Temporal Variations at the Onset of Spontaneous Acute Aortic Dissection

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SUMMARY

There have only been a few studies of the chronobiological occurrence of acute aortic dissection (AAD), and most were international and multicentered. The aim of the present study, conducted at only one center, was to determine the most frequent daily, monthly, and seasonal occurrences of AAD.

The study population included 204 patients (66.5% male) treated at our institute between January 1, 1998 and January 1, 2004. A significantly higher frequency of AAD occurred from 6:00 AM to 12:00 noon, compared with other time periods ($P < 0.001$). The results showed a significant circadian variation in AAD ($P < 0.001$) with a peak between 9:00 AM and 10:00 AM. No significant variation was found for the day of the week; however, AAD occurred most frequently on Wednesday and Monday. The frequency of AAD was found to be significantly higher during winter versus other seasons ($P < 0.001$). The analysis of monthly variations of the onset of AAD confirmed a peak in February (12.9%) and in January (12.3%).

Similar to other cardiovascular diseases, AAD exhibits significant circadian and seasonal/monthly variations. Our findings indicate that the prevention of AAD, especially during the aforementioned vulnerable periods, is possible by adequate tailoring of the treatment of hypertension, which is the main AAD predisposing factor. (Int Heart J 2006; 47: 585-595)

Key words: Aortic dissection, Initial pain onset, Circadian rhythmicity, Hypertension

ACUTE aortic dissection (AAD) is one of the most dramatic diseases in clinical medicine. It is very difficult to determine the incidence of AAD because many of the cases were misdiagnosed or missing from evidence.1-3) In the past, information was gained mostly from sporadic autopsy studies, while the newer, more comprehensive clinical or clinicopathologic studies, including the IRAD study which analyzed 464 patients from 1996 to 1998, came from large cardiovascular
referral centers.\textsuperscript{4}) Since many AAD cases are unhospitalized, a considerable number of such patients die before admission; on the other hand, attention is rarely paid, on admission, to the exact initial time of pain. It is therefore difficult to determine the exact circadian variation of the disease.

There have only been a few studies of the chronobiological occurrence of AAD, and most were international and multicentered. The aim of the present single center study was to determine the most frequent daily, monthly, and seasonal occurrences of AAD. Circadian, weekly, and circannual variations have not been adequately studied with regard to dissection type. The present study analyzed AAD temporal variations in all patients and separately by dissection type.

**METHODS**

All patients with nontraumatic AAD treated at our Institute from January 1, 1998 to January 1, 2004 ($n = 204$) were analyzed. The study was approved by the hospital ethics committee. Informed consent was obtained from all patients before enrollment. The study was conducted in accordance with the Declaration of Helsinki. Because iatrogenic dissections (2.4\%) are not subject to circadian variations, these patients were excluded from the study. Initial pain was identified prospectively on presentation or retrospectively by searching surgical, pathological, and echocardiographic databases. Acute dissection was defined as presentation within 14 days of onset of initial pain. The exact time of AAD initial pain (defined as the time reported by the patient, relatives, or witnesses) was as noted in our database. The exact time of initial pain onset was available in 79.9\% of patients, while 41 patients (the remaining 20.1\%) were excluded from the study because the exact time of AAD initial pain onset could not be identified with certainty. Each patient was categorized, according to the initial pain onset time, into 24 1-hour periods. For the analysis of circadian pattern, patients were categorized

<table>
<thead>
<tr>
<th>Sample</th>
<th>Patients, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline group</td>
<td>209 (100)</td>
</tr>
<tr>
<td>Excluded (iatrogenic dissections)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Study group</td>
<td>204 (97.6)</td>
</tr>
<tr>
<td>Circadian rhythm analysis</td>
<td></td>
</tr>
<tr>
<td>Excluded because of absence of time</td>
<td>41 (20.1)</td>
</tr>
<tr>
<td>Study group for circadian rhythm analysis</td>
<td>163 (79.9)</td>
</tr>
<tr>
<td>Weekly and monthly/seasonal analysis</td>
<td></td>
</tr>
<tr>
<td>Excluded because of lack of exact date</td>
<td>37 (18.1)</td>
</tr>
<tr>
<td>Study group seasonal analysis</td>
<td>167 (81.9)</td>
</tr>
</tbody>
</table>

**Table I. Study Population**
into 4 time periods: 6:00 AM to 11:59 AM, 12:00 noon to 5:59 PM, 6:00 PM to 11:59 PM, and 12:00 midnight to 5:59 AM.

Patients with missing data on the exact time of initial pain onset were analyzed only for weekly and seasonal rhythmicity (81.9% of 204 patients in total) (Table 1). They were all categorized into seven 1-day-of-the-week periods and twelve 1-month periods. The starting reference point was assumed to be midnight, Sunday, and December 21st for the circadian, weekly, and monthly/seasonal analysis, respectively. For the purpose of seasonal analysis, patients were grouped according to their initial pain onset into 4 groups (winter, December 21st through March 20th; spring, March 21st through June 20th; summer, June 21st through September 20th; and autumn, September 21st through December 20th).5-7)

We analyzed possible differences in circadian variation in onset of AAD with regard to the following parameters: sex (men, women), age (< 70 years, ≥ 70 years), hypertensive/normotensive, and diabetic/nondiabetic. Blood pressure was recorded on admission and the patients were assigned to one of the following 4 groups: hypertensive group, systolic pressure ≥ 150 mmHg; normotensive group, 100-149 mmHg; hypotensive group, < 100 mmHg; shock group, ≤ 80 mmHg.

A diagnosis of AAD was based on anamnestic data, clinical symptoms and signs (severe chest pain, abdominal pain, back pain, and/or acute neurologic signs), and confirmed by diagnostic methods (transthoracic echocardiography, transesophageal echocardiography, computed tomography, magnetic resonance imaging, aortography), visualisation at surgery, and/or postmortem examination. Classification of aortic dissection was based on anatomic location (Stanford classification): type A dissections (AAD A) - those involving the ascending aorta; and type B dissections (AAD B) - those not involving the ascending aorta.

The distribution of symptom onset within the 4 time-of-day intervals was tested for uniformity by the $\chi^2$ test for goodness of fit. A $\chi^2$ value large enough to reject the hypothesis implied nonuniformity. We also tested whether the frequency of AAD during the morning time period was significantly different from the other 3 time periods by using the $\chi^2$ test. The analysis of circadian rhythmicity was performed on hourly data by applying the $\chi^2$ test.

The analysis of monthly and seasonal rhythmicity was performed by using the $\chi^2$ test. Variation in the occurrence of AAD as a function of mean age was analyzed using Student's $t$ test. A $P < 0.05$ was considered significant in all tests.

**RESULTS**

Of the 204 patients with AAD in the study, type A AAD and type B AAD were present in 134 (65.7%) and 70 (34.3%) of the patients, respectively (mean age, 59.14 ± 11.76 years, 66.5% males ($P < 0.001$)). Prior hypertension history
was recorded in 96% type A AAD patients and 94.2% type B AAD patients. The majority of patients on admission (54%) were hypertensive (31.3% in AAD A, 85.7% in AAD B, $\chi^2 = 54.371, P < 0.01$). On admission, 33.1% of the patients were normotensive (51.5% in AAD A, 12.9% in AAD B, $\chi^2 = 25.366, P < 0.01$) and 9% were hypotensive (11.2% in AAD A, 1.43% in AAD B, $\chi^2 = 6.067, P < 0.05$). Shock signs on admission were present in 3.9% of patients (6% in AAD A, no shock signs in AAD B, $\chi^2 = 4.350, P < 0.05$). Diabetes mellitus (8.7%) and Marfan's syndrome (1.5%) occurred in a small minority. Initial pain occurred suddenly in 93.3% of the patients (AAD A - 95.0%, AAD B - 91.4%).

**Circadian rhythm of AAD:** AAD initial pain onset was most frequent in the period from 6:00 AM to noon ($\chi^2 = 29.81, P < 0.001$) compared with the other three 6-hour periods (Figure 1). Observed statistically by type, initial pain onset in both AAD A and AAD B was much more frequent in the period from 6:00 AM to noon than in the other 3 time periods ($\chi^2 = 12.1, P < 0.001$ and $\chi^2 = 23.6, P < 0.001$).

The statistical importance of circadian variations in the occurrence of AAD ($\chi^2 = 102.57, P < 0.01$) was confirmed in all subgroups examined, with the primary (morning) peak between 9:00 and 10:00 AM and the secondary (nocturnal) peak between 2:00 and 3:00 AM (Figure 2).

The daily peak of AAD B onset (8:00 to 9:00 AM) occurred earlier than the AAD A initial pain onset (9:00 to 10:00 AM).

The diagram shows an increase in number of AAD patients from midnight to 10:00 AM, and then a gradual decrease. Initial pain occurred within the daily interval (6:00 AM to 6:00 PM) in 71.97% of the patients, while it occurred within the nocturnal interval (6:00 PM to 6:00 AM) in 28.03% of the patients ($\chi^2 = 25.48, P < 0.001$). Most patients (74%) (69% in AAD A, 79% in AAD B) expe-
experienced aortic dissection initial pain within the first 3 hours after waking up, namely within 2 time periods (midnight to 06.00 AM - 17% of patients; 06.00 AM to noon - 43.7% of patients). The average interval from awakening to onset was 1 and hour 45 minutes in AAD B patients and 2 hours and 25 minutes in AAD A patients.

**Weekly, monthly, and seasonal variations in frequency of AAD:** No significant variation was observed in the frequency of AAD on different days of the week ($\chi^2$ test).
= 6.183; \( P \) = NS). However, the highest percentage of initial pain occurrence was noted on Wednesday (19.2\%) and then on Monday (17.4\%) (Figure 3).

Initial pain in patients with type A dissection occurred mostly on Monday (19.8\%), while it occurred mostly on Wednesday (20\%) and Friday (20\%) in those with type B dissection (Figure 3).

It was confirmed that the occurrence of AAD was statistically more important in winter months than in the other 3 seasonal periods (\( \chi^2 = 18.19, P < 0.001 \)) (Figure 4).

![Figure 4. Seasonal variation of AAD with regard to type.](image)

![Figure 5. Monthly variation in the onset of AAD initial pain with regard to type.](image)
Statistical analysis identified the occurrence of AAD mostly in winter, with a peak in February (12.9%) and January (12.3%) (Figure 5). Subgroup analysis identified that the seasonal trend was more apparent for women, those with type B aortic dissection, younger patients, patients without a history of hypertension, and nondiabetic patients.

### Table II. Most Frequent Variations in AAD A Patients, According to Subgroup

<table>
<thead>
<tr>
<th>Group</th>
<th>N (%)</th>
<th>Hour (%)</th>
<th>Daily interval (%)</th>
<th>Day (%)</th>
<th>Month (%)</th>
<th>Season (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>64.4</td>
<td>10</td>
<td>26.3</td>
<td>6:00 AM to noon</td>
<td>31.9</td>
<td>Monday</td>
</tr>
<tr>
<td>Women</td>
<td>35.6</td>
<td>9</td>
<td>14.2</td>
<td>6:00 AM to noon</td>
<td>59.1</td>
<td>Wednesday</td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>83.6</td>
<td>10</td>
<td>16.2</td>
<td>6:00 AM to noon</td>
<td>40.0</td>
<td>Monday</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>16.4</td>
<td>11</td>
<td>36.0</td>
<td>6:00 AM to noon</td>
<td>50.0</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>96.0</td>
<td>10</td>
<td>18.6</td>
<td>6:00 AM to noon</td>
<td>43.2</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Normotensive</td>
<td>4.0</td>
<td>9</td>
<td>16.2</td>
<td>6:00 AM to noon</td>
<td>36.0</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Diabetic</td>
<td>10.4</td>
<td>10</td>
<td>18.2</td>
<td>6:00 AM to noon</td>
<td>65.6</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>89.6</td>
<td>10</td>
<td>13.1</td>
<td>6:00 AM to noon</td>
<td>41.2</td>
<td>Wednesday</td>
</tr>
</tbody>
</table>

### Table III. Most Frequent Variations in AAD B Patients, According to Subgroup

<table>
<thead>
<tr>
<th>Group</th>
<th>N (%)</th>
<th>Hour (%)</th>
<th>Daily interval (%)</th>
<th>Day (%)</th>
<th>Month (%)</th>
<th>Season (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>68.6</td>
<td>8</td>
<td>14.9</td>
<td>6:00 AM to noon</td>
<td>41.6</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Women</td>
<td>31.4</td>
<td>9</td>
<td>13.6</td>
<td>6:00 AM to noon</td>
<td>45.9</td>
<td>Friday</td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>79.7</td>
<td>8</td>
<td>13.2</td>
<td>6:00 AM to noon</td>
<td>43.6</td>
<td>Wednesday</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>20.3</td>
<td>12</td>
<td>12.5</td>
<td>6:00 AM to noon</td>
<td>57.1</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>94.2</td>
<td>8</td>
<td>13.8</td>
<td>6:00 AM to noon</td>
<td>47.7</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Normotensive</td>
<td>5.8</td>
<td>11</td>
<td>25.0</td>
<td>6:00 AM to noon</td>
<td>75.0</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Diabetic</td>
<td>8.7</td>
<td>8</td>
<td>16.7</td>
<td>6:00 AM to noon</td>
<td>66.7</td>
<td>Tuesday</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>91.3</td>
<td>9</td>
<td>14.3</td>
<td>6:00 AM to noon</td>
<td>44.4</td>
<td>Wednesday</td>
</tr>
</tbody>
</table>
The highest incidences of type A AAD and type B AAD occurred in January (11.9%) and February (18.8%), respectively.

Circadian variation in the onset of AAD was analyzed according to dissection type (type A, type B) with regard to sex, age, presence/absence of hypertension history, and presence/absence of diabetes mellitus (Tables II and III).

Most patients with AAD suffered sudden onset initial pain in the chest and/or in the back (93.3%). These patients developed AAD mostly on Wednesday (19.6%) and in February (14.5%). Patients with initial pain that was not the most severe on onset (6.7%) developed AAD mostly on Friday (45.5%) and in April (36.4%).

Most AAD A (55%) and AAD B (49.1%) patients experienced the initial pain during moderate physical exertion (slow walking, showering, hair combing, dish washing). Initial pain occurred during strenuous exertion (load carrying, wood chopping, running) in 22.5% of the AAD A patients and in 20.3% of the AAD B patients. Initial pain occurred during sleep in 14.6% of the AAD A patients and in 10.3% of the AAD B patients. Initial pain occurred at rest in 4.3% of the AAD A patients and in 13.4% of the AAD B patients. Finally, 3.6% of the AAD A patients and 6.9% of the AAD B patients reported experiencing emotional stress.

**DISCUSSION**

The results of the present study indicate rhythmicity has a strong influence on the occurrence of AAD. It was demonstrated that the peak incidence of AAD occurs during early morning, when people awaken and begin their activities, ie, when they are under the highest degree of stress because of expected daily duties. By analyzing daily rhythmicity, many studies confirmed a peak of AAD onset in morning hours, as well as cyclic variability in other cardiovascular diseases. Increases in disease incidence were recorded both for other cardiovascular events and aortic dissection within the first 3 hours of awakening. This was observed both in previous studies and the present one. In the present study, circadian variations of AAD were documented in all the subgroups examined (AAD A, AAD B, men/women, hypertensive/normotensive, diabetic/nondiabetic, age under/over 70 years).

The frequent occurrence of AAD in the early morning hours is related with a surge in sympathetic activity leading to an increase in shear forces secondary to elevation in blood pressure, heart rate, and the rate of pressure change \((dP/dt)\). Pressure elevation in early morning hours acts on the aortic wall which is weakened by genetic and acquired disorders, causing triggering of AAD. Similarly, the equilibrium between thrombotic and thrombolytic factors changes in the early
morning hours, leading to an increase in hypercoagulability and lower fibrinolytic activity.\textsuperscript{9} A combination of blood pressure elevation and physical activity represents the greatest risk factor for the onset of AAD.

The present study and the study of Kojima, \textit{et al}\textsuperscript{17} both indicate that AAD occurred predominantly during the day when blood pressure variations are greatest. The daytime/night-time events ratio of 71.97\% versus 28.03\% in our study is therefore of statistical importance.

Our opinion agrees with that of Fogelholm, \textit{et al}\textsuperscript{18} who suggest in their study of subarachnoid hemorrhage that the high transient blood pressure peaks associated with physical and mental activities are a trigger for an intimal tear or rupture of the vasa vasorum within the aortic media. Krantz, \textit{et al}\textsuperscript{19} explained the circadian variation of myocardial ischemia in the same manner.

The peak of AAD onset in our study was at 10:00 AM, which coincides with the results of Gallerani, \textit{et al}\textsuperscript{20} who examined 70 patients with AAD. In the study of Sumiyoshi, \textit{et al} who examined 435 patients with AAD,\textsuperscript{21} the peak was between 8:00 AM and 11:00 AM, in December, January, and March. However, in contrast to our study and the study of Mehta, \textit{et al},\textsuperscript{9} Sumiyoshi, \textit{et al} did not analyze the differences among subgroups. In the present study, initial pain occurred mainly from 9:00 AM to 10:00 AM, while it occurred mainly in the late morning (10:00 AM to noon) in the study of Kojima, \textit{et al}\textsuperscript{17}.

Initial pain in most of our patients occurred on Wednesday (19.2\%) and Monday (17.4\%). It occurred mainly on Monday (19.8\%) in AAD A patients, and on Wednesday (20\%) and Friday (20\%) in AAD B patients. Weekly variation with a peak on Monday has also been reported in acute myocardial infarction, sudden cardiac death, and cardiac arrest.\textsuperscript{15,22,23} A lower AAD incidence on the weekend is probably due to the absence of work-related stress as well as longer sleep times (sleeping time in our patients was prolonged on weekends by 2 hours and 25 minutes). The absence of stress, which is present on working days, eliminates sudden rises and variations in blood pressure, which are 2 of the most important factors provoking the occurrence and progression of aortic dissection. As regards seasonal variation, we recorded most AAD onset cases in winter months, especially February; this was confirmed also by large studies of other cardiovascular events.\textsuperscript{7,9,24,25} Matsuo, \textit{et al}\textsuperscript{26} also reported that the occurrence of AAD was highest in the winter (January to March) and lowest in the summer (July to September). Seasonal variation with a higher incidence in winter has been reported also in acute myocardial infarction, sudden cardiac death, and cardiac arrest.\textsuperscript{23,27,28}

Subgroup analysis suggested that monthly/seasonal variations in the onset of AAD were more evident in patients under 70 years of age, women, and normotensive and nondiabetic individuals. Smaller seasonal variations of AAD onset in
older patients are related with a greater degree of autonomous dysfunction.

The AAD onset morning peak in patients over 70 years old was at 11:00 AM, which may be connected with longer parasympathetic activity and the absence of work-related responsibilities and stress. AAD occurred in our patients over 70 years old mainly from 6:00 AM to noon, while Satoshi, et al.\cite{17} reported that AAD in such patients occurred predominantly during sleep.

Some studies show the lack of periodicity for cardiovascular events among diabetic patients as opposed to nondiabetic patients.\cite{24} The present study demonstrated lower periodicity in the incidence of aortic dissection among diabetic patients; however, their number was also considerably smaller ($n = 8.7\%$).

In patients with sudden onset initial pain, AAD onset peaks occurred mainly on Wednesday and in February (winter), while in those with gradually occurring initial pain, AAD onset peaks occurred mainly on Friday and in March (spring).

**Conclusion:** It is concluded that like many other cardiovascular conditions, AAD exhibits the most significant circadian and circannual frequency of occurrence in the morning and in winter, respectively. The results of our study indicate that the prevention of AAD, especially during the aforementioned vulnerable periods, is possible by adequate tailoring of the treatment of hypertension, which is the main AAD predisposing factor.

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