Morning Blood Pressure Predicts Hypertensive Organ Damage in Patients with Renal Diseases: Effect of Intensive Antihypertensive Therapy in Patients with Diabetic Nephropathy

Satoru KURIYAMA, Yasushi OTSUKA, Rinako IIDA, Kei MATSUMOTO, Goro TOKUDOME* and Tatsuo HOSOYA*

Abstract

Blood pressure (BP) measured at home early in the morning (HBP) has been recognized as a useful predictor for organ damage and has been viewed as an important therapeutic target in patients with hypertension. The present study was aimed to determine whether this notion holds true in patients with progressive renal disease.

The study enrolled patients with mild to moderate renal impairment. They were all directed to record self-measured HBP to evaluate the adequacy of BP control. In addition to the conventional antihypertensive therapy, intensive treatment to more efficiently reduce elevated morning HBP was applied, especially in patients with diabetic nephropathy. The results were as follows:

1) The status of BP control assessed using HBP and office/clinic BP (OBP) shows predominance of morning hypertension. The prevalence of patients with well-controlled systolic HBP was 38%, those with poorly-controlled HBP 30%, masked hypertension 20% and white coat hypertension 12%.

2) Early morning systolic HBP in diabetics was significantly higher than that in non-diabetics. However, when evaluated on systolic OBP, both groups were comparable.

3) Logistic regression analysis showed that the predictive variables to explain morning hypertension (more than 130 mmHg and increased systolic HBP) were age, amount of daily urinary protein excretion and left ventricular mass index (LVMI).

4) Following conventional therapy, intensive antihypertensive therapy consisting of calcium channel blockers (CCB) and/or diuretics given in the morning, and angiotensin receptor blockers (ARB) given in the evening, together with α1-blockers given at bedtime, efficaciously reduced elevated HBP in the morning. This result was associated with significant reduction in daily urinary protein excretion and in serum plasminogen-activator inhibitor (PAI-1) concentration.

The present study indicates that, regardless of ongoing conventional antihypertensive therapy, the majority of patients with renal disease had morning hypertension, suggesting that these patients are at a higher risk for cardiovascular disease. For the purpose of improving morning hypertension, intensive treatments with combined CCB, ARB and α1-blockers could have substantial benefit on the morbidity and prognosis in patients with diabetic nephropathy.

(Internal Medicine 44: 1239–1246, 2005)

Key words: morning blood pressure, home blood pressure, diabetic nephropathy, antihypertensive agents, proteinuria, left ventricular mass index

Introduction

Owing to the popularity of medical devices for home use, BP measurements taken at home (HBP) have been viewed as an important therapeutic parameter to predict organ damage and determine patient prognosis. Indeed, HBP obtained early in the morning has been shown to have a substantial impact...
on the awareness of cardiovascular risks (1–5). In addition, many clinical reports indicate a close association between BP in the early morning and the occurrence of cardiovascular events such as myocardial infarction, cerebral apoplexy or sudden death (6–8). Recent investigations on the adequacy of BP control using HBP and office/clinic BP (OBP) performed in Japan clearly demonstrate that current antihypertensive therapy is inadequate to achieve the target goals (9, 10).

There is no doubt that hypertension observed in renal diseases is often refractory and therapy-resistant (11). Similar to the research outcomes on the brain and heart, HBP in the morning in patients with renal disease, including diabetic nephropathy, is closely associated with renal damage (12). Indeed, cardiovascular complications originating from diabetes such as retinopathy, microangiopathy, macroangiopathy and nephropathy, are normally BP dependent and frequently progress into terminal stage renal failure. Despite effort such as dietary protein and salt restriction and the use of renin-angiotensin system (RAS) inhibitors, treatment of renal diseases to retard the progression into a more advanced stage has not been successful (9–11). These unsuccessful interventions account for the growing number of patients with terminal renal failure who require dialysis. Lowering of BP is undoubtedly organ protective (13, 14). Thus, future strategies to effectively reduce elevated BP are indispensable and of particular interest.

The aim of the present study was to address whether BP control in patients with kidney diseases who had been placed on conventional medications is appropriate. Furthermore, in order to fulfill the targeted goal, application of a newly designed antihypertensive therapy to improve the BP control more efficiently was tested.

For editorial comment, see p 1211.

**Materials and Methods**

**Patients**

Enrolled in the present study were 57 patients (30 cases with type 2 diabetics, 27 non-diabetics) with renal diseases. All patients were followed on an outpatient basis at Saiseikai Central Hospital between February 2003 and September 2004. The diagnosis of type 2 diabetes mellitus was based on the World Health Organization (WHO) criteria. The diagnosis of non-diabetics was based on clinical information such as lack of fulfillment of WHO criteria for diabetes and patients’ history. Among the 27 non-diabetics, eight cases had renal biopsy-proven glomerulonephritis. Throughout the observation period, patients were required to restrict their diets as follows: calorie intake of 31–33 kcal/kg, a daily protein intake of 0.6–0.8 g/kg and a salt intake of 7 g. Patient compliance to the diet restriction was evaluated by urinary urea nitrogen and Na concentration collected every 24 hours for 2 months. For most patients, compliance to the designated diet was well maintained. OBP was measured once during each clinic visit. Patients were also required to record self-measured HBP. The HBP was measured once each morning in a sitting position within 30 minutes after awakening before taking medications, for about 2 weeks. The average of several HBP values was used for the analysis. The diagnosis of clinic hypertension (OBP 140/90 mmHg and more) was made based upon JNC/WHO criteria. Diagnosis of hypertension defined by HBP was made when patients had systolic HBP \( \geq 130 \) mmHg and/or diastolic HBP \( \geq 85 \) mmHg. When the mean HBP in the morning exceeded 130 mmHg in systolic and/or 85 mmHg in diastolic, we defined these patients as having morning hypertension. Similar to the method reported elsewhere (9, 10), the status of adequacy of BP control was evaluated by 4 different categories depending upon the relationship between HBP and OBP. The 4 categories were well-controlled BP, masked hypertension, poorly-controlled BP, and white coat hypertension. Patient characteristics with respect to the different BP control categories are shown in Table 1. All patients were treated with one or more antihypertensive drugs before the trial. The prescription decision was at the doctor’s discretion. The cardiovascular organ damage detected in this study involved the heart and kidney. Cardiac evaluation was made by left ventricular mass index (LVMI) and ejection fraction (EF) determined echocardiographically by methods reported elsewhere (15). The definition of left ventricular hypertrophy (LVH) was made when left ventricular mass index (LVMI) exceeded 135 g/m². Kidney damage was determined by the degree of daily urinary protein excretion, endogenous creatinine clearance (CrCl) and serum creatinine (Cr) concentration. The definition of kidney damage was either urinary protein exceeding 1 g/day, serum Cr concentration 2 mg/dl, or Ccr less than 30 ml/min. These measurements were made at the beginning and at the end of the observation period with a 24–36 month interval. The prevalence of cardiovascular events such as coronary heart disease (CHD), cerebrovascular diseases (CVD) or arteriosclerosis obliterans (ASO) was confirmed by medical history. Here, unless otherwise indicated, the abbreviation “BP” indicates systolic BP.

**Intensive antihypertensive therapy**

A brief protocol of the intensive antihypertensive therapy added to the conventional therapy is shown in Fig. 1. Fourteen diabetic patients with BP control categories of poor-controlled or masked hypertension previously treated with a combined therapy including calcium channel blockers (CCB) and angiotensin receptor blockers (ARB) eligible for the therapy were subjected to the following antihypertensive regimen. The intensive antihypertensive therapy consisted of a combination of CCB (amlodipine 2.5–5 mg, efonidipine 20–40 mg, cilnidipine 5 mg, benidipine 4–8 mg, manidipine 10–20 mg, nifedipine 10–20 mg) or diuretic (furosemide 40–160 mg) given in the morning after meal, as well as ARB (candesartan 4–8 mg, valsartan 40–80 mg, losartan 25–50 mg, olmesartan 40 mg) given in the evening after a meal, together with \( \alpha \)-blocker (doxazosin 1–4 mg) given at bed
time. Efficacy was observed for 24–36 months. Blood samples for serum plasminogen activator inhibitor (PAI-1), were collected between 10 AM–2 PM at the beginning and end of intensive therapy. The circulating PAI-1 concentration is known to remain constant between 9 AM–9 PM (16). The concentrations of PAI-1 were measured based upon a method reported elsewhere (17).

Statistical analysis

Unpaired and paired student t-test was applied as deemed necessary to compare the mean values using the SAS system. Correlation between the two parameters was calculated based on the Pearson’s correlation analysis. Multivariate logistic regression analysis was used to determine the contribution of the variables to the morning hypertension. The computer used for the analysis was a Dynabook Satellite 2590X (TOSHIBA). Data were presented as mean ±SD, unless otherwise indicated. A p value less than 0.05 was considered statistically significant.

Results

The characteristics of the subjects with respect to the presence of diabetes mellitus are shown in Table 2. HBP in the morning in diabetics was significantly higher than that in non-diabetics (139±14 mmHg (diabetics, n=30) vs. 131±17 mmHg (non-diabetics, n=27), p=0.046). Daily urinary protein excretion in diabetics was also greater in diabetics than in non-diabetics (2.4±2.8 g/day (diabetics, n=30) vs. 1.1±1.2 g/day (non-diabetics, n=27), p=0.028).

Figure 2 depicts the state of BP control presented as a relationship between HBP in the morning and OBP. There was a close association between the two (r=0.578, n=57, p=0.026). The prevalence of patients with well-controlled BP was 38%, those with poor-controlled BP 30%, masked hypertension 20%, and white coat hypertension 12%. This implies that half of the patients had morning hypertension.

Figure 3 depicts the state of BP management described as a relationship between diastolic HBP and diastolic OBP. Similar to systolic BP analysis (Fig. 1), there was a close relationship between the two (r=0.556, n=57, p=0.020). The prevalence of well-controlled patients was 42%, those with poor-controlled BP 26%, those with masked hypertension 24%, and those with white coat hypertension 8%. This again implies that half of the patients had morning hypertension.

Figure 4 shows the relationship between HBP and other factors representing organ damage. A positive correlation was found between HBP and LVMI (r=0.545, p=0.026), and a negative correlation was found between HBP and Cr (r=0.274, p=0.039). In contrast, no relationship was found between HBP and EF, HBP daily urinary excretion.

Table 3 shows the results of logistic regression analysis. The predictive variables for morning hypertension in patients with a HBP ≥130 mmHg were age (odds ratio (OR) 3.036, p=0.010), urinary protein excretion (OR 3.036, p=0.010), and LVMI (OR 1.083, p=0.013).

State of BP control and prevalence of organ damage was
assessed by several parameters. Cardiac damage was defined as LVMI $\geq 135$ g/m$^2$ or greater, renal damage was defined as either daily urinary protein excretion or serum creatinine concentration $>2$ mg/dl. Other organ damage was defined as a history of ASO, ischemic heart disease and/or cerebral apoplexy. When either one was found, the patient was regarded as having organ damage. Based upon these criteria, the prevalence of organ damage was 45% in well-controlled, 60% in white coat, 78% in masked and 82% in poorly controlled hypertension. Organ damage was frequently seen in masked and poorly controlled patients.

Figure 5 shows organ damage in each BP control category. LVMI in patients with masked hypertension (138±15 g/m$^2$, n=57, p=0.04) was greater in well-controlled patients (105±8 g/m$^2$, n=57). LVMI of patients with poor-controlled BP tended to be higher than those with well-controlled BP (135±24 g/m$^2$, n=57, vs. 105±8 g/m$^2$, n=57, p=0.07). Urinary protein excretion in poor-controlled patients was greater than that in well-controlled BP group (2.6±1.2 g/day, n=57 vs. 0.9±1.1 g/day, n=57, p=0.011).

Figure 6 shows the effect of intensive antihypertensive therapy.
therapy prescribed to 14 diabetic patients with nephropathy. In response to the therapy, HBP was lowered to almost normotensive range (from 140±17 to 131±14 mmHg, n=14, p=0.032). Urinary protein excretion was also reduced significantly (from 2.2±1.9 to 1.9±1.1 g/day, n=14, p=0.0001) and so was serum PAI-1 concentration (from 27±12 to 23±10 pg/ml, n=14, p=0.023). Furthermore, intensive therapy reduced the number of patients with poorly controlled and masked hypertension from 14 to 7.

**Discussion**

The main findings of the present study are 1) BP control under the concurrent antihypertensive therapy in patients with renal diseases was not appropriate, 2) diabetics have a greater HBP in the morning and increased urinary protein excretion, and predictors for morning hypertension are LVMI and urinary protein excretion, and 3) intensive antihypertensive therapy with ARB, CCB and α1-blocker is efficacious in improving morning hypertension.

**State of BP control**

To date, adequacy of BP control in general has been discussed using BP obtained at the clinic visit (OBP). However, with the advancement and popularity of hospital-based, 24-hour, ambulatory BP monitoring devices as well as home-based self-monitoring devices, the importance of the use of ambulatory BP, especially those measurements taken at home have gained attention (1–8). HBP obtained early in the morning at home by self-measurement is specifically highlighted as having a substantial impact on cardiovascular risk. Indeed, many reports indicate a close association between HBP early in the morning and occurrence of cardiovascular events (6–8, 10). In addition, cardiovascular risk is greater in patients with masked hypertension and/or those with poorly controlled than in those with a well-controlled BP (18). The J-HOME study, which measured HBP together with OBP in more than 3,400 hypertensive patients receiving antihypertensive therapy, clearly demonstrated not only that morning hypertension is still a matter of concern but also that BP control at large is quite inadequate (9). Of note is that their
results were comparable with those reported elsewhere (JMS ABPM study Wave 1) in Japan (10). The present results support these previous reports, showing that even though patients were placed on conventional antihypertensive therapy, half of them did not achieve targeted BP goals.

**Morning hypertension and organ damage**

Hypertension in association with kidney diseases is known to be therapy-resistant (11). Nocturnal decline of BP in patients with essential hypertension is often diminished as the severity progresses, and frequently inverts to a nocturnal elevation (so-called non-dipper and inverted dipper hypertension) (19, 20). This type of hypertension has a strong association with a morning rise in BP (sustained type morning hypertension) (21). In addition, cerebral stroke, coronary ischemia and sudden death are more likely to occur in the morning (6–8). GFR normally declines with age, at an estimated rate of 1 ml/min/year (22). Bakris et al suggested that if BP was controlled to 120/80 mmHg or less in patients with renal diseases, the rate of decline in GFR could remain

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>The lower limit</td>
<td>The upper limit</td>
</tr>
<tr>
<td>Age</td>
<td>3.036</td>
<td>1.319 - 6.989</td>
<td>0.010*</td>
</tr>
<tr>
<td>Gender</td>
<td>1.049</td>
<td>0.196 - 5.601</td>
<td>0.955</td>
</tr>
<tr>
<td>DM</td>
<td>1.299</td>
<td>0.320 - 5.280</td>
<td>0.714</td>
</tr>
<tr>
<td>Ccr</td>
<td>0.948</td>
<td>0.873 - 1.029</td>
<td>0.204</td>
</tr>
<tr>
<td>U prot</td>
<td>1.751</td>
<td>1.180 - 2.598</td>
<td>0.010*</td>
</tr>
<tr>
<td>LVMI</td>
<td>1.083</td>
<td>1.020 - 1.150</td>
<td>0.013*</td>
</tr>
</tbody>
</table>

Ccr: endogenous creatinine clearance, U prot: daily urinary protein excretion, LVMI: left ventricular mass index.

Figure 5. BP control categories and organ damage. Well: patients with well-controlled BP, White: those with white coat hypertension, Masked: those with masked hypertension, Poor: those with poorly-controlled BP. LVMI: left ventricular mass index, EF: ejection fraction, s-Cr: serum creatinine concentration, Ccr: creatinine clearance, U prot: daily urinary protein excretion.
within a rate of 1 ml/min/year (11). If so, vigorous antihypertensive treatment could have a strong beneficial effect on retarding the progression. A morning rise in BP is believed to act as a trigger for many vascular diseases. At present, the precise mechanisms by which morning hypertension occur are not fully understood. However, abnormalities such as an increase in sympathetic nerve activity (23), excessive activity of RAS (24), and a hypercoagulable and hypofibrinolytic state may be involved in the process (25). Recently, Kamoi et al demonstrated that elevations of HBP in the morning in patients with diabetes are strongly related to microvascular and macrovascular complications, especially nephropathy, suggesting that the control of HBP in the morning is crucial to prevent further progression of the kidney (12). The present results in patients with mild to moderately damaged renal function reinforced the previous findings that morning hypertension is strongly associated with organ damage. In Japan, as of the year 1998, diabetic nephropathy became the first causative disease. Diabetes mellitus was frequently complicated with nephropathy, progressing into terminal renal failure in a relatively short period. Kario suggested that hypertension management should be achieved by targeting a morning rise in BP (26). We agree with his proposal in this regard. Since the prevalence of morning hypertension is more frequent (Table 2), one must be alert to the more effective antihypertensive treatments for patients with diabetic nephropathy.

A new antihypertensive therapy for diabetics with morning hypertension

Irrespective of the fact that patients with poorly-controlled and masked hypertension are vulnerable for cardiovascular events (18), few strategies have been introduced to improve outcome. According to the present findings, together with previous reports, conventional antihypertensive treatment mainly reduces daytime BP but might not act effectively on nocturnal and morning hypertension (9, 10). We therefore made an attempt to prescribe a new therapy for morning hypertension, which consisted of a combination of CCB or diuretic given in the morning, and ARB given in the evening, together with \( \alpha_1 \)-blocker given at bedtime, to achieve more effective reduction in morning BP. The idea for this combination is that CCB and diuretics are volume contraction drugs, which may induce hypercoagulability, whereas ARB ameliorates the hypercoagulable state (27). Thus, the former should be administered in the morning when patients have free access to salt and water intake and the latter in the evening when one could expect the improvement of hypercoagulability seen in the morning. Moreover, \( \alpha_1 \)-blockers specifically ameliorate the hypercoagulable state by suppressing \( \alpha_1 \) receptors, platelet function and PAI-1 (28). Since the morning surge is \( \alpha_1 \) mediated (29), \( \alpha_1 \) blockers should be given at bedtime. Using this strategy, the present study showed that in response to the intensive therapy, HBP was lowered to almost 130 mmHg (Fig. 5), and a substantial
number of patients became normotensive. Reduction in daily urinary protein excretion and serum PAI-1 concentration might have a positive effect on both renal function, heart function and the hypercoagulable state.

In conclusion, the conventional antihypertensive therapy is still not appropriate to fulfill the targeted goal in patients with progressive renal disease. A new therapeutic strategy for morning hypertension consisting of CCB or diuretic in with progressive renal disease. A new therapeutic strategy is still not appropriate to fulfill the targeted goal in patients function and the hypercoagulable state.

might have a positive effect on both renal function, heart urinary protein excretion and serum PAI-1 concentration number of patients became normotensive. Reduction in daily damage and also effective in the amelioration of the increased coagulability in patients with diabetic nephropathy.

Acknowledgements: A part of this work was presented at the 102 Annual Meeting of the Japanese Society of Internal Medicine held in Osaka, Japan on April 9, 2005.

References