Endovascular Rescue Therapies for Refractory Vasospasm After Subarachnoid Hemorrhage: A Prospective Evaluation Study Using Multimodal, Continuous Event Neuromonitoring

Walid Albanna, MD*
Miriam Weiss, cand.med.*
Marguerite Müller, MD†
Marc Alexander Brockmann, MD‡
Annette Rieg, MD§
Catharina Conzen, MD*
Hans Clusmann, MD*
Anke Höllig, MD*
Gerrit Alexander Schubert, MD*

*Department of Neurosurgery, RWTH Aachen University, Aachen, Germany
†Department of Diagnostic and Interventional Neuroradiology, RWTH Aachen University, Aachen, Germany
‡Department of Intensive Care Medicine and Intermediate Care, RWTH Aachen University, Aachen, Germany

Correspondence:
Gerrit Alexander Schubert, MD,
Department of Neurosurgery, RWTH Aachen University,
Pauwelsstr. 30, 52074 Aachen, Germany.
E-mail: gerrit.schubert@me.com

Received, February 6, 2016.
Accepted, July 16, 2016.

Treatment of patients with aneurysmal subarachnoid hemorrhage (aSAH) is a multidisciplinary effort and remains a clinical challenge for its persistent high overall morbidity and mortality. Delayed cerebral ischemia as a result of clinically relevant, cerebral compromise has been shown to be a significant contributor for outcome and is thought to be caused—at least in part—by cerebral vasospasm. Therefore, medical management is aimed toward counteracting vasospasm and prevention of delayed cerebral ischemia in order to improve outcome.

OBJECTIVES

To detect clinically relevant cerebral compromise, awake patients can be monitored...
via neurological exam; however, in high-grade, unconscious, or sedated aSAH patients, monitoring is more demanding. Several invasive and noninvasive monitoring techniques are available, each with its own characteristic set of advantages and disadvantages. Perfusion delay may be detected by CT or MR perfusion imaging, and vasocostriction can be documented by digital subtraction angiography, though the hemodynamic relevance of the latter remains a matter for discussion. Continuous measurements of perfusion or oxygenation can be performed using Cerebral Blood Flow–2,3 or pO2 probes,4 and for an estimate of cerebral metabolism, microdialysis probes are available.5,7 Use of invasive techniques should comply with recent consensus recommendations.8,9

Hemodynamic augmentation and prophylactic oral administration of the calcium channel blocker nimodipine10,11 are the mainstay of current treatment efforts.12 However, in deteriorating patients refractory to these measures alone, endovascular rescue therapies (ERT) as measures of last resort can be considered.13 Though transluminal balloon or stent angioplasty (AP)14 is limited to proximal vessel segments and can cause dissection and rupture,15 it effectively restores vessel diameter, subsequently improving cerebral perfusion and clinical outcome.16,17 Intrathecal lysis (IAL) with vasodilating agents,18 though of limited efficacy if employed as a bolus or short term infusion,19,20 can be used effectively if applied continuously with a microcatheter in situ.21,22 This, however, may be associated with a different risk profile, including thromboembolism and catheter occlusion, but also the need for more rigorous circulatory support to maintain adequate perfusion pressure.

ERT are aimed at immediate improvement of cerebral blood flow and thereby oxygenation and metabolism, but the immediate effect is unclear. To assess their efficacy in real time, continuous assessment of oxygenation and metabolism as facilitated by invasive neumonitoring is essential.

In view of the limitations, the aforementioned risk profile and a questionable superiority over medical treatment alone,23 a better understanding of the mechanism and a more detailed quantification of the immediate efficacy of ERT seem warranted. It may ultimately enable us to tailor the treatment approach individually, such as timely adjustment and refinements of infusion rates (IAL) as well as consideration of further imaging studies. It is therefore the purpose of this prospective evaluation study to investigate the effect of ERT (AP, IAL) on refractory vasospasm as determined by cerebral oxygenation and metabolism.

### METHODS

#### Study Design

This is a prospective observational study of consecutive patients treated for documented aSAH at our institution from December 2014 until December 2015.

#### Setting

The study was approved by the local ethics committee (EK 602/14), and informed consent for study inclusion was obtained in all patients or their legal representatives, respectively. Demographic and clinical data were recorded, as was the modality of initial treatment, incidence of cerebral infarction occurring until the time of discharge, but unrelated to the initial procedure itself (clipping, coiling), as well as clinical outcome after 3 months (unfavourable outcome: Glasgow outcome score [GOS] 1–3, favourable outcome: GOS 4–5).

### Synopsis of Current Treatment Algorithm

All patients are treated according to the established standard operating procedure of our institution. After securing of the offending aneurysm, patients are observed on a dedicated intensive care unit and receive oral nimodipine prophylaxis and daily transcranial Doppler (TCD) measurements. Blood pressure is kept above 120 mm Hg in all patients with no upper limit (permissive hypertension).

#### Management of Neumonitoring

Patients receive invasive intracranial neumonitoring in line with recent consensus statements.9,24 Via a small craniostomy and after dural probe (Neurovent PTO, Raumedic, Helmbrechts, Germany) and a microdialysis probe for assessment of brain metabolism (71 High Cut-Off Brain Microdialysis Catheter, μdialysis, Stockholm, Sweden) are advanced about 3 to 4 cm subcortically, chosen to terminate within the vascular territory of the aneurysm and held in place by a bolt which is affixed within the craniostomy. P2O2, intracranial pressure, and cranial perfusion pressure are recorded continuously (Raumedic MPR Datalogger, Raumedic). Microdialysis probes are perfused at 0.3 μL/min with standard isotonic perfusion fluid (μdialysis), samples collected at a minimum of 3-h intervals and analyzed on site for cerebral extracellular glucose, lactate, pyruvate, glutamate, and glycerol (Iscusflex, μdialysis) or stored for later off-line analysis.

#### Management of Delayed Cerebral Ischemia

If patients show signs of clinical deterioration and other underlying etiologies (such as infection, electrolyte disturbances, and hydrocephalus) have been ruled out, hyperventilation with systolic blood pressure of greater than 180 mm Hg is induced. With persistent neurological deficit or a persistent functional deficit (decrease of ptiO2 by more than 30 mm Hg), a trend towards lower arterial pCO2 (less than 25 mm Hg), or cerebrovascular accident (CVA), nimodipine prophylaxis and daily transcranial Doppler (TCD) measurements are performed until December 2015. In all instances, vessels are slightly underdilated to prevent vessel injury.

For more generalized, distally located and/or technically inaccessible vasospasm, IAL is considered. Microcatheters (Excelsior SL10—Stryker Neurovascular; Rebar 18—Covidien/ev3, Irvine, California) are placed in the internal carotid artery just below the petrous segment or in the distal V2-segment of the vertebral artery. Through each microcatheter, nimodipine (Carinopharm, Elze, Germany; mean dose 15.6 ± 9.5 μg/kg BW/h) and heparinized saline solution are continuously infused.
Treatment Groups

For this study, treatment groups were defined as follows: AP only (ERT 1), IAL only (ERT 2), AP + IAL (ERT 3). Modality, timing, site, and duration of the intervention were documented. Continuous recording of $p_{O_2}$ was performed throughout the intervention, and microdialysates were sampled at least every 3 h. As part of our prospective study protocol, patients also underwent daily serum and cerebrospinal fluid sampling (provided an existing external ventricular or lumbar drain); samples were analyzed for glucose, lactate, c-reactive protein, S100, interleukin 6, and tumor necrosis factor $\alpha$. All ERT-related complications (dissection/perforation, infection, occlusion/thrombosis, treatment termination secondary to excessive vasopressor demand) were recorded.

For initial analysis, all ERT data were pooled irrespective of probe position in relation to ERT site or technique used; further analysis included stratification according to treatment modality (ERT 1-3) and site of intervention in relation to probe localization (probe in territory of ERT vs not in territory of ERT).

Statistical Analysis

Quantitative data are presented as mean ± standard deviation and as percentage. Student t-test, Mann–Whitney test, and 1-way ANOVA were used for comparison of quantitative parameters as applicable. Fisher’s exact and Chi-square tests were used for dichotomous criteria (Numbers®, Apple Inc., Cupertino, California; GraphPad Prism®, GraphPad Software, Inc., La Jolla, California; SAS 9.3, SAS Institute Inc., Cary, North Carolina). Statistical significance was set at $P < .05$.

RESULTS

Patient Characteristics

Thirteen consecutive patients were included for this analysis; demographic data and aneurysm treatment modality are shown in Table 1. New cerebral infarctions occurred in 46.1% of patients, resulting in mild to moderate disability in 41.7% and severe disability in 58.3% (1 patient was lost to follow-up). We recorded a total of 25 events (ERT 1: $n = 10$; ERT 2: $n = 11$; ERT 3: $n = 4$), with stratification of endovascular procedures and treatment range shown in Table 2. Overall endovascular complication rate was 10.7%: occlusion/thrombosis and removal of catheter ($n = 3, 14.2%$), termination of treatment secondary to excessive vasopressor demand ($n = 2, 9.5%$).

Effect of ERT on Tissue Oxygen Saturation

Pooled data for all ERT (Figure 1A) showed a significant increase in $p_{O_2}$ after the intervention: mean of lowest $p_{O_2}$ within 24 h before ERT was $9 ± 11$ torr ($1.2 ± 1.5$ kPa), with a significant increase to $53 ± 23$ torr ($7.1 ± 3.1$ kPa; highest mean within 24 h after ERT; $P < .001$). A comparable, significant improvement was noted irrespective of probe position in relation to ERT. Both groups featured comparable pre- and postinterventional values for $p_{O_2}$ (ns, data not shown). Probe measurements averaged over specific time intervals in relation to the intervention (Figure 1B) show a characteristic preinterventional decline in $p_{O_2}$ and consecutive improvement after the procedure which persisted over the next 36 h.

Effect of ERT on Metabolism

Pooled data for all ERT also show a significant decrease in LPR after the intervention (Figure 1C): mean of highest LPR within 24 h prior to ERT was $154.8 ± 119.1$, with a statistically significant decrease to $27.9 ± 10.7$ (lowest LPR within 24 h after ERT; $P < .001$). A comparable and statistically significant improvement was noted for both sampling sites, featuring comparable pre- and postinterventional values for LPR (ns, data not shown). Dialysis samplings averaged over specific time intervals in relation to the intervention (Figure 1D) show a preinterventional increase in LPR and consecutive improvement after the procedure, which persisted over the next 18 h.

Subgroup Analysis

Subgroup analysis accounting for the modality of ERT (AP and/or IAL) demonstrated comparable and statistically significant improvement for each modality for both oxygenation and metabolism (Figures 2A and B). Preinterventional values for $p_{O_2}$...
were comparable for all groups \((P = .41)\), with postinterventional values being significantly higher for ERT 3 than ERT 1 + 2 \((P < .05, \text{data not shown})\). ERT values for LPR were comparable without significant differences for any group, both before \((P = .16)\) and after treatment \((P = .53)\).

**Systemic Effect of ERT**

After ERT, significant improvement was noted for all locally collected metabolites (microdialysis): glucose, lactate, pyruvate, glutamate, and glycerol (Table 3). All systemic markers of metabolism and inflammation (serum, cerebrospinal fluid) failed to detect any significant change after ERT.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ERT 1</th>
<th>ERT 2</th>
<th>ERT 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ERT</td>
<td>10</td>
<td>11</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>No. of angioplasty maneuvers</td>
<td>25</td>
<td>N/A</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>Flow rate per microcatheter</td>
<td>15.6 ± 9.5 (\mu)g/kg BW/h (range: 7-37.7 (\mu)g/kg BW/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complication rate per procedure (any)</td>
<td>N/A</td>
<td>16.1% ((n = 5/31))</td>
<td>10.7% ((n = 6/56))</td>
<td></td>
</tr>
<tr>
<td>No microcathers left in Situ</td>
<td>N/A</td>
<td>14</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>ERT treatment duration per patient</td>
<td>118.6 ± 124.5 h (range 3-369 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ERT, endovascular rescue therapies; ERT 1, angioplasty only; ERT 2, continuous intraarterial lysis only; ERT 3, angioplasty and continuous intraarterial lysis; N/A, not applicable; treatment duration was defined as the time from beginning of first endovascular rescue therapies until end of intervention or removal of last microcatheter of continuous intraarterial lysis.

The following adverse events were considered an ERT-related complication: dissection (0\%), perforation (0\%), infection (0\%), occlusion/thrombosis and removal of catheter \((n = 3, 14.2\%)\), termination of treatment secondary to excessive vasopressor demand \((n = 2, 9.5\%)\), with a total complication rate of 10.7\%. Timely imaging performed after catheter occlusion and removal did not show evidence of new embolic infarction or vessel injury/occlusion.

**DISCUSSION**

In case of refractory vasospasm with significant clinical or functional deterioration, ERT such as AP or IAL are valuable treatment options. However, AP is limited to proximal vessel portions with significant risk for periprocedural complications. IAL can be associated with thrombosis and need for excessive circulatory support measures to maintain adequate perfusion pressure. Given the inherent risk profile of these procedures, a characterization and quantification of their efficacy is warranted.

Up until today, data regarding the efficacy of ERT are sparse, mostly retrospective in nature, and derived from small, descriptive case studies.\(^{16,21,25}\) Angiographic vessel diameter and cerebral circulation time\(^{25,26}\) were also used for evaluation, as were TCD or CT perfusion.\(^{27}\) TCD velocity improvements with IAL, for example, are frequently noted,\(^{28}\) but do not seem to correlate with angiographic vessel caliber, nor with clinical outcome.\(^{29}\)

**Brain Oxygen and Metabolism in SAH**

Functional parameters such as oxygenation and metabolism may provide a more direct and relevant aspect of cerebral compromise after SAH and treatment efficacy. A better understanding of the underlying physiology of AP or IAL may also be facilitated, particularly in view of simultaneous acquisition of both hemodynamic and metabolic parameters for surveillance or ERT. No study so far has investigated the effect on local oxygenation and metabolism of both AP and IAL in a prospective fashion, and a correlation with systemic parameters of metabolism and inflammation is also lacking.

In our highly selected cohort, periprocedural risk profile was low with no evidence of embolic infarction or traumatic vessel injury. Subsummation of all ERT events showed significant improvement in oxygenation in cases where conservative management failed to forestall impending ischemia. Severely compromised local metabolism returned to physiological values after ERT. Pathophysiologically, ERT can provide a substantial increase of vessel diameter, either proximally (AP) or proximally and distally (IAL), resulting in an absolute increase of flow if cerebral perfusion pressure is maintained. This targeted optimization of oxygen and glucose supply— as now documented and quantified by \(p_{\text{O}_2}\) measurement and microdialysis—is generally thought to target the causative, functional imbalance of misery perfusion after SAH, and a positive effect on outcome—though not proven—is often implied. These expectations are further supported by data implying a supplemental, direct neuroprotective effect of nimodipine.\(^{30,31}\)

**Systemic Markers of Inflammation and Metabolism in SAH**

Markers of inflammation and metabolism, however, failed to register any systemic effect of ERT, supporting the need for measurements within the target organ itself. Not all interventions were performed within the probe territory. Interestingly, no significant difference was detected whether the intervention was performed immediately proximal or contralateral/posterior to the probe, the explanation likely being 2-fold. For IAL, observation of a contralateral effect that is maintained by systemic circulation and distribution of the agent is plausible. Even with
AP, a contralateral improvement was frequently observed. We postulate that an increase in overall supply, as well as a direct improvement via collateralization were the main reasons for this observation.

**Analysis of Treatment Modality**

We also analyzed our results according to the treatment modality, with comparable improvement of oxygenation and metabolism being seen for AP, IAL, and the combination of the 2. The effect appears to be largest when proximal AP is combined with IAL, with comparable pre-ERT values suggesting an additive effect. AP alone, however, though also providing significant improvement, tended to be employed in cases with less severe compromise of oxygenation and metabolism. Interpretation is limited due to the small number of patients and interventions available for subgroup analysis. However, this observation might also reflect a treatment bias, where a single proximal procedure is chosen in cases of mild functional compromise.

**FIGURE 1.** The development of tissue oxygenation $p_{O_2}$ A, B and metabolism LPR C, D in relation to ERT (pre/post) is summarized. With regard to oxygenation, dramatic and statistically significant improvement is noted after the invention when compared to preinterventional values A, and subdifferentiation accounting for site of intervention in reference to the measuring probe (proximal to probe = "in territory"; contralateral or posterior to probe = "not in territory") also showed a comparable improvement. An exemplatory, detailed temporal course of $p_{O_2}$ is shown for probe measurements within the respective interventional territory B, illustrating a preinterventional decline in $p_{O_2}$ and consecutive improvement after the procedure. LPR is also noted to improve significantly after ERT C, irrespective of the relation of measuring probe and site of intervention. Again, a critical increase is noted before the intervention, with timely improvement of metabolism after ERT D.
and limited vasoconstriction. Cases of profound hypoperfusion, as a result of a more generalized compromise of several vessels may prompt the treating physician to opt for a combination of techniques. A more pronounced improvement in cases starting with an even poorer baseline may be the logical consequence of this scenario.

To our knowledge, this investigation comprises the largest prospective cohort to date, where endovascular rescue treatments are monitored for both local and systemic effects on oxygenation and metabolism.

In this study, improvement of both cerebral oxygenation and metabolism after ERT—but not systemic effects—were seen. New cerebral infarctions were observed in about half of all patients; patients included for this study, however, represent a subgroup at a particularly high risk for cerebral infarction and detrimental outcome, as conservative measures to maintain adequate cerebral perfusion have already failed. With that in mind, we believe that outcome results presented here are reasonable, though a direct effect of ERT on outcome cannot be deduced from these data. Invasive neuromonitoring may constitute a useful extension of our armamentarium to detect relevant functional compromise in due time, but also to monitor continuously for treatment efficacy, eventually facilitating treatment adaptation. For IAL in particular, excessive need for circulatory support due to systemic side effects of vasodilating agents is frequently observed. An individual titration toward the minimum effective dose while continuously observing oxygenation and metabolism may have the potential to further minimize the associated complication profile.

Limitations

Previous studies have analyzed their outcome,\(^2\)\(^9\) and the inconsistencies reached in their interpretation are also paying tribute to the fact that the clinical course after SAH is very heterogeneous. Extrapolation of outcome from treatment success (AP or IAL) would require a control group where treatment is withheld and considerably larger patient cohorts with identical disease characteristics and a rigorous matching process. Our outcome analysis alone therefore remains descriptive in nature. We believe, however, that it is plausible to expect a beneficial impact of ERT with functional improvement of oxygenation and metabolism and a low complication rate.

CONCLUSION

Multimodal, continuous event neuromonitoring is able to quantify treatment efficacy in SAH-related vasospasm. In our small cohort of highly selected cases, ERT was associated with improvement in cerebral oxygenation and metabolism with reasonable outcome. Event neuromonitoring may facilitate timely optimization of treatment modality and dosing according to the individual clinical course of a patient.

Disclosure

This research program is supported by the START-Program of the Faculty of Medicine, RWTH Aachen. Recording units for \(p_{\text{t}}O_2\) measurements (MPD Datalogger) were provided by the respective company (Raumedic, Helmbrechts, Germany). The authors have no additional personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

The authors present a prospective cohort analysis of 13 consecutive patients to evaluate endovascular therapies for refractory vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). Their patient cohort was observed with continuous multimodal neurophysiological monitoring, utilizing brain tissue oxygenation, intraparenchymal microdialysis, and intracranial pressure monitoring. The patients were analyzed in 3 treatment groups: (1) angioplasty only, (2) intra-arterial (IA) lysis with calcium channel antagonists (CCB), and (3) combination of both angioplasty and IA CCB. Their analysis noted improvement in local tissue oxygenation as well as improvement in microdialysate markers of tissue ischemia in all modalities, with the most pronounced improvement coming in the combination therapy group. Although measured, no improvements were observed in systemic markers of inflammation in serum or cerebrospinal fluid samples.

Delayed ischemic neurological decline after aSAH is a significant contributor to immediate and overall patient outcomes.\(^1\) The use of continuous measurements of perfusion and oxygenation has been described in the literature in the setting of aSAH in terms of estimating local cerebral metabolism.\(^2\,3\) However, it has not been widely used to guide endovascular vasospasm treatment. What the authors report is, to our knowledge, the largest prospective cohort in which patients are monitored for both local and systemic effects of cerebral oxygenation and metabolism.

This is certainly compelling and potentially useful data that could be applied in aSAH, especially in patients who do not have a reliable clinical examination. However, the present study does suffer from a small cohort, and a larger study would be useful. Nevertheless, the authors have made a credible claim for event neuromonitoring utilization in addition to transcranial Doppler in guiding endovascular vasospasm treatment.

**COMMENTS**

Despite a lack of level I evidence, endovascular treatment remains an accepted option for patients with medically refractory symptomatic vasospasm. Invasive monitoring has the potential to provide insight into the effects of endovascular treatment. The results of this study are interesting and serve as a starting point for further investigation and a better understanding of the physiological effects of endovascular treatment of vasospasm.

A drawback of this study concerns the technique that was used for infusion of calcium channel blockers. The authors placed a microcatheter in either the internal carotid artery or the vertebral artery for continuous infusion of the drug, leaving the catheter in position for an average of 118.6 h and in at least 1 patient for 369 h (15 days!). The authors did not make a convincing case that they were able to fully distinguish ischemic strokes due to vasospasm (which they report occurred in 46.1% of patients) from strokes that may have been due to the in-dwelling catheter technique. It is the opinion of these reviewers that this prolonged in-dwelling catheter technique is outside of the mainstream of neurointervention. Indeed, the authors missed an opportunity to use invasive monitoring to shed some light on the duration of the more commonly used single-injection technique for the intra-arterial infusion of drugs, which is presently poorly understood.

---


---

