Independent Associations Between Electrocardiographic Abnormalities and Outcomes in Patients With Aneurysmal Subarachnoid Hemorrhage

Findings From the Intraoperative Hypothermia Aneurysm Surgery Trial

Landis A. Coghlan, MD; Bradley J. Hindman, MD; Emine O. Bayman, PhD; Nader M. Banki, MD; Adrian W. Gelb, MB, ChB; Michael M. Todd, MD; Jonathan G. Zaroff, MD; IHAST Investigators

Background and Purpose—Electrocardiographic abnormalities are common after subarachnoid hemorrhage, but their significance remains uncertain. The aim of this study was to determine whether any specific electrocardiographic abnormalities are independently associated with adverse neurological outcomes.

Methods—This was a substudy of the Intraoperative Hypothermia Aneurysm Surgery Trial, which was designed to determine whether intraoperative hypothermia would improve neurological outcome in patients with subarachnoid hemorrhage undergoing aneurysm surgery. The outcome was the 3-month Glasgow Outcome Score treated as both a categorical measure (Glasgow Outcome Score 1 [good outcome] to 5 [death]) and dichotomously (mortality/Glasgow Outcome Score 5 versus Glasgow Outcome Score 1 to 4). The predictor variables were preoperative electrocardiographic characteristics, including heart rate, corrected QT interval, and ST- and T-wave abnormalities. Univariate logistic regression was performed to screen for significant electrocardiographic variables, which were then tested for associations with the outcome by multivariate logistic regression adjusting for clinical covariates.

Results—The study included 588 patients, of whom 31 (5%) died. There was a significant, nonlinear association between heart rate and mortality such that lowest quartile (≤60 beats/min; OR, 6.5; P=0.027) and highest quartile (>80 beats/min; OR, 8.8; P=0.006) were associated with higher risk. There was also a significant association between nonspecific ST- and T-wave abnormalities and mortality (OR, 3.1; P=0.031).

Conclusions—Bradycardia, relative tachycardia, and nonspecific ST- and T-wave abnormalities are strongly and independently associated with 3-month mortality after subarachnoid hemorrhage. Further research should be performed to determine whether there is a causal relationship between cardiac dysfunction and neurological outcome after subarachnoid hemorrhage. (Stroke. 2009;40:412-418.)

Key Words: bradycardia ■ electrocardiography ■ subarachnoid hemorrhage

Cardiac injury and dysfunction after subarachnoid hemorrhage (SAH) is a well-recognized phenomenon. In 1954, Burch described “cerebral T-wave” electrocardiographic (ECG) abnormalities in patients with stroke and noted that the findings were most marked in patients with SAH.1 Since then, diverse ECG changes have been described and occur in 25% to 90% of patients with SAH.2–4 Prior studies have described associations between ECG changes and adverse neurological outcomes after SAH, but these studies had limited power and limited ability to statistically adjust for known predictors of poor outcome after SAH.5,6–7 Because patients with more severe SAH are more likely to develop both cardiac abnormalities3,7 and poor neurological outcome,8 it has been unclear whether ECG changes are, in fact, independently associated with outcome.

The aim of this study was to test the hypothesis that ECG abnormalities occurring in patients with preoperative World Federation of Neurological Surgeons (WFNS) Class I to III SAH before surgical aneurysm clipping are independently associated with poor neurological outcome after adjustment for relevant covariates.

Materials and Methods

This was a substudy of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). IHAST was a multicenter, prospective, randomized, partially blinded clinical trial designed to determine whether mild intraoperative systemic hypothermia (33°C) would...
result in improved neurological outcome in patients undergoing surgery to treat ruptured intracranial aneurysms as compared with intraoperative normothermia. Details of trial design, patient eligibility, protocols, and outcomes have been published previously. In brief, adults with SAH and a radiographically confirmed intracranial aneurysm who were scheduled to undergo surgical treatment of the aneurysm within 14 days of SAH were eligible to participate. Other major criteria included a preoperative WFNS class of I, II, or III and the absence of endotracheal intubation at the time of study enrollment. IHAST protocols were approved by the human subjects’ committees at each participating center (n = 30) and written informed consent was obtained from either patients or their families. There were 1001 patients enrolled into IHAST. The study’s main finding was that intraoperative hypothermia did not affect neurological outcome.9

IHAST data collection included patient demographics and pre-SAH medical history. Pre-SAH hypertension was defined as being definitely or probably present. Pre-SAH coronary disease was defined as a history of one or more of the following: myocardial infarction, angina, positive stress test, or coronary revascularization. Information regarding the characteristics of the ruptured aneurysm (location, angiographic diameter) and its immediate effect (extent of subarachnoid blood [Fisher Scale],11 preoperative WFNS class,10 and National Institutes of Health Stroke Scale [NIHSS])12 were recorded before surgery. Posterior circulation aneurysms included vertebrobasilar and posterior inferior cerebellar arteries. Anterior circulation aneurysms included carotid or ophthalmic, posterior communicating, anterior choroidal, carotid bifurcation, carotid (other), middle cerebral, anterior communication, and anterior cerebral (other) arteries.

A final follow-up examination was conducted approximately 3 months after surgery by certified examiners who were unaware of intraoperative temperature management. The primary outcome measure, the 5-point modified Glasgow Outcome Score (GOS),13 was obtained in 1000 patients (1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = vegetative state, 5 = death). All deaths were reviewed and adjudicated as to primary cause by a designated physician blinded to temperature assignment and summarized using International Classification of Diseases, 10th Revision codes.

In IHAST, the occurrence of a large number of defined clinical events was prospectively documented. Examples of cardiovascular and neurological outcomes assessed on a daily basis included: congestive heart failure or pulmonary edema (by clinical assessment or chest x-ray), hypotension (undesired fall in mean arterial pressure ≤60 mm Hg for >15 consecutive minutes [or longer]), vasopressor/inotrope use to support cardiovascular function (continuously administered for >15 consecutive minutes), ventricular arrhythmia (≥3 consecutive wide complex, ≥120 ms, beats at a rate ≥100 beats/min), and cerebral infarction (neurological deficits or the presence of abnormalities on brain images indicating loss of viability).

Electrocardiographic Substudy Protocol

The ECG substudy was designed and implemented in 2001 during ongoing enrollment of IHAST. IHAST protocols did not require a preoperative ECG, although a 12-lead ECG was part of the routine preoperative assessment of the majority of patients. Therefore, IHAST centers were asked to include any preoperative ECGs that were obtained as part of routine care. To increase the likelihood of an association between ECG abnormalities and SAH, an a priori decision was made to include only patients undergoing surgery within 4 days (96 hours) of SAH. Exclusion criteria for this substudy were a pre-SAH history of arrhythmias and the presence of a temporary or permanent pacemaker.

When patients had multiple preoperative ECGs, the ECG obtained closest to the time of SAH was used for analysis. Patient identifiers were removed from the ECGs, which were then analyzed by cardiologists (J.Z., N.B.) at a single site (University of California, San Francisco), who were blinded to temperature group assignments, clinical characteristics, and outcomes. The following measurements were made for each ECG: heart rate (ventricular rate), primary rhythm, QT interval (absolute), and heart rate-corrected QT interval (QTc, Bazett’s formula). Each ECG was also characterized as to the presence of any of 7 predefined morphological abnormalities (Table 1).

To be considered abnormal, a morphological abnormality was required to be present in at least 2 leads within at least one ECG distribution. The inferior distribution included leads II, III, and aVF (augmented vector foot). The lateral distribution included leads I and aVL (augmented vector left). The anterior distribution included leads V1 to V6.

Statistical Methods

To assess the generalizability of the results, we compared the clinical characteristics of the ECG substudy population with those IHAST patients who had surgery ≤4 days after SAH but who did not have a preoperative ECG. We also compared IHAST subjects with surgery ≤4 days versus >5 days after SAH. These comparisons were made using Kruskal-Wallis and χ² tests according to the nature of each variable.

The primary aim was to test for associations between ECG variables and 2 different 3-month outcome measures: (1) GOS as a categorical outcome (1 to 5); and (2) mortality (GOS 5 versus GOS 1 to 4). Prestudy assumptions included a 10% overall study mortality, a 15% incidence of preoperative ECG abnormalities, and a 2.4-fold increased risk of all-cause mortality in patients with preoperative ST/T-wave abnormalities.3 Based on these prestudy assumptions, and an 80% power to detect a difference in all-cause mortality between groups (with ST/T abnormalities versus without ST/T abnormalities), the investigators determined a sample size of 573 ECGs would be required to obtain a statistically significant result (alpha=0.05). The study enrollment of 588 patients met this criterion.

For the primary study analysis, the Step 1 models quantified the univariate associations between the ECG variables and the 2 outcome measures (GOS 1 to 5, mortality) using Fisher exact (FE) test, analysis of variance, and t tests as determined by the nature of each variable. Each of the 7 morphological ECG abnormalities was treated as a dichotomous variable (present or absent). The rate-corrected QT interval (QTc) was used as a continuous variable. Because the relationship between heart rate and the outcomes was observed to be nonlinear by visual inspection and logistic modeling, the ventricular rate was divided into 4 quartiles (<60, 61 to 70, 71 to 80, 81 to 138 beats/min) and treated as a categorical predictor variable.

The Step 2 models used multivariate stepwise selection methods to determine which ECG variables were independent of one another in their associations with the 2 outcome measures. All ECG variables with probability values ≤0.30 were initially included in the models, but probability values <0.10 were required for variables to remain in the models.

The Step 3 models used multivariate stepwise selection methods to determine which ECG variables were independently associated with outcomes after inclusion of relevant clinical covariates. These factors were determined a priori and selected to characterize patient demographics (age, gender), aneurysm characteristics (size, location), severity of SAH (Fisher Scale), and immediate neurological sequelae (preoperative WFNS class, NIHSS [treated as a continuous variable]). Also, because IHAST patients were random-
ized to one of two intraoperative temperatures (normothermia versus hypothermia), this assignment was also included in this analysis. All of the preselected clinical covariates and all ECG variables were tested for inclusion in the final model with a probability value ≤0.30 for initial inclusion and P<0.10 for final retention.

There were complete data for all of the clinical covariates with 2 exceptions. Thirty-four patients had an incomplete NIHSS examination, almost always due to a leg that could not be moved after angiography. For these 34 patients, an imputed NIHSS score was calculated based on the NIHSS items that were present normalized to a maximum score of 42. Two patients had missing values for aneurysm angiographic diameter. An imputed value for aneurysm diameter was obtained by taking the median value of aneurysm diameter of other patients in the ECG study population who were matched for age (±5 years), gender, aneurysm location, preoperative WFNS, NIHSS, and Fisher scores.

The study also included a secondary analysis designed to explore for possible mechanisms underlying associations between the ECG variables and outcomes. For this analysis, additional multivariate models that included clinical covariates were generated using the significant ECG predictors from the primary analysis (heart rate, QTc, nonspecific ST/T-waves) and the predefined cardiovascular and neurological hospital outcomes (see “Methods”).

All statistical analyses were performed on SAS 9.1.3 Service Pack XP_PRO Platform. Logistic regression models reported ORs, 95% CIs, and a probability value <0.05 was considered statistically significant.

**Results**

There were 778 patients who underwent surgery within 4 days of their SAH. The clinical characteristics and outcomes are shown in Table 2 and these did not differ significantly among patients who did (n=588 [76%]) and did not (n=190 [24%]) have preoperative ECGs. The 222 IHAST subjects who had surgery ≥5 days after SAH had lower preoperative WFNS, Fisher, and NIHSS scores in comparison to those subjects having surgery within 4 days. No patients were excluded from the study on the basis on a history of arrhythmia or a pacemaker.

In the ECG subpopulation, 378 (64%) had a good 3-month outcome (GOS 1) and 31 (5%) died. In 23 patients (74%), neurological injury (cerebral infarction, cerebral edema, intracranial hypertension, hydrocephalus, and so on) was the primary cause of death. Of these 23 patients, 2 had fatal anoxic brain injury after resuscitation from cardiac arrest. Of the remaining 8 patients, 2 deaths were due to sepsis and its sequelae, and 6 deaths were primarily on a respiratory basis (including 2 patients with fatal pulmonary emboli). Of the 6 patients dying primarily on a respiratory basis, 3 had coexisting neurological injuries. Therefore, neurological injuries were the primary or contributing cause of death in 26 (84%) of the patients. Bradycardia and hypotension were coded as minor contributors to death in one patient each.

Table 3 summarizes the study’s ECG findings. At least one morphological ECG abnormality was present in 468 patients (80%) and a total of 907 different abnormalities were present. The most common abnormality was nonspecific ST/T-wave changes (NSSTTWA) followed by ST elevation, T-wave inversion, and ST depression. ECG abnormalities were most commonly observed in the anterior leads. There were no significant associations between the number or type of observed ECG abnormalities and either the preoperative WFNS or Fisher class. Compared with a published study of preoperative ECGs in patients undergoing any type of noncardiac surgery (with a mean age of 60 years), the SAH study patients were more likely to have an abnormal ECG (80% versus 25%) and ST depression (7% versus 3%) but less likely to have Q waves (6% versus 10%).

For the primary analysis, the Step 1 models showed that for GOS (1 to 5), ST depression had a significant univariate association with outcome (FE P=0.026), and both NSSTTWA (FE P=0.085) and QTc (analysis of variance P=0.051) had nonsignificant associations. Four ECG variables had significant univariate associations with mortality (GOS 5): NSSTTWA (FE P=0.020), ST depression (FE P=0.047), heart rate (FE P=0.019), and QTc (t test P=0.038).

The Step 2 models, designed to test the independence of the ECG variables from each other (but without inclusion of clinical covariates), showed that for GOS (1 to 5), ST depression (OR, 2.0; CI, 1.2 to 3.5; P=0.011) and QTc (OR, 1.004 per 1-ms increase; CI, 1.000 to 1.009; P=0.043) were significantly associated outcomes and Q/QS waves had a nonsignificant association (OR, 1.7; CI, 0.9 to 3.0; P=0.076). Both NSSTTWA (OR, 3.0; CI, 1.1 to 8.1; P=0.026) and QTc (OR, 1.009 per 1-ms increase; CI, 1.002 to 1.016; P=0.018) were significantly associated with mortality.

The results for the Step 3 GOS (1 to 5) model, that included clinical covariates, are shown in Table 4. Age, preoperative WFNS, posterior aneurysm location, and aneurysm size were significant and independent predictors of GOS score. In this model, there was only a nonsignificant association between QTc and GOS score.

The results for the Step 3 mortality model, that included clinical covariates, are shown in Table 5. Age and preoperative WFNS grade were the only clinical variables that remained in this model. Heart rate had a nonlinear relationship with mortality such that second quartile rates (61 to 70 beats/min) were associated with lowest risk, and both the lowest and highest heart rate quartiles were associated with increased mortality (Figure). There was also a significant association between NSSTTWA and mortality; QTc had a nonsignificant association.

Secondary analyses explored associations between the ECG predictors (heart rate, QTc, and NSSTTWA) and cardiovascular and neurological hospital outcomes. There was a significant association between QTc and postoperative hypotension (OR, 1.011 per 1-ms increase; CI, 1.00 to 1.02; P=0.048), which occurred in 16 (3%) of the ECG study subjects. There was also an association between top quartile heart rates and treatment with vasopressors or inotropes for cardiovascular indications (heart rate >80 versus 61 to 70; OR, 2.5; CI, 1.3 to 5.0; P=0.008). Finally, the presence of NSSTTWA was associated with the use of vasopressors for cardiovascular indications (OR, 2.2; CI, 1.2 to 4.1; P=0.010) and with pulmonary edema (OR, 1.9; CI, 1.0 to 3.5; P=0.043).

**Discussion**

The primary result of this study is that preoperative bradycardia (heart rate ≤60 beats/min), relative tachycardia (heart rate >80 beats/min), and NSSTTWA were associated with increased mortality in patients with SAH treated with surgical aneurysm clipping. These associations were independent of
clinical covariates known to predict outcome after SAH, including age, aneurysm location, Fisher Scale, preoperative WFNS, and NIHSS. In fact, the ORs for these ECG predictors were similar in magnitude to those observed for age and WFNS. It is notable that aneurysm size and location, Fisher Scale, and NIHSS were not significantly associated with mortality, suggesting that the ECG findings may actually have greater prognostic value than many of the more standard clinical measures. There were also nonsignificant associations between increasing QTc and both the categorical GOS and mortality outcomes.

These findings are novel compared with prior reports and are likely attributable to the unique design of this study. Specifically, this is the largest study of this type to date and, in contrast to prior studies, the ECG data were collected prospectively and characterized based on predefined criteria. In addition, the outcomes and adverse events were assessed prospectively. This is the first study to quantify the associa-
lations between ECG findings and clinical outcome after comprehensive adjustment for clinical factors known to affect outcome. The study’s prospective design also allowed for exploration of mechanisms underlying the associations between the ECG variables and clinical outcomes.

The study’s results are clinically relevant and applicable to the majority of patients with mild to moderate SAH (preoperative WFNS Grade 1 to 3). The preoperative presence of bradycardia, relative tachycardia, or NSSTTWA identifies patients at risk of poor outcome, independent of other clinical factors. The study’s secondary analyses suggest that NSSTTWA, relative tachycardia, and a prolonged QTc interval may identify patients who are more likely to have

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1-year increase</td>
<td>1.025 (1.011–1.040)</td>
</tr>
<tr>
<td>WFNS: II versus I</td>
<td>2.4 (1.0–5.5)</td>
</tr>
<tr>
<td>WFNS: III versus I</td>
<td>10.9 (3.5–33.4)</td>
</tr>
<tr>
<td>NSSTTWA</td>
<td>3.1 (1.1–8.6)</td>
</tr>
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<td>QTc per 1-ms increase</td>
<td>1.007 (0.999–1.015)</td>
</tr>
<tr>
<td>HR 81–138 versus 61–70</td>
<td>8.8 (1.8–42.3)</td>
</tr>
</tbody>
</table>

Table 4. Multivariate Predictors of Mortality (GOS 5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1-year increase</td>
<td>1.04 (1.01–1.07)</td>
<td>0.023</td>
</tr>
<tr>
<td>WFNS: II versus I</td>
<td>2.4 (1.0–5.5)</td>
<td>0.048</td>
</tr>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>NSSTTWA</td>
<td>3.1 (1.1–8.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>QTc per 1-ms increase</td>
<td>1.007 (0.999–1.015)</td>
<td>0.095</td>
</tr>
<tr>
<td>HR 71–80 versus 61–70</td>
<td>3.9 (0.8–20.0)</td>
<td>0.104</td>
</tr>
<tr>
<td>HR 81–138 versus 61–70</td>
<td>8.8 (1.8–42.3)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*OR indicates relative odds of mortality.
†Omnibus P value for WFNS <0.001 with 2 degrees of freedom.
‡Heart rate in beats per minute. Omnibus P value for HR = 0.040 with 4 degrees of freedom.

Model c statistic = 0.671.

Table 3. Preoperative ECG Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundamenta rhythm</td>
<td>Normal sinus 421 (72%)</td>
</tr>
<tr>
<td></td>
<td>Sinus bradycardia, &lt;60 124 (21%)</td>
</tr>
<tr>
<td></td>
<td>Sinus tachycardia, ≥100 27 (5%)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation 6 (1%)</td>
</tr>
<tr>
<td></td>
<td>Other supraventricular rhythm 10 (2%)</td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>Mean±SD 72±15</td>
</tr>
<tr>
<td></td>
<td>Median 70</td>
</tr>
<tr>
<td></td>
<td>Quartile ranges 36–60, 61–70, 71–80, 81–138</td>
</tr>
<tr>
<td>QT interval–absolute, msec</td>
<td>Mean±SD 402±49</td>
</tr>
<tr>
<td></td>
<td>Median 397</td>
</tr>
<tr>
<td></td>
<td>Range 264–700</td>
</tr>
<tr>
<td>Corrected QT interval (QTc), msec</td>
<td>Mean±SD 433±39</td>
</tr>
<tr>
<td></td>
<td>Median 427</td>
</tr>
<tr>
<td></td>
<td>Range 350–658</td>
</tr>
<tr>
<td>QTc &gt;440, N (%)</td>
<td>205 (35%)</td>
</tr>
</tbody>
</table>

Table 4. Multivariate Predictors of GOS Score (1 to 5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR* (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
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<td>0.104</td>
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</tbody>
</table>

*OR indicates relative odds of a single category increase (worsening) in GOS score.
†Omnibus P value for WFNS <0.001 with 2 degrees of freedom.
‡Heart rate in beats per minute. Omnibus P value for HR = 0.040 with 4 degrees of freedom.

Model c statistic = 0.671.
On the one hand, patients with SAH that affect heart rate should be reassessed. A prolonged QTc should probably be followed with increased vigilance for the development of cardiovascular instability. It is notable that a prolonged QTc has been shown to be associated with early cardiac morbidity and mortality after ischemic stroke.15 In the present study, 35% of patients had a prolonged QTc (>400 ms).

In this study population, the great majority of deaths were on a neurological basis. The associations between the ECG predictors and the need for vasopressors for cardiovascular indications suggest that there is an important link between cardiovascular performance and neurological outcome after aneurysmal SAH. These findings are consistent with other studies, which have shown that tachycardia, hypotension, and reduced cardiac index are associated with adverse outcome after SAH, possibly by reducing cerebral perfusion pressure during periods of cerebral vasospasm.16,17

The ECG findings may not precede cardiac dysfunction, however. It is possible that tachycardia, bradycardia, and ST- and T-wave abnormalities could be manifestations of neurocardiogenic injury occurring early after SAH. The pathophysiology of neurocardiogenic injury has been well described and appears to be related to excessive cardiac sympathetic stimulation early after brain injury.18–22 In the present study, ECG abnormalities were most commonly observed in the anterior leads, consistent with prior studies that demonstrated that the anterior and anteroseptal walls of the left ventricle are most likely to be affected by neurocardiogenic injury.23,24

Based on the results of this study, therapeutic options for patients with SAH that affect heart rate should be reassessed. On the one hand, β-blockers may be cardioprotective during the period of high sympathetic outflow early after SAH and may limit relative tachycardia. Older clinical trials suggested a beneficial role for β-blockers in the care of patients with SAH.25,26 However, the association between bradycardia and mortality in the present study suggests that excessive heart rate-lowering could be harmful after SAH. Further clinical research in this area is required.

This study does have limitations. Because all of the patients had SAH, the prevalence of ECG abnormalities could not be compared with a control group such as patients admitted to the hospital with other noncardiac conditions. IHAST excluded patients with severe SAH (preoperative WFNS >3) who typically have more neurocardiogenic injury and worse outcomes.8,27 It is unknown how including these patients would have affected the results. The study included only one ECG per patient and recent studies have suggested that serial ECG acquisition is more sensitive in the detection of ECG abnormalities.28

A large number of ECGs in this study had NSSTTWA in comparison to specific repolarization abnormalities such as ST depression or T-wave inversion. Therefore, there was more statistical power to find associations between NSSTTWA and the outcomes in comparison to specific abnormalities, which may be more clinically applicable. There was a nonsignificant association between ST depression and GOS in the multivariate analysis. It is possible but unproven that NSSTTWA, as defined by this study, is a surrogate for any type of repolarization abnormality in predicting adverse outcomes after SAH.

In summary, preoperative bradycardia, relative tachycardia, and NSSTTWA on ECG are independently associated with increased mortality after SAH of mild to moderate severity. These findings add to the growing body of evidence, which indicates that there are important relationships between cardiovascular dysfunction and neurological outcomes after SAH. Further mechanistic and trial-based research is required to determine whether these relationships are causal in nature.

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