Examining the Relationship Between Triggering Activities and the Circadian Distribution of Acute Aortic Dissection

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ABSTRACT

Background and Objectives: There are limited data examining triggering activities and circadian distribution at the onset of acute aortic dissection (AAD) in the context of diagnostic and anatomical classification. The aim of this study was to further investigate this relationship between triggering activities and circadian distribution at the onset of AAD according to diagnostic and anatomical classification. Subjects and Methods: A total of 166 patients with AAD admitted to Kyungpook National University Hospital between July 2001 and June 2009 were included. To assess the influence of diagnostic and anatomical classification, we categorized the patients into intramural hematoma (IMH) group (n=67)/non-IMH group (n=99) and Stanford type A (AAD-A, n=94)/type B (AAD-B, n=72). To evaluate circadian distribution, the day was divided into four 6-hour periods: night (00-06 hours), morning (06-12 hours), afternoon (12-18 hours), and evening (18-00 hours). Results: Most (72%) AAD episodes were related to physical (53%) and mental activities (19%), with about one-third occurring during the afternoon, and only 12% occurring at night. No differences in triggering activities or circadian distribution were observed among the groups. Waking hours including morning, afternoon, and evening correlated with triggering activities (p=0.003). These relationships were observed for the non-IMH (p=0.008) and AAD-B (p=0.003) cases. The remaining categories had similar relationships, but did not reach statistical significance. Conclusion: Our findings suggest differences in the relationship between triggering activities and the circadian distribution of the onset of AAD according to diagnostic and anatomical classification. (Korean Circ J 2010;40:565-572)

KEY WORDS: Dissection; Aorta; Circadian rhythm.
Although in some cases IMH may rapidly regress, it may also proceed to dissection or aortic rupture.\(^{11}\) Patients with IMH show different clinical features and have a much better prognosis with medical treatment compared to those with classic AAD.\(^{12-14}\) In the context of limited available data, we hypothesized that there would be differences in triggering activities and their circadian distribution between patients with IMH and classic AAD. In the present study we investigated triggering activities and the circadian distribution of the onset of AAD. Our aim was to elucidate the relationship between both parameters in an analysis of subgroups sorted according to AAD anatomical location and the presence or absence of IMH.

**Subjects and Methods**

**Study design and population**

Because traumatic or iatrogenic dissections are not influenced by chronobiologic patterns, these patients were excluded from the analysis. One hundred eighty-seven consecutive AAD patients who were admitted to Kyungpook National University Hospital between July 2001 and June 2009 were included in the present study. Twenty-one patients whose triggering activities or onset time of AAD were uncertain were excluded from further analysis. In total, 166 patients with AAD were included in this study. The data were retrospectively collected from hospital medical records. The diagnosis of AAD was based on clinical symptoms/signs including severe chest pain, back pain, abdominal pain, neurological signs, typical findings on computed tomography (CT), and transesophageal echocardiography. Cases of IMH were included in the present study. IMH was defined as a hemorrhage contained within the medial layer of the aortic wall with crescentic or circular thickening \(\geq 7\) mm, without intimal flap or intimal tear.\(^{15,16}\) To assess the influence of anatomical location, we divided the patients into Stanford type A dissection (AAD-A) defined as AAD involving the ascending aorta, and type B dissection (AAD-B) defined as AAD occurring distal to the left subclavian artery.\(^{10}\) To evaluate the seasonal distribution of onset of AAD, the year was divided into four seasons: spring (March-May), summer (June-August), autumn (September-November), and winter (December-February). To evaluate the circadian distribution of onset of AAD, the day was divided into four 6-hour periods: night (00-06 hours), morning (06-12 hours), afternoon (12-18 hours), and evening (18-00 hours). The protocol was reviewed and approved by the institutional review board. Written informed consent was obtained for all patients enrolled in the study.

**Statistical analysis**

The data were analyzed using the Statistical Package for the

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**Table 1. Baseline characteristics of patients with acute aortic dissection according to Stanford classification and the presence or absence of intramural hematoma**

|                      | All (n=166) | AAD-A group (n=94) | AAD-B group (n=72) | p     | Non-IMH group (n=99) | IMH group (n=67) | p     |
|----------------------|-------------|--------------------|--------------------|-------|----------------------|------------------|-------|
| Age (year)           | 58.8±13.3   | 59.0±12.8          | 58.7±14.4          | 0.901 | 54.4±13.5            | 65.4±10.6        | <0.001|
| Age >60 (year), n (%)| 84 (51)     | 51 (54)            | 33 (46)            | 0.282 | 38 (38)              | 46 (69)          | <0.001|
| Male gender, n (%)   | 85 (51)     | 39 (41)            | 46 (64)            | 0.004 | 64 (65)              | 21 (31)          | <0.001|
| Height (cm)          | 164.4±9.9   | 163.0±9.8          | 164.6±9.7          | 0.034 | 167.8±8.7            | 159.4±9.4        | <0.001|
| BMI (kg/m\(^2\))     | 24.0±2.9    | 24.2±2.9           | 23.7±3.0           | 0.317 | 24.1±3.0             | 23.6±2.8         | 0.294 |
| Final diagnosis, n (%)|           |                    |                    |       |                      |                  |       |
| IMH                  | 67 (40)     | 33 (35)            | 34 (47)            | 0.115 |                      |                  |       |
| Anatomical location, n (%)|     |                    |                    |       |                      |                  |       |
| Stanford A           | 94 (57)     |                    |                    |       | 61 (62)              | 33 (49)          | 0.115 |
| Symptoms/signs, n (%)|           |                    |                    |       |                      |                  |       |
| Chest pain           | 90 (54)     | 63 (67)            | 27 (38)            | <0.001| 60 (61)              | 30 (45)          | 0.045 |
| Back pain            | 40 (24)     | 13 (14)            | 27 (38)            | <0.001| 21 (21)              | 19 (28)          | 0.291 |
| Abdominal pain       | 26 (16)     | 10 (11)            | 16 (22)            | 0.042 | 14 (14)              | 12 (18)          | 0.512 |
| Neurologic sign      | 14 (8)      | 11 (12)            | 3 (4)              | 0.083 | 10 (10)              | 4 (6)            | 0.347 |
| Risk factors, n (%)  |           |                    |                    |       |                      |                  |       |
| Hypertension         | 113 (68)    | 61 (65)            | 52 (72)            | 0.315 | 58 (59)              | 55 (82)          | 0.001 |
| Marfan syndrome      | 5 (3)       | 2 (2)              | 3 (4)              | 0.653 | 5 (5)                | 0 (0)            | 0.082 |
| Surgery, n (%)       | 93 (56)     | 84 (89)            | 9 (13)             | <0.001| 64 (65)              | 29 (43)          | 0.007 |
| In-hosp mortality, n (%)| 11 (7)    | 8 (9)              | 3 (4)              | 0.352 | 9 (9)                | 2 (3)            | 0.202 |

Values are given as number or mean \(±\) standard deviation. AAD-A: Stanford type A aortic dissection, AAD-B: Stanford type B aortic dissection, BMI: body mass index, IMH: intramural hematoma, In-hosp mortality: in-hospital mortality.
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The Social Sciences (SPSS) software (version 15.0; SPSS, Inc., Chicago, IL, USA) was used to analyze the data. Continuous variables were expressed as mean ± standard deviation, while categorical variables were given as number (percentage). The Student's t-test was employed for comparison of continuous variables, and Chi-square analyses were used for comparison of categorical variables. The distribution of triggering activities at the onset of AAD within four 6-hour periods was tested for uniformity in the overall population and in the various patient subgroups by the Chi-square test for goodness of fit. A Chi-square value large enough to reject the null hypothesis implied nonuniformity. A 2-sided p<0.05 was considered statistically significant.

**Results**

**Baseline characteristics of patients with acute aortic dissection**

The baseline characteristics of patients with AAD are listed in Table 1. The average age of study patients was 59±14 years. No significant difference was found in gender proportions. Chest pain (51%) was the most common symptom, while hypertension (68%) was the most common risk factor for AAD. Most cases of AAD (95%) were detected by CT. Surgery was performed on 93 patients (56%). Eleven patients (7%) expired during hospitalization.

**Triggering activities and the chronobiological distribution of the onset of acute aortic dissection**

Triggering activities at the onset of AAD are shown in Tables 2 and 3. Most AAD cases (n=120, 72%) were related to physical (n=88, 53%) and mental (n=32, 19%) activities. The chronobiological distribution of the onset of AAD is reported in Table 2 and Fig. 1. In terms of seasonal distribution, AAD occurred most frequently in winter (33%) followed by spring (26%), autumn (22%), and summer (19%). In terms of month-
ly distribution, AAD occurred most frequently in December and January (11%, respectively), and least frequently in August (4%), closely followed by September (5%). There was homogeneity in the weekly distribution. In terms of the circadian distribution, AAD occurred most frequently at 12-14 hours (13%) followed by 18-20 hours (11%), 14-16 hours (11%), 16-18 hours (10%), 20-22 hours (10%), and 06-08 hours (10%). Therefore, about one-third of AAD episodes occurred during the afternoon, with the least (12%) occurring at night.

Relationship between triggering activities and the circadian distribution of the onset of acute aortic dissection

The relationship between triggering activities and the circadian distribution of the onset of AAD is reported in Fig. 2. Triggering activities were related to circadian distribution (p=0.003) (Fig. 2A). At night, AAD occurred frequently in patients with no triggering activities, whereas during the waking hours, AAD occurred frequently in patients with physical or mental activity. Baseline characteristics according to Stanford classification are listed in Table 1. Compared with the AAD-B group, the AAD-A group involved more women (p=0.042). However, there was no significant difference in inhospital mortality between the two groups (p=0.352).

Triggering activities and the chronobiological distribution of the onset of acute aortic dissection according to Stanford classification

Differences in triggering activities and the chronobiological distribution of the onset of AAD between patients with AAD-A and AAD-B are shown in Table 2. No significant difference was observed between the two groups in triggering factors. Compared with the AAD-B group, onset in the AAD-A group occurred more frequently during the autumn/winter (p=0.008). However, there was no significant difference in circadian distribution between the two groups (p=0.248).

The relationship between triggering activities and the circadian distribution of the onset of acute aortic dissection-subgroup analysis according to Stanford classification

The relationship between triggering activities and the circadian distribution of the onset of AAD according to Stanford classification is reported in Fig. 2. Although there was a relationship between triggering activities and the circadian distribution of the onset of AAD for the AAD-B group (p=0.003)
(Fig. 2C), the relationship in the AAD-A group (p=0.197) did not reach statistical significance (Fig. 2B).

Baseline characteristics according to the presence or absence of intramural hematoma

Baseline characteristics according to the presence or absence of IMH are listed in Table 1. Compared with the non-IMH group, the IMH group was older (p<0.001) with significantly more women (p<0.001), history of hypertension (p=0.001), and a significantly lower frequency of surgery (p=0.007). However, there was no significant difference in in-hospital mortality between the two groups (p=0.202).

Triggering activities and the chronobiological distribution of the onset of acute aortic dissection according to the presence or absence of intramural hematoma

Differences in triggering activities and chronobiological distribution at the onset of AAD according to the presence or absence of IMH are shown in Table 2. No significant difference in triggering factors was observed between the two groups. Furthermore, there was no significant difference in circadian distribution (p=0.100) or seasonal distribution (p=0.236) between the two groups.

The relationship between triggering activities and the circadian distribution of the onset of acute aortic dissection-subgroup analysis according to the presence or absence of intramural hematoma

The relationship between triggering activities and the circadian distribution of the onset of AAD according to the presence or absence of IMH is reported in Fig. 2. The relationship between triggering activities and the circadian distribution of the onset of AAD in the Stanford type A group (p=0.197), but the difference did not reach statistical significance (B). The relationship between triggering activities and the circadian distribution of AAD onset held for the Stanford type B group (p=0.003) (C). The relationship between triggering activities and the circadian distribution of the onset of AAD held for the non-intramural hematoma group (p=0.008) (D). There was a trend towards a relationship between triggering activities and circadian distribution of the onset of AAD in the intramural hematoma group (p=0.102), but the difference did not reach statistical significance (E). The distribution of triggering activities of the onset of AAD within four 6-hour periods was tested for uniformity in the overall population, and in the patient’s subgroups by the Chi-square test for goodness of fit. A Chi-square value large enough to reject the hypothesis implied nonuniformity.

**Discussion**

The results of this study demonstrate that there is a signifi-
cadian variation in the occurrence of AAD, with a primary morning peak (08-11 hours) and a secondary evening peak (17-19 hours). As mentioned earlier, an increase in BP is considered one of the most important risk factors for AAD. BP rapidly increases after 07 hours and reaches a peak at mid-morning (around 10 hours), later peaking again in the evening (16-19 hours) in hypertensive and normotensive subjects. The circadian variation of BP may be a possible explanation for the daily distribution of AAD onset.

Compared with the AAD-B group, the AAD-A group experienced chest pain more frequently, and back and abdominal pain less frequently. It is reasonable that AAD-A involving the anterior portion of the aorta is more frequently associated with chest pain, while AAD-B, which involves the posterior and inferior portion of aorta, would be more frequently associated with back and abdominal pain. Interestingly, the present study finds that AAD-A is more frequent in female. A recent study showed that there was female bias in the occurrence of AAD-A, but the difference was not statistically significant. These biases could be explained by older age and a tendency towards a history of high BP among females, as hypertension plays the most important role in the pathogenesis of AAD, and increases with age. However, there are no significant differences between the two groups regarding triggering factors in this study. Kojima et al. also demonstrated that triggering activities did not differ between the AAD-A and AAD-B groups. Moreover, this study found no difference in circadian distribution between the two groups. There are limited studies investigating a possible correlation between the anatomical location of AAD and its chronobiological distribution, and the fact that we found no significant difference may explain lack of published studies.

There was little data available examining triggering activities and the chronobiological distribution of the onset of AAD according to the presence or absence of IMH. In this study, no significant difference was observed between the two groups in triggering activities or the circadian distribution of the onset of AAD, although patients with IMH were older, more frequently female, and had a history of hypertension. However, one of the most important factors for the occurrence of AAD is an increase of BP, not a history of hypertension. Therefore, it is possible that there were no significant differences in essential mechanisms of AAD occurrence, such as BP increase, in the presence or absence of IMH.

The present study demonstrates that the occurrence of triggering activities was related to circadian distribution. AAD occurred less frequently in patients with triggering activities at night, whereas it occurred more frequently in patients with physical or mental activities during waking hours including morning, afternoon, and evening. Kojima et al. showed that daytime events were significantly more related to physical or mental activities than nighttime events (95% vs. 70%, p<0.001).
It is well known that BP exhibits circadian variation\textsuperscript{9,10}. In a previous study, higher physical and mental activity levels also showed a pattern similar to that of elevation of BP\textsuperscript{9,10}. The circadian variation of BP together with increased physical and mental activity may be a possible explanation for the daily pattern of onset of AAD. There have been limited studies about the relationship between the circadian distribution and triggers of AAD onset in the context of anatomical location and the presence or absence of IMH. To the best of our knowledge, this study is the first one to reveal that the relationship between circadian distribution and triggering activities holds for AAD-B and non-IMH cases, whereas there is no significant relationship between the two parameters in AAD-A and IMH cases. We suppose that AAD-A and IMH could be influenced by another mechanism, which underlies the relationship between the two parameters. Therefore, further studies on the relationship between the two parameters according to anatomical location and the presence or absence of IMH are needed to confirm our results.

**Study limitations**

There are some potential limitations to the present study. First, there may be some selection bias because we collected data retrospectively from hospital medical records. Second, we did not assess the activity level of each patient, although physical activity seems to be an important triggering factor for AAD. Third, the timing of onset of AAD might be different from the real time of occurrence because we collected data retrospectively, as previously mentioned. However, this disparity would not influence the relationship between triggering activities and circadian distribution because of its lack of significant importance in the study design. Finally, we could not measure BP at the time of the occurrence of AAD. We therefore could not investigate an accurate relationship between BP and triggering activities or circadian distribution.

**Conclusion**

Most AAD is caused by triggering activities. Triggering activities are related to the circadian distribution of the onset of AAD. The circadian distribution of the onset of AAD does not differ according to anatomical classification or the presence or absence of IMH. This relationship also holds for non-IMH patients and those with AAD-B.

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**REFERENCES**

1) Mittelman MA, Maclure M, Toffler GH, Serwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. N Engl J Med 1993:329:1677-83.
2) Willich SN, Lewis M, Löwel H, Arntz HR, Schubert F, Schröder R. Physical exertion as a trigger of acute myocardial infarction. N Engl J Med 1993:329:1684-90.
3) Kuznts DS, Kop WJ, Gabbay FH, et al. Circadian variation of amбулatory myocardial ischemia: triggering by daily activities and evidence for an endogenous circadian component. Circulation 1996;93:1364-71.
4) Kono T, Morita H, Nishina T, et al. Circadian variations of onset of acute myocardial infarction and efficacy of thrombotic therapies. J Am Coll Cardiol 1996;27:774-8.
5) Marchant B, Ranjayalaks K, Stevenson R, Wilkinson P, Timmis AD. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmental temperature. Br Heart J 1993:69:385-7.
6) Guecchi-Ruscone T, Picaullaga E, Guzzetti S, Contini M, Montano N, Nicolis E. Morning and Monday: critical period for the onset of acute myocardial infarction. The GISLI 2 Study experience. Eur Heart J 1994:15:882-7.
7) Willich SN, Levy D, Rococo MB, Toffler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardio1987;60:801-6.
8) Gallerani M, Portaluppi F, Maida G, et al. Circadian and circannual rhythmicity in the occurrence of subarachnoid hemorrhage. Stroke 1996;27:1793-7.
9) Kojima S, Sumiyoshi M, Nakata Y, Daida H. Triggers and circadian distribution of the onset of acute aortic dissection. Circ J 2002:66:232-5.
10) Mehta RH, Mannfredini R, Hassan F, et al. Chronobiological patterns of acute aortic dissection. Circulation 2002:106:1110-5.
11) Kim JK, Park SW, Jeong JO, et al. Clinical features and prognosis of acute aortic intramural hemorrhage compared with those of acute aortic dissection: a single center experience. Jpn Heart J 2001:42:91-100.
12) Hwang GS, Kim YH, Lee HS, et al. Clinical comparison of aortic intramural hemorrhage with aortic dissection involving the ascending aorta. Korean Circ J 2000;30:440-7.
13) Song JK, Kim HS, Song JM, et al. Multicenter longitudinal follow-up clinical study comparing the natural course of medically-treated patients with aortic dissection and aortic intramural hematoma. Korean Circ J 2001:31:592-601.
14) Lee IS, Kang DH, Song JK, et al. Clinical and echocardiographic outcome of aortic intramural hemorrhage compared with acute aortic dissection. Korean Circ J 1998;28:749-56.
15) Mohr-Kahaly S, Erbel R, Kearney P, Path M, Meyer J. Aortic intramural hemorrhage visualized by transesophageal echocardiography: findings and prognostic implications. J Am Coll Cardiol 1994:23:655-64.
16) Nienaber CA, von Kodolitsch Y, Petersen B, et al. Intramural hemorrhage of the thoracic aorta: diagnostic and therapeutic implications. Circulation 1995;92:1465-72.
17) Harris KM, Braveman AC, Gutierrez FR, Barzilai B, Dávila-Román VG. Transesophageal echocardiographic and clinical features of aortic intramural hematoma. J Thorac Cardiovasc Surg 1997;114:619-26.
18) Sueyoshi E, Matsusaka Y, Sakamoto I, Uetani M, Hayashi K, Narimatsu M. Fate of intramural hematoma of the aorta: CT evaluation. J Comput Assist Tomogr 1997;21:931-8.
19) Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway NE. Management of acute aortic dissections. Ann Thorac Surg 1970:10:237-47.
20) Matsu H. The thrombosed type of aortic dissection: its clinical features and diagnosis. Int J Angiol 1998;7:329-34.
21) Tsurujo Mar, Yamao T, Miximo M, Foredinsson M, Kallj S, Uusitalo A. Blood pressure and heart rate variability and reactivity as related to daily activities in normotensive men measured with 24-h intra-arterial recording. J Hypertens 1991:9:665-73.
22) Fogelholm RR, Turjanmaa VM, Naitila MT, Munro KE, Sama S. Diurnal blood pressure variations and onset of subarachnoid haem-
23) Sumiyoshi M, Kojima S, Arima M, et al. Circadian, weekly, and seasonal variation at the onset of acute aortic dissection. Am J Cardiol 2002;89:619-23.

24) Izzo JL Jr, Larrabee PS, Sander E, Lillis LM. Hemodynamics of seasonal adaptation. Am J Hypertens 1990;3:405-7.

25) Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. Circulation 2004;109:3014-21.