Abstract: Objective: To investigate the impact of anxiety symptoms on the circadian rhythm of blood pressure in patients with hypertension. Methods: The 24 h ambulatory blood pressure was compared between patients with hypertension and generalized anxiety disorder, and patients with hypertension only. Results: The mean day-time and night-time systolic (SBP, 156.6±11.0 and 149.6±12.4 mm Hg, respectively) blood pressure in patients with both hypertension and anxiety was greater than in patients with hypertension only (143.2±15.0 and 126.0±10.8 mm Hg, respectively, P<0.01). The mean day-time and night-time diastolic blood pressure (DBP, 101.5±10.1 and 96.9±17.6 mm Hg, respectively) in the hypertension and anxiety group was also greater than in the hypertension only patients (94.1±10.9 and 77.4±10.2 mm Hg, respectively, P<0.01). SBP and DBP dipping was found in 87.5% and 80.1% of the hypertension only patients, as compared with 16.6% and 21.4% respectively, of the hypertension and anxiety patients (P<0.01). Conclusions: The presence of anxiety symptoms is associated with a higher level of blood pressure in hypertensive patients. Anxiety symptoms are also associated with a diminished circadian rhythm of blood pressure. The clinical significance of the reduced blood pressure dipping at night requires further investigation.

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Generalized anxiety disorder and the circadian rhythm of blood pressure in patients with hypertension

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Running title: anxiety symptoms and hypertension

There is no conflict to interest from any of the authors of the manuscript.
Abstract

Objective: To investigate the impact of generalized anxiety disorder (GAD) on the circadian rhythm of blood pressure in patients with hypertension. Methods: The 24 h ambulatory blood pressure was compared between patients with hypertension and GAD, and patients with hypertension only. Results: The mean day-time and night-time systolic (SBP, 156.6±11.0 and 149.6±12.4 mm Hg, respectively) blood pressure in patients with GAD was greater than in the no-GAD group (143.2±15.0 and 126.0±10.8 mm Hg, respectively, P<0.01). The mean day-time and night-time diastolic blood pressure (DBP, 101.5±10.1 and 96.9±17.6 mm Hg, respectively) in the GAD group was also greater than in the no-GAD group (94.1±10.9 and 77.4±10.2 mm Hg, respectively, P<0.01). SBP and DBP dipping was found in 87.5% and 80.1% of the hypertension only patients, as compared with 16.6% and 21.4% respectively, of the hypertension and GAD patients (P<0.01). Conclusions: The presence of GAD is associated with a higher level of blood pressure in hypertensive patients. GAD is also associated with a diminished circadian rhythm of blood pressure. The clinical significance of the reduced blood pressure dipping at night requires further investigation.

Key Words: generalized anxiety disorder, hypertension, ambulatory blood pressure.
Key points

1. Blood pressure during sleep at night is generally lower than in the daytime.

   The impact of generalized anxiety disorder on the circadian rhythm of blood pressure is unknown.

2. Our study showed that the mean day-time and night-time systolic and diastolic blood pressure in patients with both hypertension and generalized anxiety disorder was greater than in the hypertension only patients.

3. In patients with both hypertension and generalized anxiety disorder, there was a remarkable reduction in the decline or dipping of blood pressure at night.

   Reduced dipping of blood pressure is known to be associated with an increased risk of cardiovascular complications from hypertension.

4. This study demonstrates that generalized anxiety disorder has significant impact on the circadian rhythm of blood pressure in hypertensive patients.
Introduction

Hypertension is one of the most common chronic diseases in the developed countries, with a prevalence of 25-28% in the adult population [1]. Hypertension is associated with several major cardiovascular complications such as heart failure, myocardial infarction and renal dysfunction [1]. Anxiety symptoms due to generalized anxiety disorder are found in approximately 12% of patients with hypertension [2]. In normotensive subjects, anxiety symptoms are associated with the development of hypertension in the later years of life [3-5]. Cross-sectional analysis also shows a significant correlation between anxiety symptoms and the level of hypertension in all age groups [6-8]. The average systolic blood pressure in the patients with moderate to severe anxiety symptoms was higher than that of the non-anxiety patients [2]. In addition, patients with anxiety symptoms were more likely to have severe hypertension and less likely to achieve optimal blood pressure control [2].

Blood pressure in healthy subjects and patients with hypertension is known to have a circadian rhythm. Systolic (SBP) and diastolic blood pressure (DBP) a few hours into sleep at nights falls to the lowest point during the day (dipping). There is a marked surge in blood pressure in the morning hours coinciding with the transition from sleep to wakefulness [9]. Hypertensive patients without the nocturnal fall in blood pressure are more likely to suffer from cardiovascular events than those with the night dip [10]. The primary purpose of this study is to evaluate whether the presence of generalized anxiety disorder (GAD) has any impact on the circadian rhythm of blood pressure in hypertensive patients.
Patients and methods

Patient selection

This study was approved by the institution review board of Liaocheng People’s Hospital. Informed consent was obtained from all participants before the study. Between January 2002 and December 2006, about 1,010 patients with established diagnosis of hypertension (blood pressure $\geq 140/90$ mm Hg at the time of the initial diagnosis) were screened for anxiety symptoms by at our cardiology clinics. Patients with anxiety symptoms were first assessed by a Zung [11] self-rating anxiety scale (SAS). SAS is a 20 item instrument with a minimum and the maximum response from each patient of 20 and 80, respectively. GAD was suggested if the raw score was more than 40 [11]. The patients with a high SAS score were then assessed by a non-psychiatrist using a structured clinical interview for DSM-IV to confirm or to exclude GAD [12].

Among these participants, 56 (28 males, average age 54.7±8.1 years, range 36-72) met the DSM IV criteria for GAD. During the screening phase, the first 56 (27 males, average age 55.3±9.2 years, range 37-70 years, $p>0.05$) hypertensive patients who had no GAD were also recruited as control group.

Physical examination, blood biochemistry, ECG, chest X-ray and echocardiography were performed in all patients. Patients with target organ damages such as renal dysfunction, ventricular hypertrophy, ventricular dilation or dysfunction, were excluded from the study. Patients with other chronic illnesses such as diabetes or respiratory diseases were also excluded from this study.
**Ambulatory monitoring of blood pressure**

All antihypertensives were ceased seven days before the ambulatory monitoring. The 24 h blood pressure monitoring was performed with a SpaceLabs 90207 device (SpaceLabs Medical, Redmond, WA), recording blood pressure every 20 min between 7 am and 9 pm, and every 30 min between 9 pm and 7 am.

**Data analysis**

The following parameters were obtained from the ambulatory blood pressure data: 1) mean day-time systolic and diastolic blood pressure (dSBP and dDBP); 2) mean night-time systolic and diastolic blood pressure (nSBP and nDBP); 3) SBP and DBP load, which was defined as the percentage of SBP that exceeded 140 mm Hg, and percentage of DBP that exceeded 90 mm Hg during day-time (7 am- 9 pm) and night-time (9 pm to 7 am); 5) Nocturnal blood pressure reduction was calculated as a percentage of mean night-time blood pressure decline compared with mean day-time blood pressure: \([\frac{\text{mean day-time blood pressure} - \text{mean night-time blood pressure}}{\text{mean day-time blood pressure}}] \times 100\). According to the criterion of Verdecchia and colleagues [12], hypertensive patients with a nocturnal reduction in average day-time systolic blood pressure and diastolic blood pressure of less than 10% were classified as non-dippers, while those with night-time reduction of 10% or more were classified as dippers.

Data were expressed as means ±SD. Differences in blood pressure between groups were analyzed by student t test. Categorical data were analyzed by
Chi-square test.  $P<0.05$ was considered statistically significant.

**Results**

*General findings*

None of the patients had detectable complications from hypertension, such as renal failure, coronary artery disease, myocardial infarction, left ventricular dysfunction, retinal disease or stroke.  As shown in Table 1, there was no significant difference in patient’s age and sex between the two groups.  Calcium channel blockers were the most commonly used anti-hypertensive drugs.  Most patients were managed with a single drug but four patients in the GAD group and five patients in the no-GAD group used a combination of calcium channel blockers and diuretics (7.1% vs 8.9%, $P>0.05$).  There was no significant difference in the types of antihypertensive drugs between the two groups (Table 1, $P>0.05$).

Most patients reported sleep well at night during the blood pressure monitoring phase.  Seven patients (12.5%) from the GAD group and five patients (8.9%, $P>0.05$) from the non-anxiety group administered temazepam to assist with their sleep.

The average Zung anxiety score in the GAD group was significantly higher than in the no-GAD group (Table 1, $P<0.01$).

*Comparison of average day time and night time blood pressure*

In the hypertension and GAD group, the mean SBP and DBP during day-time and at night was greater than in the no-GAD group (Table 2, $P<0.01$).
The percentage of patients with blood pressure load during 24 hours, day-time and night-time in the GAD group was also greater than in the no-GAD group (Table 3, \(P<0.01\)).

**Blood pressure dipping**

SBP dipping in the no-GAD and GAD group was 87.5% and 16.0% respectively \((P<0.01)\). DBP dipping in the two groups was 80.1% and 21.4%, respectively \((P<0.01)\).

The mean SBP and DBP during 24 hours monitoring is demonstrated in Fig 1. The dipping in both SBP and DBP at midnight shown in no-GAD group was absent in the GAD group.

**Discussion**

The circadian rhythm of blood pressure in hypertensive patients without target organ damages is similar to healthy subjects. There are two peaks during the day, between 6 and 10 am, and between 4-6 pm, and a trough at midnight [13]. This typical variation pattern has also been demonstrated in hypertensive only patients in the present study (Fig 1). The circadian rhythm of blood pressure during the day and night is related to the release pattern of catecholamines, which is higher during the day and lower at nights and the reduction in blood pressure at midnight is largely due to the reduced sympathetic activities [14].

Our previous study on almost 900 patients has shown that about 12% of
hypertensive patients without major end-organ damages suffered from GAD [2]. We have also demonstrated that female gender, duration of hypertension, and previous hospitalizations are independent predictors of anxiety symptoms in the hypertensive patients [2]. To the best of our knowledge, there have been no previous studies on the impact of GAD on the circadian rhythms of SBP and DBP.

In patients with hypertension and GAD, the dipping in SBP at nights, which is commonly seen in hypertensive patients without GAD, was lost in about 84% of patients, whereas dipping in DBP was absent in more than a third. The blood pressure load in hypertensive patients with GAD was also higher than in the no-GAD patients.

The reasons for the higher proportion of non-dippers in the patients with GAD are unclear. Antihypertensive drugs are unlikely to have caused this because all drugs were discontinued for a week before the blood pressure was recorded, and the type of drugs used was similar between the two groups. It is believed that patients with GAD have enhanced sympathetic activities which may have caused the imbalance between sympathetic and parasympathetic systems during day and night [15], contributing to the non-dipping of blood pressure in patients with both hypertension and GAD.

The loss of normal circadian rhythm of blood pressure may have important clinical implications. It is known that the loss of the reduction in blood pressure at night is associated with increased risk of cardiovascular events in hypertensive patients. On average, each 5% decrease in the decline in nocturnal systolic/diastolic
blood pressure is associated with an approximately 20% greater risk of cardiovascular mortality [13]. Even when 24 h blood pressure values are within the normal range, diminished nocturnal decreases in systolic/diastolic blood pressure are associated with an increased risk of cardiovascular mortality [13]. In the present study, whether the cardiovascular risks in the patients with anxiety symptoms are increased remain to be seen.

In conclusion, ambulatory blood pressure monitoring has revealed that the mean day-time and night-time blood pressure in patients with both hypertension and GAD is higher than in patients with hypertension only. The circadian rhythm of blood pressure commonly seen in hypertension only patients is absent in the majority of patients with both hypertension and GAD. The clinical significance of these new findings needs to be further investigated.
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Anxiety but not depression is associated with elevated blood pressure in a community


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Table 1. Comparison of clinical features and antihypertensive drugs between generalized anxiety disorder (GAD) and no-GAD groups.

<table>
<thead>
<tr>
<th></th>
<th>GAD (n=56)</th>
<th>No-GAD (n=56)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex males, average</td>
<td>28</td>
<td>27</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.7±8.1 (36-72)</td>
<td>55.3±9.2 (37-70)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Years of hypertension</td>
<td>8.2±7.1</td>
<td>7.6±7.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>3 (5.4%)</td>
<td>2 (3.6%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diuretics</td>
<td>13 (23.1%)</td>
<td>15 (26.8%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ACEI</td>
<td>12 (21.4%)</td>
<td>14 (25.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>32 (57.1%)</td>
<td>30 (53.6%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>SAS score</td>
<td>47.9±5.8</td>
<td>31.2±5.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

SAS: Zung Anxiety Self-assessment score.
Table 2. Comparison of mean daytime and nighttime blood pressure between the No-GAD and GAD groups.

<table>
<thead>
<tr>
<th></th>
<th>Day SBP</th>
<th>Night SBP</th>
<th>Day DBP</th>
<th>Night DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-GAD (n=56)</td>
<td>143.2±15.0</td>
<td>126.0±10.8</td>
<td>94.1±10.9</td>
<td>77.4±10.2</td>
</tr>
<tr>
<td>GAD (n=56)</td>
<td>156.6±11.0**</td>
<td>149.6±12.4**</td>
<td>101.5±10.1**</td>
<td>96.9±17.6**</td>
</tr>
</tbody>
</table>

**P<0.01 compared with the no-GAD group.
Table 3. Comparison of blood pressure load between No-GAD and GAD groups.

<table>
<thead>
<tr>
<th></th>
<th>SBP load</th>
<th></th>
<th>DBP load</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Night</td>
<td>Day</td>
<td>Night</td>
</tr>
<tr>
<td>No-GAD</td>
<td>45%</td>
<td>11%</td>
<td>54%</td>
<td>12%</td>
</tr>
<tr>
<td>(n=56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>67%**</td>
<td>70%**</td>
<td>73%**</td>
<td>69%**</td>
</tr>
<tr>
<td>(n=56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P<0.01
Figure legend

Figure 1. Comparison of the ambulatory blood pressure between the no-GAD (HPT) and GAD groups (A).
Figure 1.