Electrocardiographic Changes Predict Angiographic Vasospasm After Aneurysmal Subarachnoid Hemorrhage

George M. Ibrahim, MD; R. Loch Macdonald, MD, PhD

Background and Purpose—Early identification of patients at risk of angiographic vasospasm after aneurysmal subarachnoid hemorrhage (SAH) may mitigate its sequelae. One mechanism that may contribute to angiographic vasospasm is increased central sympathetic activity, which is also thought to cause electrocardiographic (ECG) changes after SAH. Here, we perform the first study to determine the association between ECG changes and angiographic vasospasm after SAH.

Methods—Exploratory analysis was performed on 413 patients from CONSCIOUS-1, a prospective randomized trial of clazosentan for the prevention of angiographic vasospasm. ECGs were obtained within 24 hours of aneurysm rupture and during the vasospasm risk period. Angiographic vasospasm was assessed using catheter angiography at baseline and 7 to 11 days after SAH. Multivariate logistic regression was used to identify significant associations.

Results—The most prevalent finding on ECG both immediately following SAH and during the vasospasm risk period was QT prolongation (42% and 25%, respectively). A prolonged QT interval and tachycardia on the baseline ECG were associated with angiographic vasospasm (OR, 1.86; 95% CI, 1.00–3.45; and OR, 10.83; 95% CI, 1.17–100.50, respectively). QT prolongation on ECG during the vasospasm risk period was also associated with angiographic vasospasm (OR, 3.53; 95% CI, 1.67–7.39). No ECG findings were associated with delayed ischemic neurological deficit, but tachycardia and ST changes were associated with worse clinical outcome.

Conclusions—QT prolongation and tachycardia on ECG were independently associated with angiographic vasospasm after aneurysmal SAH on multivariate analysis.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00111085.

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Key Words: subarachnoid hemorrhage ■ electrocardiography ■ vasospasm ■ angiography ■ neurogenic stunned myocardium
sured by the modified Rankin Scale score, were also correlated with ECG changes.

Methods

Study Population
We conducted a post hoc analysis of 413 subjects enrolled between January 2005 and March 2006 onto CONSCIOUS-1, a prospective, randomized, double-blinded phase IIIB trial evaluating the efficacy of clazosentan in preventing angiographic vasospasm.7 The methods and results have been published.7

Clinical Assessment
All patients with computed-tomography-confirmed SAH were admitted to the respective neurological units and underwent microsurgical clipping or endovascular coiling as deemed appropriate by the treating physician. The severity of the subjects’ presenting symptoms was classified based on the World Federation of Neurosurgical Societies (WFNS) scale.8 All subjects were monitored for development of DIND, which was defined as neurological worsening of ≥2 points on the modified Glasgow Coma Scale, or an increase of ≥2 points in the abbreviated National Institutes of Health Stroke Scale lasting >2 hours.9 At 12 weeks postSAH, the subjects’ modified Rankin Scale score was calculated with poor clinical outcome, which was defined as outcomes worse than moderate disability.10

Electrocardiography
An ECG was obtained for all patients within 24 hours of aneurysm rupture and during the time of risk of angiographic vasospasm, defined as 7 to 11 days following SAH. For this analysis, we included also ECG performed 4 to 7 days after SAH. The frequency of abnormal findings on ECG in rate, rhythm, ST-segment, intervals, and T-waves was reported based on these ECG recordings, not on continuous ECG recording. Tachycardia was defined as a heart rate of >100 beats/minute, and bradycardia as <60 beats/minute. ST-segment elevation and depression were defined as deviations of 1 mm above and below the baseline, respectively. The frequency of nonspecific ST-changes was also documented. A QT interval, corrected for heart rate >410 ms and a QRS interval >100 ms were considered abnormal, respectively. All ECGs were interpreted by the treating physicians.

Serum Potassium
As serum potassium has been previously reported as an independent risk factor for ECG changes following SAH,11 we incorporated the electrolyte levels on presentation in the statistical models that included baseline ECG changes. Hypokalemia and hyperkalemia were defined as potassium levels <3.2 mmol/L and >5.5 mmol/L, respectively. The mean time between SAH ictus and bloodwork was 23.5 ± 18.2 hours.

Radiology
All patients underwent catheter angiography within 48 hours of aneurysm rupture, and then at 7 to 11 days postSAH. Angiographic vasospasm was determined by the percentage of change in arterial diameter between baseline and follow-up angiograms as follows: none (0%–25%), mild (26%–50%), moderate (51%–75%), and severe (76%–100%). Computed tomography scans were performed at baseline, 24 to 48 hours after the aneurysm-securing procedure, 6 weeks postaneurysmal rupture, and again as deemed necessary by the treating physicians. The extent of SAH was quantified using the Hijdra scale, which evaluates the amount of clot in 10 fissures and cisterns.12 All images were reviewed centrally by 2 independent, blinded reviewers with adjudication of disagreements on angiographic vasospasm.
proportion of patients with bradycardia decreased since the baseline ECG (P=0.07). When ECG abnormalities were analyzed by aneurysm location, there was a trend toward greater frequency of nodal rhythms in patients with anterior circulation aneurysms compared with posterior circulation (P=0.07). No other associations between ECG abnormalities and aneurysm location were identified.

### Angiographic Vasospasm

In the binary logistic regression model, variables that were found to be significantly associated with mild, moderate, or severe angiographic vasospasm (Table 3) were female sex (OR, 2.32; 95% CI, 1.27–4.23), high subarachnoid clot burden (OR, 2.41; 95% CI, 1.39–4.19), WFNS grade 4–5 (OR, 3.15; 95% CI, 1.57–6.33), clipping versus coiling (OR, 2.32; 95% CI, 1.27–4.23), WFNS grade 4–5 (OR, 2.41; 95% CI, 1.39–4.19), high subarachnoid clot burden, and clipping versus coiling.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline ECG (%)</th>
<th>ECG During Vasospasm Risk Period (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia (HR &gt;100 beats/min)</td>
<td>9 (4)</td>
<td>24 (10)</td>
<td>0.53</td>
</tr>
<tr>
<td>Bradycardia (HR&lt;60 beats/min)</td>
<td>44 (17)</td>
<td>25 (10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal</td>
<td>12 (6)</td>
<td>14 (6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td>0.80</td>
</tr>
<tr>
<td>ST Segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspecific changes</td>
<td>24 (9)</td>
<td>37 (15)</td>
<td>0.59</td>
</tr>
<tr>
<td>Depression</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Elevation</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Intervals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT</td>
<td>106 (42)</td>
<td>62 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Widened QRS</td>
<td>9 (4)</td>
<td>8 (3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Inverted T-waves</td>
<td>12 (5)</td>
<td>10 (4)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

### Delays Ischemic Neurological Deficit

There were no findings on ECGs that independently predicted DIND (Table 4). The most significant predictor of DIND was the presence of mild, moderate, or severe angiographic vasospasm (OR, 69.87; 95% CI, 9.14–534.27). Higher WFNS score (OR, 2.58; 95% CI, 1.11–5.99) and higher subarachnoid clot burden (OR, 2.63; 95% CI, 1.11–6.22) were also predictive of DIND.

### Clinical Outcome

Factors associated with poor clinical outcome on multivariate analysis (Table 5) included WFNS grades 4 or 5 (OR, 4.80; 95% CI, 2.32–9.92), as well as angiographic vasospasm (OR, 2.19; 95% CI, 1.02–4.71) and DIND (OR, 4.13; 95% CI, 1.81–9.40). Tachycardia and ST changes on ECG during the vasospasm risk period predicted poor outcome (OR, 2.82; 95% CI, 1.09–7.34; and OR, 2.90; 95% CI, 1.23–6.82, respectively).
nerve fibers mainly originating in the superior cervical ganglion.15,16 Although the pathogenesis of vasospasm is complex and only partially understood, there is evidence to suggest that sympathetic hyperactivity is 1 mechanism contributing to this phenomenon. In 1 study, patients with symptomatic cerebral vasospasm showed improvements in cerebral perfusion following ipsilateral locoregional cervical sympathetic block.8 Furthermore, Yasargil performed surgical ablation of periadventitial sympathetic fibers, resulting in chronic denervation during craniotomy for ruptured aneurysms, and reported low rates of angiographic vasospasm.17 It follows, therefore, that ECG manifestation of increased central activity, such as depolarization abnormalities, may serve as surrogate markers of cerebrovascular vasospasm. Interestingly, despite improvements in perfusion in the aforementioned study, proximal vessel caliber did not increase following sympathetic nerve fibers mainly originating in the superior cervical ganglion.15,16 Although the pathogenesis of vasospasm is complex and only partially understood, there is evidence to suggest that sympathetic hyperactivity is 1 mechanism contributing to this phenomenon. In 1 study, patients with symptomatic cerebral vasospasm showed improvements in cerebral perfusion following ipsilateral locoregional cervical sympathetic block.8 Furthermore, Yasargil performed surgical ablation of periadventitial sympathetic fibers, resulting in chronic denervation during craniotomy for ruptured aneurysms, and reported low rates of angiographic vasospasm.17 It follows, therefore, that ECG manifestation of increased central activity, such as depolarization abnormalities, may serve as surrogate markers of cerebrovascular vasospasm. Interestingly, despite improvements in perfusion in the aforementioned study, proximal vessel caliber did not increase following sympathetic
The finding that QT prolongation is the most prevalent ECG finding after SAH is in keeping with published series. Prospective studies have previously concluded that ECG changes are mainly seen in the early stages; however, we show that the proportion of certain findings (tachycardia and nonspecific ST-changes) actually increase in interval between baseline and the vasospasm risk period. In our multivariate model, we included numerous variables that have been previously linked to ECG changes after SAH following a thorough literature review, including sex and aneurysm location.

Previous studies have linked various ECG findings to poor outcomes on multivariate analysis, including cardiac arrhythmias (prevalence of approximately 4% in 1 series). Other ECG findings linked to poor outcome include bradycardia, relative tachycardia, and ST- and T- wave abnormalities. One observational study identified a tilt toward depressed sympathovagal balance, as determined by heart rate variability, as a contributor to poor outcome after SAH. To our knowledge, only 1 previous study identified the QT interval as an independent predictor of in-hospital mortality; however, as the investigators did not account for vasospasm or DIND, it is difficult to know whether patients with QT interval were less likely to survive because of symptomatic vasospasm and DIND. In contrast, another previous study corroborated our results that QT prolongation is not associated with outcome after SAH.

The association in the current study between prolonged QT interval and angiographic vasospasm may explain the findings of Ichinomiya and colleagues who found that a prolonged QT interval (>448 ms) at 7 days postaneurysm rupture was a predictor of neurological outcome. This group furthermore found that improvement in QT prolongation was associated with favorable outcome, suggesting a role for angiographic vasospasm as a mechanistic explanation. A significant limitation of previous studies is the lack of assessment of angiographic data to diagnose vasospasm. For example, Brouwers and colleagues found that fast rhythm disturbances correlated with poor outcome, but not cerebral ischemia; but, they did not directly assess arterial luminal narrowing. The current article therefore bridges a gap in knowledge between ECG findings and angiographic vasospasm.

It has been postulated that in the presence of known vasospasm, ECG abnormalities may identify patients who will go on to develop cerebral ischemia. This may be related to poor cardiac output as a result of neurogenic stunned myocardium, which may increase the risk of delayed cerebral ischemia from existing vasospasm. Supporting the physiological role for ECG abnormalities as markers of poor cardiac output, it has been previously reported that QT dispersion may be a marker of cardiorespiratory compromise; and QT prolongation, in addition to T-wave inversion, is a sensitive marker of abnormal wall motion on echocardiography after SAH. However, in a prospective study of 121 patients designed to test the association between cardiac abnormalities and delayed cerebral ischemia, no such relationship was identified. Similarly, we find that no ECG abnormalities were associated with risk of DIND in the current patient cohort, although several ECG findings were associated with the presence of angiographic vasospasm.

The main limitation of this study is our inability to account for the administration of cardiotoxic drugs, which may influence ECG changes; however, in 1 study, ECG changes were independent of plasma norepinephrine levels. Another limitation is that clazosentan was associated with a higher incidence of hypotension than was placebo in CONSCIOUS-1, and this might influence ECG changes. Conversely, analysis only of the placebo patients had similar findings in this data. Clazosentan is not known to have any direct effects on ECG. Our strengths include the availability of catheter angiography on all subjects for the evaluation of angiographic vasospasm and systematic and consistent collection of outcome variables. Furthermore, we present one of the largest series evaluating ECG changes in SAH patients, and the only such series evaluating the association between ECG change and vasospasm.

Conclusion
Abnormalities on ECG, such as QT prolongation and tachycardia, are independently associated with angiographic vasospasm. Tachycardia and nonspecific ST-segment changes are also significantly associated with poor outcome.

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None.

Disclosures
Actelion Pharmaceuticals Ltd was the sponsor of the CONSCIOUS-1 trial; the company provided the authors with the trial data set, but had no role in this exploratory analysis nor in the development of the article. The data analysis and writing are the work of the authors. Dr Macdonald is a consultant for Actelion and is chief scientific officer of Edge Therapeutics, Inc.

References


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