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Clinical Article

ECG abnormalities in predicting secondary cerebral ischemia after subarachnoid haemorrhage

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Summary

Background. Electrocardiographic (ECG) abnormalities frequently occur after subarachnoid haemorrhage (SAH), and have been linked with poor outcome. The pathogenesis behind this relation is unclear. We hypothesized that cardiac dysfunction may contribute to the development of delayed cerebral ischemia (DCI) and investigated if electrocardiographic repolarization abnormalities on admission, representing this cardiac dysfunction, are related to DCI. We also assessed the additional value of ECG characteristics to establish prognosticators for clinical outcome (WFNS, age and Hijdra score).

Method. In a series of 121 consecutive patients with aneurysmal SAH we related individual repolarization-like ECG changes (ST and T-wave changes, QTc prolongation, a U-wave) to the occurrence of DCI by means of Cox proportional hazard modelling and to poor outcome (death or dependence) with logistic regression analysis. We used ROC curves to assess the additional prognostic value of the most important ECG characteristics to established prognosticators.

Findings. Only ST segment depression had a statistically significant relationship with the occurrence of DCI (HR 2.4 [95%CI 1.2–4.9]) in univariate analysis. In a similar analysis ST-elevation (OR 4.9; [95%CI 0.99–24.0]), ST-depression (OR 10.6; [95%CI 2.3–48.8]), T-wave inversion (OR 2.5; [95%CI 1.1–5.5]) and ischemic like ECG abnormalities (OR 8.3; [95%CI 3.0–22.2]) were significantly related to poor outcome. In multivariate models with extension of these ECG characteristics for establishing prognosticators the AUC of the ROC improved from 0.81 to 0.84.

Conclusions. ECG abnormalities did not contribute to the prediction of DCI and have limited value in prognosticating poor outcome. The occurrence of DCI is not the explanation of this relationship between ECG characteristics and outcome.

Keywords: Subarachnoid haemorrhage; electrocardiogram; delayed cerebral ischemia; outcome.

Introduction

Electrocardiographic (ECG) repolarization changes occur in three quarters of patients with subarachnoid haemorrhage (SAH) irrespective of the presence or absence of previous cardiac disease [8]. Most frequent are QTc prolongation, ST segment deviation, an inverted T wave or the occurrence of an abnormal U wave. ECG abnormalities in the acute stage of SAH are usually attributed to autonomic imbalance, in particular to direct autonomic discharge to the heart or to increased levels of circulating catecholamines [18].

The ECG changes found early after SAH have been linked to outcome in some studies investigating this relationship [2, 4, 7, 9–12, 19, 21] (Table 1). The pathogenesis behind this relation has not been elucidated. We hypothesized that ECG changes might increase the risk of delayed cerebral ischemia (DCI) and thereby explain the relation between ECG changes and poor outcome. The ECG changes often include repolarization abnormalities and these are associated with transient myocardial dysfunction. This myocardial dysfunction results in hemodynamic instability and contributes to pulmonary edema [16]. The combination of hemodynamic instability and reduced oxygenation may contribute to the development of DCI, especially because cerebral autoregulation is disturbed after SAH [13, 15, 17].

The aim of this study was to investigate the prognostic value of repolarization abnormalities observed at baseline 12-lead ECG for the occurrence of DCI in patients with SAH. Additionally we investigated whether electrocardiographic repolarization abnormalities have additional prognostic information for clinical outcome in addition to established prognos-

Table 1. *Literature reporting outcome in the period with brain CT*

References and Year study	No. of patients	Repolarization abnormalities	Outcome event	Outcome correlation	Details
2; 1986–1987*	61	QTc, ST↓, T↓↑, U, P↑, PR	poor outcome and DCI	no relation individual ECG abn; cardiac ischemia adds to value of clinical criteria for predicting poor outcome	14 > 24 h of SAH admission; stratified for GCS and blood on CT
21; 1991–1996	58	ST↑↓, T↓	in hospital all cause and cardiac mortality	univariate relationship with combination of ECG abn; multivariately not	
7; 1997–1999#	122	QTc, ST↑↓, T↓↑ inverted U, Q, ECG score	in hospital mortality	QTc and ECG score most significant prognosticator in multivariate analyses	ECG score (total number of leads with Q, ST↓, T↓)
4; <1991	45	QTc, ST↑↓, T↓↑, U	in hospital mortality	no relationship	10 patients no SAH; ECG: mean 5 days after SAH
10; 1999–2000#	97	QTc, ST↑↓, T↓↑, U	in hospital death	ST↓ significant relation; OR 17.7 (95%CI:1.6–880.1)	70 (42%) missing ECG18 of 97 no aneurysm
19; 2001-ongoing*,#	100	QTc, ST↑↓, T↓, U	in hospital mortality	no relationship	computerized ECG measurement
11; 1977–1983	100	QTc, ST↑↓, T↓↑, U, Q, PR	in hospital death and angiographic vasospasm	ST↓, QTc and Q with outcome; abnormal ECG with angiographic vasospasm	no standard CT
12; <1995 (3 years of study)	70	QTc, ST↑↓, T↓↑, U, P, PR	in hospital outcome (neurological deficit) and angiographic vasospasm	no relationship	pre operative ECG; 25 > 36 h after SAH
9; <1995 (6 years of study)#	23	ST↑	symptomatic vasospasm (no further classification)	no relationship	only 4 with vasospasm; all 23 had ST↑ out of 226 not specified patients

* Prospective study; # only admission ECG.

ticators such as the clinical condition on admission and the amount of extravasated blood on the initial brain CT.

Methods and materials

Study population

We studied a consecutive series of 148 patients with SAH who had been admitted within 4 days after onset of SAH to the Westeinde hospital in the Hague between January 2000 and July 2002. From this series we excluded 9 patients with a non-aneurysmal perimesencephalic haemorrhage, 3 patients with complete left bundle branch block and 3 patients with a history of heart disease, as well as 12 patients who had no ECG recording on the day of admission. The remaining 121 patients had an SAH with an aneurysmal pattern of haemorrhage on CT. In 28 of these patients no intra-arterial angiography had been performed because of a poor clinical condition from the outset. These 28 patients all died early during their hospital course. In 3 other patients no aneurysm was detected in two angiographic evaluations. No patient used class I or III anti-arrhytmic drug or digoxin, which may alter the cardiac repolarization. All patients were treated according to standard intensive care guidelines during at least two weeks after their hospitalization. This protocol consisted of absolute bed rest, oral nimodipine, an oral antiepileptic drug and intravenous administration of fluid aiming at normovolemia. We refrained from antihypertensive medication unless in case of extreme values or impeding end-organ failure.

Data collection

An admission 12-lead ECG of each patient was analyzed by an experienced electrocardiographer who was blinded to the patient's condition. In general, ST elevation or depression greater than 0.1 mV in limb leads or 0.2 mV in pre-cardial leads were defined as an abnormal finding. A T wave was defined as inverted if less than 0.1 mV in depth, and as peaked if greater than 1 mV. T wave abnormalities were assessed in leads I, II, aVL, aVF and V_{2-6}. The occurrence of a U wave was recorded. The corrected QT (QTc) interval was calculated by Bazett's formula [1] from an average of 3 complexes in lead II and was considered abnormal if it was longer than 0.42 s in men and 0.43 s in women. Occurrences of ischemic like ECG abnormalities were also recorded. We defined ischemic like ECG abnormalities as the presence of ST depression or T wave inversion, or both in at least two leads.

The clinical condition on admission was evaluated according to the WFNS classification [5].

A distinction was made between good neurological condition (WFNS I, II, or III) and poor neurological condition (WFNS IV or V) on admission. The amount of subarachnoid blood was assessed according to the classification of Hijdra [6]. Subarachnoid blood in 10 cisterns or fissures and in 4 ventricles on CT was evaluated semi quantitatively as scores ranging from 0 to 3. Each cistern, fissure or ventricle was graded separately according to the amount of extravasated blood. We calculated the total sum score of blood in the basal cisterns (range 0–30) and ventricles (range 0–12) and dichotomized these at their median value.

The outcomes of interest were the occurrence of DCI and poor clinical outcome (death or dependence). DCI was considered definite in case of a new hypodense lesion on the CT scan together with a gradual developing focal deficit, impairment of consciousness, or both in a

patient with no other explanation for this event. Clinical features without hypodensities revealed by a CT scan were scored as probable DCI. In all analyses, definitive and probable DCI were combined.

Based on clinical status at 3 months after onset, we evaluated outcome according to the 5 point Rankin scale [20]. We qualified the scores 0–3 as good outcome and the scores 4, 5 and death as poor outcome. A score of 0–3 points means that the patient is independent for activities of daily life. Rebleeding was defined as a sudden clinical deterioration with evidence of new blood on CT in comparison with a previous scan.

Data analysis

Descriptive statistics were used to report the number and type of ECG abnormalities.

We related the occurrence of DCI to baseline characteristics (WFNS, amount of blood on baseline CT and age) and to the individual ECG abnormalities (ST depression or elevation, a peaked T or T wave inversion and a U wave) of admission ECG by means of Cox proportional hazards modelling, which yields hazard ratios (HR). HRs may be interpreted as relative risks; [3] these were considered statistically significant if the 95% confidence interval (CI) did not include 1. Next we developed multivariate models with forward selection. The first model was based on WFNS, age and Hijdra score (model M1); secondly we extended it with the individual ECG abnormalities (M2). Variables were retained in the model if the corresponding p-value was <0.10. We evaluated the discriminating power of the models with the area under the curve (AUC) of the corresponding receiver operator characteristic curve (ROC). An AUC can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction). In additional analyses the combined ischemic like ECG abnormalities were entered in a third model (M3) together with the baseline characteristics and the individual ECG abnormalities. In the analyses for DCI, patients were recorded at the time of rebleeding, death or at discharge.

We also looked for the relation between ECG characteristics and poor clinical outcome with logistic regression modelling, which yields crude odds ratios. For multivariate analyses a similar strategy as for the analysis of DCI was used.

Results

The baseline characteristics of the included patients are listed in Table 2. Twenty-five (20.7%) patients had no repolarization abnormalities on the admission electrocardiogram. The most frequent abnormalities were ST depression, T wave inversion, a peaked T wave, the presence of a U wave or QTc prolongation. A U wave was found in 52% of admission electrocardiograms.

DCI

Of the individual ECG characteristics, only ST segment depression predicted the occurrence of DCI (HR 2.4 [95%CI, 1.2–4.9]) (Table 3). No other baseline characteristic or the combined ischemic like ECG changes had a statistically significant relation with DCI in univariate analysis. Because ST depression was the only variable with a statistically significant association with DCI we refrained from multivariate analyses. The AUC of the ROC for ST depression was 0.53 (95%CI 0.42–0.63).

Table 2. *Patient characteristics*

Total 121 patients	
Age	
Mean (sd)	54.7 (12.9)
Female gender n (%)	90 (74%)
WFNS at admission n (%)	
– I	37 (31%)
– II	26 (21%)
– III	13 (11%)
– IV	17 (14%)
– V	28 (23%)
Hijdra score	
– Cisternal score	median (range) 18 (0–30)
– Ventricular score	median (range) 2 (0–12)
*Electrocardiographic findings**	
– ST elevation	10 (8%)
– ST depression	17 (14%)
– T wave inversion	38 (31%)
– Peaked T wave	21 (17%)
– QTc prolongation	16 (13%)
– U wave	63 (52%)
– Ischemic like ECG abnormalities	33 (27%)
Outcome events	
– DCI	52 (43%)
– Poor outcome	58 (48%)
– Rebleeding	12 (10%)

* Some patients had more abnormalities on their ECG so total exceeds 100%.

Table 3. *Predictors for the occurrence of DCI in the univariate analyses*

Variable	Hazard ratio	95%CI
ST depression	2.4	1.2–4.9
ST elevation	2.1	0.7–5.7
T wave inversion	0.9	0.5–1.7
Peaked T wave	0.7	0.3–1.5
U wave	0.7	0.4–1.3
QTc prolongation	1.0	0.5–2.3
Ischemic like ECG abnormalities*	1.3	0.7–2.4
WFNS	0.7	0.4–1.4
Female sex	0.5	0.4–1.6
Age	0.99	0.97–1.01
Hijdra score		
– Cisternal score > median	1.4	0.8–2.4
– Ventricular score > median	1.5	0.9–2.6

* ST segment depression or T wave inversion, or both in at least two leads.

Clinical outcome

In the univariate analyses ST elevation, ST depression, T wave inversion, a peaked T wave and the occurrence of

Table 4. *ECG changes and baseline clinical characteristic and their relation to poor outcome in univariate analyses*

	Odds ratio	95%CI
ST elevation	4.9	0.99–24.0
ST depression	10.6	2.3–48.8
T wave inversion	2.5	1.1–5.5
Peaked T wave	0.4	0.1–1.03
U wave	0.4	0.2–0.9
QTc prolongation	1.1	0.9–3.2
Ischemic like ECG abnormalities*	8.3	3.0–22.2
Age (continuous)	1.04	1.01–1.07
WFNS ≥ 4	8.1	3.4–19.0
Hijdra score		
– Cisternal score above median	2.8	1.4–5.9
– Ventricular score above median	8.6	3.7–19.5

* ST segment depression or T wave inversion, or both in at least two leads.

Table 5. *Multiple logistic regression on selected variables for outcome*

Variable	M1		M2		M3	
	OR	95%CI	OR	95%CI	OR	95%CI
WFNS ≥ 4	3.3	1.1–9.6	4.3	1.4–13.7	3.1	0.99–9.9
Hijdra score						
– Cisternal score >18	2.7	1.2–6.4	–	–	–	–
– Ventricular score >2	4.3	1.5–12.0	3.6	1.2–10.6	3.2	1.1–9.5
ST depression			6.2	1.2–33.7	–	–
Peaked T wave			0.3	0.1–0.9	–	–
U wave			0.4	0.2–0.98	0.4	0.1–0.9
Ischemic like ECG abnormalities					5.2	1.7–15.9
AUC of ROC	0.81	0.74–0.89	0.84	0.77–0.91	0.84	0.74–0.89

Variables were excluded from the model if the corresponding $p > 0.10$.

a U wave were related to outcome (Table 4). A peaked T wave and a U wave were related to a favourable outcome.

Established prognostic factors such as WFNS, age, and the amount of blood on CT (model M1) predicted the occurrence of poor outcome in this group of patients as well. In multivariate model M1 (established prognosticators) WFNS and Hijdra score were retained, but not age (Table 5). Upon extension with the individual (marginal) statistically significant ECG variables (M2) only WFNS score, Hijdra ventricular score, ST depression, a peaked T wave and a U wave were retained in the model. In subsequent extension of this model with combined ischemic like ECG abnormalities (M3) to this model the WFNS score, Hijdra ventricular score, U wave and the combined ischemic like ECG abnormalities were retained. The AUC of the ROC for model M1 was 0.81 and that for models M2 and M3 0.84 (Fig. 1).

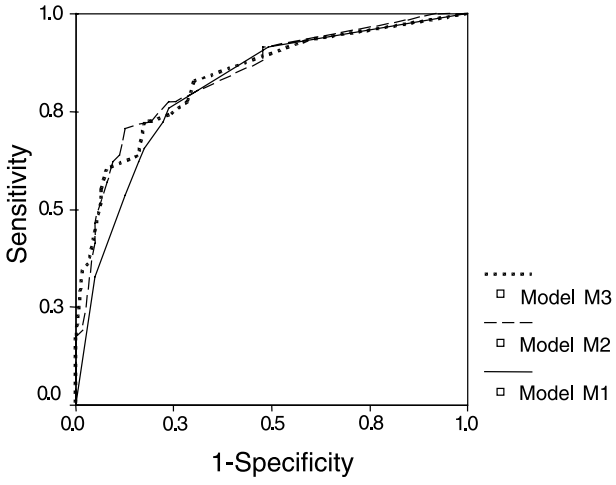

Fig. 1. ROC curves of Model M1, M2 and M3 in predicting outcome. *M1* WFNS and Hijdra score, *M2* WFNS, Hijdra ventricular score, ST depression, peaked T wave and U wave, *M3* WFNS, Hijdra ventricular score, U wave and ischemic like abnormalities

Discussion

We found that ECG characteristics do not contribute to the prediction of DCI. Although ST depression had a statistically significant relationship with the occurrence of DCI in univariate analysis, the importance of ST depression for prognosticating DCI is negligible.

Our secondary aim was prognosticating poor outcome. ST depression and in subsequent analyses a combination of ischemic ECG abnormalities appeared independent predictors of poor outcome. The additive prognostic information of these ECG variables for poor outcome is limited.

In the acute stage after SAH autonomic instability and an excess of catecholamines frequently lead to ECG and cardiac enzyme changes as an expression of temporary cardiac dysfunction. The electrocardiogram provides a simple tool to screen patients for cardiac dysfunction. In previous studies with SAH patients, ST elevation, T wave inversion and QTc prolongation appeared to be related to transient cardiac dysfunction, [9, 14] and cardiac dysfunction has been found to be an independent prognostic factor for the occurrence of DCI [15].

Only one study investigated the relation of serial acquired ECG abnormalities to the occurrence of DCI [2]. The authors found no predictive effect of individual ECG abnormalities on DCI. Several explanations for the weak relation between ECG abnormalities and DCI may

exist. Firstly, ECG abnormalities may not be sufficiently accurate markers for the identification of myocardial damage that leads to DCI. Secondly, myocardial dysfunction leading to DCI may occur in the absence of ECG changes. Thirdly, ECG abnormalities do not necessarily reflect impaired autoregulation. An impaired autoregulation in combination with a reduced perfusion pressure and reduced cardiac output is associated with an increased risk of DCI [13].

Numerous reports have described ECG changes after SAH that are associated with poor outcome. Many of these studies were small and sometimes hampered by exclusion of many patients, and are therefore difficult to extrapolate to other series of SAH patients. Most studies (Table 1) concluded that there was a relation of the clinical condition on admission or the amount of extravasated blood and the presence of ECG abnormalities. This probably explains that the additional prognostic value of ECG abnormalities to the clinical condition on admission and the amount of extravasated blood on outcome was limited in our study. Only three studies took these prognostic baseline characteristics into account [2, 7, 21]. These three studies, primarily focusing at case fatality rates, suggested an additional effect of a combination of ischemic like ECG abnormalities to the clinical condition on admission and the amount of extravasated blood. In a retrospective cohort study with 122 patients a combination of a pathological Q wave, ST depression and T inversion was the most powerful risk factor for in hospital mortality in a multivariate model also including Hunt and Kosnik, QTc interval, age and sex [7]. The additional prognostic value of this combined ECG score was not investigated in that study.

A limitation of our study is the partly retrospective data collection. However, 75% of the data were prospectively acquired and we admitted all SAH patients to the ICU for at least 2 weeks with standard daily treatment. Except for 12 patients with missing ECG's a complete dataset of all other consecutive SAH patients was available. Clinical condition on admission and outcome of the 12 patients with missing ECG's were comparable with the other patients. It is unlikely that excluding these patients influenced our results significantly. A potential drawback is that the study ECG was performed not immediately in some patients but up to 4 days after SAH onset. Almost all patients (120) were admitted within 48 hours of haemorrhage and in none of the patients the DCI preceded the first ECG study.

We investigated only the admission ECG and excluded patients with already known cardiac disease. Thereby we excluded other causes of ECG changes such as medical treatment (inotropic support). In our study we took as one of the outcomes DCI, and not vasospasm. Vasospasm does not always lead to DCI or clinical features and is therefore a less relevant outcome from a clinical point of view.

In addition to the prognostic effect of ST depression and ischemic like ECG abnormalities for poor outcome, the occurrence of a U wave and a peaked T wave significantly predicted a favourable outcome. No other study mentioned this protective effect of individual ECG abnormalities. We find it difficult to explain this observation.

In conclusion ST depression and ischemic like ECG abnormalities are independent predictors of a poor outcome, but the relation of these individual ECG parameters with poor outcome is not explained by the occurrence of DCI. The additional value of ECG abnormalities to baseline characteristics in prognosticating outcome appeared to be limited.

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Comment

The authors highlight well the issues of ECG changes after subarachnoid hemorrhage, which as they note occur in up to three-quarters of patients with subarachnoid hemorrhage. The thought that they could use the ECG to try to predict who might develop cerebral vasospasm is an interesting one, but is so nonspecific that one would be surprised if they found a tight correlation between the two occurrences.

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