Clinical Article
J Korean Neurosurg Soc 62 (5) : 519-525, 2019
https://doi.org/10.3340/jkns.2019.0061 pISSN 2005-3711 eISSN 1598-7876

Relationship between Circadian Variation in Ictus of Aneurysmal Subarachnoid Hemorrhage and Physical Activity

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Objective : The circadian pattern of the onset time of aneurysmal subarachnoid hemorrhage (aSAH) has been reported by various authors. However, the effect of the degree of physical exertion on the circadian pattern has not been studied in detail. Therefore, we conducted this study to investigate the effect of physical exertion on the circadian pattern of aSAH.

Methods : Of the 335 patients presenting with aSAH from January 2012 to December 2017, 234 patients with identifiable onset time and metabolic equivalent (MET) values were enrolled. The onset time of aSAH was divided into 4-hour intervals. The patient's physical exertion was then assessed on a scale between 1 and 8 METs using generally accepted MET values, and categorized into two groups—light exertion (1 to 4 METs) and moderate to heavy exertion (5 to 8 METs)—to determine the effect of the degree of physical exertion on the onset time distribution of aSAH. Multivariate analysis was used to calculate the odds ratio (OR) between the two groups to determine the effect of the degree of physical exertion on each set of time periods.

Results : There was a definite bimodal onset pattern that peaked at 08:00–12:00 hours followed by 16:00–20:00 hours ($p<0.001$). MET values at all time intervals were found to be significantly higher than the night time (00:00–04:00 hours) values ($p<0.031$). The MET value distribution showed a unimodal pattern that slightly differed from the bimodal distribution of the onset time of aSAH. There were no significant differences in the ORs of each time interval according to the degree of the MET value.

Conclusion : This study reaffirmed that aSAH occurs in a bimodal pattern, especially showing the highest prevalence in the morning. Although aSAH could be related to daily activity, there were no significant changes in diurnal variations affected by the degree of physical exertion.

Key Words : Subarachnoid hemorrhage · Epidemiology · Physical exertion · Risk factors.

INTRODUCTION

The onset time of aneurysmal subarachnoid hemorrhage (aSAH) has been reported to show a circadian pattern[6,11,16,20-23], and several studies have analyzed the correlation between the circadian pattern of aSAH and conventional risk factors[2,3,5,11,23]. These studies focused on the possibility of providing pharmacologic protection or lifestyle modification against

• Received : March 4, 2019 • Revised : April 29, 2019 • Accepted : May 7, 2019
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the risk factors that promote the onset of aSAH during high-risk times of the day. Previously published studies have shown that the 2-peak temporal pattern of aSAH is independent of conventional risk factors such as hypertension, diabetes mellitus, cigarette smoking, and alcohol intake[23]. However, the correlation between the circadian pattern of aSAH and physical exertion, which is a modifiable risk factor, has not been adequately assessed. A better understanding of the effect of physical exertion on the circadian variation in aSAH onset can facilitate manipulation of temporal risk factors or lifestyle modification during the high-risk period.

This paper presents a single-center study conducted to investigate the effects of conventional risk factors as well as physical activity on circadian rhythmicity of aSAH. We also investigated whether clinical (Hunt-Hess Grade) severity varied by the time of the rupture.

MATERIALS AND METHODS

Study population

This study was approved by the Institutional Review Board of Ulsan University Hospital (IRB No. 2019-03-001). In this retrospective, single-center hospital-based study, we included a consecutive series of 335 patients with aSAH admitted through the Emergency Room to the Department of Neurosurgery in our institute from January 2012 to December 2017 on the basis of Electronic Medical Records. Of the 335 patients, 228 had obvious onset times within the hour, and six other patients could be predictably identified within a daily phase. The remaining 101 patients with no identifiable onset time and metabolic equivalent (MET) values were excluded from further analysis. aSAH was defined as spontaneously and rapidly developing headache with neurological symptoms caused by bleeding into the subarachnoid space due to aneurysmal rupture. Clinical diagnosis was based on computed tomography (CT) or magnetic resonance imaging (MRI). In all the patients, the presence of the ruptured aneurysm was confirmed by transfemoral cerebral angiography. Patients whose hemorrhage originated from causes other than an intracranial aneurysm were excluded. All the admitted patients were assessed using the Glasgow coma scale and Hunt-Hess scale. Admission CT scans were classified using the modified Fisher grading scale. All times of onset were recorded on a military time clock (00:00–23:59 hours). The onset time of aSAH was categorized into six daily phases with 4-hour intervals : the night phase (00:00 to 04:00), 04:00 to 08:00, 08:00 to 12:00, 12:00 to 16:00, 16:00 to 20:00, and 20:00 to midnight. Based on the data available in the Electronic Medical Records, baseline demographics, past medical history, and precise time of onset were abstracted using the following characteristics : age, sex, hypertension history, smoking status (divided into non-smokers and current smokers), and heavy alcohol consumption (defined as ≥150 g alcohol consumption per week). The patient's degree of physical exertion at the time of the symptoms was also recorded in the Electronic Medical Record. Physical activity was then assessed on a scale between 1 and 8 score using generally accepted MET values and categorized into two groups: light exertion (1 to 4 METs) and moderate to heavy exertion (5 to 8 METs)[2,15].

Statistical analysis

Assuming that the onset of the aSAH had no relation to the time of day, the onset time would be evenly distributed throughout the day. The frequency of observed cases in each 4-hour interval over 24 hours was compared with the expected frequency to determine if onset times were evenly distributed using a χ^2 goodness-of-fit test.

The proportions of aSAH were measured across each time phase and stratified by age, gender, degree of physical exertion (MET value), Hunt-Hess Grade (HHG), hypertension, smoking status, and heavy alcohol consumption. Age was categorized as <65 years and ≥65 years. MET value was categorized as light exertion (1 to 4 METs) and moderate to heavy exertion (5 to 8 METs). HHG was categorized as HHG 1–3 and HHG 4–5. Confidence intervals (CIs) for proportions were calculated by Wilson's method. The degrees of physical exertion (MET values) were modeled as independent variables for calculating the respective odds ratios (ORs). The OR with 95% CI of aSAH occurring in each phase versus the night was calculated using multinomial logistic regression. For comparison of the MET values according to time phases, the MET values for each phase were analyzed by the analysis of variance (ANOVA) test. Statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) and R package (ver 3.5.0; R foundation for Statistical Computing).

Table1. Baseline characteristics of included patients with aneurysmal subarachnoid hemorrhage

Variable	Value	Remarks
Sex		
Male	95 (40.6)	
Female	139 (59.4)	
Mean age (years)	54.12±11.96	54 (19–86)*
Age (years)		
<65	191 (81.6)	
≥65	43 (18.4)	
Rupture time interval		
00:00–04:00	10 (4.3)	
04:00–08:00	30 (12.8)	
08:00–12:00	77 (32.9)	
12:00–16:00	36 (15.4)	
16:00–20:00	51 (21.8)	
20:00–24:00	30 (12.8)	
HHG		
1	1 (0.4)	
2	47 (20.1)	
3	117 (50.0)	
4	59 (25.2)	
5	10 (4.3)	
MET score		
1	25 (10.7)	
2	57 (24.4)	
3	54 (23.1)	
4	22 (9.4)	
5	33 (14.1)	
6	29 (12.4)	
7	12 (5.1)	
8	2 (0.9)	
MET score group		
Light exertion	158 (67.5)	
Moderate to heavy	76 (32.5)	
HTN		
(-)	141 (60.3)	
(+)	93 (39.7)	
Current smoking	163 (81.2)	
(-)	44 (18.8)	
(+)		
Heavy alcohol consumption		
(-)	190 (81.2)	
(+)	44 (18.8)	

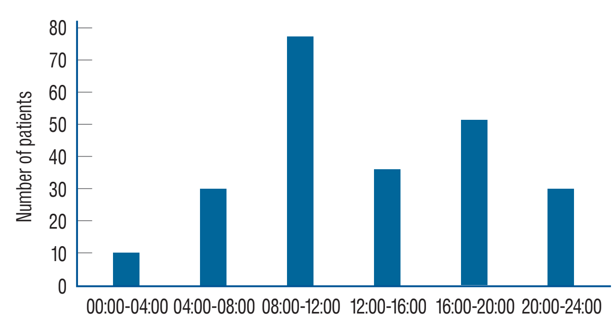
Values are presented as mean±standard deviation or number (%). *Median (minimum-maximum). HHG : Hunt-Hess grade, MET : metabolic equivalent, HTN : hypertension

RESULTS

The mean age of patients with aSAH was 54.12±11.96 years (standard deviation, 11.96 years). Of the patients, 40.6% were male, 18.4% were elderly (≥65 years), 29.5% had high grade aSAH (HHG, 4–5), and 32.5% belonged to the moderate to heavy exertion group (Table 1). In terms of the onset time of aSAH, there was a definite daily variation pattern over time (χ^2=68.94, df=5, p<0.001) (Fig. 1). The highest number of patients (32.9%) reported onset times between 08:00 and 12:00 hours, with peak occurrence between 11:00 and 12:00. The lowest peak was noted between midnight and 04:00, the night time. In all patients with aSAH, the 08:00–12:00 peak was much higher in comparison with the night phase (00:00–04:00) (OR, 7.70; 95% CI, 3.97–16.69).

When the onset time frequency was stratified by various demographic factors (Table 2), the lowest number of cases occurred in the night phase (00:00–04:00 hours) and the highest one at 08:00–12:00 hours among all subgroups except the old age group (≥65 years). In addition, the diurnal pattern that shows peaks at 08:00–12:00 hours followed by 16:00–20:00 hours was persisted except for patients without hypertension.

MET values for all time intervals were found to be statistically significantly higher when compared to the night time values (p=0.031), as seen in Fig. 2. The distribution of MET values also showed a peak at 08:00–12:00 hours followed by 12:00–16:00 hours. This was slightly different from the bimodal distribution of onset time of aSAH, which showed



No. of patients	10	30	77	36	51	30
%	4.3	12.8	32.9	15.4	21.8	12.8

Fig. 1. Distribution of number of the observed cases with aneurysmal subarachnoid hemorrhage according to the rupture time. Bar graph showing distribution of number of the observed cases with aneurysmal subarachnoid hemorrhage with known times of onset. Null hypothesis of uniformity is rejected (χ^2=68.94, df=5, p<0.001).

peaks at 08:00–12:00 hours followed by 16:00–20:00 hours.

Based on the analysis of whether the degree of MET value has impact on aneurysm rupture time, the moderate to heavy exertion group had an OR of 2.69 compared to the light exertion group at 08:00–12:00 hours (Table 3). But there was no statistically significance (p=0.229). Although patients with moderate to heavy exertion have an increased OR in all the subgroups, there was no statistical meaning.

DISCUSSION

In this study, diurnal variation of onset time of aSAH, specifically a bimodal distribution, was observed, and this diurnal variation was also seen in all subgroups. These findings are analogous to other studies around the world that show an increase in the frequency in the morning[6,7,9,10,16,20,21,23]. In addition, there was a preponderance in the morning hours, regardless of age, sex, or other traditional risk factors, which was also in accordance with the findings of most previous re-

Table 2. Proportion of aSAH cases across the six time blocks stratified by sex, age, stroke severity (HHG), MET score, and hypertension, diabetes mellitus, dyslipidemia, current smoking, and heavy alcohol consumption statuses

	Total	00:00–04:00	04:00–08:00	08:00–12:00	12:00–16:00	16:00–20:00	20:00–24:00
All cases	234	4.3 (2.3–7.7)	12.8 (9.1–17.7)	32.9 (27.2–39.2)	15.4 (11.3–20.6)	21.8 (17.0–27.5)	12.8 (9.1–17.7)
Sex							
Male	95	4.2 (1.6–10.3)	10.5 (5.8–18.3)	40.0 (30.7–50.1)	17.9 (11.5–26.8)	16.8 (10.6–25.6)	10.5 (5.8–18.3)
Female	139	4.3 (2.0–9.1)	14.4 (9.5–21.2)	28.1 (21.3–36.0)	13.7 (8.9–20.4)	25.2 (18.7–33.0)	14.4 (9.5–21.2)
Age							
<65 years	191	4.7 (2.5–8.7)	12.6 (8.6–18.0)	35.1 (28.7–42.1)	14.1 (9.9–19.8)	20.4 (15.3–26.7)	13.1 (9.0–18.6)
≥65 years	43	2.3 (0.4–12.1)	14 (6.6–27.3)	23.3 (13.2–37.7)	20.9 (11.4–35.2)	27.9 (16.7–42.7)	11.6 (5.1–24.5)
HHG							
1–3	165	2.4 (0.5–6.1)	12.7 (8.5–18.7)	35.2 (28.3–42.7)	15.8 (11.0–22.1)	21.2 (15.7–28.1)	12.7 (8.5–18.7)
4–5	69	8.7 (4.0–17.7)	13.0 (7.0–23.0)	27.5 (18.4–39.0)	14.5 (8.1–24.7)	23.2 (14.8–34.4)	13.0 (7.0–23.0)
MET score							
Light exertion	158	5.1 (2.6–9.7)	14.6 (9.9–20.9)	29.1 (22.6–36.6)	15.2 (10.4–21.6)	22.8 (16.9–29.9)	13.3 (8.9–19.5)
Moderate to heavy exertion	76	2.6 (0.7–9.1)	9.2 (4.5–17.8)	40.8 (30.4–52.0)	15.8 (9.3–25.6)	19.7 (12.3–30.0)	11.8 (6.4–21.0)
HTN							
(-)	141	5.0 (2.4–9.9)	10.6 (6.6–16.8)	34.0 (26.7–42.2)	20.6 (14.7–28.0)	19.9 (14.1–27.2)	9.9 (6.0–16.0)
(+)	93	3.2 (1.1–9.1)	16.1 (10.0–24.9)	31.2 (22.7–41.2)	7.5 (3.7–14.7)	24.7 (17.1–34.4)	17.2 (10.9–26.1)
DM							
(-)	222	4.5 (2.5–8.1)	12.6 (8.9–17.6)	32.9 (27.0–39.3)	16.2 (11.9–21.6)	20.7 (15.9–26.5)	13.1 (9.3–18.1)
(+)	12	0.0 (0.0–24.2)	16.7 (4.7–44.8)	33.3 (13.8–60.9)	0.0 (0.0–24.2)	41.7 (19.3–68.0)	8.3 (1.5–35.4)
Dyslipidemia							
(-)	176	3.4 (1.6–7.2)	13.6 (9.3–19.5)	35.2 (28.6–42.5)	15.9 (11.2–22.0)	18.8 (13.7–25.2)	13.1 (8.9–18.8)
(+)	58	6.9 (2.7–16.4)	10.3 (4.8–20.8)	25.9 (16.3–38.4)	13.8 (20.6–43.8)	31.0 (20.6–43.8)	12.1 (6.0–22.9)
Current smoking							
(-)	163	3.1 (1.3–7.0)	12.9 (8.6–18.9)	32.5 (25.8–40.0)	16.0 (11.1–22.3)	23.9 (18.0–31.0)	11.7 (7.6–17.5)
(+)	71	7.0 (3.0–15.4)	12.7 (6.8–22.4)	33.8 (23.9–45.4)	14.1 (7.8–24.0)	16.9 (9.9–27.3)	15.5 (8.9–25.7)
Heavy alcohol consumption							
(-)	190	3.7 (1.8–7.4)	13.7 (9.5–19.3)	30.5 (24.4–37.4)	16.8 (12.2–22.8)	23.2 (17.7–29.7)	12.1 (8.2–17.5)
(+)	44	6.8 (2.3–18.2)	9.1 (3.6–21.2)	43.2 (29.7–57.8)	9.1 (3.6–21.2)	15.9 (7.9–29.4)	15.9 (7.9–29.4)

Values are presented as number or % (95% confidence interval). HHG : Hunt-Hess grade, MET : metabolic equivalent, HTN : hypertension, DM : diabetes mellitus ports[6,13,21,23].

Although some studies have shown that physical activity is a precipitating factor for aSAH, the effect of physical activity on the etiology of aSAH and the underlying mechanism have not been clearly defined[14,18]. Anderson et al.[2] described that moderate to extreme physical exertion tripled the risk of aSAH. On the other hand, Abbott et al.[1] studied the impact of baseline physical activity on subarachnoid hemorrhage in men. In that study, men were divided into three groups—inactive, partially active, and active—and excessive levels of subarachnoid hemorrhage were noted in inactive older men.

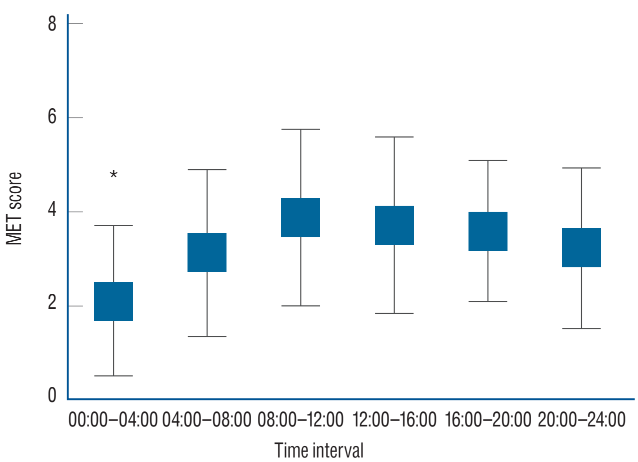


Fig. 2. Differences in metabolic equivalent (MET) scores in relation to time intervals. The mean value of MET scores shows a peak at 08:00–12:00 hours followed by 12:00–16:00 hours. *Post-hoc* analysis demonstrates that MET score at 00:00–04:00 is significant lower when compared to that for all other time intervals. *p=0.031.

Unlike Anderson's study, it means that a certain level of physical activity has a preventive effect. However, these two studies showing the opposite effects of physical activity on the occurrence of aSAH did not show the effect of physical exertion on the diurnal variation of aSAH. In our study, moderate to heavy physical exertion had no significant effect on diurnal variation. Although our study also did not measure all extrinsic or endogenous factors, an important aspect of our study is to confirm whether physical exertion affects diurnal variation. In our study, the distribution of MET values showed a unimodal distribution, which could be attributable to the higher levels of activity at day time. However, the circadian pattern of aSAH showed a bimodal distribution, which was different from the unimodal distribution pattern of MET values. The other peak of aSAH occurrence in the afternoon (16:00–20:00) could be affected by other factors than physical exertion. As mentioned earlier, it is known that regular physical activity has a preventive effect against stroke[4,8,12,17,19,24]. Thus, the degree of baseline activity in patients may have affected the result as a confounding factor. Consequently, our study has shown that there is no significant change in diurnal variations according to the degree of physical exertion.

This study had some limitations. First, the MET value does not reflect other physiological mechanisms. It does not objectively score the effects of other activities, such as the Valsalva maneuver, which can increase intracranial pressure as well as systemic activities associated with blood pressure. Second, the evaluation of patients with high severity who could not be appropriately interviewed was insufficient. Although it is likely

Table 3. The ORs and 95% CI values according to the differences in MET scores at each rupture time interval with the night time value used as reference

Rupture interval time	Variable	B	SE	OR	95% CI	*p*-value
04:00–08:00*	MET : light exertion			Reference		
	MET : moderate to heavy	0.197	0.901	1.217	0.208–7.114	0.827
08:00–12:00	MET : light exertion			Reference		
	MET : moderate to heavy	0.992	0.824	2.696	0.536–13.554	0.229
12:00–16:00	MET : light exertion			Reference		
	MET : moderate to heavy	0.693	0.866	2.000	0.366–10.919	0.423
16:00–20:00	MET : light exertion			Reference		
	MET : moderate to heavy	0.511	0.848	1.667	0.316–8.787	0.547
20:00–24:00	MET : light exertion			Reference		
	MET : moderate to heavy	0.539	0.885	1.714	0.302–9.719	0.543

*Reference category : 00:00–04:00. OR : odds ratio, CI : confidence interval, MET : metabolic equivalent, B : beta, SE : standard error that the response of the companion is similar to the actual patient in such cases, taking into account personal habits and medical conditions, in some cases, it is possible that the intensity of the physical exertion has not been properly recorded. Third, we only considered the degree of physical exertion at the onset time of aSAH, as discussed above. Fourth, our investigation showed the limitations of selective bias and compound effect inherent to single-center, retrospective analyses. A randomized controlled trial involving a large-scale multicenter study should be conducted in the future to collect more data concerning the effect of physical exertion on the circadian pattern of aSAH.

CONCLUSION

The circadian pattern of the onset time of aSAH was also noted in our study. However, there were no significant changes in diurnal variations in relation to the degree of physical exertion.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : SCK, JML
Data curation : JML, NYJ, ESP
Formal analysis : JML, NYJ
Methodology : SCK, JBP, HBS, IUL
Project administration : SCK
Visualization : JML, NYJ
Writing - original draft : JML
Writing - review & editing : SCK, NYJ

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