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Fluctuating Electrocardiographic Changes Predict Poor Outcomes After Acute Subarachnoid Hemorrhage

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Background: Electrocardiogram (ECG) abnormalities following aneurysmal subarachnoid hemorrhage (SAH) have been well documented. Evidence suggests that ECG changes and cardiac dysfunction worsen outcome. Determining which patients are at most risk is unclear but important to ascertain.

Methods: We prospectively studied clinical markers, cardiac abnormalities, and clinical outcomes in 20 patients admitted within 48 hours of aneurysmal SAH. All patients had ECGs prior to surgical clipping, during the clipping surgery, and during the postoperative period.

Results: The aneurysm was located in the anterior circulation in 17 patients (85%) and in the posterior circulation in 3 patients (15%). Abnormal ECG changes in patients with acute SAH were observed, with a total incidence rate of 65%. The incidence of T wave abnormalities was 53.8% among the patients with ECG changes, 46.2% had ST segment change, and 30.8% had QT interval prolongation. Of the 13 patients with ECG changes, 4 (30.8%) had fluctuating ECG abnormalities (an abnormality that presented and disappeared during the study period or changed in character). All 4 patients with fluctuating ECG changes had a poor outcome (100%) compared to 3 of the 9 patients (33.3%) patients with fixed abnormalities ($P<0.05$).

Conclusion: The unique finding in this study that has not been reported previously in the literature is the contribution of dynamic ECG changes to the prognosis for good recovery from aneurysmal SAH. In our group, all the patients who had ECG changes that fluctuated from one abnormal change to another had a poor outcome. The etiology of this finding is not clear but may open the door to further study into the pathogenesis of cardiac changes in aneurysmal SAH. The clinical utility of the variability of ECG abnormalities needs to be validated in a larger cohort of patients with longer follow-up than was possible in this study.

Keywords: *Aneurysm, cardiovascular abnormalities, electrocardiography, mortality, subarachnoid hemorrhage*

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INTRODUCTION

The incidence of subarachnoid hemorrhage (SAH) from intracranial aneurysm is estimated to be 6-28 per 10,000 population.[1] SAH produces significant morbidity and mortality in patients, and only an estimated one-third of patients with SAH will survive functionally. Unique pathophysiologic changes occur after the rupture of an intracranial aneurysm. Although many of these changes occur in the brain, distant effects such as cardiac abnormalities are also commonly seen. Electrocardiogram (ECG) abnormalities, including changes in ST segment and T wave, prolonged QT interval (QTc), and P wave abnormalities, occur in 50%-100% of patients during the acute stage of SAH.[2,3] ECG changes usually occur during the first 42 hours after SAH, but their duration is variable, and ECG usually returns to normal by 6 weeks after the event.[4] Evidence suggests that cardiac dysfunction is an independent risk factor for death and disability in aneurysmal SAH.[5,6]

The ECG changes associated with aneurysmal SAH can be confusing to clinicians because they may be of cardiac origin or neutrally mediated electrophysiologic effects.[7] Ibrahim and Macdonald demonstrated that ECG changes can occur with angiographic vasospasm after SAH.[8] However, Huang et al reported that in patients with SAH, the occurrence of nonspecific ST segment or T wave changes and prolonged QTc assessed early in the

emergency department are independently associated with in-hospital mortality.[9]

Despite the link between poor outcome and cardiac abnormalities, the outcomes of individual patients with cardiac dysfunction are quite variable. We noted that some patients in the operating room had dynamic changes in their ECG during surgical clipping of the cerebral aneurysm. Consequently, we designed this study to prospectively analyze whether these dynamic changes were associated with worse outcomes in patients with aneurysmal SAH. Our hypothesis was that the dynamic changes in the ECG during the perioperative period can predict outcome for patients with aneurysmal SAH.

METHODS

For this prospective observational study, we collected data on 20 adult patients who underwent surgical clipping of a ruptured cerebral aneurysm within 48 hours of SAH. The diagnosis was confirmed by computed tomography scan. Patients with known previous heart disease or history of cardiac arrhythmia were excluded from the study. The study was approved by the human subjects review board (institutional review board) at a tertiary university hospital in Egypt.

Data collected included demographic information and imaging data for aneurysm size. A standard 12-lead ECG was done once daily for the 3 days preoperatively, 2 hours after induction of general anesthesia in the operating room, and 1 day postoperatively. The intraoperative ECG was not done during the critical times of the surgery: induction of anesthesia, skin incision, aneurysm manipulation, or clipping. All patients had continuous ECG monitoring during the study period. We defined an abnormal ECG as a constant change for >30 minutes in at least 2 leads that was not explained by other factors. We excluded brief ECG changes and those related to certain surgical events. To ensure consistency in lead placement for all ECG recordings of the patient during the study period, we marked the skin on each patient's chest. A cardiologist and experienced consultant anesthesiologist interpreted the ECG changes.

ECG abnormalities in acute aneurysmal SAH were classified according to morphology (P wave, Q wave, QRS complex, ST segment, T wave, and U wave); impulse conduction (PR interval, QRS complex, and QT segment); and rhythm (sinus tachycardia, sinus bradycardia, atrioventricular nodal rhythm, atrial premature contractions, atrial flutter or fibrillation, ventricular premature contractions, and ventricular tachycardia or fibrillation). ECG changes were documented if the abnormality was present in at least 2 leads and was consistently noted for 2 hours (intermittent and recurrent changes for 30 minutes were documented as positive).

Clinical severity of the SAH was measured by the Hunt and Hess grading system, with grades 1 and 2 considered good, and grades 3, 4, and 5 considered poor. Aneurysms <12 mm in diameter were categorized as small, those 12-24 mm as large, and those >24 mm as giant.

Neurologic assessment of patients was done according to the Glasgow Coma Scale 3 days preoperatively and 1 day postoperatively.

Information from the blood evaluation for myocardial injury was also collected (creatine kinase and the MB fraction [CK-MB]), as well as blood pressure, heart rate, and central venous pressures. Hypotension was defined as systolic pressure <90 mmHg and diastolic pressure <60 mmHg. Hypertension was defined as 2 consecutive blood pressure readings >160/100 mmHg.

Table 1. Patient Characteristics

Variable	All Patients n=20
Age, years, mean ± SD	47.2 ± 12.8
Weight, kg, mean ± SD	76.85 ± 11.9
Hypertension, n (%)	7 (35%)
Diabetes mellitus, n (%)	2 (10%)
Smoking, n (%)	4 (20%)

Poor outcome was defined as death prior to hospital discharge or discharge to a nursing home. Good outcome was defined as discharge home or to a rehabilitation center.

Statistical analysis was done using a commercially available statistical package (SPSS; IBM). Means and standard deviations are used to describe quantitative data. Categorical data were analyzed using chi-square, Fisher exact test, or Z-test to test the difference between distributions among the study subgroups. For continuous variables, the 2-tailed unpaired *t* test was used to test the significance of the difference between 2 group means, and the 2-tailed paired *t* test was used to test the significance of changes between the preoperative, intraoperative, and postoperative means. *P* values <0.5 were considered significant.

RESULTS

Twenty patients (12 females and 8 males) 18-70 years of age (mean 47.2 ± 12.8 years) with aneurysmal SAH within 48 hours of admission were included in the study (Table 1). Patients were classified into 2 groups according to the presence of ECG abnormalities at any time during the study period. Seven (35%) patients had normal ECGs throughout the entire study, while 13 patients (65%) had some ECG abnormalities during the study period. Seven (53.8%) had T wave abnormalities, 6 (46.2%) had ST segment changes, 4 (30.8%) had QTc segment prolongation, 4 (30.8%) had sinus tachycardia, 3 (23.1%) had U waves present, 3 (23.1%) had sinus bradycardia, 3 (23.1%) had frequent ventricular premature contractions, and 1 patient (7.7%) had a nonspecific change in ECG. Four patients (30.8%) had ECG changes that fluctuated among the preoperative, intraoperative, and postoperative ECG time points (ie, the type of abnormality changed between time points).

There were no significant differences between patients with ECG abnormalities vs patients without ECG abnormalities in age; weight; and history of diabetes mellitus, smoking, and hypertension ($P>0.05$). Baseline imaging showed 17 patients (85%) had aneurysms in the anterior circulation (middle cerebral, posterior communicating artery, or anterior communicating artery), and 3 patients (15%) had posterior circulation artery aneurysms. Fifteen patients (75%) had large or giant aneurysms. Seven patients (35%) had a baseline Hunt and Hess clinical grade of 1, 5 patients (25%) had grade 2, 2 patients (10%) had grade 3, 3 patients

Table 2. Relationship Between Electrocardiogram (ECG) Abnormalities and Aneurysm Size and Clinical Grade

	Patients with Abnormal ECGs n=13	Patients with Normal ECGs n=7	Total
Size of Aneurysm[a]			
Small	2	3	5
Large and giant	11	4	15
Hunt and Hess Grade[b]			
1, 2	6	6	12
3, 4, 5	7	1	8

[a]Aneurysms <12 mm in diameter were categorized as small, those 12-24 mm as large, and those >24 mm as giant.
[b]Clinical severity of the subarachnoid hemorrhage was measured by the Hunt and Hess grading system, with grades 1 and 2 considered good, and grades 3, 4, and 5 considered poor.

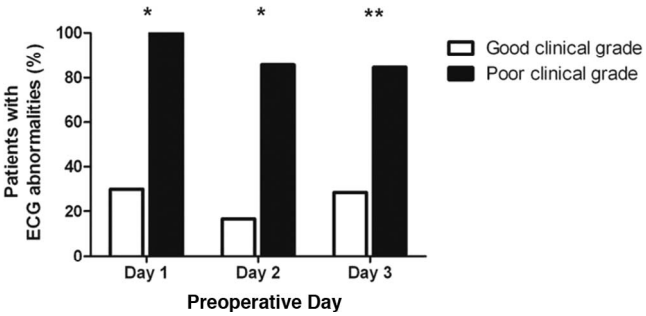

Figure. Percentages of patients with good clinical grade (Hunt and Hess grades 1 and 2) and poor clinical grade (Hunt and Hess grades 3, 4, and 5) aneurysmal subarachnoid hemorrhage who developed electrocardiographic (ECG) abnormalities during the 3-day preoperative period. The differences between groups were statistically significant on all 3 days (*$P<0.01$, **$P<0.05$).

(15%) had grade 4, and 3 patients (15%) had grade 5 (Table 2).

As shown in the Figure, during the 3-day preoperative period, the incidence of ECG abnormalities was higher among patients with poor Hunt and Hess clinical grades than among patients with good clinical grades on the first day of hospitalization (100% vs 30%, respectively; $P<0.01$), on the second day (85.7% vs 16.6%, respectively; $P<0.01$), and on the third day of hospitalization (84.6% vs 28.6%, respectively; $P<0.05$). Postoperatively, no difference was detected in the incidence of ECG changes between patients with low clinical grades and patients with high clinical grades.

The incidence of ECG changes increased in patients who had lower grades on the Glasgow Coma Scale, meaning that neurologic status was worse among patients in the abnormal ECG group compared to patients in the normal ECG group.

We further categorized the patients depending on their score on the Glasgow Coma Scale. Patients in category I had a Glasgow Coma Scale score of 15, while patients in categories II, III, and IV had Glasgow Coma Scale scores <15. All the patients in the normal ECG group were in category I or II; all the patients in categories III and IV had ECG changes.

We compared the incidence of ECG abnormalities between patients in category I and patients in categories II, III, and IV (Table 3). On the first day of hospitalization, the incidence of ECG changes was 30% among patients in category I and 100% among patients in other categories. This difference was statistically significant ($P<0.01$). On the second day of hospitalization, the incidence was 16.6% among patients in category I and 85.7% among patients in the other categories. This difference was also statistically significant ($P<0.01$). On the third day of admission, the incidence was 28.6% among patients in category I and 84.6% among patients in the other categories, and this difference too was statistically significant ($P<0.05$). One day postoperatively, however, the incidence of ECG abnormalities was 60% among patients in category I and 66.6% among patients in the other categories. This difference was not statistically significant ($P>0.05$).

The incidence of CK elevation in patients with abnormal ECGs was 69% compared to 0% in patients without ECG abnormalities ($P<0.05$). The peak elevation occurred 3-4 days after onset of hemorrhage. The mean value of CK-MB was not significantly different in the 2 groups ($P>0.05$).

Patients in the abnormal ECG group were hemodynamically less stable than patients with normal ECGs. Blood pressure was initially elevated in 5 patients (38.5%) with abnormal ECGs compared to 1 patient (14.3%) in the normal ECG group. Hypotension developed in 3 patients in the abnormal ECG group (23.1%). Heart rate and central venous pressure remained within normal range in all patients.

Outcome at the time of discharge was not related to the mere presence of an abnormality on ECG. The incidence of poor outcome was higher in the group with ECG abnormalities, but the trend was not statistically significant ($P>0.05$). The presence of fluctuating ECG changes during the study period was a strong predictor of poor outcome. All 4 patients who had fluctuating ECG changes had a poor outcome (100%) compared to patients who had ECG abnormalities but no fluctuation (33.3%, $P<0.05$) (Table 4).

DISCUSSION

The association of aneurysmal SAH with electrocardiographic abnormalities has been recognized for many years. In their experiments with animals, Offerhaus and van Gool attributed ECG changes and subendocardial lesions similar to those induced by aneurysmal SAH to increased levels of catecholamines.[10] Hawkins and Clower proposed a direct tissue toxic effect of norepinephrine after finding elevated levels of norepinephrine in myocardial tissue post–aneurysmal SAH.[11] On the other hand, Karch and Billingham showed that a contraction band necrosis represents the most likely pathologic substrate of myocardial injury in aneurysmal SAH.[12] Other studies have linked cardiac dysfunction and poor outcome.[5,6] Coghlan and colleagues concluded that bradycardia, relative tachycardia, and nonspecific ST segment and T wave abnormalities are strongly and independently associated with 3-month mortality after SAH.[13]

In our cohort of patients, we found an association between ECG changes and the severity of the injury

Table 3. Percentages of Patients with Electrocardiogram (ECG) Abnormalities According to Glasgow Coma Scale Category

	Incidence of ECG Abnormalities			
	Preoperative Day 1	Preoperative Day 2	Preoperative Day 3	Postoperatively
Category I	30%	16.6%	28.6%	60%
Categories II, III, and IV	100%	85.7%	84.6%	66.6%
P Value	<0.01	<0.01	<0.05	>0.05

Note: Category I includes patients with a Glasgow Coma Scale score of 15. Categories II, III, and IV include patients with a Glasgow Coma Scale score <15.

(assessed by Hunt and Hess grade), premorbid hypertension, and CK elevation although not all associations reached statistical significance. We believe that the myocardial enzyme elevation is not from acute myocardial infarction but rather indicates low-grade myocardial damage caused by sustained sympathetic stimulation from cerebral lesions. This myocardial damage may not influence the wall motion or short-term outcome. In 2012, the VISION[14] team reported the peak postoperative troponin T measurement during the first 3 days after surgery was significantly associated with 30-day mortality. We believe postoperative cardiac enzyme measurements in patients who have ECG changes after SAH can enhance risk stratification after surgery.

The unique finding in this study that has not been reported previously in the literature is the contribution of dynamic changes in the ECG to the prognosis for good recovery from aneurysmal SAH. In our group, all the patients who had ECG changes that fluctuated from one abnormal change to another had a poor outcome. The etiology of this finding is not clear but may open the door to further study into the pathogenesis of cardiac changes in aneurysmal SAH. The animal and human studies to date have implicitly assumed that the injury to the myocardium occurs at the time of the hemorrhage and that the ECG changes we see are the sequelae of this early event. Our study may suggest that injury to the cardiac conduction system may be an ongoing process in some patients, meaning that interventions may be available to counteract the detrimental neurologic changes. Conversely, these data could suggest that the initial injury to the heart is greater in patients who later develop fluctuating ECG findings and have poor outcomes. This finding is not well supported by the literature in myocardial ischemia in which the electric abnormalities are typically monomorphic and localized to the area of infarction. Further study is necessary to determine the mechanisms that lead to fluctuating ECG changes in patients with aneurysmal SAH. In our study, patients with dynamic changes in ECG had worse outcomes than patients with fixed ECG abnormalities. Consequently, we suggest that patients with dynamic changes should be vigilantly followed with continuous ECG monitoring.

It is unclear if and why the period around surgery is important for ECG changes. On the one hand, our study was constructed around the surgical intervention and may only reflect the changes that occur early after SAH. In contrast, surgery could act as a kind of stress test that uncovers autonomic instability after SAH. Also, it is possible that some process around surgery affects some patients and not others irrespective of SAH, although the association with poor outcome would suggest that the association is not trivial.

This study has several limitations. This was an observational study with a small cohort of patients. The advantage of the patient population is that the treatment of the aneurysm was uniform. In current practice, >50% of ruptured aneurysms are treated with coil embolization. In the university hospital where this study was performed, coil embolization was not a treatment option. A second limitation is that outcome was measured at the time of discharge. Follow-up for several months may be needed to confirm outcomes. Unfortunately, follow-up information for this study cohort was not available. The clinical utility of the variability of ECG abnormalities needs to be validated in a larger cohort of patients with longer follow-up.

Table 4. Patient Outcomes

	Patients with Abnormal ECGs n=13		
Outcome	Fixed Change n=9	Fluctuating Change n=4	Patients with Normal ECGs n=7
Poor outcome, n (%)	3 (33.3%)	4 (100%)	1 (14.3)
Good outcome, n (%)	6 (66.7%)	0	6 (85.7%)

ECGs, electrocardiograms.

CONCLUSION

The results of our study suggest that patients with aneurysmal SAH who have fluctuating ECG abnormalities have poor outcomes compared to patients with consistently abnormal ECGs. We believe that elevated cardiac enzymes and fluctuating ECGs after surgery strongly predict poor outcomes for patients after SAH.

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REFERENCES

1. Sacco RL, Wolf PA, Bharucha NE, et al. Subarachnoid and intracerebral hemorrhage: natural history, prognosis, and precursive factors in the Framingham study. *Neurology*. 1984 Jul;34(7):847-854.

2. Salvati M, Cosentino F, Ferrari M, et al. Electrocardiographic changes in subarachnoid hemorrhage secondary to cerebral aneurysm. Report of 70 cases. *Ital J Neurol Sci*. 1992 Jun;13(5): 409-413.
3. Mayer SA, LiMandri G, Sherman D, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. *J Neurosurg*. 1995 Nov;83(5): 889-896.
4. Lanzino G, Kongable GL, Kassell NF. Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 1994 Jul:6(3):156-162.
5. Naidech AM, Kreiter KT, Janjua N, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. *Circulation*. 2005 Nov 1;112(18): 2851-2856.
6. Sakr YL, Lim N, Amaral AC, et al. Relation of ECG changes to neurological outcome in patients with aneurysmal subarachnoid hemorrhage. *Int J Cardiol*. 2004 Sep;96(3):369-373.
7. Liu Q, Ding YH, Zhang JH, Lei H. ECG change of acute subarachnoid hemorrhagic patients. *Acta Neurochir Suppl*. 2011;111:357-359. doi: 10.1007/978-3-7091-0693-8_60.
8. Ibrahim GM, Macdonald RL. Electrocardiographic changes predict angiographic vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2012 Aug;43(8):2102-2107. doi: 10.1161/STROKEAHA.112.658153.
9. Huang CC, Huang CH, Kuo HY, Chan CM, Chen JH, Chen WL. The 12-lead electrocardiogram in patients with subarachnoid hemorrhage: early risk prognostication. *Am J Emerg Med*. 2012 Jun;30(5):732-736. doi: 10.1016/j.ajem.2011.05.003.
10. Offerhaus L, van Gool J. Electrocardiographic changes and tissue catecholamines in experimental subarachnoid hemorrhage. *Cardiovasc Res*. 1969 Oct;3(4):433-440.
11. Hawkins WE, Clower BR. Myocardial damage after head trauma and simulated intracranial hemorrhage in mice: the role of the autonomic nervous system. *Cardiovasc Res*. 1971 Oct;5(4): 524-529.
12. Karch SB, Billingham ME. Myocardial contraction bands revisited. *Hum Pathol*. 1986 Jan;17(1):9-13.
13. Coghlan LA, Hindman BJ, Bayman EO, et al; IHAST Investigators. Independent associations between electrocardiographic abnormalities and outcomes in patients with aneurysmal subarachnoid hemorrhage: findings from the intraoperative hypothermia aneurysm surgery trial. *Stroke*. 2009 Feb;40(2): 412-418. doi: 10.1161/STROKEAHA.108.528778.
14. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012 Jun 6;307(21):2295-2304. doi: 10.1001/jama.2012.5502.

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