Serial Electrocardiographic Recording in Aneurysmal Subarachnoid Hemorrhage

P.J.A.M. Brouwers, MD, E.F.M. Wijdicks, MD, D. Hasan, MD, M. Vermeulen, MD, E.F.D. Wever, MD, H. Frericks, MD, and J. van Gijn, MD

We prospectively studied serial electrocardiograms in 61 patients with aneurysmal subarachnoid hemorrhage. Electrocardiographic changes were related to the initial level of consciousness, to subsequent events, and to outcome after 3 months. All 61 patients had at least one abnormal electrocardiogram, but cardiac disease did not contribute directly to morbidity or mortality. Fast rhythm disturbances, ischemic changes, or both on the electrocardiograms were significantly correlated with poor outcome but not with specific outcome events, particularly not with rebleeding or cerebral ischemia. The Glasgow Coma Scale score on admission and the amount of cisternal and (to a lesser extent) intraventricular blood on the initial computed tomogram were also significantly correlated with poor outcome, but these factors only partially confounded the relation between electrocardiographic abnormalities and poor outcome. We conclude that in patients with aneurysmal subarachnoid hemorrhage, electrocardiographic abnormalities do not herald impending cardiac disease but indirectly reflect adverse intracranial factors. Electrocardiographic abnormalities may therefore have some independent value in predicting poor outcome. (Stroke 1989;20:1162-1167)

Numerous reports1-11 have described electrocardiographic (ECG) changes in aneurysmal subarachnoid hemorrhage (SAH) that are associated with poor outcome3,7,8,11 and are often attributed to a systemic release of catecholamines, leading to focal subendocardial damage.2,4,5,8 The most prominent ECG changes, seen in >50% of the patients, are ST–T segment changes, U wave abnormalities, and a large variety of rhythm disturbances.4,5,8,9

It has been suggested that serious arrhythmias and ischemic ECG changes predispose to cardiac mortality in SAH.7,8,11-14 On the assumption that inhibition of the enhanced sympathetic discharge might improve outcome in SAH, two double-blind randomized studies have been performed,15,16 but mortality was not reduced. Moreover, in a prospective series of 254 patients, only two patients with ventricular fibrillation were found.17

The studies performed thus far might be reconciled if ECG abnormalities and the underlying damage to the myocardium did not contribute directly to poor outcome, but merely reflected severe intracranial disease. We investigated this possibility in a prospective series of 61 patients with aneurysmal SAH by means of serial ECG recording, close clinical observation, computed tomography (CT scanning), and standard assessment of outcome.

Subjects and Methods

Between June 1986 and June 1987 in two university hospitals, we prospectively studied a series of 69 consecutive patients (43 patients in Rotterdam and 26 in Utrecht) who had symptoms and signs of SAH and CT evidence of aneurysmal SAH. In the only patient in whom the CT scan was normal, we relied on blood and blood pigments in the cerebrospinal fluid. All 69 patients were admitted to the study ≤72 hours after the presenting SAH, after giving informed consent. Eight of the 69 patients were subsequently excluded from the study because of a negative angiogram (seven) or an arteriovenous malformation (one). Of the 61 remaining patients, in 45 (74%) angiography or autopsy demonstrated an aneurysm; in the other 16 patients, angiography and surgery were contraindicated because of advanced age (>70 years) or impaired level of consciousness. Nevertheless, a ruptured aneurysm was considered highly probable in these 16 patients due to the presence of blood in the interhemispheric, suprasel-
lar, or sylvian cisterns and to the absence of evidence of any other cause of the SAH.18,19

During the first 4 days after admission, all 61 patients were treated with tranexamic acid, 6 g/day i.v. in six doses. In a separate study about plasma volumes, 19 patients were randomized to additional treatment with fludrocortisone, 0.2 mg i.v. twice a day for 12 days. These drugs are not known to affect ECG findings. All 61 patients were kept on a fluid intake of at least 3 l/day20,21 and received no antihypertensive drugs.22

During the study period, which lasted 12 days or until death or surgery, all 61 patients were under close observation in an intensive care or high-dependency unit. The level of consciousness on admission was scored according to the 14-point Glasgow Coma Scale (GCS).23 We also obtained daily measurements of serum electrolytes, and any disturbance (especially a low serum potassium concentration) was immediately corrected. Thirty patients were operated upon at approximately Day 12 after the presenting SAH.

CT scanning was performed on admission and was repeated every week or when the patient's condition deteriorated. The amount of intraventricular blood on the baseline CT scan (at admission) was scored separately for each of the four ventricles on a scale of 0 (no blood) to 3 (completely filled with blood) points; frank intraventricular hemorrhage was defined as a sum score of ≥3 points. The amount of cisternal blood on the baseline CT scan was similarly scored from 0 to 3 points for 10 different basal cisterns and fissures.24 The baseline CT scans were scored simultaneously by two observers who were blinded to the ECG findings.

Cerebral infarction, rebleeding, and acute hydrocephalus were strictly defined.24,25 Outcome was assessed at 3 months according to the 5-point Glasgow Outcome Scale26 by neurologists who were unaware of the ECG and CT scan findings. For the purpose of analysis we categorized the outcomes on this scale as poor (death/persistent vegetative state/severe disability) and good (moderate disability/good recovery) outcome.

The ECG was continuously monitored in all 61 patients. A standard 12-lead ECG was scored daily in Utrecht and three times per week in Rotterdam during the study period. If rhythm disturbances were seen on the monitor, they were recorded and collected for later review by a trained nursing staff accustomed to working with ECG monitoring. Six months after completion of the study, the ECG and rhythm strips were interpreted by one investigator, with final corrections from a second investigator who was blinded to the CT scan findings, clinical characteristics, and outcome. Table 1 shows the classification system used.27,28 Sinus tachycardia, atrial flutter or fibrillation, supraventricular tachycardia, supraventricular extrasystole, and ventricular arrhythmias were considered to be fast rhythm disturbances. When an ischemic ST segment, ischemic T wave, or transient pathologic Q wave was seen, cardiac ischemia was considered to be present.

We used nonparametric tests to explore the associations between cardiac and neurologic variables. We analyzed distributions in 2 x 2 tables with Fisher's exact test. The Mann-Whitney U test was used to compare unpaired samples because of the small sample size and because we assumed that the values were not normally distributed; if there were too many ties, we used the test of Yates and Cochran. Probability values were calculated by two-sided tests. All six possible determinants of outcome were dichotomized (GCS score: normal (14) vs. decreased level of consciousness (<14 points); cisternal blood: 0–20 vs. 21–30 points; intraventricular blood: <3 vs. ≥3 points; and cardiac ischemia, fast rhythm disturbances, or both: present vs. not present). We chose the risk-ratio

| Table 1. Patients with Electrocardiographic Abnormalities on at Least One Recording After Aneurysmal Subarachnoid Hemorrhage |
|-----------------|-----------------|
| Abnormality                        | n   |
| Sinus bradycardia (<60 beats/min)   | 31  |
| Ischemic S-T segment*               | 31  |
| Ischemic T wave†                    | 29  |
| Prominent U wave‡                   | 27  |
| Q-Tc interval prolongation          | 24  |
| Left ventricular hypertrophy sign§  | 22  |
| Flat or isoelectric T wave          | 17  |
| Sinus tachycardia (>100 beats/min)  | 12  |
| Short P-R interval (<0.12 sec)      | 10  |
| Supraventricular extrasystole       | 9   |
| Ventricular arrhythmias†            | 9   |
| Other arrhythmias§                  | 9   |
| Long P-R interval (>0.20 sec)       | 9   |
| Transient pathologic Q wave (infarct Q)# | 8   |
| Bundle branch block                 | 7   |
| Peaked P wave                       | 7   |
| Tall T wave                         | 7   |
| Atrial flutter, fibrillation, or supraventricular tachycardia | 4   |
| Broad P wave                        | 3   |

Number out of 61 patients. Where no specifications are given, abnormalities were defined according to Robles de Medina.23

*Horizontal or down-sloping S-T segment with or without ST-J depression and upward convexity of S-T segment with or without ST-J elevation.

†Positive – negative T wave, symmetrical negative T wave in I, II, or V 5-6, tall positive symmetrical T wave, especially together with prolonged Q-Tc, interval.

‡>25% of highest T wave in precordial leads.

§SV1 + RV5,6 > 35 mm.

||Ventricular premature beats (Lown and Wolf27 Classes 1–4), ventricular tachycardia (Lown and Wolf27 Class 5 and torsades des points), ventricular flutter, and ventricular fibrillation.

#Sinoatrial block, sinus arrest (>4 sec), sinus arrhythmia, second- or third-degree atrioventricular block, and idioventricular rhythm.

#Deep and broad transient Q wave >0.04 sec wide and/or with amplitude of >25% of R wave in same lead with normal septal activation in I, aVL, and V 5-6.
TABLE 2. Electrocardiographic Abnormalities Present on at Least One Recording in Seven Autopsied Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast rhythm disturbances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular extrasystole</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ischemic S-T segment</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Ischemic T wave</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Transient pathologic Q wave</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cardiac ischemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Prominent U wave</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>QTc interval prolongation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Left ventricular hypertrophy sign</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Flat or isoelectric T wave</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other arrhythmias (sinus arrhythmia)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Long P-R interval</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 1 shows the incidence of the various ECG abnormalities. In 58 of the 61 patients, the ECG abnormalities first appeared within 3 days after the SAH. The ECG abnormalities changed to other abnormalities, without any consistent order, and then disappeared during the study period.

Individual ECG abnormalities were not predictive of the risk of acute hydrocephalus, cerebral ischemia, rebleding, or poor outcome. Potentially dangerous arrhythmias or actual death due to heart disease did not occur in any patient during the first 4 weeks after the initial SAH. Nevertheless, of seven autopsied patients who died of intracerebral complications, four showed subendocardial bleeding and fibrosis. After correction for the number of recordings, ECG abnormalities in these four patients were both more numerous and more varied than in the other three patients (Table 2).

Of the 61 patients, 47 (77%) were entered into the study ≤24 hours, 10 (16%) 24-48 hours, and four (7%) 48-72 hours after the SAH. All 61 patients had at least one abnormal ECG. Of 368 recordings, 318 (86%) were abnormal. Of 32 patients with fast rhythm disturbances, cardiac ischemia, or both and poor outcome, 28 died (15 of rebleeding, four of infarction, three of hydrocephalus, one of the direct effect of the primary SAH, one of postoperative subdural hematoma, and four of other causes; these four included one patient who died of myocardial infarction and one with "sudden death," both after >1 month), three were severely disabled (one as a result of the primary SAH, one as a result of rebleeding, and one as a result of postoperative subdural hematoma), and one patient survived in a persistent vegetative state as a direct effect of the primary SAH. Fast rhythm disturbances and its combination with cardiac ischemia were associated not only with poor outcome, but also with a number of baseline characteristics such as a GCS score of <14, frank intraventricular hemorrhage (score ≥3), and a history of hypertension or cardiovascular disease (Table 3). The first two associations alerted us to possible confounding of the predictive power of fast rhythm disturbances or its combination with cardiac ischemia by intracranial factors.

Fast rhythm disturbances and its combination with cardiac ischemia were not significantly associated with the amount of cisternal blood on the baseline CT scan (z=1.52, p=0.13 and z=1.54, p=0.13, respectively, by the Mann-Whitney U test). With regard to the possible confounding influence of the baseline CT scan features, we found nonsignificant associations of cardiac ischemia with frank intraventricular hemorrhage (p=0.09) and with the amount of cisternal blood (z=1.74, p=0.08 by the Mann-Whitney U test).

A GCS score of <14 and a baseline CT scan with >20 points of cisternal blood were associated with poor outcome (28 of 36 vs. seven of 25: RR=2.8, 95% CI 1.4-5.3 and 22 of 29 vs. 13 of 32: RR=1.9, 95% CI 1.2-3.0, respectively). The relation between frank intraventricular hemorrhage and poor out-
TABLE 3. Baseline Clinical Characteristics and Outcome Events in 61 Patients with Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Baseline Clinical characteristics</th>
<th>Total (N=61)</th>
<th>Fast rhythm disturbances (n=24, 39%)</th>
<th>Cardiac ischemia (n=45, 74%)</th>
<th>Both (n=21, 34%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glasgow Coma Scale score &lt;14</strong></td>
<td>36</td>
<td>19 53†</td>
<td>28 78</td>
<td>16 44†</td>
</tr>
<tr>
<td><strong>Age &gt;50 yr</strong></td>
<td>41</td>
<td>20 49</td>
<td>33 80</td>
<td>18 44</td>
</tr>
<tr>
<td><strong>History of hypertension or cardiovascular disease</strong></td>
<td>21</td>
<td>13 62†</td>
<td>19 90</td>
<td>12 57§</td>
</tr>
<tr>
<td><strong>Computed tomographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged lateral ventricles</td>
<td>18</td>
<td>9 50</td>
<td>12 67</td>
<td>8 44</td>
</tr>
<tr>
<td>Enlarged third ventricle</td>
<td>21</td>
<td>11 52</td>
<td>15 71</td>
<td>9 43</td>
</tr>
<tr>
<td>Frank intraventricular hemorrhage (≥3 points)</td>
<td>15</td>
<td>10 67‡</td>
<td>14 93</td>
<td>9 60§</td>
</tr>
<tr>
<td><strong>Amount of cisternal blood &gt;20 points</strong></td>
<td>29</td>
<td>13 45</td>
<td>25 86</td>
<td>12 41</td>
</tr>
</tbody>
</table>

Outcome events:
- Cerebral infarction: 13 2 15 10 77 1 8
- Rebleeding: 20 10 50 15 75 8 40
- Acute hydrocephalus: 15 5 33 9 60 4 27
- Poor outcome: 35 19 54# 30 86** 17 49††

% of total for that row.
*tp<0.025, 0.05, respectively, different from % of overall total by Yates and Cochran test.
§tp<0.025, 0.01, 0.05, respectively, different from % of overall total by Fisher’s exact test.
#Risk ratio (RR) 1.8, 95% confidence interval (CI) 1.2–2.8.
**RR 2.1, 95% CI 1.02–4.5.
††RR 1.8, 95% CI 1.2–2.7.

As GCS score was the strongest indicator of poor outcome in SAH, in keeping with earlier studies,32,33 we performed a stratified analysis of fast rhythm disturbances, cardiac ischemia, and both after adjusting for GCS score (Table 4). We checked for effect modification first.31,34-35 Table 4 shows that there was little variation over the strata, which was confirmed by a formal test for homogeneity of effect (for fast rhythm disturbances: χ²=0.44, 1 df, p=0.8; for cardiac ischemia: χ²=0.224, 1 df, p=0.6; for both: χ²=0.022, 1 df, p=0.9). Comparison of the Mantel-Haenszel pooled estimates from Table 4 with the crude estimates from Table 3 shows that cardiac ischemia was slightly confounded by GCS score (RR decreased from 2.1 to 1.9) and that fast rhythm disturbances (RR 1.4 instead of 1.8) and its combination with cardiac ischemia (RR 1.5 instead of 1.8) were moderately confounded by GCS score.

**Discussion**

All 61 patients had ECG abnormalities of a changing character, which have been described before in patients with SAH, although the definitions differed.1-11,36-41 A number of ECG abnormalities may have been missed in one of the two centers as a result of its lower frequency of ECG recording. Nevertheless, we considered it reasonable to combine the data since rhythm abnormalities were detected by continuous ECG monitoring and since nonrhythm abnormalities usually lasted >1 day.

Individual ECG abnormalities were not obviously related to the amount of cisternal or intraventricular blood on the baseline CT scan or to specific complications such as infarction, rebleeding, acute hydrocephalus, or to outcome in general. On the other hand, we did find poor outcome to be associated with the broader categories of fast rhythm disturbances, cardiac ischemia, or both.

Despite these associations of ECG abnormalities with outcome, we did not find a direct contribution of cardiac disease to mortality, in keeping with previous studies.15,17,42,43 In the only patient with proven myocardial infarction and in one other patient who was found dead in bed, >1 month had passed since the presenting SAH. Moreover, severe intracranial damage, reflected by a baseline GCS score...
of <14, was also significantly correlated with poor outcome. Correction for GCS score showed that the prognostic power of ECG abnormalities depended partially on the level of consciousness. In the absence of a direct effect of heart disease on outcome, it is probable that the remaining predictive power of ECG abnormalities also depends on intracranial factors. However, these are less easy to identify because the amount of cisternal blood on the baseline CT scan was related to outcome but not to ECG abnormalities, while the opposite applied to frank intraventricular hemorrhage. We therefore conclude that ECG abnormalities in SAH indirectly reflect intracranial damage or dysfunction, but that this general association cannot be explained by a simple combination of specific intracranial factors.

The prognostic value of ECG abnormalities has been described.3,7-9 In a series of 40 patients Cruickshank et al7 found that the two patients who had pathologic Q waves and one of the three patients with S-T segment elevations died. Melin and Fogelholm8 demonstrated a significant relation between sinus tachycardia and death ≤ 7 days after SAH; however, their patients were retrospectively studied, with only one ECG recording and without correction for possible confounding factors such as the level of consciousness. Galloon et al10 demonstrated that changing ECG abnormalities were a bad prognostic sign, even if compared with patients who had persistently abnormal ECGs; unfortunately, these authors did not define either the ECG abnormalities or the outcome events.

Postmortem investigation of the heart10,44-47 and cardiac enzyme measurements3,46,48-50 have made it likely that ECG abnormalities after SAH can be explained by subendocardial ischemia, small hemorrhages, or focal necrosis of the heart. We could confirm this finding in four of our seven autopsied patients. Recently, left ventricular wall motion abnormalities were observed in an echocardiographic study of the heart in patients with SAH.51 There is increasing evidence that the structural damage to the myocardium results from high levels of catecholamines, especially norepinephrine,2,38,45,52-55 caused by either systemic hypertensive effects such as left ventricular strain5,56 or by direct toxicity.14,38,54 Experimental work implicates damage to the hypothalamus as the cause of an increase in sympathetic tone.47,53,57,58 This notion is supported by postmortem studies.15,58,59

We conclude that ECG abnormalities in patients with SAH are more important as indicators of intracranial disease than as predictors of potentially fatal heart disease. Nevertheless, we think that serial ECG recording can be useful because fast rhythm disturbances, cardiac ischemia, or both add to the value of clinical criteria in predicting poor outcome. The same applies to the amount of cisternal blood and frank intraventricular hemorrhage on the admission CT scan, but the prognostic value of ECG and radiologic factors was not identical in our study.

References
22. Wijdicks EFMM: Hyponatremia, volume status and blood pressure following aneurysmal subarachnoid hemorrhage
47. Hammermeister KE, Reichenbach DD: QRS changes, pulmonary edema, and myocardial necrosis associated with subarachnoid haemorrhage. Am Heart J 1969;78:94-100

KEY WORDS • coronary disease • electrocardiography • subarachnoid hemorrhage
Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage.
P J Brouwers, E F Wijdicks, D Hasan, M Vermeulen, E F Wever, H Frericks and J van Gijn

*Stroke*. 1989;20:1162-1167
doi: 10.1161/01.STR.20.9.1162

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/9/1162

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/