gabriel Contreras2, Chris Streather1, David Oliveira1 and Stephen Nelson1

1Department of Renal Medicine and Transplantation, St George’s Hospital Medical School, London, UK and 2Division of Nephrology, University of Miami, Miami, FL, USA

Abstract

Background. Elevated pulse pressure (PP) is an indicator of poor outcome in hypertensives in the general population and on haemodialysis. The prognostic value of PP in pre-dialysis patients with chronic kidney disease (CKD) stages 4/5 and its interaction with renin–angiotensin system (RAS) inhibitors is unknown.

Methods. This retrospective study of 349 patients from the pre-dialysis clinic analysed the effect association of PP and RAS inhibition on adverse outcomes in CKD stages 4/5. Primary endpoints were a composite of death or dialysis.

Results. At baseline, 349 patients (63% males, 34% diabetics) were aged 60±0.8 years (mean±SEM) with systolic blood pressure (SBP) 149±1.3 mmHg, diastolic BP (DBP) 83±0.7 mmHg, PP 66±1.0 mmHg, creatinine 442±16 μmol/l and haemoglobin 10.7±0.1 g/dl. Patients were followed up for 297±19 days and 93% took one to seven (2.45±0.07) antihypertensives. At presentation, the adverse outcome group had higher SBP (151±1.5 vs 145±2.4 mmHg; P<0.05), proportion of diabetes (39% vs 23%; P<0.05) and creatinine (478±22 vs 354±11 μmol/l; P<0.05), but lower haemoglobin (10.6±0.1 vs 11.2±0.2 g/dl; P<0.05). PP increased with age (r²: 0.4; P<0.0001). PP >80 mmHg was associated with adverse outcome (Kaplan–Meier survival analysis, log-rank test P<0.05). In a model of proportional hazards regression, adjusted for age, baseline creatinine, diabetes and haemoglobin, elevated PP was associated with poorer outcome (hazards ratio: 1.09; 95% confidence interval: 1.01–1.18; P<0.05) and angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use was beneficial (hazards ratio: 0.73; 95% confidence interval: 0.53–0.99; P<0.05).

Conclusions. The study demonstrates that elevated PP indicates high risk of death or dialysis and the benefit of blockade of the RAS is independent of the baseline PP in patients with CKD stages 4/5.

Keywords: chronic kidney disease; pulse pressure; renin–angiotensin system; hypertension; ACE inhibitors; renal failure

Introduction

Chronic kidney disease (CKD) is a major public health problem [1]. The number of patients with CKD is large and associated healthcare costs are considerable [1,2]. The progression of the kidney disease and its associated cardiovascular complications are the major causes of morbidity and mortality [3,4]. This holds true for all stages of kidney disease, including the end stage requiring renal replacement therapy.

The burden of hypertension is present at all stages of CKD. The knowledge of the mechanism and implications of elevated blood pressures in CKD is evolving. We and others have shown that pulse pressure is a reliable indicator for increased mortality in patients on maintenance haemodialysis [5–7]. This could be a reflection of increased arterial stiffness, which has been demonstrated to be associated with mortality in patients with end-stage renal disease [8]. However, the significance of pulse pressure in pre-dialysis, CKD patients has not been studied. Furthermore, the mechanism of generation of arterial stiffness and high pulse pressure in CKD is unknown. In patients with essential hypertension, the activation of the renin–angiotensin system has been proposed to be involved in the aetiology of increased arterial stiffness [9].

Correspondence and offprint requests to: Debasish Banerjee, MD, MRCP, Consultant Nephrologist and Honorary Senior Lecturer, Renal Medicine and Transplantation, St George’s Hospital, Blackshaw Road, London SW17 0QT, UK. Email: Debasish.Banerjee@stgeorges.nhs.uk

© The Author [2005]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.

For Permissions, please email: journals.permissions@oxfordjournals.org
The study was conducted to determine the significance of elevated pulse pressure and benefits of inhibition of the renin–angiotensin system in predialysis patients with CKD stages 4 and 5.

Subjects and methods

The study population consisted of all patients followed up in the pre-dialysis clinic of St George’s Hospital between December 1996 and April 2004. Data were collected for all 349 patients from their case notes and audit sheets. Fifteen patients were excluded from the study by virtue of pre-emptive transplantation. Patients were followed from presentation to death, progression of renal disease to dialysis or until April 2004. Thus, patients without events were followed up from their presentation to the clinic until 1 April 2004. The progression of renal disease was defined as the deterioration of renal function resulting in the initiation of dialysis, on advice from a multidisciplinary team including physicians, nurses and dieticians. Ethical approval for the retrospective study was obtained from the Wandsworth Local Ethics Research Committee. The blood pressure values used for the study were determined at baseline at the pre-dialysis clinic in patients resting in a sitting posture for 15 min by trained nurses using a mercury sphygmomanometer. For the purpose of the study, patients who were on angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARB) at presentation were considered to be treated with these agents during the entire study period. The dose and duration of therapy were not considered to be treated with these agents during the entire study period. The groups with or without adverse outcomes (death or progression of renal disease needing dialysis) were compared using two-sample t-test and Wilcoxon rank sum test for the continuous variables. The categorical variables were compared using chi-square test. Blood pressure variables were correlated with age using Pearson correlation coefficient. Survival analysis was conducted with Kaplan–Meier survival function and log-rank test. A proportional hazards regression was used to determine the associations of pulse pressure and inhibition of the renin–angiotensin system with outcomes, adjusting for age, diabetes, serum creatinine and haemoglobin. All statistical analyses were conducted using Statistix 7 (Analytical Software, USA, 2002).

Results

The baseline demographic and clinical characteristics are as shown in Table 1. A total of 349 patients were followed up for a mean duration of 297 ± 19 days (median: 163 days; range: 2–248 days). The most common cause of CKD was diabetes (30%) followed by hypertension (17%), chronic glomerulonephritis (12%) and polycystic kidney disease in (9%). The 15 patients (4.3%) excluded by virtue of pre-emptive transplantation were much younger (42 ± 4 years) with better blood pressure control [systolic blood pressure (SBP): 141 ± 6 mmHg; pulse pressure: 67 ± 5 mmHg]. The pre-emptive transplant group was excluded to avoid selecting a rather different, healthier CKD patient group. Sixty-seven per cent of the patients had an adverse outcome with 17 (4.9%) deaths and 218 (62.5%) patients progressing to dialysis. The remaining 99 (28.4%) patients were followed up without adverse events. The median of follow-up intervals for the groups were 178 days for no adverse event, 134 days for patients going onto dialysis and 363 days for non-survivors.

At presentation, the adverse outcome group had higher blood pressure (SBP 151 ± 1.5 vs 145 ± 2.4 mmHg; P < 0.05), number of patients with diabetes (39% vs 23%; P < 0.05) and creatinine (478 ± 22 vs 354 ± 11 μmol/l; P < 0.05), but lower haemoglobin (10.6 ± 0.1 vs 11.2 ± 0.2 g/dl; P < 0.05). The pulse pressure increased with age in the entire population (r²: 0.4; P < 0.0001). Patients with pulse pressure >80 mmHg had a poorer event-free survival (log rank P < 0.05), as shown in Figure 1. The higher SBP was more important for the adverse outcomes than lower diastolic blood pressure (DBP) (Table 1). Also, pulse pressure correlates better with SBP (r² = 0.70, P < 0.001) than DBP (r² = 0.004, P = 0.73).

Isolated systolic hypertension (SBP ≥ 140 mmHg; DBP < 90 mmHg) was prevalent in 40% of the entire population. However, in a proportional hazards regression analysis adjusting for age, baseline creatinine, haemoglobin, diabetes and use of ACE inhibitor/ARB, isolated systolic hypertension did not have any significant effect on adverse outcome.

Forty-three per cent of the entire population was treated with an ACE inhibitor or ARB. Use of ACE inhibitor or ARB was associated with improved outcomes, as evident from Figure 2 (log rank P < 0.05).

In a proportional hazards model, high pulse pressure, age, high creatinine and low haemoglobin at baseline were predictors of poor outcome. The use of ACE inhibitor/ARB was associated with reduced risk of death or need of dialysis (Table 2).

Table 1. Clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n = 334)</th>
<th>Group with adverse outcome (n = 235)</th>
<th>Group without adverse outcome (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 0.8</td>
<td>60 ± 1.0</td>
<td>63 ± 1.6</td>
</tr>
<tr>
<td>Gender male (%)</td>
<td>63</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>34</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>10.7 ± 0.09</td>
<td>10.6 ± 0.11</td>
<td>11.2 ± 0.17</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>36.2 ± 0.3</td>
<td>36.2 ± 0.4</td>
<td>36.1 ± 0.6</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>442 ± 16</td>
<td>478 ± 21</td>
<td>354 ± 11</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.3 ± 0.01</td>
<td>2.3 ± 0.01</td>
<td>2.3 ± 0.02</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.6 ± 0.02</td>
<td>1.7 ± 0.03</td>
<td>1.4 ± 0.03</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>30.1 ± 1.4</td>
<td>31.7 ± 1.8</td>
<td>26.5 ± 2.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>149 ± 1</td>
<td>151 ± 2</td>
<td>145 ± 2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>83 ± 1</td>
<td>84 ± 1</td>
<td>82 ± 1</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>66 ± 1</td>
<td>68 ± 1</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Use of ACE/ARB (%)</td>
<td>44</td>
<td>44</td>
<td>52</td>
</tr>
</tbody>
</table>

Values represent means±SEM.

*p < 0.05.

PTH, parathyroid hormone; ACEI; ACE inhibitor.
The results of the study establish that elevated pulse pressure is associated with increased probability of reaching adverse endpoints, including death and progression of renal disease requiring dialysis in pre-dialysis patients with CKD stages 4/5. The use of ACE inhibitors/ARBs was associated with better event-free survival.

The lack of information on the presence and the magnitude of proteinuria in the study limits its ability to explore the relationship of the use of ACE inhibitors/ARBs and proteinuria. The beneficial effects of lipid-lowering agents, aldosterone-receptor blockers and control of secondary hyperparathyroidism were not explored in the study. Another limitation of the study was the lack of information on the past history of cardiovascular events and hyperlipidaemia, which may have an effect on adverse outcome.

There were more patients with diabetes in the adverse outcome group, but the lack of association of diabetes in the proportional hazards model could be explained by the relationship of diabetes with other variables in the analysis and fewer patients with diabetes.

Though hypertension is an undisputed conventional risk factor in the general population, its role in CKD patients on maintenance haemodialysis has been a subject of controversy for a considerable length of time [10,11]. Previous studies have even demonstrated that elevated systolic blood pressure was associated with improved outcomes in patients on haemodialysis [12]. However, more recently, elevated pulse pressure has been shown to be consistently associated with higher mortality in patients on maintenance haemodialysis [5–7]. The findings are similar to those in the elderly population (in contrast to the younger population), where pulse pressure holds a stronger relationship with mortality than SBP or DBP [13]. In the present study, pulse pressure is independently related to adverse outcome in pre-dialysis patients, CKD 4/5. These observations suggest differing pathophysiological mechanisms behind the generation of elevated blood pressure in different study populations. There is accumulating evidence from clinical and laboratory studies that the vascular pathology behind the generation of high blood pressure could be different in differing patient groups. For example, concentric hypertrophy of small- to medium-sized arteries in a young patient of essential hypertension is different from the stiffening of central arteries in an elderly with isolated systolic hypertension [14].

The generation of hypertension in CKD (including haemodialysis) patients involves several possible mechanisms. Volume overload related to salt ingestion, activation of the renin–angiotensin system, up-regulation of the sympathetic nervous system, endothelial dysfunction and generation of reactive oxygen species with down-regulation of the nitric oxide system have all been implicated [9]. Though arterial stiffness is known to be a promoter of systolic hypertension and high pulse pressure, the exact mechanism of generation of this stiffness with CKD is not known [14]. All of the above-mentioned pathways could be involved in the generation of stiffness.

The adverse consequences of high pulse pressure on the cardiovascular system are related to its haemodynamic effects. Elevated pulse pressure in CKD has been shown to be associated with left ventricular hypertrophy and, possibly, cardiomyopathy with cardiac dilatation if persistent [14]. With stiffened arteries

**Fig. 1.** Event-free survival by different pulse pressure groups (blue = <80 mmHg, red = >80 mmHg). Log-rank test P < 0.05 (For the colour versions of this figure please see the supplementary data at NDT online).

**Fig. 2.** Event-free survival with use of ACE inhibitor/ARB (red = with ACEI/ARB, blue = without ACEI/ARB). Log-rank test P < 0.05 (For the colour versions of this figure please see the supplementary data at NDT online).

**Table 2.** Proportional hazards regression: effect of baseline clinical characteristics on primary endpoints

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% LL</th>
<th>95% UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse pressure per 10 mmHg</td>
<td>1.09</td>
<td>1.01</td>
<td>1.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.73</td>
<td>0.53</td>
<td>0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age per 1 year</td>
<td>0.98</td>
<td>0.98</td>
<td>0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.02</td>
<td>0.73</td>
<td>1.41</td>
<td>0.37</td>
</tr>
<tr>
<td>Creatinine per 100 μmol</td>
<td>1.04</td>
<td>1.00</td>
<td>1.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haemoglobin per g/dl</td>
<td>0.89</td>
<td>0.88</td>
<td>0.89</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

HR, hazards ratio; LL, lower limit; UL, upper limit; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

**Discussion**

The results of the study establish that elevated pulse pressure is associated with increased probability of reaching adverse endpoints, including death and progression of renal disease requiring dialysis in pre-dialysis patients with CKD stages 4/5. The use of ACE inhibitors/ARBs was associated with better event-free survival.
the heart pumps against a non-expansile central blood compartment, i.e. against an increased after load, which leads to left ventricular hypertrophy and left ventricular dysfunction. As a consequence of limited distensibility of central arteries in systole impairing the storing of blood for diastolic flow, the DBP remains low. Thus, the perfusion of cardiac muscle, which happens in diastole, is diminished.

Benefits of inhibition of the renin–angiotensin system have been demonstrated in patients on haemodialysis [15,16]. Studies have also demonstrated that inhibition of the renin–angiotensin system improves arterial stiffness [17]. The present study suggests that the benefit of blockade of the renin–angiotensin system is independent of the baseline pulse pressure. However, due to the lack of prospective follow-up data on pulse pressure, the study is limited in its ability to rule out a possible beneficial effect of ACE inhibitor/ARB on pulse pressure.

Though not suggested by the present study, it may be possible that inhibition of the renin–angiotensin system renders the central arteries more distensible and, thereby, overcomes the above-mentioned hemodynamic consequences of elevated pulse pressure. On the other hand, it can be postulated that the high pulse pressure could be a reflection of another more elementary process that causes myocardial and vascular damage per se. Thus, it is possible that the benefits of inhibition of the renin–angiotensin system could be due to its effects on the cardiovascular system independent of arterial stiffness. The possible relationship of renin–angiotensin activation and arterial stiffness needs further investigation.

The study demonstrates that elevated pulse pressure is associated with poorer outcomes and that inhibition of the renin–angiotensin system is protective. However, these results have triggered several questions regarding the mechanism of generation of pulse pressure and the role of inhibition of the renin–angiotensin system in this process in CKD.

Conflict of interest statement. None declared.

References

10. Ogden LG, He J, Lydick E, Whelton PK. Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. Hypertension 2000; 35: 539–543

Accepted in revised form: 23.11.05

Received for publication: 24.11.04

D. Banerjee et al.