Trigger Factors and Their Attributable Risk for Rupture of Intracranial Aneurysms

A Case-Crossover Study

Monique H.M. Vlak, MD; Gabriel J.E. Rinkel, MD, PhD; Paut Greebe, RN, PhD; Johanna G. van der Bom, MD, PhD; Ale Algra, MD, PhD

Background and Purpose—Little is known about activities that trigger rupture of an intracranial aneurysm. Knowledge on what triggers aneurysmal rupture increases insight into the pathophysiology and facilitates development of prevention strategies. We therefore aimed to identify and quantify trigger factors for aneurysmal rupture and to gain insight into the pathophysiology.

Methods—During a 3-year period, 250 patients with aneurysmal subarachnoid hemorrhage completed a structured questionnaire regarding exposure to 30 potential trigger factors in the period soon before subarachnoid hemorrhage (hazard period) and for usual frequency and intensity of exposure. We assessed relative risks (RR) of rupture after exposure to triggers with the case-crossover design comparing exposure in the hazard period with the usual frequency of exposure. Additionally, we calculated population-attributable risks.

Results—Eight triggers increased the risk for subarachnoid hemorrhage: coffee consumption (RR, 1.7; 95% CI, 1.2–2.4), cola consumption (RR, 3.4; 95% CI,1.5–7.9), anger (RR, 6.3; 95% CI, 4.6–25), startling (RR, 23.3; 95% CI, 4.2–128), straining for defecation (RR, 7.3; 95% CI, 2.9–19), sexual intercourse (RR, 11.2; 95% CI, 5.3–24), nose blowing (RR, 2.4; 95% CI, 1.3–4.5), and vigorous physical exercise (RR, 2.4; 95% CI, 1.2–4.2). The highest population-attributable risks were found for coffee consumption (10.6%) and vigorous physical exercise (7.9%).

Conclusions—We identified and quantified 8 trigger factors for aneurysmal rupture. All triggers induce a sudden and short increase in blood pressure, which seems a possible common cause for aneurysmal rupture. Some triggers are modifiable, and further studies should assess whether reduction of exposure to these factors or measures preventing sudden increase in blood pressure decrease the risk of rupture in patients known to have an intracranial aneurysm. **(*Stroke*. 2011;42: 1878-1882.)**

Key Words: intracranial aneurysm ■ subarachnoid hemorrhage ■ risk factors ■ rupture ■ stroke prevention

Approximately 2% of the population has an intracranial aneurysm (IA), but only few IA rupture.[1,2] With the increasing use of neuroimaging techniques, more incidental aneurysms are being detected.[3]

The risk of rupture of an IA is composed of "chronic" risk factors, such as being female, age, and hypertension,[4] and "trigger" factors, which cause the actual rupture. Activities such as physical exercise, sexual activity, alcohol use, smoking, emotional stress, and a Valsalva maneuver often precede rupture,[5–8] but the triggering potential of most factors has not been quantified. Only physical exercise has been associated with an elevated risk for aneurysmal rupture.[5,9]

The case-crossover design enables studying the effect of transient exposure to potential trigger factors on the risk of an acute event, such as subarachnoid hemorrhage (SAH), by comparing exposure in a period soon before the event with the patient's usual frequency of exposure.[10] Insight into trigger factors and into the pathophysiology of aneurysmal rupture helps to develop strategies to reduce the risk of rupture. We therefore aimed to identify and quantify trigger factors for rupture of IA and to determine their attributable risks.

Subjects and Methods

Design and Study Population

We performed a case-crossover study among patients with aneurysmal SAH admitted in the Utrecht Stroke Center and who were 18 years of age or older. Informed consent was given by either patient or proxy. Aneurysmal SAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological

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From the Utrecht Stroke Center (M.H.M.V., G.J.E.R., P.G., A.A.), Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, the Netherlands; Julius Center for Health Sciences and Primary Care (M.H.M.V., A.A.), University Medical Center, Utrecht, the Netherlands; Department of Clinical Epidemiology (J.G.v.d.B., A.A.), Leiden University Medical Center, Leiden, the Netherlands.

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Correspondence to Ale Algra, MD, PhD, Department of Neurology and Julius Center, University Medical Center Utrecht, Room STR 7.140, Mailbox STR 6.131, PO Box 85500, 3508 GA Utrecht, the Netherlands. E-mail a.algra@umcutrecht.nl

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signs with subarachnoid blood proven by CT or lumbar puncture and radiologically proven IA. The study protocol was approved by our Medico-Ethical Review Committee.

Few proxies of seriously ill or deceased patients consented to participate and completed the questionnaire. Based on these initial experiences, we decided to only include patients who could complete the questionnaire themselves or with the help of a proxy. We compared medical record notes for activities at the time of onset of SAH (eg, sexual activity, toilet use, sleep, exercise) of patients included in our study and those with aneurysmal SAH who were not included.

Procedures

A structured questionnaire that was used previously in the Stroke Onset Pilot Study was translated into Dutch and adapted for SAH.[11,12] The time of onset of SAH was defined as the time of the symptoms that led to referral. Data were obtained on the activities at onset, demographics, medical and family history, and site of the aneurysm. For all potential trigger factors, patients were asked about exposure in the past year, usual frequency of exposure, and presence of exposure in the "hazard period." The hazard periods were predefined according to the estimated duration of effect of each potential trigger factor: 1 hour for coffee or cola consumption, smoking, Valsalva maneuver, heavy lifting, emotions, sexual activity, temperature change (eg, sauna use or a cold shower), and vigorous to extreme physical exercise (metabolic equivalent of task $\geq$6);[13] 4 hours for cocaine, marijuana, and sildenafil use; and 24 hours for fever, a flu-like disease, and alcohol use. Patients were asked about exposure in the hazard period and for the last time of exposure before onset of SAH to check the consistency of answers about exposure in the hazard period. If answers were inconsistent, then the data of that patient were not used in the main analysis of that particular factor.

If patients were unable to complete the questionnaire during the hospitalization period, then they were asked to bring the completed questionnaire to their first check-up. If patients forgot to bring it, then they received a copy and were asked to return it by postal mail.

Data Analysis

The ratio of the observed exposure frequency in the hazard period (before the onset of SAH) and the expected frequency was used to calculate relative risks (RR) with corresponding 95% CI.[14,15] Expected frequencies were calculated with the usual annual frequency of exposure.

We calculated that assuming a type 1 error of 5%, 80% power, and an exposure in the hazard period of 10% of the population, a sample size of 200 patients would be large enough to calculate RR of 2.2 with sufficient precision. To check the consistency of the results from our main analysis, we performed 4 sensitivity analyses. First, an analysis (sensitivity analysis [SENS] 1) was performed using only the yes-or-no question on exposure in the hazard period and disregarding the question about last time of exposure. Patients who were excluded from the main analysis because of inconsistent answers on exposure in hazard period and last time of exposure were now included. In a second sensitivity analysis, patients with inconsistent data were first assumed to be exposed in the hazard period (SENS2A), and then assumed not to be exposed (SENS2B). Assuming 6 hours of sleep and less exposure to most triggers, an analysis was performed maximizing the number of exposed hours to 18 hours per day, excluding patients whose SAH occurred between midnight and 6:00 AM (SENS3).

Assuming a hazard period of 24 hours for alcohol, patients who drink $\geq$1 glass of alcohol per day are considered to be always exposed. Considering their usual frequency, these patients will often also report exposure in the hazard period. In the case-crossover design, patients who report exposure in the hazard period and are considered always exposed do not contribute to the RR.[16] Therefore, we changed the hazard period for alcohol to 6 hours (SENS4A) and 2 hours (SENS4B). Now, only patients who drink $\geq$4 glasses of alcohol per day (SENS4A) or $\geq$12 glasses of alcohol per day (SENS4B) are considered always exposed and more patients contribute to the RR.

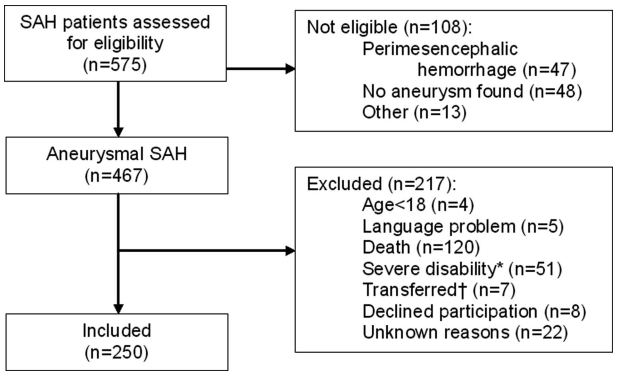

Figure. Flowchart of patient inclusion. SAH indicates subarachnoid hemorrhage. *Critically ill without sufficient recovery for participation. †Transferred to another hospital before being asked to participate.

The fraction of patients with SAH that can be attributed to a particular trigger factor, the population-attributable risk, is calculated as follows: population-attributable risk=prevalence of exposure(RR$-$1)/[prevalence of exposure(RR$-$1)$+$1].[17] The prevalence of exposure for each factor was calculated as the mean number of exposures per year and divided by the annual number of hazard episodes.

Results

The characteristics of the 250 included patients (Figure) are given in Table 1. The activities reported in the medical records were similar for patients who were included in our study and those who were not (data not shown). Fifty percent of the surveys were completed within 3 weeks (range, 1 day–34 weeks).

Table 2 summarizes the exposures and RR for all potential trigger factors. Coffee consumption is used as an example to explain the data presentation in detail; the analysis for all factors was performed in a similar way. For coffee consumption, data were used from 197 patients. Fifty-three patients gave incomplete answers (either on average exposure or the hazard period) or inconsistent data. Of the 197 patients who provided consistent data, 169 patients had consumed coffee in the past year and 28 had not. Using the assumption of a 1-hour exposure period of coffee, none of the 169 patients were all-day drinkers (ie, $\geq$24 cups/day). The risk of rupture of an IA was 1.7-times (95% CI, 1.2–2.4) higher in the hour after drinking a cup of coffee compared with no coffee.

Similarly, we found elevated RR for drinking cola, nose-blowing, straining for defecation, startling, anger, sexual intercourse, and vigorous to extreme physical exercise (metabolic equivalent of task $\geq$6). In contrast, we found a decreased RR for all types of alcohol. The RR essentially did not change when comparing patients who completed the questionnaire before and after 6 weeks (data not shown).

Sensitivity analyses are given in Table 3 and Supplemental Table I (http://stroke.ahajournals.org). In the sensitivity analysis limited to the yes-or-no question on exposure in the hazard period (SENS1), the RR increased for all triggers. In the sensitivity analysis in which patients with inconsistent data were considered exposed (SENS2A) or not exposed (SENS2B) in the hazard period, all factors that were statisti-

Table 1. Baseline Characteristics of the 250 Patients

Characteristic	Patients (n=250)
Men, n (%)	62 (24.8)
Mean age, y	54.7
Time from SAH to survey, n (%)	
<2 wk	80 (32.0)
2–6 wk	68 (27.2)
≥6 wk	102 (40.8)
Site symptomatic aneurysm, n (%)	
Anterior circulation	224 (89.6)
Posterior circulation	26 (10.4)
Cigarette smoking, n (%)	
Never	53 (20.8)
Past	42 (16.8)
Current <20 cigarettes/d	85 (33.6)
Current ≥20 cigarettes/d	70 (28.0)
Alcohol, n (%)§	
0 units/wk	52 (21.6)
1–12 units/wk	143 (59.3)
≥12 units/wk	46 (19.1)
Vigorous physical exercise, n (%)†	
≥3 times/wk	51 (23.2)
<3 times/wk	72 (32.7)
Never	97 (44.1)
Medical history, n (%)	
SAH	5 (2.0)
Hypertension‡	66 (26.6)
Heart disease‡	15 (6.0)
Diabetes‡	6 (2.4)
Positive family history, n (%)	
SAH‡§	12 (4.8)
ADPKD	1 (0.4)

ADPKD indicates autosomal-dominant polycystic kidney disease; SAH, subarachnoid hemorrhage.

*Including anterior cerebral artery, anterior communicating artery, and pericallosal artery.

†Vigorous physical exercise was defined as metabolic equivalent of task ≥6; 12% missing data.

‡<5% missing data.

§At least 1 first-degree relative with SAH.

cally significant in the original analysis remained significant (Supplemental Table I).

When reducing the maximum number of exposed hours per day to 18 hours (SENS3), the RR remained statistically significant, except for liquor consumption and sneezing (Supplemental Table I). The RR of beer, wine, liquor, and all types of alcohol consumption in general remained <1 when the hazard period was 6 hours (SENS4A), but not when it was 2 hours (SENS4B; Table 3).

Population-Attributable Risk

The population-attributable risks associated with trigger factors for SAH are shown in Table 4. Trigger factors that contributed most to ruptures of IA were drinking coffee (10.6%) and physical exercise (7.9%).

Table 2. Relative Risks for Potential Trigger Factors for Rupture of Intracranial Aneurysms

Risk Factors*	Included in Analysis (Always Exposed, Exposed in Hazard Period)	Not Exposed in Past Year	No or Inconsistent Data	RR (95% CI)
Caffeine				
Coffee	169 (0, 48)	28	53	1.7 (1.2–2.4)
Tea	100 (0, 6)	116	34	0.7 (0.3–1.5)
Cola	92 (0, 8)	135	23	3.4 (1.5–7.9)
Alcohol				
All types	128 (78, 64)	52	70	0.2 (0.1–0.2)
Beer	88 (23, 22)	143	19	0.2 (0.1–0.4)
Wine	139 (62, 51)	86	25	0.1 (0.1–0.2)
Liquor	76 (14, 15)	154	20	0.3 (0.1–0.5)
Smoking				
Cigarettes	119 (24, 80)	103	28	1.1 (0.8–1.6)
Cigar	13 (0, 2)	230	7	1.0 (0.2–5.6)
Drugs				
Marijuana	6 (0, 2)	241	3	1.4 (0.4–5.4)
Temperature				
Temperature change	38 (0, 2)	199	13	2.9 (0.6–14)
Flu-like illness	79 (0, 1)	134	37	2.4 (0.3–16)
Valsalva maneuver				
Sneezing	116 (0, 3)	34	100	0.5 (0.2–1.3)
Coughing	88 (0, 7)	55	107	1.4 (0.6–3.3)
Nose-blowing	113 (0, 12)	49	88	2.4 (1.3–4.5)
Straining for defecation	87 (0, 5)	117	46	7.3 (2.9–19)
Lifting >50 kg	23 (0, 0)	209	18	—
Lifting >25 kg	69 (0, 2)	150	43	0.8 (0.2–2.9)
Lifting >12.5 kg	150 (2, 7)	65	56	0.7 (0.4–1.4)
Emotions				
Startling	55 (0, 2)	148	47	23.3 (4.2–128)
Anger	66 (0, 2)	149	35	6.3 (1.6–25)
Sexual activity				
Intercourse	113 (0, 8)	85	52	11.2 (5.3–24)
Masturbation	40 (0, 8)	155	55	5.9 (0.8–42)
Physical exercise				
MET ≥6	115 (0, 11)	88	47	2.4 (1.4–4.2)
MET ≥7	30 (0, 1)	177	43	3.5 (0.5–25)

CI indicates confidence interval; MET, metabolic equivalent of task; RR, relative risk.

*No RR could be calculated for cocaine use, sildenafil use, consumption of Red Bull® (Red Bull GmbH, Santa Monica, CA) energy drink beverage, or fever because no patients were exposed in the hazard period.

Discussion

Our study shows that drinking coffee or cola, nose-blowing, straining for defecation, startling, anger, sexual intercourse, and vigorous to extreme physical exercise were all associated with the triggering of aneurysmal rupture. For drinking coffee, the population-attributable risk was >10%; for all other triggers, it was less.

Table 3. Relative Risks With Hazard Periods of 2, 6, and 24 Hours for Beer, Wine, Liquor, and All Types of Alcohol

	Alcohol Hazard Period		
Risk Factor	24-h RR (95% CI)	6-h RR (95% CI)	2-h RR (95% CI)
All types	0.2 (0.1–0.2)	0.2 (0.1–0.4)	0.9 (0.5–1.6)
Beer	0.2 (0.1–0.4)	0.1 (0.0–0.6)	0.1 (0.0–1.3)
Wine	0.1 (0.1–0.2)	0.4 (0.2–0.6)	1.1 (0.6–2.1)
Liquor	0.3 (0.1–0.5)	0.3 (0.1–0.9)	1.3 (0.4–4.5)

CI indicates confidence interval; RR, relative risk.

Previously, a case-crossover study on trigger factors for SAH showed a 2.7-fold increase in the risk of aneurysmal rupture in the 2 hours after moderate to extreme physical exercise (metabolic equivalent of task ≥5), which is comparable with the RR of 2.4 we found.[9] However, another case-crossover study showed a 15-fold increase of SAH in the minutes after vigorous to extreme exercise (metabolic equivalent of task ≥6).[5] The risk of rupture is possibly the highest in the first 15 minutes and subsides in time thereafter.

A case-control study found an increased risk for SAH in the initial 3 hours after cigarette smoking (odds ratio, 7.0; 95% CI, 3.7–13.1).[6] We found no triggering effect of cigarette use, and neither did another case-crossover study.[9] These contradicting results are probably explained by the difference in design. First, the case-control study used control subjects from the general population, of which only 2% harbor IA and are at risk for SAH.[2] Second, patients with SAH have a different risk factor profile than the general population. There were twice as many subjects who smoked heavily in the SAH population than in the control population. The higher proportion of subjects who smoke in the SAH population 3 hours before SAH compared with the control group may reflect the difference in smoking habits between the 2 populations. In the case-crossover design, there is no bias regarding smoking status because it compares the exposure to smoking in the hazard period with that in a control period for the same patient.

Table 4. Relative Risks, Prevalence, and Population-Attributable Risk Associated With Trigger Factors for Rupture of Intracranial Aneurysms

Risk Factor	RR (95% CI)	% of Population Exposed	Prevalence (%)*	PAR (%)
Coffee	1.7 (1.2–2.4)	88.1	17.5	10.6
Cola	3.4 (1.5–7.9)	42.8	1.5	3.5
Nose-blowing	2.4 (1.3–4.5)	73.7	4.1	5.4
Strain	7.3 (2.9–19)	47.3	0.6	3.6
Startling	23.3 (4.2–128)	29.2	0.1	2.7
Anger	6.3 (1.6–25)	33.5	0.2	1.3
Sexual intercourse	11.2 (5.3–24)	59.1	0.4	4.3
Physical exercise†	2.4 (1.4–4.2)	58.1	6.1	7.9

CI indicates confidence interval; PAR, population-attributable risk; RR, relative risk.

*Percent of the population that is exposed in any given hour.

†Metabolic equivalent of task ≥6.

Immediately after the SAH, patients are seriously ill and a considerable proportion never recovers. Inevitably, this has led to some limitations in our study. First, it has resulted in an interval between the SAH and completion of the questionnaire of >2 weeks for two-thirds of the patients. The retrospective assessment, the time lapse between SAH, and completion of the questionnaire and specifically asking for exposure in a prespecified period may have led to recall bias. Second, the inclusion of patients in relatively good clinical condition could have led to survival bias if certain triggers affect prognosis after SAH. However, we found no significant difference between activities from the medical records of patients who were included in our study and those who were not. Also, a previous study interviewing proxies for patients with poor outcome found no difference in risks after exposure to physical exercise when using patient or proxy-derived data.[9] For other trigger factors, this has not been investigated. A third limitation is the assumption of a 24-hour hazard period for alcohol. Many patients who reported exposure in the hazard period had a daily intake of ≥1 glass per day and therefore did not contribute to the RR in the main analysis. We analyzed the effect of these patients on our primary results by using different hazard periods and found that the risks of alcohol change according to the presumed exposure time. Risks are higher soon after alcohol ingestion and decrease thereafter. A previous case-crossover study also found a decreased risk of aneurysmal rupture during the initial 2 hours after alcohol consumption, although this decrease was not statistically significant.[9] The effects of dosage and time lapse since alcohol intake on acute risk of SAH remain unclear and should be further investigated.

The strengths of our study are the use of the case-crossover design (no control selection bias), the inclusion of patients with a proven aneurysmal SAH (no misclassification bias), and the inclusion of patient-derived data (increasing reliability and completeness of data). The large number of included patients and consistency of the results in the sensitivity analyses support the robustness of our results.

Because blood pressure and intra-arterial pressure are directly related, an increase in blood pressure increases the transmural pressure, which is a risk factor for aneurysmal rupture.[18] Several of the factors we investigated are known to cause a short-lasting and sudden increase in blood pressure.[19–24] Our data support the view that a sudden and short-lasting increase in blood pressure caused by daily activities is a relevant pathophysiological pathway for aneurysmal rupture. Many of the trigger factors we found concern lifestyle, which may have implications for patients with an unruptured IA or for SAH patients awaiting treatment. Reducing caffeine consumption or treating constipated patients with unruptured IA with laxatives may lower the risk of SAH. Although physical exercise has a triggering potential, we do not advise refraining from physical exercise because it is also an important factor in lowering the risk of other cardiovascular diseases.[25] Whether prescribing antihypertensive drugs to patients with unruptured IA is beneficial in

terms of preventing aneurysmal rupture and other cardiovascular diseases should be studied in randomized trials.

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Disclosure

None.

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