

Cardiac Arrhythmias after Subarachnoid Hemorrhage: Risk Factors and Impact on Outcome

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Key Words

Arrhythmia, risk factors · Atrial fibrillation · Subarachnoid hemorrhage · Outcome predictors

Abstract

Objective: Serious cardiac arrhythmias have been described in approximately 5% of patients after subarachnoid hemorrhage (SAH). The aim of this study was to identify the frequency, risk factors and clinical impact of cardiac arrhythmia after SAH. **Methods:** We prospectively studied 580 spontaneous SAH patients and identified risk factors and complications associated with the development of clinically significant arrhythmia. Multiple logistic regression analysis was used to calculate adjusted odds ratios for the effect of arrhythmia on hospital complications and 3-month outcome, as measured by the modified Rankin Scale, after controlling for age, neurological grade, APACHE-2 physiologic subscore, brain herniation and aneurysm size. **Results:** Arrhythmia occurred in 4.3% (n = 25) of patients. Atrial fibrillation and flutter were the most common arrhythmias, occurring in 76% (n = 19) of these patients. Admission predictors of cardiac arrhythmia included older age, history of arrhythmia and ab-

normal admission electrocardiogram (all p < 0.05). After adjusting for length of stay, hospital complications associated with arrhythmia included myocardial ischemia, hyperglycemia, and herniation (all p < 0.05). Arrhythmia was associated with an excess ICU stay of 5 days (p = 0.002). After adjusting for other predictors of outcome, arrhythmia was associated with an increased risk of death (adjusted OR 8.0, 95% confidence interval 1.9–34.0, p = 0.005), and death or severe disability (adjusted OR 6.9, 95% confidence interval 1.5–32.0, p = 0.014). **Conclusions:** Clinically important arrhythmias, most often atrial fibrillation or flutter, occurred in 4% of SAH patients. Arrhythmias are associated with an increased risk of cardiovascular comorbidity, prolonged hospital stay and poor outcome or death after SAH, after adjusting for other predictors of poor outcome. Copyright © 2008 S. Karger AG, Basel

Introduction

Cardiac abnormalities following subarachnoid hemorrhage (SAH) are well described. Electrocardiogram (ECG) changes, including P wave abnormalities, pro-

longed QTc interval, ST segment and T-wave changes, occur in over 50% of patients [1–3], often in the first few days after SAH onset, and are associated with poor neurologic grade on admission [4].

Between 50 and 100% of patients experience cardiac rhythm disturbances during the acute phase of SAH. The majority of these abnormalities are benign, with sinus tachycardia, sinus bradycardia, and premature atrial and ventricular beats being the most common. Only 1–4% of patients experience a clinically significant arrhythmia, such as ventricular tachycardia or atrial tachyarrhythmias [5–10]. Predictors of serious cardiac arrhythmias remain poorly defined, and their impact on clinical outcome is unknown. In this study we sought to identify the prevalence, risk factors, hospital complications associated with arrhythmia and impact on long-term outcome of cardiac arrhythmias after SAH. We hypothesized that, though uncommon, clinically significant arrhythmias are associated with increased hospital complications, prolonged length of stay and worse outcome.

Methods

Patient Population

The Columbia University SAH Outcomes Project prospectively enrolled 580 consecutive patients with spontaneous SAH admitted to the Neurologic Intensive Care Unit between July 1, 1996 and May 1, 2002. The diagnosis of SAH was established on the basis of admission computed tomography (CT) or by xanthochromia of the cerebrospinal fluid. Both aneurysmal and non-aneurysmal cases of spontaneous SAH were included in this analysis. Exclusion criteria included: secondary SAH from trauma, arteriovenous malformation or other causes; age <18 years; admission >14 days after SAH onset, or no ECG available for review.

Clinical Management

The management of SAH patients at our institution has been described in detail previously [11, 12]. Phenytoin was administered for a median of 7 days and levels were checked regularly to maintain a serum concentration between 10 and 20 mg/dl [13]. All patients received 0.9% normal saline at 1 mg/kg/h and supplemental 5% albumen was administered as needed to maintain normovolemia (central venous pressure 5–8 mm Hg). Patients who developed symptomatic vasospasm, defined as neurologic deterioration not explained by other causes, were treated with vasopressors (either phenylephrine or norepinephrine) to maintain a systolic blood pressure between 160 and 220 mm Hg, adjusted to clinical response.

Clinical and Radiographic Assessment

Admission clinical status was evaluated with the Hunt-Hess scale and the Acute Physiology and Chronic Health Evaluation (APACHE)-2 physiologic subscore (calculated by subtracted Glasgow Coma Score from the APACHE-2 score). We defined hy-

potension as a systolic blood pressure ≤ 90 mm Hg, pulmonary edema was defined as the presence of characteristic radiographic infiltrates in the setting of hypoxia, and we considered myocardial infarction/ischemia (MI) to be evidence of cardiac injury (based on ECG, troponin and echocardiographic data judged not to be secondary to neurogenic injury by a study team of physicians in weekly conference). We examined medications, procedures, elevated volume status (defined by central venous pressure ≥ 8 mm Hg, and ≥ 1 liter net volume intake in 24 h prior to arrhythmia onset) and electrolyte levels within 24 h of arrhythmia onset. Abnormal values were defined by our laboratory's lower limit of normal, including a potassium <3.6 mg/dl, magnesium <1.5 mg/dl, phosphorus <2.5 mg/dl and calcium <8.4 mg/dl or ionized calcium <1.12 mg/dl. An abnormal troponin level was defined as >0.2 ng/ml. Total phenytoin levels within 24 h of development of arrhythmia were recorded, as were average phenytoin levels over the course of hospitalization.

Cardiac Monitoring

All patients underwent continuous cardiac rhythm monitoring while in the neuro-ICU. ECGs were routinely obtained at admission and then periodically, as determined by the treating physician. Serial troponin levels and echocardiography were performed when ECGs were abnormal, in patients with a prior history of cardiac disease, or in the setting of cardiovascular symptoms such as chest pain, hypotension, or pulmonary edema. Ejection fraction (EF) was assessed by transthoracic (and/or transesophageal) echocardiography, and was dichotomized as normal (EF $\geq 50\%$) versus abnormal.

Blinded Cardiac Assessment

Serial ECGs for all patients coded with arrhythmia by the treating physician were independently assessed by a board-certified cardiologist (DS), blinded to the clinical characteristics and outcome status of the patient. Patients coded as experiencing an arrhythmia, but who did not have ECGs available for review, were excluded from the present analysis. Admission ECGs and all follow up ECGs were assessed. We defined clinically significant arrhythmia as any rhythm disturbance other than sinus tachycardia, sinus bradycardia, or sinus rhythm with premature atrial or ventricular complexes.

Outcome Measures

Survival and functional outcome was assessed at 3 months using the modified Rankin Scale (mRS; 0 = full recovery, 6 = death); poor outcome was defined as severe disability or death (mRS score 4–6). Median excess ICU and hospital length of stay (LOS) were calculated by comparing the median LOS of patients with arrhythmia to those without.

Statistical Analysis

Continuous variables were dichotomized based on clinical cut-points or median values. The association of arrhythmia with candidate demographic and clinical variables was assessed in a univariate analysis using binary logistic regression. Variables found to be significant on univariate analysis were then entered by hand into a multiple logistic regression model based on clinical relevance of each variable. A multivariate model addressing the association of arrhythmia and in-hospital complications was constructed, adjusting for hospital LOS. Finally, a multivariate mod-

el examining the effect of arrhythmia on 3-month outcome was created, after controlling for other predictors of outcome including age, Hunt-Hess grade, aneurysm size, herniation and APACHE-2 physiologic subscore [11, 14]. Elevated intracranial pressure and low EF did not predict outcome on univariate analysis and were not included in the multivariate model. The variable for clinically significant arrhythmias was added individually to this model to calculate adjusted odds ratios for the strength of association of arrhythmia with 'death' and 'severe disability or death' (mRS 4–6). Tests for interactions were performed for all significant variables in the multivariable models. Significance was set at $p < 0.05$ for all analyses.

Results

Of 580 SAH patients enrolled in our database, 8% ($n = 46$) were coded as having an arrhythmia sometime during their hospital stay. Ten patients did not have ECGs available for review. After excluding patients with sinus bradycardia, sinus tachycardia or sinus rhythm with or without premature ventricular or apical complexes, 4.3% ($n = 25$) of patients in the cohort had a verified clinically significant arrhythmia. Among this group the mean age was 53 years (range 20–89), and 68% were female. The majority of patients underwent aneurysm clipping (81%). The type of aneurysm repair (surgical clipping vs. endovascular coiling) was not associated with an increased risk of arrhythmia. The median number of different arrhythmias per patient was 1 (range 1–4) and the median number of days of arrhythmia per patient was 2.5 (range 1–41). Arrhythmia developed a median of 3 days after SAH onset (range 0–30). The most common type of arrhythmia was atrial fibrillation or flutter (76%) and only 16% of patients experienced a ventricular arrhythmia (table 1).

Admission predictors for arrhythmia were examined (table 2). An abnormal ECG (such as left or right axis deviation, PR segment abnormality, ST segment elevation or depression, T-wave abnormality, QTc prolongation or bundle branch block) at admission was found in 92% of patients who developed an arrhythmia and independently predicted arrhythmia [adjusted OR 9.4, 95% confidence interval (CI) 2.2–40.5, $p = 0.002$]. On the cardiologist's review of admission ECGs among arrhythmia patients, a prolonged QTc >500 ms was seen in 16% of patients, ST segment abnormalities were seen in 67% and T-wave inversion was seen in 25%. Though a cardiac history of coronary artery disease, angina or MI were associated with the development of a clinically significant arrhythmia during hospitalization on univariate analysis, only a history of arrhythmia remained an independent

Table 1. Types of arrhythmia among 25 patients with SAH

Type of arrhythmia	n	%
Atrial fibrillation or atrial flutter	19	76
Junctional rhythm	4	16
Pauses	4	16
Supraventricular tachycardia	3	12
Asystole	3	12
Bigeminy	2	8
Ectopic atrial pacemaker	1	4
Multifocal atrial tachycardia	1	4
Non-sustained ventricular tachycardia	1	4
Sustained ventricular tachycardia	1	4
2nd degree heart block Mobitz I	1	4
2nd degree heart block Mobitz II	1	4
3rd degree heart block	1	4
Torsade de pointes	0	0
Ventricular fibrillation	0	0

predictor on multivariate analysis (adjusted OR 9.1, 95% CI 2.7–30.7, $p < 0.001$). All 5 patients (20%) with a history of arrhythmia had atrial fibrillation in the past, but 2 of these 5 developed other arrhythmias including atrial flutter, second degree heart block and junctional rhythm.

Clinical treatments associated with the development of arrhythmia were recorded. Among those with arrhythmia, 24% received hypertensive, hypervolemia therapy (HHT) to treat symptomatic vasospasm, 48% received an intravenous pressor and 4% received hypertonic saline prior to the time the arrhythmia developed. Twenty percent of patients with arrhythmia were in volume overload at the time of arrhythmia onset (table 3). There was no significant association between the development of arrhythmia and HHT. Mean phenytoin levels were not significantly associated with arrhythmia. The most common electrolyte abnormality was hypokalemia, which occurred in 28% of arrhythmia patients. An elevated troponin or CK-MB occurred in 24% of patients.

Recurrent arrhythmia occurred in 72% of our cohort. Despite treatment, 44% continued to have arrhythmias. The most common arrhythmias to recur were atrial fibrillation or flutter (56%) and ventricular arrhythmias (11%). Treatments included digoxin in 10 patients (40%), diltiazem in 7 patients (28%), metoprolol in 4 patients (16%), amiodarone in 4 patients (16%), procainamide in 1 patient (4%), lidocaine in 1 patient (4%) and atropine in 1 patient (4%).

Several medical complications were significantly associated with arrhythmia after adjusting for hospital

Table 2. Admission risk factors for arrhythmia among SAH patients

	Entire cohort (n = 580)		Arrhythmia group (n = 25)		OR (95% CI)	p
	n	%	n	%		
Demographics						
Age >53 years	300	52	21	84	5.1 (1.7–15.2)	0.003*
Gender (female)	392	68	19	76	1.5 (0.6–3.9)	0.374
Race (non-white)	284	49	6	24	0.3 (0.1–0.8)	0.015
Medical history						
Hypertension	266	46	19	76	5.5 (1.8–16.4)	0.002
Coronary artery disease/angina	31	5	3	12	3.5 (1.0–12.9)	0.057
Arrhythmia	18	3	4	16	9.1 (2.7–30.7)	<0.001*
CHF	12	2	1	4	2.7 (0.3–22.3)	0.351
Myocardial infarction	22	4	3	12	4.9 (1.3–18.4)	0.017
Thyroid dysfunction	32	6	1	4	0.9 (0.1–7.2)	0.946
Admission radiographic data						
SAH sum score ≥ 15	225	38	20	80	5.0 (1.7–14.8)	0.004
IVH present	281	49	19	76	3.9 (1.4–10.5)	0.008
ICH present	96	17	5	20	1.3 (0.5–3.5)	0.650
Aneurysm size ≥ 10 mm	117	20	8	32	2.2 (0.9–5.4)	0.093
Admission clinical data						
Hunt-Hess score	337	58	19	76	1.4 (1.0–1.9)	0.033
Loss of consciousness	224	39	16	64	4.3 (1.7–11.2)	0.003
Seizure at ictus	5	9	9	16	2.4 (0.8–7.4)	0.132
APACHE-2 subscore ≥ 5	303	52	18	72	2.6 (1.0–6.8)	0.045
Abnormal admission ECG	320	55	23	92	9.4 (2.2–40.5)	0.002*

* p value significant on multivariate analysis. CHF = Congestive heart failure; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

LOS, these included hyperglycemia, brainstem compression from herniation and MI (table 4). Of those who developed MI, the mean troponin level was 9.2 ng/ml (range 0–22.2 ng/ml). Three patients with MI had normal transthoracic echocardiography and 3 had mild to moderate reductions in EF with anterior-septal or septal hypokinesis. A transthoracic or transesophageal echocardiogram was performed in 38% of the entire cohort and in 76% of those who developed an arrhythmia. Of those who underwent echocardiography, an EF <50% was seen in 21% of the entire cohort and in 11% of those who developed an arrhythmia. There was no significant association between an EF <50% and arrhythmia (OR 0.4, 95% CI 0.1–1.9, $p = 0.265$). Similarly, EF <50% was not a significant predictor of outcome. Four of the 25 arrhythmia patients (16%) experienced a cardiac arrest at some point during their hospitalization. Though none of the patients who arrested died in the hospital, 3 (75%) were

dead at 3 months and 1 was severely disabled. No patients with arrhythmia experienced renal failure and there was no significant association of arrhythmia with blood stream infection or sepsis. The only neurologic complication associated with arrhythmia was herniation (table 4).

Sixteen of 25 (64%) patients who experienced an arrhythmia were dead at 3 months and 1 was severely disabled. Of all patients with arrhythmia who died, 50% died of direct effects of the initial SAH, 17% died of medical complications (including arrhythmia), 17% died of cerebral edema, 8% died of rebleeding, and 8% died of various other causes. After controlling for age, Hunt-Hess grade, clinical herniation, aneurysm size, and APACHE-2 physiologic subscore, clinically significant arrhythmias remained independently predictive of death (adjusted OR 8.0, 95% CI 1.9–34.0, $p = 0.005$) and severe disability or death (mRS 4–6; adjusted OR 6.9, 95% CI

Table 3. Hospital risk factors among arrhythmia cohort

	n	%
Medications		
Intravenous pressor	12	48
Hypertonic saline	1	4
Elevated total phenytoin level >20 mg/dl	1	4
Diuretic	6	24
Albuterol	4	16
Nicotine patch	1	4
Electrolyte and lab abnormalities		
Potassium <3.6 mg/dl	7	28
Phosphorus <2.5 mg/dl	4	16
Magnesium <1.5 mg/dl	0	0
Calcium <8.4 mg/dl or ionized calcium <1.12 mg/dl	4	16
Elevated troponin or CK-MB	6	24
Volume status		
Central venous pressure ≥8 mm Hg	8	32
>1 liter net volume input in previous 24 h	6	24
Procedures/therapies		
Central line	9	36
Pulmonary artery catheter	2	8
Therapeutic hypothermia	0	0

1.5–32.0, $p = 0.014$) at 3 months (table 5). We examined the effect of subtypes of arrhythmia (i.e. atrial or ventricular arrhythmias) on outcome, but did not find any significant associations.

A significantly longer ICU LOS was associated with the occurrence of a clinically significant arrhythmia. The median ICU LOS in those with arrhythmia was 13 days, compared to 8 days in the patients without arrhythmia ($p = 0.002$); the median hospital LOS in those with arrhythmia was 15 days, compared to 13 days in the patients without arrhythmia ($p = 0.132$).

Discussion

In this inception cohort study we were able to demonstrate that arrhythmia following SAH is associated with a high rate of mortality and predicts poor functional outcome at 3 months, after adjusting for neurological grade and severity of clinical illness (APACHE-2 physiological subscore), age, herniation and aneurysm size. Our study is the first, to our knowledge, to show that clinically sig-

Table 4. Hospital complications associated with arrhythmia, adjusted for hospital length of stay

	Entire cohort		Arrhythmia group		Adjusted OR (95% CI)	Adjusted p
	n	%	n	%		
Medical complication						
Ejection fraction <50%	46	8	3	12	0.4 (0.1–1.9)	0.285
Cardiac arrest	57	10	4	16	2.0 (0.6–6.0)	0.238
Blood stream infection	48	8	3	12	1.4 (0.4–4.8)	0.639
Hypotension ^a	105	18	8	32	2.2 (0.9–5.2)	0.082
Anemia requiring transfusion	209	36	14	56	2.1 (0.9–5.1)	0.099
Fever >38.3°C	310	54	19	76	2.4 (0.8–6.8)	0.089
DVT	23	4	2	8	1.7 (0.4–7.9)	0.502
Hyperglycemia >11.1 mmol/l	174	30	13	52	2.7 (1.2–6.1)	0.020*
MI/Ischemia	35	6	7	28	6.7 (2.6–17.4)	<0.001*
Pulmonary edema	82	14	7	28	2.2 (0.8–5.6)	0.110
Neurologic complication						
Symptomatic vasospasm	95	16	7	28	1.7 (0.7–4.3)	0.269
Herniation	89	15	8	32	3.4 (1.4–8.3)	0.008*
Cerebral infarction	208	36	11	44	1.2 (0.5–2.9)	0.610
Seizures	31	5	2	8	1.3 (0.3–6.0)	0.726
Aneurysm rebleed	58	10	1	8	0.8 (0.2–3.4)	0.732

Adjusted for ICU LOS. MI = Myocardial infarction; DVT = deep vein thrombosis.

* p value significant on multivariate analysis.

^a Defined as sustained systolic blood pressure <90 mm Hg.

Table 5. Adjusted outcomes at 3 months among SAH patients with clinically significant arrhythmia

Outcome at 3 months	Entire cohort		Arrhythmia group		Adjusted OR (95% CI)	Adjusted p
	n	%	n	%		
Dead (mRS 6)	119	21	16	64	8.0 (1.9–34.0)	0.005*
Severely disabled or dead (mRS 4–6)	151	26	17	68	6.9 (1.5–32.0)	0.014*

Outcome adjusted for age, Hunt-Hess grade, aneurysm size, APACHE-2 physiologic subscore and brain herniation. mRS = Modified Rankin Scale.

* p value significant on multivariate analysis.

nificant arrhythmias are predictive of mortality as well as disability after SAH. Previous studies have yielded conflicting results regarding the clinical importance of various cardiac abnormalities after SAH. Tachyarrhythmias and cardiac ischemia have been related to poor outcome after SAH, though this association was less robust after controlling for admission Glasgow Coma Scale score and Fisher grade [1]. While ECG abnormalities were found to predict outcome in another study, this association lost significance when a multivariate model was applied [15]. Similarly, others have not been able to find a significant relationship between ECG abnormalities and outcome after SAH, after controlling for established predictors of poor outcome [4, 16]. Elevated troponin was independently predictive of death or severe disability at 14 days after SAH in one study, but this effect was lost at 3 months [17]. Though 50% of patients who died succumbed to the direct effects of the initial bleeding, 17% died of medical complications, including arrhythmia.

Though some studies have described rates of arrhythmia after SAH of 30% and higher, these studies included patients with sinus bradycardia and tachycardia and premature atrial and ventricular complexes [4, 6]. The rates of clinically significant arrhythmia, as defined in this paper, are similar to those seen in the literature. We observed a higher rate of atrial fibrillation and flutter than has been previously described in other SAH arrhythmia cohorts. While 76% of our group developed atrial fibrillation or flutter, this rhythm was observed in only 10% of SAH patients with arrhythmia in another study [5]. In mixed ICU populations, clinically significant tachyarrhythmias occur in up to 20% of patients overall, with atrial fibrillation occurring most frequently [18]. In our study, recurrent arrhythmias (particularly atrial fibrillation or flutter) were common despite treatment, suggest-

ing that more aggressive management of arrhythmia may be warranted.

Predictors for the development of arrhythmia in our cohort included older age, abnormal ECG at admission and a history of arrhythmia. Though worse neurological grade and APACHE-2 physiologic subscores were significant risk factors for the development of arrhythmia on univariate analysis, this effect was not sustained on multivariate analysis. Arrhythmia does not merely reflect degree of critical illness. Pre-existing cardiac disease was not independently associated with arrhythmia, suggesting that a history of cardiac disease alone does not explain a predisposition to arrhythmia. Risk factors for tachyarrhythmias amongst critically ill surgical ICU patients include sepsis, elevated CVP, acute renal failure, anemia requiring transfusion and poor APACHE-2 scores [18–20]. We were unable to find any of these associations in our neurologically ill SAH patients [19].

Neurologically ill patients differ from general critically ill patients in several ways. Elevated catecholamine levels and hypothalamic dysfunction have been described in SAH patients compared with controls and have been associated with both ECG abnormalities and tachyarrhythmias [21–23]. Hyperglycemia, which can occur in response to an acute catecholamine surge or generalized stress response following neurologic injury was noted to be associated with arrhythmia in our cohort [14, 24, 25]. Some arrhythmias may be related, in part, to HHT therapy used to treat symptomatic vasospasm, as both intravenous pressors and volume expansion, which are known risk factors for supraventricular tachyarrhythmias, were used frequently in the patients who developed arrhythmia. We were unable to detect a significant relationship between HHT and arrhythmia, but this may be due to insufficient power. Though elevated phenytoin levels can

be associated with arrhythmia, we did not observe this association in our cohort.

Interestingly, arrhythmia was significantly associated with brainstem compression from herniation. Increased ICP and physical compression of brainstem and hypothalamic autonomic centers in herniating patients can trigger catecholamine responses that could instigate an arrhythmia.

The ICU LOS was significantly prolonged in patients who developed arrhythmia compared to the rest of the cohort. Though it is not possible to determine whether prolonged LOS predisposed patients to arrhythmia or if arrhythmia itself was causal, the fiscal implications of prolonged LOS are profound.

There are several limitations to this study which should be mentioned. First, we only had echocardiographic data in 38% of our cohort. However, no other studies, to our knowledge, have examined EF and the occurrence of arrhythmia after SAH; as such, we are the first to explore this relationship. We did not have complete time-locked

data on IV pressor or hypertonic saline use in the cohort as a whole, and this limited our ability to compare the effects of these medications in those with arrhythmia and those without. We also did not have complete data on troponin levels.

In summary, although clinically significant arrhythmias are relatively uncommon after SAH, they are associated with a high mortality rate, and serious cardiac and neurological comorbidity. Older patients with a history of arrhythmia or an abnormal ECG on admission should undergo close cardiac monitoring, and the presence of rhythm disturbances should prompt aggressive measures to treat MI, maintain a normal cardiac rhythm and minimize autonomic stress, when present.

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