Repolarization Abnormalities in Patients with Subarachnoid and Intracerebral Hemorrhage: Predisposing Factors and Association with Outcome

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BACKGROUND: Electrocardiographic (ECG) abnormalities are frequent in patients with intracranial insult. In this study, we evaluated the factors predisposing to the repolarization abnormalities, i.e., prolonged corrected QT (QTc) interval, ischemic-like ECG changes and morphologic end-repolarization abnormalities, and examined the prognostic value of these abnormalities in patients with subarachnoid and intracerebral hemorrhages requiring intensive care.

METHODS: This was a prospective, observational clinical study in a university-level intensive care unit. Clinical characteristics, the level of consciousness, and findings in primary head computed tomography were recorded on admission. The study period was divided into three 2-day sections. In each section, a 12-lead ECG, transthoracic echocardiography, the results of standard blood electrolytes and cardiac troponin I, as well as the rate of vasoactive and sedative drug infusions were recorded. Repolarization abnormalities such as prolongation of the QTc interval (millisecond), ischemic-like ECG changes, and morphologic end-repolarization abnormalities (present/absent) were evaluated and analyzed. The 1-year functional outcome was determined using the Glasgow Outcome Score.

RESULTS: During the 2-year study period, 108 patients were included in the study. Different repolarization abnormalities were frequent in both types of hemorrhage. Prolongation of the QTc interval was predisposed by female gender (β, 24.5; P = 0.010) and the use of propofol (β, 30.5; P = 0.001). The predisposing factor for ischemic-like ECG changes were male gender (odds ratio [OR], 5.9; P = 0.003) and for morphological end-repolarization abnormalities aneurysmatic bleeding (OR, 13.0; P = 0.002). Ischemic-like ECG changes were common, in 87/108 patients during the study period, and were associated with a poorer 1-year functional outcome (OR, 4.7; lower 95% confidence interval, 1.5; P = 0.010).

CONCLUSIONS: Each repolarization abnormality has characteristic predisposing factors. Ischemic-like ECG changes are common and are associated with a poorer 1-year functional outcome. (Anesth Analg 2013;116:190–7)

Electrocardiographic (ECG) changes are frequently seen in patients with intracranial insult.1,12 There are several reports on ECG abnormalities in patients with subarachnoid hemorrhage (SAH)3,4 but only a few in patients with intracerebral hemorrhage (ICH).5,6 Likewise, data on nontraumatic intracranial hemorrhage (SAH, ICH, and intraventricular hemorrhage [IVH]),7,8 as a whole, are scarce, and data considering the effect of repolarization abnormalities on the long-term outcome of these patients are contradictory.4,11–13 Repolarization abnormalities such as a prolongation of the QT interval and changes in the ST segment and T wave morphology are the most common ECG alterations in patients with SAH10 and ICH.9 The mechanisms of these abnormalities are not completely understood, but they are thought to be related to the sympathetic overactivity induced by the intracranial hemorrhage. Injury in the rightsided insular area has particularly been noted to be associated with ECG alterations,2,3,14,15 In addition, female gender and hypokalemia (potentially manifested by the hyperadrenergic state)16 have been reported to be independent risk factors for QT prolongation in patients with SAH.17 An association between QT prolongation and ischemic-like ECG changes with prior coronary artery disease has been reported in patients with ICH.1 On the other hand, there are reports of ECG abnormalities in patients with ICH in the absence of prior heart disease. It is thought that the same mechanisms that act in SAH are also prevalent in these patients.7,8 There are, however, insufficient data concerning...
the type and the incidence of ECG changes and the predisposing factors for ECG alterations in different type of intracranial hemorrhages, nor an association with outcome.

The aim of this study was to evaluate the factors predisposing to repolarization abnormalities, i.e., prolonged corrected QT (QTc) interval, ischemic-like ECG changes, and morphologic end-repolarization abnormalities, and to examine the prognostic value of these abnormalities in SAH and ICH patients requiring intensive care.

METHODS
Patients
This prospective, single-center study was approved by the Ethics Committee of the Oulu University Hospital, and written informed consent was obtained from the patient or a legal surrogate in all cases. This was an observational study of patients admitted to the tertiary level intensive care unit (ICU) over a 2-year period, from December 2007 to December 2009. All patients admitted to the ICU with non-traumatic intracranial hemorrhage during the study period were screened. Exclusion criteria included an intracranial hemorrhage resulting from tumor, arteriovenous malformation, or recent head/neck operation, age <18 years, and an ICU admission delay from hospital admission >48 hours.

Patient characteristics, including age, sex, and medical history, were recorded. The level of consciousness on hospital admission or before sedation was assessed using the Glasgow Coma Score.18 Data considering ICU scores were retrieved from a prospectively collected electronic patient database (Critical Care Information Management System [CCIMS], Clinisoft, GE, Helsinki, Finland), in which the Acute Physiology And Chronic Health Evaluation II score19 is recorded on admission, as is the daily Sequential Organ Failure Assessment score.20

Head computed tomography (CT) scan was performed on admission, and the diagnosis of intracranial hemorrhage was established. SAH and IVH were classified according to the Hijdra SAH CT score,21 and the ICH volume (in milliliters) was calculated (d1 × d2 × d3 [3 perpendicular diameters, d]). Diffuse cerebral edema, acute hydrocephalus, and midline shift were dichotomized as present or absent. The etiology of the hemorrhage was recorded based on the data from head CT scans, CT angiographies, digital subtraction angiographies, and operation and autopsy reports. On the basis of these findings, patients were divided into 2 groups: the SAH/IVHx group included patients with aneurysmatic SAH or IVH and perimesencephalic SAH, whereas the ICH/IVHy group was composed of patients with primary and secondary ICH or IVH.

Clinical Management
During the ICU stay, all patients were treated according to our normal clinical practice, consistent with the latest guidelines.22–24 Patients with aneurysmatic hemorrhage were treated by an endovascular or surgical method in the early phase. IV nimodipine was used, and normovolemic was maintained to minimize the risk for the development of vasospasm. The mean arterial blood pressure was individually targeted from 60 to 80 mm Hg. When intracranial pressure was monitored, the calculated cerebral perfusion pressure (cerebral perfusion pressure = mean arterial blood pressure – intracranial pressure) was generally targeted to be >60 mm Hg. The calibration of the intracranial and arterial pressure transducers was performed at the level of patient’s eye angle, as in our clinical practice. Vasooactive drugs and fluid administration were guided by the patients’ hemodynamics. The blood hematocrit level was maintained >0.30, the blood glucose level was 6.0 to 8.0 mmol/L, and electrolytes were within the normal range. A normothermic body temperature was targeted.

Study Protocol
The study period started on the day of ICU admission (day 0) and lasted 5 days thereafter (days 1–5), unless the patient died or was transferred to another hospital. It was divided into three 2-day sections: T1: days 0 to 1; T2: days 2 to 3; and T3: days 4 to 5. Twelve-lead ECGs and blood samples were taken, and transthoracic echocardiography (TTE) was performed at least once in each section. According to the study protocol and our clinical practice, blood samples (such as cardiac troponin I [cTnI]), magnesium, and glomerulus filtration rate were taken every 6 hours. Levels for potassium <3.5 mmol/L, ionized calcium <0.9 mmol/L, and magnesium <0.70 mmol/L were defined as being decreased. The glomerulus filtration rate was estimated using the Cockcroft–Gault formula (1.15 × [140 Age] × Weight [kg] / P-Krea [mmol / L], × 0.85 in female patients),25 and <60 mL/min was defined as being decreased. cTnI was measured using an immunofluorometric method (Innotrac Aio™, Inntrac Diagnostics OY, Turku, Finland), and a result >0.06 μg/L was defined as being elevated. The use and the rate of vasooactive (norepinephrine, dobutamine, and nimodipine) and sedative (propofol) drug infusions at the time of the ECG were recorded.

The prospectively collected ECGs were retrospectively manually analyzed by 2 observers (EJ and MV) for rhythm, heart rate, PQ interval duration, QRS interval duration and morphology, QT interval duration, ST segment changes, and T and U wave abnormalities. The Sokolow–Lyon criteria were used to identify left ventricular (LV) hypertrophy. The QT interval was measured using the tangent method and corrected (QTc) for heart rate by the Bazett formula. Repolarization abnormalities were defined and analyzed in 3 categories according to the following criteria: (1) prolonged QTc: the maximal QTc >440 ms in male patients and >470 ms in female patients; (2) ischemic-like ECG changes: ST segment elevation and depression ≥0.1 mV in limb leads and ≥0.2 mV in chest leads, inverted (negative) T wave in any lead apart from aVR and V1; and (3) morphologic end-repolarization abnormalities: biphasic, 2-peak or tall T wave or separated U wave ≥0.1 mV.

TTE was performed by 1 of the authors (EJ), and the global LV function was determined by measuring the ejection fraction (EF) of the LV. It was categorized in 3 classes: (1) EF ≥50%; (2) EF 40% to 49%; and (3) EF < 40%. An EF < 50% was defined as global LV dysfunction.
The 1-year functional outcome was assessed using the Glasgow Outcome Score (GOS). Data were collected by telephone interview with the patient or a surrogate by 2 of the authors (EJ and MV) and dichotomized as good (GOS 4–5: no to moderate disability) or poor (GOS 1–3: severe disability, vegetative state, death). Data considering the cause of death were received from the official national database (Statistics Finland, Helsinki, Finland). On the basis of the data, the causes of death were categorized as cardiac and noncardiac. Patients with the decision to withdraw life support (neurologically hopeless prognosis) were recorded.

Statistical Analysis
The SPSS (version 15.0, SPSS Inc., Chicago, IL) and SAS (version 9.2, SAS Institute Inc., Cary, NC) software were used for statistical analysis. Summary measurements were expressed as a mean with SD or as a median with 25th to 75th percentile, unless otherwise stated.

Continuous variables were analyzed using the Student t-test or the Mann–Whitney U test. The χ² test or the Fisher exact test were used for categorical variables.

The analyses of repeatedly measured data were performed to test the possible differences in repolarization abnormalities between the SAH/ICH and ICH/IVH, groups during the study period. Repeatedly measured variables were analyzed by a linear random coefficients model (continuous variables) or by a generalized linear random effects model with Gaussian quadrature for integral approximation (dichotomous variables). In both mixed models, the unstructured covariance pattern was specified for random effects, and the following P-values are reported: \( P_g \) (\( P_{\text{inter}} \)), the overall change over measurement points; \( P_g+ \) (\( P_{\text{group}} \)), the average difference between groups; and \( P_{g+t} \) (\( P_{\text{group}\times\text{time}} \)), group–time interaction, that is, the difference between groups over time. Residual versus predicted value plots were performed to assess the normality of the residuals, and they were reasonably close to normally distributed.

Multivariate linear and logistic regression models were built to identify the predisposing factors for repolarization abnormalities (the length of QTc interval, ischemic-like ECG changes, and morphologic end-repolarization abnormalities) and association with a poorer outcome (GOS 1–3). The variables tested were entered into the model one at a time, and the variables in the final models were chosen based on the \( P \)-value (\( P < 0.05 \)), or the variables affecting the value of coefficient of determination (\( r^2 \)) in the linear regression model (>10% change) and –2x log likelihood functions between 2 subsequent models in logistic regression models (\( P < 0.05 \) according to \( \chi^2 \) test for the difference, with degrees of freedom = 1). Age and gender were used as adjusting factors, and they were left in the model if they were statistically significant. The interaction terms between the variables at the final regression models were created, and each of the interaction terms was found nonsignificant (all \( P > 0.15 \)). The linearity assumption of the continuous variable age in the logistic regression model was evaluated by adding polynomial terms of (centered) age into the model. The variables tested in the regression models for the evaluation of predisposing factors for each repolarization abnormality were demographics, the type and the aneurysmatic etiology of bleeding and the level of consciousness on admission, cTnI elevation and LV dysfunction at the time or before the ECG recording, and electrolyte concentrations and the use of infused drugs (norepinephrine, dobutamine, nimodipine, and propofol) at the time of ECG recording.

Two-tailed \( P \)-values were reported. Due to several dependent analyses performed, the significance level was set to \( P \leq 0.01 \).

RESULTS
During the 2-year study period, 191 patients with nontraumatic intracranial hemorrhage were treated in our ICU, and 108 of these patients were included in the analyses. The flow chart of the study is shown in Figure 1. Sixty-six (61%) patients had an SAH/IVH, type of hemorrhage, and 59 (89%) of the patients were aneurysmatic. An ICH/IVH, type of hemorrhage was diagnosed in 42 (39%) patients, of which 4 had aneurysmatic bleeding without an SAH component, as observed in the primary head CT scan.

Clinical characteristics, data concerning the ICU stay, and neurosurgical interventions are presented in Table 1 and online supplemental Tables S1 and S2, (Supplemental Digital Content 1, http://links.lww.com/AA/A473). Except for better level of consciousness on admission in SAH/IVH, patients, there were no differences in clinical characteristics between the groups.

Figure 1. Flow chart of the study. ICU = intensive care unit; AVM = arteriovenous malformation.
Table 1. Clinical Characteristics According to the Type of Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>SAH/IVH&lt;sub&gt;n = 66&lt;/sub&gt;</th>
<th>ICH/IVH&lt;sub&gt;n = 42&lt;/sub&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>57.3 (11.6)</td>
<td>57.5 (12.2)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>34 (52)</td>
<td>22 (52)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>40 (61)</td>
<td>26 (62)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>26 (39)</td>
<td>15 (36)</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart disease, n (%)</td>
<td>8 (12)</td>
<td>7 (17)</td>
<td>0.5</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Prior medications, n (%)</td>
<td>29 (44)</td>
<td>19 (45)</td>
<td>0.9</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>12 (18)</td>
<td>9 (21)</td>
<td>0.7</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>7 (11)</td>
<td>0</td>
<td>0.041</td>
</tr>
<tr>
<td>Digitalis, n (%)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>0.6</td>
</tr>
<tr>
<td>The level of consciousness on admission, n (%)</td>
<td>19.5 (6.6)</td>
<td>20.9 (6.2)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

SAH = subarachnoidal hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage; GCS = Glasgow Coma Score; APACHE = Acute Physiology And Chronic Health Evaluation.

ECG findings during the study period are presented in Table 2. ECGs were available for review as follows: all 3 in 82 patients, 2 in 23 patients, and 1 in 3 patients. Ninety-eight patients (91%) had normal sinus rhythm in all analyzed ECGs. The heart rate increased, and the duration of the PQ and QRS intervals decreased during the follow-up. The QTc interval was prolonged in at least 1 ECG during the study period in 60 (91%) patients with SAH/IVH, and in 41 (98%) patients with ICH/IVH, (P = 0.2). The frequency and the progression of different repolarization abnormalities were equal between the groups.

The predisposing factors for the repolarization abnormalities are presented in Table 3. Prolongation of the QTc interval was predisposed by female gender (β, 24.5; lower 95% confidence interval [CI], 6.0; P = 0.010) and the use of propofol (β, 30.5; lower 95% CI, 12.2; P = 0.001). The predisposing factor for ischemic-like ECG changes was male gender (odds ratio [OR], 5.9; lower 95% CI, 1.8; P = 0.003), and for morphologic end-repolarization abnormalities, it was aneurysmatic bleeding (OR, 13.0; lower 95% CI, 2.7; P = 0.002). In addition, cTnI elevation may have been a predisposing factor for QTc prolongation and ischemic-like ECG changes, as well as aneurysmatic bleeding for QTc prolongation, but the sample size was too small to determine these findings. There was also an inverse association between nimodipine use and ischemic-like ECG changes, as well as unconsciousness and morphologic end-repolarization abnormalities.

TTE was performed in all patients at time point T1, in which the frequency of global LV dysfunction was the highest: EF ≥50%, 85 (79%); EF 40% to 49%, 17 (16%) and EF < 40%, 6 (6%). Ischemic-like ECG changes were more frequent in patients with global LV dysfunction (18/22 [82%] vs 49/83 [59%]; P = 0.048). The other repolarization abnormalities were not associated with global LV dysfunction (data not shown).

The 1-year GOS is presented in Table 4. The mortality rate was 18% (12/66) in the SAH/IVH group and 29% (12/42) in the ICH/IVH group. Of 17 patients, life support was withdrawn in 16 because of poor neurologic prognosis.

<table>
<thead>
<tr>
<th>Type</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>P&lt;sub&gt;group&lt;/sub&gt;</th>
<th>P&lt;sub&gt;time&lt;/sub&gt;</th>
<th>P&lt;sub&gt;group-time&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm, mean (SD)</td>
<td>SAH/IVH&lt;sub&gt;n = 64&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 41&lt;/sub&gt;</td>
<td>72 (14)</td>
<td>78 (19)</td>
<td>0.37</td>
<td>0.003</td>
</tr>
<tr>
<td>Sinus rhythm, n (%)</td>
<td>SAH/IVH&lt;sub&gt;n = 61&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>71 (16)</td>
<td>74 (14)</td>
<td>77 (16)</td>
<td>0.69</td>
</tr>
<tr>
<td>PQ interval, mean (SD)</td>
<td>SAH/IVH&lt;sub&gt;n = 49&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>148 (29)</td>
<td>140 (26)</td>
<td>138 (22)</td>
<td>0.48</td>
</tr>
<tr>
<td>QRS duration, mean (SD)</td>
<td>SAH/IVH&lt;sub&gt;n = 49&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>153 (36)</td>
<td>146 (33)</td>
<td>144 (31)</td>
<td>0.15</td>
</tr>
<tr>
<td>Normal QRS morphology, n (%)</td>
<td>SAH/IVH&lt;sub&gt;n = 42&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 30&lt;/sub&gt;</td>
<td>62 (97)</td>
<td>59 (97)</td>
<td>58 (98)</td>
<td>0.054</td>
</tr>
<tr>
<td>QTc max, ms, med (25th–75th)</td>
<td>SAH/IVH&lt;sub&gt;n = 49&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>493 (465–536)</td>
<td>470 (434–526)</td>
<td>459 (429–487)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Ischemic-like ECG changes, n (%)</td>
<td>SAH/IVH&lt;sub&gt;n = 49&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>40 (63)</td>
<td>39 (64)</td>
<td>37 (63)</td>
<td>0.73</td>
</tr>
<tr>
<td>MERA, n (%)</td>
<td>SAH/IVH&lt;sub&gt;n = 49&lt;/sub&gt;</td>
<td>ICH/IVH&lt;sub&gt;n = 37&lt;/sub&gt;</td>
<td>44 (69)</td>
<td>54 (89)</td>
<td>49 (83)</td>
<td>0.086</td>
</tr>
</tbody>
</table>

T<sub>1</sub>, days 0–1, ECG n = 105: SAH/IVH<sub>n = 64</sub>, ICH/IVH<sub>n = 41</sub>; T<sub>2</sub>, days 2–3, ECG n = 98: SAH/IVH<sub>n = 61</sub>, ICH/IVH<sub>n = 37</sub>; T<sub>3</sub>, days 4–5, ECG n = 92: SAH/IVH<sub>n = 59</sub>, ICH/IVH<sub>n = 33</sub>.

ECG = electrocardiography; SAH = subarachnoidal hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage; QTc = QT interval corrected by Bazett formula; MERA = Morphological End-repolarization Abnormalities.
during the hospitalization. All these patients died. There was 1 cardiac-caused death in a patient with prior severe coronary artery disease, whose life support was withdrawn because of poor prognosis caused by the severe heart disease, age, and neurologic deficit. Data regarding functional outcome were received from all 84 of the patients surviving the first year after the insult, and it was poorer in patients in the ICH/IVH group. Ischemic-like ECG changes were common in 87 of 108 patients during the study period. These changes were associated with a poorer 1-year functional outcome in the entire study group (OR, 4.7; lower 95% CI, 1.5; P = 0.010) as well as in the nonwithdrawn patients (OR, 8.5; lower 95% CI, 1.7; P = 0.010; Table 5).

**DISCUSSION**

The main findings of this study were given as follows: (1) there were no differences in the frequency, the type, or the progression of different repolarization abnormalities between the SAH/IVH and the ICH/IVH groups; (2) each repolarization abnormality had characteristic predisposing factors; and (3) ischemic-like ECG changes were common and associated with a poorer 1-year functional outcome.

Repolarization abnormalities were equally frequent in the SAH/IVH and the ICH/IVH groups in our study. This supports the argument that they are related to the location and extent of the brain lesion rather than to the exact mechanism of the cerebrovascular insult. On the other hand, there has been a trend from the first reports showing that these abnormalities are more frequent in patients with SAH. One explanation could be the probability of a more severe global brain injury, which was observed in our study with a higher frequency of diffuse brain edema in the SAH/IVH group. Nevertheless, in our study, the only difference between the SAH/IVH and ICH/IVH groups was in the frequencies of morphologic end-repolarization abnormalities, which were slightly more frequent in the SAH/IVH group and predisposed to by aneurysmatic bleeding. The rupture of an aneurysm probably has a specific disruptive effect on the balance of the autonomic nervous system, but comparative studies in patients with different types and etiologies of hemorrhage are lacking.

In this study, the prolongation of the QTc interval reached a maximum within 2 days of the insult and shortened thereafter in both groups. This has been demonstrated in patients with SAH. In contrast, morphologic end-repolarization abnormalities were delayed, being most frequent and prominent 2 to 3 days after the insult. This unique finding indicates that these abnormalities are obviously triggered by the hemorrhage, although the exact mechanism of the progression is unclear.

The lengthening of the QTc interval was predisposed by female gender and the use of propofol. Female gender is associated with prolonged QT intervals in healthy subjects and in patients with SAH, but a novel finding in our study was that propofol lengthened QTc intervals. This could explain the sensitivity of this patient population, with an already prolonged QT interval, to malignant ventricular arrhythmias—1 symptom described in propofol infusion

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**Table 3. Predisposing Factors for Repolarization Abnormalities in Multivariable Linear and Logistic Regression Models Using QTc Interval as a Linear Variable and Ischemic-like ECG Changes and Morphologic End-Repolarization Abnormalities as Binary Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β/odds ratio (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc interval, ms*</td>
<td>Gender, female 24.5 (6.0–43.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>Ischemic-like electocardiograph changes, n = 87 (81%)†</td>
<td>Aneurysmatic bleeding 19.6 (0.92–38.2)</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>Cardiac troponin I &gt;0.06 μg/L 19.9 (0.72–39.0)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>Use of nimodipine 30.5 (12.2–48.8)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Gender, male 5.9 (1.8–18.7)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Cardiac troponin I &gt;0.06 μg/L 3.6 (1.0–12.9)</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>Use of propofol 0.32 (0.11–0.95)</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Aneurysmatic bleeding 13.0 (2.7–63.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>MERA, n = 92 (85%)‡</td>
<td>GCS 13–15 1.0</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>GCS 7–12 0.31 (0.06–1.6)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>GCS 3–6 0.21 (0.05–0.95)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

QTc = QT interval corrected by Bazett formula; ECG = electrocardiographic; MERA = Morphological End-repolarization Abnormalities; GCS = Glasgow Coma Score.

*R² 0.24.

†–2 Log likelihood 89.08.

‡–2 Log likelihood 68.76

*The level of consciousness on admission, compared with those with GCS 13–15.

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**Table 4. 1-Year Functional Outcome Defined by Glasgow Outcome Score, Categorization of Death in Nonsurviving Patients and Withdrawn Decisions According to the Type of Hemorrhage**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SAH/IVH</th>
<th>ICH/IVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>39 (59)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>5 (good recovery)</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>4 (moderate disability)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Poor</td>
<td>27 (41)</td>
<td>29 (69)</td>
</tr>
<tr>
<td>3 (severe disability)</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>2 (vegetative state)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1 (dead)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Withdrawn*</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

GOS = Glasgow Outcome Score; SAH = subarachnoidal hemorrhage; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage.

*All withdrawn patients died.
syndrome. We did not, however, find any correlation between the duration of the QTc interval and the rate of propofol infusion (data not shown). Although the association between QTc prolongation and ventricular arrhythmias were not noted in patients with SAH, propofol should be used cautiously with moderate infusion rates. In addition, the QT interval should be monitored frequently in patients with intracranial hemorrhage and prolonged QTc interval based on data regarding patients with long QT syndrome, case reports in patients with propofol-related infusion syndrome, and the present results.

The frequency of the ischemic-like ECG changes did not depend on the type of hemorrhage. In our study, ischemic-like ECG changes were associated with an elevation in cTnI levels in a logistic regression model. In addition, an association with global LV dysfunction was noted. These findings indicate that ischemic-like ECG changes may be caused by myocardial injury. Our findings are supported by the recent findings by Hasegawa et al. in patients with ICH. In their study, ECGs were only analyzed on arrival, which may have caused an underestimation of these abnormalities, as seen in the lower rates of these abnormalities compared with ours. It was also notable that the intracranial insult was more severe (lower Glasgow Coma Scores on admission and larger ICH volumes) in the patients in our study.

Myocardial injury after intracranial insult is supposed to be multifactorial caused by the direct cardiac toxicity of nor-epinephrine released from intracardiac nerve endings, systemic hyperadrenergic state, and coronary vasospasm. The histopathology of myocardial necrosis is called coagulative myocytolysis and is characterized by an excessive calcium influx and early myocyte calcification. Interestingly in this study, we noted that nimodipine use was inversely associated with ischemic-like ECG changes. Theoretically, this could be explained by the vasodilating effects of nimodipine on coronaries as well as on the cerebral arteries and/or by the inhibition of excessive calcium influx into the myocytes. This, however, needs further evaluation for confirmation.

Morphologic end-repolarization abnormalities were observed less frequently among patients who were unconscious on admission. This could be explained by the need for sedation, intubation, and mechanical ventilation in these patients, which may have protected the heart by depressing the hemorrhage-induced sympathetic storm. This supports previous findings demonstrating that sympathomimetic stimulation especially causes detectable changes in the ECG during end-repolarization.

We demonstrated that ischemic-like ECG changes were associated with a poorer 1-year functional outcome, which supports the findings by Coghlan et al., although the patients studied had aneurysmatic SAHs with a shorter follow-up time of 3 months. The results in the meta-analysis performed by van der Bilt et al. from the same patient population also agree with ours. In some studies, cTnI elevation has been reported to be associated with a poor outcome. In our study, cTnI was not related to a poor outcome; instead, cTnI elevation was associated with ischemic-like ECG changes. In summary, according to our study results with only 1 cardiac-caused death, the myocardial injury and dysfunction after intracranial bleeding, presenting as ischemic-like ECG changes, are rarely fatal. Instead, as demonstrated in our study, ischemic-like ECG changes are associated with impaired functional outcome. Therefore, early detection of these manifestations and evaluation of the need for supportive therapy are essential. The cardioprotective effects of β-blockers have been demonstrated in SAH patients, which is also theoretically reasonable for the catecholamine-induced nature of cardiac manifestations. In practice, however, these patients often need exogenous vasopressors for hypotension or even inotropic drugs for cardiac failure, and the use of β-blockers is questionable in these situations.

The main limitation of the present study was that only patients with severe ICH requiring neurosurgical interventions or support of vital functions (e.g., mechanical ventilation and hemodynamic support) were included in the study. According to previous studies in patients with SAH, these patients often have the most severe cardiovascular disorders, but one needs to be cautious when extrapolating the results to a population with a less severe ICH. Second, patients with impaired renal function were included in the study, which may have affected the results regarding cTnI elevation. The effects of the ECG findings are, however, supposed to be minor, and troponin elevation has been noted to be valuable in predicting cardiac events, even in patients with renal failure. Third, the categorization of hemorrhages into 2 classes (SAH/IVH, and ICH/IVH) did not consider the effect of IVH on the outcome. It was, however, tested in the logistic regression models as an isolated dichotomous variable and did not achieve statistical significance. In addition, the sample size of this study was quite small, and the categorization of patients into >2 groups was not reasonable. Last, there were some missing data in this study, caused mainly by practical and logistical reasons (4 patients died, 3 patients were withdrawn, and 7 patients were transferred to another hospital during days 0 to 5 after ICU admission).
In conclusion, different repolarization abnormalities were frequent in both the SAH/IVH and ICH/IVH groups, without differences in the type and progression of these abnormalities. The predisposing factors for QTc prolongation were female gender and the use of propofol, whereas male gender predisposed ischemic-like ECG changes. Morphologic end-repolarization abnormalities were predisposed by aneurysm rupture. In different repolarization abnormalities, only ischemic-like ECG changes were associated with a poorer 1-year functional outcome.

DISCLOSURES
Name: Eija Junttila, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Eija Junttila has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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REFERENCES


