Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: the role of coagulation and fibrinolysis

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Early increased cortisol level is associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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Abstract

Background and purpose
In patients with aneurysmal subarachnoid hemorrhage (SAH) hyperglycemia, hypertension, and endothelium dysfunction are associated with the occurrence of delayed cerebral ischemia (DCI). Since these are physiological reactions of increased cortisol secretion, the purpose of the present study was to investigate whether increased serum cortisol levels after SAH are associated with the occurrence of DCI.

Methods
Blood samples were obtained at standard intervals after SAH. DCI was defined as the gradual onset of new focal neurological impairment and/or a decreased level of consciousness of at least 2 points as recorded on the Glasgow Coma Scale.

Results
Thirty-one patients were included. Eleven patients (35%) developed DCI. Patients with DCI had a significantly higher median cortisol level two days after SAH than patients without DCI (1026 nmol/l [range 408-1280 nmol/l] vs. 716 nmol/l [range 50-1164 nmol/l] respectively, p=0.006). The logistic model revealed a significant (p=0.021) univariate association between the first cortisol assessment and DCI occurrence. An increase of 250 nmol/l in early cortisol level was associated with a 2.42 (95% CI 1.14–5.14) times increased odds on DCI occurrence. The association remained significant after adjusting (in separate models) for the known predictors of DCI occurrence (amount of blood on admission CT scan using the Hijdra score, loss of consciousness during ictus, and admission GCS).

Conclusions
Increased serum cortisol levels early after SAH are associated with DCI occurrence, and therefore can be a useful risk indicator in clinical practice.
Cortisol is a glucocorticoid hormone which is secreted during a stress response. Physiological reactions of increased cortisol secretion include hyperglycemia, hypertension, and endothelium dysfunction.\(^1\) Since in patients with aneurysmal subarachnoid hemorrhage (SAH) hyperglycemia, hypertension, and endothelium dysfunction are associated with the occurrence of delayed cerebral ischemia (DCI), an increased stress response could play a pivotal role in the development of DCI.\(^2^-^5\) To our knowledge this has never been investigated before, and therefore the purpose of the present study was to investigate the prognostic value of increased serum cortisol levels after aneurysmal SAH on DCI occurrence.

## Methods

We used data and serum samples from a single-center, prospective, randomized, double-blind, placebo-controlled trial investigating the effect of simvastatin on endothelial function, coagulation, fibrinolysis, and inflammation in patients with SAH.\(^6\) This study was registered in the International Standard Randomised Controlled Trial registry (number ISRCTN45662651) and approved by the local Institutional Review Board. In short, consecutive patients with SAH in the last 72 hours presenting at the Academic Medical Center, Amsterdam, the Netherlands, were randomized to receive 80 mg simvastatin or placebo until day 14 after SAH. In the former study, use of simvastatin did not influence any parameters of endothelial function, coagulation, fibrinolysis, and inflammation, and no effect was observed on TCD vasospasm and clinical signs of DCI.\(^5\) Therefore, all patients of the former study, except one patient who had no aneurysm on angiography, were eligible for inclusion in the present study.

DCI was defined as the gradual onset of new focal neurological impairment and/or a decreased level of consciousness of at least 2 points as recorded on the Glasgow Coma Scale (GCS), either with cerebral infarction on CT scan compatible with clinical presentation or proven at autopsy, or in case no CT scan or autopsy was obtained, suspect for infarction with exclusion of other causes by appropriate laboratory studies.

On admission, the amount of cisternal and ventricular blood on admission CT scan was calculated using the Hijdra score.\(^7\) Blood samples were obtained at standard intervals: 2±1, 4±1, 7±1, 10±1, 14±1, and 17±1 days after SAH, between 8:00 and 9.30 AM to avoid diurnal fluctuations of serum markers. During the first blood withdrawal at day 2, and the last at day 17 after SAH, patients did not use study medication. In case of hospital discharge before day 17, no further samples were obtained.

## Statistics

To investigate differences in baseline characteristics between patients with and without DCI we used the unpaired \(t\)-test, Mann-Whitney test, \(\chi^2\) or Fisher’s exact test, where appropriate.
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The possible difference in cortisol levels over time between the groups of patients with and without DCI was investigated with a linear mixed effects model, using the nlme package in the R statistical program. In this model, the parameters that describe the development of cortisol level over time (the intercept and slope) were allowed to differ per individual. Based on the results from the mixed model approach, we subsequently tested the prognostic value of early cortisol levels on DCI occurrence using a logistic model (SPSS 16.0). Subsequently, we extended this logistic model by adjusting (in separate models) for the known predictors of DCI occurrence (amount of blood on admission CT scan using the Hijdra score, loss of consciousness during ictus, and admission GCS).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=31)</th>
<th>No DCI (n=20)</th>
<th>DCI (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, year (SD)</td>
<td>53 (11)</td>
<td>52 (11)</td>
<td>55 (10)</td>
<td>0.52*</td>
</tr>
<tr>
<td>N of women (%)</td>
<td>19 (61)</td>
<td>13 (65)</td>
<td>6 (55)</td>
<td>0.71†</td>
</tr>
<tr>
<td>N of patients with history of hypertension (%)</td>
<td>6 (19)</td>
<td>4 (20)</td>
<td>2 (18)</td>
<td>&gt;0.99†</td>
</tr>
<tr>
<td>Median WFNS-score on admission (range)</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
<td>3 (1-5)</td>
<td>0.27‡</td>
</tr>
<tr>
<td>Median GCS score on admission (range)</td>
<td>14 (5-15)</td>
<td>14 (5-15)</td>
<td>13 (5-15)</td>
<td>0.32‡</td>
</tr>
<tr>
<td>N of patients with initial GCS score of 15 (%)</td>
<td>9 (29)</td>
<td>6 (30)</td>
<td>3 (27)</td>
<td>&gt;0.99†</td>
</tr>
<tr>
<td>N of patients with focal neurological impairment (%)</td>
<td>9 (29)</td>
<td>5 (25)</td>
<td>4 (36)</td>
<td>0.68†</td>
</tr>
<tr>
<td>N of patients with loss of consciousness during ictus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- yes (%)</td>
<td>17 (55)</td>
<td>10 (50)</td>
<td>7 (64)</td>
<td>0.71†</td>
</tr>
<tr>
<td>- no (%)</td>
<td>12 (39)</td>
<td>8 (40)</td>
<td>4 (36)</td>
<td></td>
</tr>
<tr>
<td>- unknown (%)</td>
<td>2 (7)</td>
<td>2 (10)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure on admission (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systolic</td>
<td>161 (34)</td>
<td>156 (32)</td>
<td>171 (38)</td>
<td>0.28*</td>
</tr>
<tr>
<td>- diastolic</td>
<td>91 (18)</td>
<td>90 (14)</td>
<td>95 (25)</td>
<td>0.53*</td>
</tr>
<tr>
<td>Median Hijdra-score admission CT-scan (range)</td>
<td>23 (2-37)</td>
<td>23 (2-37)</td>
<td>28 (17-31)</td>
<td>0.06‡</td>
</tr>
</tbody>
</table>

Location of aneurysm

<table>
<thead>
<tr>
<th></th>
<th>Total (n=31)</th>
<th>No DCI (n=20)</th>
<th>DCI (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- anterior circulation (%)</td>
<td>27 (87)</td>
<td>17 (85)</td>
<td>10 (91)</td>
<td>&gt;0.99†</td>
</tr>
<tr>
<td>- posterior circulation (%)</td>
<td>4 (13)</td>
<td>3 (15)</td>
<td>1 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients using simvastatin during hospitalisation (%)

<table>
<thead>
<tr>
<th>Total (n=31)</th>
<th>No DCI (n=20)</th>
<th>DCI (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (48)</td>
<td>9 (45)</td>
<td>6 (55)</td>
<td>0.61§</td>
</tr>
</tbody>
</table>

Legends: DCI = delayed cerebral ischemia; SD = standard deviation; GCS = Glasgow Coma Score; WFNS = World Federation of Neurological Surgeons; * = based on Student’s t-test; † = based on Fisher’s exact test; ‡ = based on Mann-Whitney U test; § = based on χ²

Based on the results from the mixed model approach, we subsequently tested the prognostic value of early cortisol levels on DCI occurrence using a logistic model (SPSS 16.0). Subsequently, we extended this logistic model by adjusting (in separate models) for the known predictors of DCI occurrence (amount of blood on admission CT scan using the Hijdra score, loss of consciousness during ictus, and admission GCS).
Results

After written informed consent was obtained, 31 patients were included in this study. Baseline characteristics are listed in the Table. Twenty-four patients (77%) were coiled and 7 patients (23%) were clipped. Median day of aneurysm treatment after SAH was day one (range 0-30). Eleven patients (35%) developed DCI. Signs of DCI started at a median of 6 days (range 4-10 days). No significant differences were observed in baseline characteristics between patients with and without DCI occurrence, although a clear trend was observed toward higher admission CT scan Hijdra-scores in the group of patients with DCI (p=0.06).

For cortisol, there was a significant difference between the groups of patients with and without DCI. Patients who developed DCI had a significantly higher median cortisol level 2 days after SAH than patients who did not develop DCI (1026 nmol/l [range 408-1280 nmol/l] vs. 716 nmol/l [range 50-1164 nmol/l] respectively, p=0.006). Over time the difference between the two groups decreased (p-value for difference in slope 0.04) (Figure).

Since the linear mixed model showed that cortisol levels 2 days after SAH were higher in the DCI group, we also tested the prognostic value of first cortisol assessment on DCI occurrence.
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The logistic model revealed a significant (p=0.021) univariate association between the first cortisol assessment and DCI occurrence, with an odds ratio per unit cortisol of 1.004. This means that an increase of for instance 250 nmol/l in early cortisol level reflects a 2.42 (95% CI 1.14–5.14) times increased odds on DCI occurrence. The association remained significant after adjusting (in separate models) for the most important predictors of DCI occurrence (amount of cisternal and ventricular blood on admission CT scan, loss of consciousness during ictus, and admission GCS (p-values for cortisol in these multivariate logistic models 0.05, 0.02 and 0.03, respectively).

Discussion

To our knowledge, this is the first study to show that increased cortisol levels early after SAH are of prognostic value for the occurrence of DCI. The association between cortisol and DCI remained significant after adjusting in separate models for other known predictors of DCI occurrence, namely the amount of cisternal and ventricular blood on admission CT scan, loss of consciousness during ictus, and a low Glasgow Coma Score on admission.

Several previous studies investigated cortisol levels in SAH patients, but never in relation to the occurrence of DCI. Some studies showed that serum levels of cortisol were increased after SAH, especially early after the hemorrhage. Associations have been found with electrocardiographic abnormalities, and with poor outcome and mortality rates. Another study investigated the relation between cortisol and the occurrence of angiographic vasospasm. In that study, increased mean cortisol levels were observed in patients with impaired levels of consciousness and in patients with vasospasm, especially before onset of spasm. However, data were difficult to interpret since a mean cortisol level was calculated from all available measurements.

How can an increased stress response, as reflected by increased cortisol levels, lead to DCI? Previous studies showed that aneurysmal SAH often results in ischemia of the hypothalamus. Hypothalamic stimulation results in a stress response, with increased cortisol levels mediated by the pituitary adrenocortical axis. In turn, an increased stress response results in endothelium dysfunction. Therefore, in aneurysmal SAH, an increased stress response might aggravate endothelium dysfunction and thereby promote the development of DCI. This hypothesis is supported by the results from an autopsy study which showed that almost all patients with hypothalamic lesions after SAH have widespread ischemic lesions in the cortex.

Our study has some limitations that need to be addressed. First, blood samples were derived from a study investigating the effects of simvastatin, and one could argue that our results represent an effect caused by the simvastatin treatment. However blood samples in this exploratory study were assessed at standard intervals, and simvastatin use did not show an
Cortisol levels are associated with DCI
effect of simvastatin on serological parameters, nor on DCI or TCD vasospasm. Moreover, the study medication was started after the first blood withdrawal at day 2 after SAH. Although simvastatin has been associated with a reduction of DCI, a recent phase II study did not show a beneficial effect.\textsuperscript{17-19} Furthermore, a recent retrospective study showed that the rate of radiographic vasospasm, symptomatic vasospasm, delayed cerebral infarction, and clinical outcome did not change after implementation of statins in the routine treatment of SAH patients.\textsuperscript{20,21} Second, since we measured cortisol levels two days after admission, it could be that an even stronger association with DCI could be found when cortisol was measured directly after admission. Third, the sample size was too small for one multivariate model, which we solved by adjusting for three possible confounders separately.

We conclude that increased serum cortisol levels early after SAH are associated with DCI occurrence. Since serum can easily be obtained and cortisol concentrations easily measured, elevated cortisol levels in the acute phase can be a useful risk indicator in clinical practice. Finally, our results suggest that the increased stress response as represented by elevated cortisol levels after aneurysmal SAH deserves further exploration as a possible treatment target to prevent DCI.
References


Cortisol levels are associated with DCI

