Atmospheric Pressure Variation is a Delayed Trigger for Aneurysmal Subarachnoid Hemorrhage

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OBJECTIVE: There is an ongoing search for conditions that induce spontaneous subarachnoid hemorrhage (SAH). The seasonal pattern of SAH is shown in a large meta-analysis of the literature, but its explanation remains undecided. There is a clear need for sound meteorologic data to further elucidate the seasonal influence on SAH. Because of the stable and densely monitored atmospheric situation in the north of the Netherlands, we reviewed our unique cohort on the seasonal incidence of SAH and the association between SAH and local atmospheric changes.

METHODS: Our observational cohort study included 1535 patients with spontaneous SAH admitted to our neurovascular center in the north of the Netherlands between 2000 and 2015. Meteorologic data could be linked to the day of the ictus. To compare SAH incidences over the year and to test the association with meteorologic conditions, incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) were used, calculated by Poisson regression analyses.

RESULTS: Atmospheric pressure variations were significantly associated with aneurysmal SAH. In particular, the pressure change on the second and third day before the ictus was independently correlated to a higher incidence of aneurysmal SAH (IRR, 1.11; 95% CI, 1.00–1.23). The IRR for aneurysmal SAH in July was calculated 0.67 (95% CI, 0.49–0.92) after adjustment for temperature and atmospheric pressure changes.

CONCLUSIONS: Atmospheric pressure variations are a delayed trigger for aneurysmal SAH. Also, a significantly decreased incidence of aneurysmal SAH was noted in July.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating type of stroke, although the case fatality is decreasing. Therefore, more knowledge on the pathophysiology and development of cerebral aneurysm is required, including risk factors contributing to the rupture of aneurysms. Established risk factors for SAH are hypertension, alcohol excess, and smoking.

A seasonal pattern in incidence of SAH has been observed. Conflicting data have been published regarding the relation between temperature and incidence of SAH. Some studies found a relation between SAH and atmospheric pressure changes, whereas others did not. In a large meta-analysis of 72,694 patients, no direct relation was found between occurrence of SAH and atmospheric pressure or temperature changes, which has led to the assumption that meteorologic factors do not explain the seasonal occurrence of SAH. However, the review was based on heterogeneous data from low-quality articles, with small or heterogeneous cohorts or inaccurate weather data. Because the individual constituents of a meta-analysis define its overall quality, this situation leads to results that are not generalizable.

Our SAH referral region in the north of the Netherlands has no altitude differences and is located at sea level, which makes it...
homogeneous for atmospheric pressure and temperature. Also, detailed meteorologic data are available from many automated weather stations in the referral area, allowing accurate meteorologic measurements to be linked to an individual patient. This factor prompted us to perform a detailed review on the seasonal variation in SAH incidence. In addition, we analyzed the association between SAH and temperature and atmospheric pressure. The unique combination of detailed information about patients with SAH and local meteorologic conditions at the time of the ictus distinguishes our study from previously reported studies.

METHODS

Patients
All consecutive patients with spontaneous SAH referred to our academic neurovascular center in Groningen between January 2000 and December 2015 were included in this study. Over the years, clinically relevant data were collected in a prospectively kept database. SAH was confirmed with computed tomography. Additional angiographic imaging (computed tomography angiography and/or conventional angiography) was performed to determine the presence of an aneurysm. Patients with SAH caused by an arterial dissection were excluded, as well as pediatric patients. A cohort of 1535 patients with SAH were eligible.

Given the design of the study and the fact that patients were treated according to standard clinical care, the research ethical board decided that informed consent was not required.

Meteorologic Data
All patients with SAH in the north of the Netherlands (Groningen, Friesland, and Drenthe provinces) are referred to the neurovascular unit of the University Medical Center in Groningen. This district covers an area of 8902 km² with a temperate climate, harboring no differences in altitude. It is located at sea level. At the end of the study period, there were 1,718,390 inhabitants in this area according to the Central Bureau of Statistics in the Netherlands.

Quality-controlled meteorologic data were retrieved from the weather station at Eeldere Airport of the Royal Netherlands Meteorological Institute. Data from this station are typical for the entire study region. Meteorologic data included mean atmospheric pressure, daily highest and lowest atmospheric pressure, mean temperature, and daily maximum and minimum temperature. In the Netherlands, the seasons are winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).

Statistical Analysis
Categorical data are presented as number and percentages. Continuous variables are presented as mean with standard deviation or median with interquartile range, depending on the normality of the data. Group differences are tested using χ² tests or 2-sample unpaired t tests. The day of onset of SAH was used to count the number of patients presenting with SAH for each day between 2000 and 2015. The incidences of SAH during months of the year were compared using incidence rate ratio (IRR) with corresponding 95% confidence intervals (CIs), calculated by univariate Poisson regression analyses. Furthermore, univariate Poisson regression analyses were used to assess the relationship between SAH and change in atmospheric pressure (maximum—minimum atmospheric pressure per day) and change in temperature (maximum—minimum temperature per day) at the day of SAH and 1 day, 2 days, and 3 days before the ictus. Month of the year, change in atmospheric pressure, and change in temperature were combined in a multivariate Poisson regression analysis to test the independency of the variables. Before these analyses, a log transformation on the change in atmospheric pressure and change in temperature was performed. All analyses were performed for SAH as a group and separately for aneurysmal SAH and nonaneurysmal SAH. A P value <.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, New York, USA).

RESULTS

Patients
In the cohort of 1535 patients, 62% of patients were female and mean age was 56 years.

A symptomatic aneurysm was diagnosed in 1242 patients (Table 1). The mean variation in daily atmospheric pressure over the year was 6.2 hPa; the mean difference in daily temperature over the year was 8.3°C.

Month of the Year
Figure 1 shows the cumulated SAH percentage, both aneurysmal and nonaneurysmal, per month over the period 2000–2015. The lowest SAH percentage occurs in July. When tested in the univariate Poisson regression analysis (Table 2), the IRR of all SAH in July was calculated as 0.89 (95% CI, 0.89–0.89), due to a similar significant association in the subgroup of aneurysmal SAH (IRR, 0.61; 95% CI, 0.45–0.82). For nonaneurysmal SAH, there was no significant difference in incidence among the months of the year.

Atmospheric Pressure and Temperature
Figure 2A shows the total number of SAHs per month, both aneurysmal and nonaneurysmal, plotted with the mean daily atmospheric pressure in the period 2000–2015. The IRRs for the association between SAH and change in atmospheric pressure are shown in Table 3. A 1-hPa change in atmospheric pressure was significantly associated with an increased risk of SAH 2 days later (IRR, 1.11; 95% CI, 1.03–1.19). Also, a change of 1 hPa in the third day before the ictus increases the risk of SAH (IRR, 1.08; 95% CI, 1.01–1.16). Combination of the results of the second and third day before SAH yielded the same significant association. Again, these results were mainly found in the subgroup of aneurysmal SAH.

Figure 2B shows the total number of SAH per month, both aneurysmal and nonaneurysmal, plotted with the mean daily temperature in the period 2000–2015. The IRRs for the
association between SAH and change in temperature are shown in Table 4. A change of 1°C 1 day before the ictus decreases the risk of SAH with an IRR of 0.89 (95% CI, 0.82–0.98). The initial 2 days before the ictus combined yielded a similar significant association between change in temperature and SAH (IRR, 0.86; 95% CI, 0.77–0.97), which once more was a result of the subgroup analysis of aneurysmal SAH. For nonaneurysmal SAH, no significant association between change in temperature and bleeding was found.

Multivariate Poisson Regression
Table 5 presents the result of the multivariate Poisson regression analysis. The IRR of aneurysmal SAH in July remains significantly lower compared with other months (IRR, 0.67; 95% CI, 0.49–0.92). The variation in atmospheric pressure the second and third day before the ictus remained associated with higher incidence of aneurysmal SAH (IRR, 1.11; 95% CI, 1.00–1.23). This association was independent of the month of the year.

DISCUSSION
In this review of a large single-center study of 1535 patients with SAH, we found that a variation in atmospheric pressure provokes the occurrence of aneurysmal SAH 2 and 3 days later. This association was calculated independent of month of the year. Furthermore, we found that there are significantly fewer SAHs in July (which is midsummer in our geographic area). None of these findings was consistent with nonaneurysmal SAH. The unique combined homogeneity of the study region and our detailed database add to the existing literature on SAH and climate.

Atmospheric Pressure and Temperature
We found that a variation in atmospheric pressure significantly increases the risk of aneurysmal SAH 2 and 3 days later. Previous research21,22 showed that decreased atmospheric pressure results in significant inhibition of interleukin-1β, an inflammatory factor which is a key mediator in aneurysm growth. We hypothesize that atmospheric pressure changes trigger the inflammation process in the aneurysm wall, which subsequently increases the risk of rupture 2 and 3 days after the exposure. Although speculative, another explanation is that atmospheric pressure has an effect on blood pressure and venous return, which increases the risk on SAH caused by an augmented pressure on the aneurysm wall.14,17

In our study, an independent association of change in temperature and incidence of SAH was not found, despite many other studies.5,7,9,12,18 Variation in temperature was associated with SAH in a univariate analysis, but combined with month of the year and atmospheric pressure, it disappeared. This finding suggests that temperature changes go along with atmospheric pressure changes. Hence, it is not temperature that influences the aneurysm, but rather atmospheric pressure. Nevertheless, it could be that the temperature variation in our region is too small. In Baltimore, Maryland, USA, steep changes in temperature might explain why there was an association of SAH and temperature in that area.8 Again, a possible effect of temperature

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>All SAH, n = 1535 (100%)</th>
<th>Aneurysmal SAH, n = 1242 (81%)</th>
<th>Nonaneurysmal SAH, n = 293 (19%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>945 (62)</td>
<td>823 (66)</td>
<td>122 (41)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>56 (12.3)</td>
<td>56 (12.4)</td>
<td>57 (11.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>344 (22)</td>
<td>302 (24)</td>
<td>42 (14)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Previous SAH, n (%)</td>
<td>29 (2)</td>
<td>28 (2)</td>
<td>1 (&lt;1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pressure, hPa</td>
<td>1014.8 (9.8)</td>
<td>1015.2 (1008.9–1015.2)</td>
<td>984.2</td>
<td>1048.1</td>
</tr>
<tr>
<td>Change in pressure/day (hPa)</td>
<td>6.2 (4.3)</td>
<td>5.1 (3.1–8.2)</td>
<td>0.7</td>
<td>42.9</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>9.9 (6.3)</td>
<td>10.1 (5.5–14.8)</td>
<td>−19.5</td>
<td>35.4</td>
</tr>
<tr>
<td>Change in temperature/day (°C)</td>
<td>8.3 (3.8)</td>
<td>7.9 (5.3–10.9)</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Frequency of SAH per day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Number of days</td>
<td>4517</td>
<td>1136</td>
<td>177</td>
<td>11</td>
</tr>
</tbody>
</table>

SAH, subarachnoid hemorrhage.
*Group differences were tested with the χ² test.
†Group differences were tested with the 2-sample unpaired t test.
‡Change in pressure = maximum − minimum atmospheric pressure at the day of SAH.
§Change in temperature = maximum − minimum temperature at the day of SAH.

The association between SAH and change in temperature are shown in Table 4. A change of 1°C 1 day before the ictus decreases the risk of SAH with an IRR of 0.89 (95% CI, 0.82–0.98). The initial 2 days before the ictus combined yielded a similar significant association between change in temperature and SAH (IRR, 0.86; 95% CI, 0.77–0.97), which once more was a result of the subgroup analysis of aneurysmal SAH. For nonaneurysmal SAH, no significant association between change in temperature and bleeding was found.
is explained by its effect on blood pressure. Low temperatures induce peripheral vasoconstriction, leading to increased blood pressure.\textsuperscript{9,23}

**Month of the Year**

Consistent with our findings, many other investigators have reported a declined incidence of SAH in the summer.\textsuperscript{9,11,19,24-26} In our analysis, temperature and atmospheric pressure variation could not explain this seasonal difference. In the literature, some other suggestions have been put forward. Lai et al.\textsuperscript{10} suggested that the decrease of SAH in the summer might be mediated by increased exposure to sunlight. Subsequently, Guan et al.\textsuperscript{27} found higher incidence of hypovitaminosis D in their cohort of treated cerebral aneurysms. Vitamin D receptors play an important role in the expression of vascular endothelial growth factor and enzymes that affect the development and remodeling of vessels, such as metalloproteinases. Vitamin D also has antiproliferative effects on smooth muscle cells in the walls of arteries, in addition to potent anti-inflammatory effects.\textsuperscript{28} Lack of vitamin D may induce an inflammatory process in the aneurysm wall that increases the risk of rupture. On the other hand, Feigin et al.\textsuperscript{25} reported an increase of aneurysmal SAH in winter in the southern hemisphere and specifically a decrease in July, which is the month with the second lowest monthly sunshine hours.

Another explanation of the seasonal pattern might be influenza activity.\textsuperscript{14,19} Influenza epidemics occur less in summer than in the other seasons. Also, Backes et al.\textsuperscript{4} showed in a large study an increased incidence of SAH during epidemic influenza, independent of temperature. Influenza is known to trigger multiple inflammatory factors, particularly tumor necrosis factor \(\alpha\), which is an important modulator in the formation and rupture of aneurysms.\textsuperscript{4,13,29,30}

Furthermore, a parameter that has often been studied in SAH is humidity. However, only a few investigators have reported a relationship with the incidence of SAH. Hughes et al.\textsuperscript{9} found that humidity correlates with SAH incidence. It has been suggested that humid environments cause an expansion of plasma blood volume and therefore increase blood pressure and thus the risk of SAH.\textsuperscript{9,31}

Summer vacations often occur in July. However, it is not likely that the catchment population in July decreases significantly, mainly because the Netherlands have a spreading system for the school summer vacations. The dates of the vacation vary each year and are equally spread over July and August, depending on the region of the country. Furthermore, the average age of patients with SAH is 56 years. In general, these people do not

**Figure 1.** Total number of subarachnoid hemorrhages (SAHs), aneurysmal SAHs, and nonaneurysmal SAHs in the period 2000–2015 per month.
depend on school vacations because their children are older. Our northern region is a popular summer destination for the entire country, so the population might shift but does not decrease significantly.

As suggested by Steenhuijsen et al., it would be interesting to have information about seasonal changes in blood pressure because hypertension is a well-known risk factor for SAH. It is possible that summer may induce changes in behavior affecting arterial blood pressure and subsequently SAH.

**Comparison with Other Studies**

Compared with other studies, there are some interesting remarks that may color the interpretation and generalizability of previous studies. In our study, the day of the ictus was taken into account.

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**Table 2. Poisson Regression Analysis Examining the Association Between Month of the Year and the Incidence of Subarachnoid Hemorrhage**

<table>
<thead>
<tr>
<th>Month</th>
<th>All SAH</th>
<th>Aneurysmal SAH</th>
<th>Nonaneurysmal SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>January</td>
<td>1.05</td>
<td>0.83—1.33</td>
<td>0.68</td>
</tr>
<tr>
<td>February</td>
<td>0.98</td>
<td>0.71—1.30</td>
<td>0.26</td>
</tr>
<tr>
<td>March</td>
<td>1.07</td>
<td>0.86—1.36</td>
<td>0.55</td>
</tr>
<tr>
<td>April</td>
<td>0.92</td>
<td>0.72—1.18</td>
<td>0.5</td>
</tr>
<tr>
<td>May</td>
<td>0.88</td>
<td>0.68—1.12</td>
<td>0.29</td>
</tr>
<tr>
<td>June</td>
<td>0.97</td>
<td>0.76—1.23</td>
<td>0.77</td>
</tr>
<tr>
<td>July</td>
<td>0.68</td>
<td>0.53—0.89</td>
<td>0.05</td>
</tr>
<tr>
<td>August</td>
<td>1.02</td>
<td>0.81—1.30</td>
<td>0.86</td>
</tr>
<tr>
<td>September</td>
<td>1.01</td>
<td>0.80—1.28</td>
<td>0.93</td>
</tr>
<tr>
<td>October</td>
<td>0.9</td>
<td>0.71—1.15</td>
<td>0.42</td>
</tr>
<tr>
<td>November</td>
<td>1.13</td>
<td>0.89—1.42</td>
<td>0.32</td>
</tr>
<tr>
<td>December</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Coefficients are represented as IRRs. SAH, subarachnoid hemorrhage; IRR, incidence rate ratio; CI, confidence interval.

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**Figure 2.** (A) Mean daily atmospheric pressure and total subarachnoid hemorrhages in the period 2000–2015 per month. (B) Mean daily temperature and total subarachnoid hemorrhages in the period 2000–2015 per month.
account, whereas in other studies the day of the SAH was not known and the day of presentation in the hospital or the call of the ambulance was analyzed.3,4,7,8 It is known that ictus and presentation at the hospital can differ, especially in milder cases of SAH.

In addition, in previous studies,4,9,10,18 the meteorologic data per week or even per month were used, which makes it difficult to determine a possible association. Because physiologic changes caused by weather changes occur in a short time, increased incidence of rupture would be expected within days. Therefore, our use of detailed meteorologic data for each day over the past 15 years, directly linked to the day of ictus of each patient, is superior.

Furthermore, an important strength of our study is that it was conducted in a homogeneous area for both temperature and pressure. Also, our calculations were based on first-hand data about the ictus (exact time and place) and the local meteorologic details. In contrast, some other studies included patients with SAH with incorrect or unspecified meteorologic data.8,12,32

Limitations
Some limitations of our study also need to be addressed. First, our prospectively collected data were analyzed retrospectively. Furthermore, we were not able to link the possible confounders such as age, gender, and hypertension to the Poisson regression

<table>
<thead>
<tr>
<th>Table 3. Poisson Regression Analysis Examining the Association Between the Log-Transformed Change in Atmospheric Pressure Compared with Previous Days and the Incidence of Subarachnoid Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All SAH</strong></td>
</tr>
<tr>
<td><strong>IRR</strong></td>
</tr>
<tr>
<td>LogΔP*</td>
</tr>
<tr>
<td>LogΔP1</td>
</tr>
<tr>
<td>LogΔP2</td>
</tr>
<tr>
<td>LogΔP3</td>
</tr>
<tr>
<td>LogΔP23</td>
</tr>
</tbody>
</table>

Coefficients are represented as IRRs. SAH, subarachnoid hemorrhage; IRR, incidence rate ratio; CI, confidence interval.

*ΔP = maximum − minimum atmospheric pressure at the day of SAH.
†P1 = 1 day before SAH.
‡P2 = 2 days before SAH.
§P3 = 3 days before SAH.
||P23 = day 2 and day 3 before SAH.

<table>
<thead>
<tr>
<th>Table 4. Poisson Regression Analysis Examining the Association Between the Log Transformation of Change in Temperature and the Incidence of Subarachnoid Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All SAH</strong></td>
</tr>
<tr>
<td><strong>IRR</strong></td>
</tr>
<tr>
<td>LogΔT*</td>
</tr>
<tr>
<td>LogΔT1</td>
</tr>
<tr>
<td>LogΔT2</td>
</tr>
<tr>
<td>LogΔT3</td>
</tr>
<tr>
<td>LogΔT12</td>
</tr>
</tbody>
</table>

Coefficients are represented as IRRs. SAH, subarachnoid hemorrhage; IRR, incidence rate ratio; CI, confidence interval.

*ΔT = maximum − minimum temperature at the day of SAH.
†T1 = 1 day before SAH.
‡T2 = 2 days before SAH.
§T3 = 3 days before SAH.
||T12 = first 2 days before SAH.
analysis. As in many other studies, deaths before presentation in the hospital were not included.

CONCLUSIONS

Atmospheric pressure variations are a delayed trigger for aneurysmal SAH. Also, a significantly decreased incidence of aneurysmal SAH was noted in July, which could not be explained by atmospheric pressure and temperature variations.

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