Circadian Variation of Acute Aortic Dissection

Significance of Blood Pressure Dipping Pattern

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Summary

Acute aortic dissection (AAD) is a life-threatening cardiovascular disease with high mortality. Hypertension is a well known risk factor of AAD. There have been previous reports about the association between circadian variation of blood pressure (BP) and cardiovascular events. However, little is known about the association between the onset-time of AAD and circadian variation of BP. The purpose of this study was to clarify the characteristics of circadian variation of BP in AAD and its relation to the onset-time of this disease. This study included type B spontaneous AAD patients who were referred to our institution and treated conservatively between January 2008 and June 2013. Patients with type A AAD, secondary to trauma, and type B AAD which preceded surgical intervention were excluded. Data were retrospectively collected from the hospital medical records. Sixty-eight patients with type B AAD were enrolled. The distribution of the circadian pattern in the study patients was as follows: extreme-dipper, 0% (none); dipper, 20.6% (n = 14); non-dipper, 50% (n = 34); riser, 29.4% (n = 20). Non-dipper and riser patterns were more frequently observed compared with other population studies reported previously. Moreover, no patient in the dipper group had night-time onset while 31.5% of the patients in the absence of nocturnal BP fall group (non-dipper and riser) did (P = 0.01). Absence of a nocturnal BP fall was frequently seen in AAD patients. Absence of a nocturnal BP fall may be a risk factor of AAD. Circadian variation of BP may also affect the onset-time of type B AAD. (Int Heart J 2015; 56: 324-328)

Key words: Ambulatory blood pressure monitoring

Acute aortic dissection (AAD) is a life-threatening cardiovascular disease with high mortality.1-8 Population-based studies suggest the incidence of AAD is about 3 cases per 100,000 people per year.2,9 In a review of 464 patients from the International Registry of Acute Aortic Dissection (IRAD), overall in hospital mortality was 27.4%.1 Hypertension is a known risk factor of AAD.2,3,9,10 There have been reports about the association between circadian variation of blood pressure (BP) and cardiovascular events.11-15 In normal subjects, BP decreases during sleep by 10% to 20% and increases promptly on waking. However, a variety of abnormal diurnal variation patterns have been described. Kario, et al reported that 27% of ischemic strokes occurred during sleep in the extreme-dipper group in their study.11

Circadian variation in the onset-time of AAD has been reported.16-23 Sumiyoshi, et al reported that circadian variation was observed at the onset of AAD, with a primary morning peak (8:00-11:00 AM) and a secondary peak in the evening (5:00-7:00 PM).17 They reported that the circadian variation of BP may be a possible explanation for the daily pattern in the onset of AAD.

Little is known about the association between the onset-time of AAD and circadian variation of BP. The purpose of this study was to clarify the characteristics of circadian variation of BP in AAD and its relation to the onset-time of this disease.

Methods

Study population: Type B spontaneous AAD patients who were referred to our institution and treated conservatively between January 2008 and June 2013 were enrolled. The inclusion criteria were 1) spontaneous type B AAD presenting within 14 days of symptom onset, 2) diagnosis confirmed by computed tomography with contrast confirmation of dissected aorta, and 3) ambulatory blood pressure monitoring (ABPM) was performed during the post-acute phase. Patients with type A AAD, secondary to trauma, and type B AAD which preceded surgical intervention were excluded. Data were retrospectively collected from the hospital medical records. This study was performed in accordance with the Helsinki Declaration.
Ambulatory blood pressure monitoring protocol and circadian variation of blood pressure: ABPM was performed with an automatic device (TM-2431; A & D, Tokyo), which recorded BP and heart rate (HR) every 30 minutes in the evening and every 60 minutes at night. Nocturnal systolic blood pressure (SBP) fall was calculated as previously described. We classified the subtypes of nocturnal SBP fall as follows: extreme-dipper (≥ 20% nocturnal SBP fall), dipper (nocturnal SBP fall ≤ 10% but < 20%), non-dipper (nocturnal SBP fall ≥ 0% but < 10%), riser (nocturnal SBP fall < 0%). We combined the non-dipper with the riser patients into an absence of nocturnal BP fall group. Daytime was defined as 6:01 AM-10:00 PM, and night-time as 10:01 PM-6:00 AM.

Definitions of underlying diseases: Definitions of the clinical criteria were as follows: hypertension: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or medical treatment for hypertension before admission; dyslipidemia: low-density lipoprotein (LDL)-cholesterol level ≥ 140 mg/dL or treatment for dyslipidemia before admission; diabetes mellitus: hemoglobin A1c level (Japan Diabetes Society: JDS) > 6.5% or treatment for diabetes mellitus before admission.

Statistical analysis: The baseline characteristics and ABPM were compared between the dipper group and absence of nocturnal BP fall group. The unpaired \( t \) test (Student’s \( t \)-test) or Mann-Whitney \( U \) test was performed for continuous variables. The chi-square test or Fischer’s exact probability test was performed for categorical variables. All statistics were performed using SPSS 18.0/Windows SPSS, Inc., (Chicago, IL, USA) statistical software. A \( P \) < 0.05 was considered statistically significant.

RESULTS

There were 115 patients with spontaneous type B AAD in this study period. Thirty-nine patients did not receive ABPM and 8 patients were excluded because the onset-time could not be definitively identified. Finally, 68 patients with type B AAD were enrolled (Figure 1). The distribution of the dipping pattern in the study patients was as follows: extreme-dipper, 0% (none); dipper, 20.6% (n = 14); non-dipper, 50% (n = 34); riser, 29.4% (n = 20). The average time from onset to ABPM was 14.8 ± 22.8 days.

The baseline characteristics of the study population and medication at ABPM are shown in Table. There were no significant differences in the background characteristics between the 2 groups except for the use of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin 2 receptor blocker.

Table. Patient Characteristics and Medication at Ambulatory Blood Pressure Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Dipper n = 14</th>
<th>Absence of nocturnal BP fall n = 54</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.9 ± 11.0</td>
<td>62.3 ± 13.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>9/14 (64.3%)</td>
<td>32/54 (59.3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.9 ± 3.8</td>
<td>24.1 ± 4.7</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>13/14 (92.9%)</td>
<td>48/54 (88.9%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Anti-hypertensive agent, n (%)</td>
<td>5/13 (38.4%)</td>
<td>15/48 (31.3%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>1/12 (8.3%)</td>
<td>1/44 (2.3%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1/12 (8.3%)</td>
<td>19/49 (38.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>DeBakey type 3A, n (%)</td>
<td>2/14 (14.3%)</td>
<td>6/54 (11.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td>DeBakey type 3B, n (%)</td>
<td>12/14 (85.7%)</td>
<td>48/54 (88.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Peak CRP, mg/dL</td>
<td>10.6 ± 6.8</td>
<td>11.4 ± 4.8</td>
<td>0.14</td>
</tr>
<tr>
<td>HbA1c, JDS, %</td>
<td>5.4 ± 0.6</td>
<td>5.2 ± 0.5</td>
<td>0.26</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>113.4 ± 12.9</td>
<td>111.0 ± 32.0</td>
<td>0.68</td>
</tr>
<tr>
<td>Cr, mg/dL</td>
<td>0.79 ± 0.18</td>
<td>0.71 ± 0.22</td>
<td>0.26</td>
</tr>
<tr>
<td>eGFR, mL/minute/1.73m²</td>
<td>72.3 ± 17.6</td>
<td>84.8 ± 25.6</td>
<td>0.29</td>
</tr>
<tr>
<td>ACE-I or ARB, n (%)</td>
<td>13/14 (92.9%)</td>
<td>31/54 (57.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>14/14 (100%)</td>
<td>52/54 (96.3%)</td>
<td>0.63</td>
</tr>
<tr>
<td>CCB, n (%)</td>
<td>14/14 (100%)</td>
<td>50/54 (92.6%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>1/14 (7.1%)</td>
<td>16/54 (29.6%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Oral anti-hyperglycemic drug, n (%)</td>
<td>0/14 (0%)</td>
<td>1/54 (1.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Anti-platelet drug, n (%)</td>
<td>2/14 (14.3%)</td>
<td>2/54 (3.7%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Anti-coagulant drug, n (%)</td>
<td>1/14 (7.1%)</td>
<td>1/54 (1.9%)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or percentages. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; BP, blood pressure; CCB, Ca-channel blocker; Cr, creatinine; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; and JDS, Japan Diabetes Society.
(ARB) at ABPM. ACE-I or ARB use in the dipper group was significantly higher than in the absence of nocturnal BP fall group.

The circadian variation of AAD is shown in Figure 2. There were two peaks (morning: 8:00-9:00 AM and evening: 5:00-6:00 PM) in the onset-time of type B AAD. The associations of the circadian variation in the onset-time of AAD and dipping pattern of BP are presented in Figure 3 and Figure 4. The onset-time of AAD was in the night-time in 17 patients (25%). The number of patients whose onset was in the night-time was significantly less in the dipper group than in the absence of nocturnal BP fall group ($P = 0.01$).

**Discussion**

In this study, 79.4% of type B AAD patients were in the absence of nocturnal BP fall group (non-dipper and riser pattern). There was significantly less onset of AAD in the night-time in the dipper group. The dipping pattern of BP was associated with the onset-time of AAD.

In this study, 50% of the patients were non-dipper type and 29.4% were riser type. No patient was classified as an extreme-dipper. The non-dipper and riser patterns were more frequently observed compared with other population studies reported previously. Kario, et al reported that the distribution of dipping pattern was as follows; extreme-dipper, 17% ($n = 97$); dipper, 40% ($n = 230$); non-dipper, 32% ($n = 185$); riser, 11% ($n = 63$). In the Ohasama study, Metoki, et al performed ABPM in 1430 Japanese subjects. The distribution in their study was as follows; extreme-dipper, 18% ($n = 252$); dipper, 49% ($n = 701$); non-dipper, 27% ($n = 389$); riser, 6% ($n = 88$). Although our data are different from the distribution of dipping patterns in population studies, there was a possible association between the circadian variation of BP and the occurrence of AAD.

Independent of the degree of hypertension, non-dipping is a risk factor for heart failure and other cardiovascular complications. Metoki, et al reported that inverted dippers (risers) or non-dippers tended to be at a relatively higher risk for cerebral infarction. Ingelsson, et al. reported that the presence of “non-dipping” blood pressure was associated with an increased risk of congestive heart failure. In previous studies, little was reported about the association of the circadian variation of BP and AAD. The absence of nocturnal BP fall may be a risk factor of AAD.

Our data showed that the dipping pattern of BP was associated with the onset-time of AAD. In the dipper group no patient had night-time onset while 31.5% of the patients in the absence of nocturnal BP fall group did. This study was the first to report on the association between the onset-time of AAD and circadian variation of BP. In this study, there were two peaks (8:00-9:00 AM and 5:00-6:00 PM) in onset-time of type B AAD. Circadian variation of AAD onset has been previously reported. Sumiyoshi, et al demonstrated that circadian variation of AAD was observed with a morning peak (8:00-11:00 AM) and a secondary evening peak (5:00-7:00 PM). Galllerni, et al investigated the circadian variation of spontaneous acute events in the thoracic aorta. They reported that there was a primary peak of onset in the morning hours (around 10:00 AM) and a secondary peak in the evening (8:00 PM).
The distributions in these studies were similar to that of our study. Metha, et al reported that two potentially synergistic mechanisms may play a role in the occurrence of chronobiological periodicity.15,16 They reported that these include rhythmic variation in the sympathovagal balance and in the hemorheologic properties of circulating blood. Kojima, et al reported that the onset of AAD was predominantly during the day (6:00 AM - 6:00 PM) and the daytime events were significantly more related to physical or mental activity than the night-time events.21 Our data suggest that the dipping pattern of BP was associated with circadian variation in the frequency of type B AAD.

Several studies have attempted to improve the dipping pattern of BP.25,26 Hermida, et al reported that bedtime valsartan administration improves the diurnal/nocturnal blood pressure ratio to a more dipper profile.26 They also reported that bedtime administration of nifedipine decreased the prevalence of a non-dipper BP pattern. 26 Rakugi, et al reported that once daily administration of azilsartan improved the non-dipping pattern in nocturnal hypertension.26 Bedtime administration of an ARB and Ca-channel blocker (CCB) may improve the non-dipping of BP. Although an association between normalization of dipping pattern and reduction in cardiovascular risk has not been fully established, improvement of dipping pattern may reduce the risk of AAD. Further studies will be necessary to elucidate the hypothesis. Study limitations: This study has several limitations. First, it was a retrospective study. Second, the sample size was small. Because our sample size was small, we divided the patients into two groups (dipper group and absence of nocturnal BP fall group) instead of three groups (dipper, non-dipper, riser group).

Third, there was a possibility of selection bias. Because we excluded the patients who did not receive the ABPM, patients with a severe condition were excluded. Also, there was no valid internal control group who received ABPM in the non-AAD population. Furthermore, the findings of this study were not adjusted for the possible confounding effect of anti-hypertensive medications. Since the ABPM was performed after induction of antihypertensive medications, it remains possible that the antihypertensive medications may have altered the circadian blood pressure variation. Because cessation of anti-hypertensive medications meant the patient would be at risk of developing the AAD, we could not discontinue the antihypertensive medications before the ABPM. Finally, we included a single ABPM measurement in this study. Since the reproducibility of ABPM is not satisfactory, 21 it may be difficult to determine the nocturnal dipping pattern from a single ABPM measurement.

Conclusions: Absence of a nocturnal BP fall was frequently seen in AAD patients. Absence of a nocturnal BP fall may be a risk factor of AAD. Circadian variation of BP may also affect the onset-time of type B AAD.

Disclosure

No conflict of Interest.

References

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