Noradrenaline concentrations and electrocardiographic abnormalities after aneurysmal subarachnoid haemorrhage

P J A M Brouwers, H G M Westenberg, J Van Gijn

Abstract
Serial ECGs and serial assessment of plasma noradrenaline concentrations were carried out in 37 consecutive patients with aneurysmal subarachnoid haemorrhage and 18 operated controls.

Electrocardiographic abnormalities reflecting possible signs of cardiac ischaemia occurred significantly more often in patients than in controls. By contrast, plasma noradrenaline concentrations were much higher in controls than in patients. Plasma noradrenaline concentrations were higher in patients with poor outcome, particularly after the third day, but showed covariance with established predictors of outcome such as the Glasgow coma scale score on admission, the amount of extravasated blood on the initial CT, and age.

In conclusion, high plasma noradrenaline concentrations do not explain the occurrence of electrocardiographic abnormalities, and are not useful as independent predictors of poor outcome or secondary complications.

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In patients with aneurysmal subarachnoid haemorrhage (SAH), abnormalities on ECG predict poor outcome, to some extent independently. This applies particularly to signs of cardiac ischaemia. These changes on ECG do not herald impending heart disease but reflect adverse intracranial factors.1 The changes indicate myocardial damage, which in turn would result from high plasma noradrenaline concentrations, mediated by either systemic hypertensive effects leading to left ventricular strain, or by direct toxicity.2 Hypothalamic damage has been implicated as the cause of raised concentrations of plasma noradrenaline,3,4 either indirectly, through the adrenal glands, or directly, via release of noradrenaline by sympathetic nerve terminals in the myocardium.2

In this study we set out to investigate the association between noradrenaline, ECG changes (particularly cardiac ischaemia), and outcome characteristics. To distinguish between non-specific stress of disease (also present in SAH) and noradrenaline released as a result of hypothalamic damage in SAH, we introduced a control group of patients who had undergone elective surgery of the mandible (pain) and who had to remain on an intensive care unit (stress) for at least one day.

Patients and methods
We prospectively studied a series of 37 consecutive patients with clinical and radiological evidence of aneurysmal SAH.5,6 All patients were admitted within 72 hours of the presenting haemorrhage. Twenty five patients underwent aneurysm surgery at about day 12 after the presenting SAH.

The level of consciousness on admission was assessed with the 14 point Glasgow coma scale score.7 The amount of intraventricular blood on the admission CT was graded separately for each of the four ventricles on a semiquantitative scale of 0 (no blood) to 3 (completely filled with blood). The amount of cisternal blood on the admission CT was similarly graded from 0 to 3 for 10 different basal cisterns and fissures.8,9 Intracerebral haematoma was recorded as present or absent.

A standard 12 lead ECG at rest was obtained daily during the study period, which lasted 12 days or until rebleeding, surgery, or death. The leads were newly attached for each recording. Six months after completion of the study, the ECGs were interpreted according to previously described criteria,10 11 by one investigator who was blinded to all other findings. If an ECG characteristic was identified on any day it was considered present in that particular person. An ischaemic ST segment, ischaemic T wave, or transient pathological Q wave were counted as signs of cardiac ischaemia.

Cerebral infarction was defined as the gradual development of focal neurological signs, deterioration in conscious level, or both, with infarction confirmed by CT or necropsy.12 Outcome was assessed at three months according to the five point Glasgow outcome scale.13 We reduced the outcome
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Noradrenaline categories on this scale to two: poor outcome (death, or persistent vegetative state, or severe disability) or good outcome (moderate disability or good recovery).

Blood samples were collected from an indwelling catheter at 8.00 am after 20 minutes of supine rest. We obtained daily measurements of electrolytes and cardiac enzymes. The assessment of creatine kinase myocardial band fraction was not influenced by the presence of creatine kinase brain band fraction. Plasma was collected for measurement of cortisol and noradrenaline concentrations on days 1, 3, 6, 9, and 12 after admission. Any disturbance in the concentration of electrolytes, especially of potassium, was immediately corrected.

The control group consisted of 18 patients who were included one day after elective surgery of the mandible. They remained intubated for 24 hours after the operation. All left the hospital in good condition within three weeks. In the control group the same ECG (daily) and laboratory measurements (days 1, 3, 6, 9, and 12) were performed except for those of plasma cortisol.

Plasma noradrenaline concentrations (normal value 200–400 pg/ml) were determined by means of high pressure liquid chromatography.

Distributions in $2 \times 2$ contingency tables were tested with a 2 tailed $x^2$ test. The changes in plasma noradrenaline concentrations were analysed by means of multivariate analysis of variance with repeated measures of the factor time. The contrasts at the different days were assessed by Tukey's multicomparison test. Bartlett's test for homogeneity of group variances was performed on all measures. Skewed data were log transformed before the statistical analysis.

**Results**

Of the 37 patients, 24 were entered into the study within 24 hours, 10 patients between 24 and 48 hours, and three patients between 48 and 72 hours after SAH.

The table shows that there were no significant differences between patients and controls with regard to the proportions with abnormal mean enzyme concentrations over the first 12 days of the study, and with regard to general characteristics. Of the 125 ECG recordings performed in controls, 58 (46%) showed one or more abnormalities. In 12 of the 18 controls a preoperative ECG was available and in nine of these 12 we found new ECG abnormalities after operation, but in all cases these disappeared on later ECGs. Of the 337 ECGs performed in patients, 273 (81%) were abnormal; all had at least one abnormal ECG. Virtually all ECG abnormalities changed to other abnormalities, without any consistent order, and disappeared during the study period in 25 of the 37 patients.

Abnormalities on ECG indicating cardiac ischaemia occurred significantly more often in patients than in controls (table), 38 associations between ECG abnormalities, especially cardiac ischaemia, and electrolyte disturbances could be detected.

Plasma noradrenaline concentrations were nearly always above normal in the first 12 days of the study. In controls plasma noradrenaline concentrations were higher than in patients, except for the first day (figure, left panel). This difference was significant on days 2, 3, 6, and 9 ($P < 0.02$).

There was little association between abnormal laboratory findings for enzymes and cortisol (average for 12 days) on the one hand and cardiac ischaemia on the other. In controls there were few abnormal laboratory findings. Patients and controls with cardiac ischaemia had higher concentrations of noradrenaline than those without. For patients the pattern analysis factors were statistically significant ($P$ values 0.05–0.0001). The figure (right panel) shows the time course for noradrenaline in patients according to outcome, and in controls. Patients with a good outcome showed no rise in plasma noradrenaline values over time, whereas patients with a poor outcome and controls did; this difference was significant on day 12 only ($P < 0.03$).

As a large amount of subarachnoid blood on admission CT is a powerful predictor of poor outcome, the noradrenaline values over time were stratified for the amount of subarachnoid blood ($\leq 20$ and $> 20$; range 0–30) on admission CT. After the third day, plasma noradrenaline values were higher in patients with a large amount of subarachnoid blood but this difference was statistically significant only on day 12 ($P < 0.04$). When the noradrenaline concentrations were also stratified for Glasgow coma scale score (14 and <14), intraventricular blood ($\leq 2$ and $>$; range 0–12), intracerebral haematomata (no or yes), or age ($\leq 53$ and $>$53), all curves strongly resembled the right panel of the figure, which implies covariation. We performed
Plasma noradrenaline concentrations (mean (SEM)) over time in patients with a subarachnoid haemorrhage (□) and in controls (△). In the right panel the patient group is stratified for outcome (poor outcome □, good outcome ○). *Significant difference between the groups on that particular day. Horizontal lines are the limits of normal values.

135 CT scans. A combination of rebleeding and infarction occurred in five patients. The occurrence of infarction or rebleeding was not related to the concentrations of noradrenaline.

Discussion
Most patients with SAH as well as controls had increased noradrenaline concentrations on most days, although the variance of these values was large. Patients and controls were both exposed to pain and to the stress of an intensive care unit, which allowed us to distinguish changes in noradrenaline concentrations from hypothalamic damage, expected only in patients with SAH. There were no obvious differences between patients and controls with regard to severity of pain or to prescribed medication. Controls had the highest values of plasma noradrenaline, probably explained by strong physical stress resulting from operation.

Individual ECG abnormalities were not obviously related to clinical and radiological characteristics at baseline, as described before. Therefore we used a combination of ECG abnormalities as possible indices of cardiac ischaemia, the broader category of which is known to be related to outcome. As patients and controls were comparable with regard to age, cardiovascular history, and blood pressure, we assumed that the proportion of pre-existent ECG abnormalities in both groups was also similar. Nevertheless, we found twice as many abnormal ECGs in patients as in controls.

Despite the high plasma noradrenaline in controls, cardiac ischaemia was much rarer than in patients with SAH. This difference in occurrence of cardiac ischaemia and plasma noradrenaline concentrations between the groups was large and significant. Therefore we think that, although plasma noradrenaline concentrations reflect myocardial noradrenaline concentrations only indirectly and probably incompletely, high plasma noradrenaline concentrations in patients with SAH are not a sufficient explanation for the development of cardiac ischaemia, by contrast with generally held beliefs. Grad et al. also concluded that ECG changes did not depend on raised plasma noradrenaline concentrations, but they did not adjust for clinical and radiological factors, or study a control group. Theoretically, we may have missed a very early rise in noradrenaline as a result of the primary impact of the haemorrhage on the hypothalamus, but as 65% of the patients were entered in the study within 24 hours of the haemorrhage this is unlikely.

The association between increased cardiac enzymes and cortisol on the one hand and cardiac ischaemia on the other was marginal; apparently structural damage of the myocardium can often be mild (normal enzymes), and still cause signs of cardiac ischaemia on the ECG.

Cardiac ischaemia is associated with poor outcome, but in a previous study we showed that this association is indirect, in that ECG changes reflect the impact of the primary bleeding, perhaps via hypothalamic damage, that results in increased secretion of noradrenaline. In the first three days of our study period there were no significant differences in noradrenaline concentrations between patients with good and poor outcome; from day 6 onwards the differences in noradrenaline concentrations between patients with good and poor outcome became more clear. Stratification for known predictors of poor outcome (Glasgow coma scale score <14, amount of subarachnoid blood >20, amount of intraventricular blood >2, presence of an intracerebral haematoma, or age >53 years), however, showed that noradrenaline concentrations are not independently related to outcome. In addition the clinical and radiological factors have more practical value as predictors of poor outcome than increased noradrenaline concentrations, as they can be obtained on the day of admission.
The cause of delayed cerebral ischaemia after SAH is largely unknown. Although noradrenaline has often been implicated as the causative factor, we were not able to find an association between raised plasma noradrenaline and infarction in our patient group, which is in agreement with another recent study. The occurrence of rebleeding was not associated with raised noradrenaline either.

In conclusion, raised plasma noradrenaline concentrations after SAH do not explain cardiac ischaemia. Both factors should be considered indirect measures of cerebral damage (probably via hypothalamic damage). Therefore, the prediction of complications and poor outcome from the Glasgow coma scale score and the CT findings on admission is more relevant, more accurate, and more practical than assessment of noradrenaline or identification of ECG abnormalities.