Effects of Induced Hypertension on Cerebral Perfusion in Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage
A Randomized Clinical Trial

Celine S. Gathier, MD; Jan Willem Dankbaar, MD, PhD; Mathieu van der Jagt, MD, PhD; Bon H. Verweij, MD, PhD; Annemarie W. Oldenbeuving, MD, PhD; Gabriel J.E. Rinkel, MD, FRCPE; Walter M. van den Bergh, MD, PhD; Arjen J.C. Slooter, MD, PhD; for the HIMALAIA Study Group*

Background and Purpose—The presumed effectiveness of induced hypertension for treating delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage is based on uncontrolled case-series only. We assessed the effect of induced hypertension on cerebral blood flow (CBF) in aneurysmal subarachnoid hemorrhage patients with delayed cerebral ischemia in a randomized clinical trial.

Methods—Aneurysmal subarachnoid hemorrhage patients were randomized to induced or no induced hypertension (control group) at delayed cerebral ischemia onset. CBF was assessed, blinded for treatment allocation, with computed tomographic perfusion in standardized predefined regions at delayed cerebral ischemia onset and after 24 to 36 hours of study treatment. Mean arterial blood pressure was compared between groups (linear mixed model). The primary outcome measure was the difference in change in overall CBF (Mann–Whitney U test).

Results—Mean arterial blood pressure was, on average, 12 mm Hg (95% confidence interval, 8.6–14.5) higher in the hypertension group (n=12) than in the control group (n=13). Change in overall CBF (mL/100g per s) was −8.5 (range, −42 to 30) in the control group and 0.1 (range, −31–43) in the hypertension group (P=0.25).

Conclusions—Change in overall CBF did not differ to a statistically significant extent between the groups. Based on our results, 225 to 250 patients per group are needed to find a statistically significant difference in change in overall CBF between induced hypertension and no hypertension.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT0161323.

Key Words: arterial pressure | cerebral infarction | hypertension | randomized controlled trial | subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) contributes to poor outcome after aneurysmal subarachnoid hemorrhage and may occur when the cerebral blood flow (CBF) no longer meets the demand of the brain tissue in the setting of impaired cerebrovascular autoregulation. Vasospasm is an important cause of DCI, and for many decades, the so-called triple-H therapy is used to target this potential cause of DCI. Of this triple-H therapy, induced hypertension seems most promising in increasing CBF to improve symptoms of DCI, but its presumed effectiveness is based on uncontrolled case-series only. We performed a randomized controlled trial to assess the effect of induced hypertension on CBF with computed tomographic perfusion (CTP) in patients with DCI after aneurysmal subarachnoid hemorrhage.

Methods

Study Design and Patients
From 2009 to 2015, we performed this study as part of a multicenter randomized controlled trial on the effectiveness of induced hypertension on clinical outcome. The study was approved by the relevant medical ethics committees (MEC 10–157). Inclusion and exclusion criteria and informed consent procedure were published previously. DCI was defined as a decrease of ≥1 point on the Glasgow Coma
Intention to Treat
Crossover Case Excluded

Table 1. Patient Characteristics Per Group

<table>
<thead>
<tr>
<th></th>
<th>No Induced Hypertension (n=13)</th>
<th>Induced Hypertension (n=12)</th>
<th>Excluded Patients (n=11)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>59 (10.7)</td>
<td>54 (10.4)</td>
<td>68 (9.2)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>11 (85)</td>
<td>7 (58)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Hypertension before aSAH (%)</td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Antihypertensive medication at admission (%)</td>
<td>0</td>
<td>1 (8)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>WFNS score &gt;3 (%)</td>
<td>5 (38)</td>
<td>7 (58)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Aneurysm anterior circulation (%)</td>
<td>8 (62)</td>
<td>11 (92)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Hijdra sumscore &gt;median of 27.5 (%)</td>
<td>6 (46)</td>
<td>7 (58)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Aneurysm treatment: clip/coil (%)</td>
<td>7 (54)/6 (46)</td>
<td>6 (50)/6 (50)</td>
<td>2 (18)/9 (62)</td>
</tr>
<tr>
<td>ICH present (%)</td>
<td>4 (31)</td>
<td>3 (25)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>1 (8)</td>
<td>0</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Age-adjusted bicaudate index &gt;1 (%)</td>
<td>4 (31)</td>
<td>5 (42)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Onset DCI, days after aSAH, mean (SD)</td>
<td>6.5 (4.1)</td>
<td>5.4 (2.0)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Time between CTP1 and CTP2, h, mean (SD)</td>
<td>33 (8.7)</td>
<td>32 (7.3)</td>
<td>37 (11.3)†</td>
</tr>
<tr>
<td>MAP at baseline, mean (SD)</td>
<td>99 (10.7)</td>
<td>100 (15.2)</td>
<td>95 (12.2)†</td>
</tr>
</tbody>
</table>

*aSAH indicates aneurysmal subarachnoid hemorrhage; CTP1, computed tomographic perfusion during clinical deterioration; CTP2, CTP 24–36 hours after randomization; DCI, delayed cerebral ischemia; ICH, intracerebral hematoma; MAP, mean arterial blood pressure; and WFNS, World Federation of Neurosurgical Societies.

*D patients randomized to induced hypertension and 6 patients randomized to the control group.
†Available for 6 patients.

Scale sumscores of balance scores, with exclusion of any other explanation for the deterioration, such as (increasing) hydrocephalus, recurrent bleeding, epilepsy (electroencephalography performed in case of suspicion of epilepsy), an infectious disease with associated decrease in consciousness level, hypoglycemia (<3.0 mmol/L) or hyponatremia (<125 mmol/L), metabolic encephalopathy caused by renal or hepatic failure or any other possible cause for deterioration as judged by the treating physician.

All eligible aneurysmal subarachnoid hemorrhage patients of whom informed consent was obtained on admission were randomized at random block size of 8.

Interventions

Hypertension was induced for at least 24 to 48 hours with norepinephrine in the intensive care unit until improvement of neurological deficits, occurrence of a complication, a maximum mean arterial blood pressure (MAP) of 130 mmHg, or a maximum systolic blood pressure of 230 mmHg.4

In the control group, MAP was not raised, but a MAP <80 mm Hg was avoided with vasopressors. In this group, patients were managed either at a medium care unit or intensive care unit. In intensive care unit–patients, MAP was continuously measured intra-arterially. Only the hourly, nurse-validated measurements were obtained for statistical analyses. In patients in the control group who remained in the medium care unit, blood pressure was measured noninvasively, at least every 4-hourly. All patients were treated with oral nimodipine, which was started directly after hospital admission and continued during the entire admission period and received fluids aiming for normovolemia.

CTP Imaging Protocol and Evaluation

All patients underwent CTP imaging at the time of clinical deterioration (CTP1) and after 24 to 36 hours of study treatment (CTP2), all performed on a 64- or 128-multidetector CT-scanner (Philips Healthcare, Best, the Netherlands; Siemens, Den Haag, The Netherlands), covering 40 to 80 mm, at the level of the basal ganglia and lateral ventricles.

All CTP scans were reconstructed at 5-mm slices and transferred to a workstation (IntelliSpace Portal; Philips Healthcare). CBF was

Table 2. Differences in Change in CBF Values Between the Groups

<table>
<thead>
<tr>
<th></th>
<th>No Induced Hypertension (n=13)</th>
<th>Induced Hypertension (n=12)</th>
<th>Crossover Case Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intention to Treat</td>
<td>Crossover Case Excluded</td>
<td></td>
</tr>
<tr>
<td>Change in overall CBF</td>
<td>−8.5 (−42 to 30)</td>
<td>−9.7 (−42 to 30)</td>
<td>−9.7 (−42 to 30)</td>
</tr>
<tr>
<td></td>
<td>(−31 to 43)</td>
<td>(−31 to 43)</td>
<td>(−31 to 43)</td>
</tr>
<tr>
<td>Change in lowest CBF</td>
<td>1.0 (−23 to 41)</td>
<td>1.9 (−23 to 41)</td>
<td>1.9 (−23 to 41)</td>
</tr>
<tr>
<td></td>
<td>11.2 (−23 to 50)</td>
<td>10.3 (−23 to 50)</td>
<td>11.2 (−23 to 50)</td>
</tr>
<tr>
<td>Change in largest CBF</td>
<td>0.1 (−1.0 to 1.7)</td>
<td>0.2 (−1.0 to 1.7)</td>
<td>0.2 (−1.0 to 1.7)</td>
</tr>
<tr>
<td></td>
<td>0.0 (−1.5 to 2.6)</td>
<td>0.0 (−1.5 to 2.6)</td>
<td>0.0 (−1.5 to 2.6)</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow (ml/100g/min).
*Mann–Whitney U test.
estimated, blinded for treatment allocation, in 12 predefined regions of interest drawn in cortical gray matter and basal ganglia.

As primary outcome, we calculated the mean absolute CBF of all regions of interest (overall CBF) at CTP1 and CTP2 per patient. Change in overall CBF between these time points was subsequently calculated and compared between groups.

Furthermore, as secondary outcome measures, we compared between the groups the change in CBF in the patients’ region of interest with the lowest absolute value of CBF at CTP1 (lowest CBF) and assessed relative measurements by comparing between the groups the change in the patients’ lowest interhemispheric CBF ratio (reflecting the largest perfusion asymmetry) between the timepoints (largest CBF asymmetry).
Sample Size and Statistical Analysis
We calculated that a sample of 26 patients (13 per group) would yield a power of 80%, at a significance level of 0.05, to detect a 60% absolute difference in improvement in overall CBF in the hypertension group versus the control group. For this explanatory study, we primarily performed on-treatment analyses, but an intention-to-treat analysis was additionally performed in case of crossover of patients. MAP over time was compared between groups (linear mixed model). The difference between groups in change in overall CBF, lowest CBF, and largest CBF asymmetry was analyzed (Mann–Whitney U test). Per group, the difference in overall and lowest CBF between CTP1 and CTP2 was assessed (Wilcoxon signed-rank test; post hoc analysis).

Results
Of 36 randomized patients, 11 were excluded because one or both of the CTP scans were not performed (n=4); one of the CTP scans failed because of movement artifacts or insufficient contrast arrival (n=2) or the CTP scans were not suitable for postprocessing (n=5), leaving 25 patients with 50 CTP scans included in the study. Thirteen patients were randomized to induced hypertension and 12 to no hypertension (Table 1). One patient randomized to induced hypertension never received hypertension induction because cardiac ultrasound, performed before the intervention because of low venous oxygen saturation, revealed a previously unknown cardiomyopathy. Induced hypertension was judged contraindicated by the treating physician. This patient was primarily analyzed in the control group, but an intention-to-treat analysis and analysis with exclusion of this patient were additionally performed.

Between CTP1 and CTP2, the MAP was, on average, 12 mm Hg (95% confidence interval, 8.6–14.5 mm Hg) higher in the hypertension group than in the control group. All patients in the hypertension group were still receiving induced hypertension at time of CTP2.

Change in overall CBF (ml/100g/min) was 0.1 (−31 to 43) in the hypertension group versus −8.5 (−42 to 30) in the control group (P=0.25). Secondary outcome measures did not differ significantly between the groups either, and all results remained similar with intention-to-treat analysis and analysis with exclusion of this patient were additionally performed.

Individual mean values of overall and lowest CBF are shown in the Figure. Only in the hypertension group, there was a trend toward improved CBF at CTP2 in the lowest perfused region.

Serious adverse events occurred in the hypertension and control group as follows: death 2 versus 1, pneumothorax 1 versus 0, atrial fibrillation 1 versus 0, myocardial ischemia 1 versus 0.

Discussion
We investigated the effects of induced hypertension alone because hypervolemia and hemodilution were earlier found not promising in increasing CBF.3 CTP is of practical use and provides accurate estimation of CBF.5

Several limitations of our study are inherent to using CTP. By assessing CBF in predefined regions, we might have missed areas with more severe perfusion deficits. Selecting regions in visible areas of hypoperfusion could result in more pronounced changes in CBF but also observer bias. Second, although perfusion measurements with CTP have been validated,6 exact quantification remains difficult. For this reason, we also analyzed relative CBF measurements by comparing both hemispheres. However, when solely using this approach, bilaterally decreased perfusion can be missed.

Furthermore, 11 patients were excluded from the study because of unavailable CTP data. However, because in most cases exclusion was caused by technical problems, we believe the CTP data were missing at random and the likelihood of selection bias to be low. The greater proportion of high-grade WFNS (World Federation of Neurosurgical Societies) patients in the hypertension group may, however, have biased the results. Patients in the hypertension group were more often admitted to the intensive care unit than patients from the control group. As outcome assessment was blinded, it is unlikely that this would have affected our results.

Strengths of the study are the randomized controlled design allowing for more firm conclusions than in previous uncontrolled studies, and the achievement of a significantly higher MAP in the hypertension group.

Our findings do not support the use of induced hypertension to augment overall CBF in aneurysmal subarachnoid hemorrhage patients with DCI. However, a small effect cannot be definitively excluded because a trend was seen in improved CBF in areas with lowest perfusion. This might be of clinical interest, as hypoperfused areas might progress to infarction if not treated. Induced hypertension might thus be beneficial in improving CBF in regions with impaired perfusion. Based on our results, 225 to 250 patients per group would be needed to find a statistically significant difference in change in overall CBF between induced hypertension and no hypertension.

Appendix
Ale Algra, Walter M. van den Bergh, Gus N. Beute, Bert A. Coert, Jan Willem Dankbaar, Ruben Dammers, Diederik W.J. Dippel, Clemens M.F. Dirven, Celine S. Gathier, Janneke Horn, Mathieu van der Jagt, Marcella C. Müller, Jozef Kesecioglu, Fop van Kooten, Aad van der Lugt, Annemarie W. Oldenbeuving, Bram van der Pol, Gabriel J.E. Rinkel, Gerwin Roks, Willem J. van Rooij, Irene C. van der Schaaf, Arjen J.C. Slooter, Menno Sluzewski, W. Peter Vandertop, Bon H. Verweij.

Disclosures
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4. Gathier CS, van den Bergh WM, Slooter AJ; HIMALAIA-Study Group. HIMALAIA (Hypertension Induction in the Management of


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