“**DE**layed **C**erebral **I**schemia **B**eyond **E**ndolumina**L** spasmolysis and induced hypertension”
(DECIBEL)

NCT: Not assigned

Date: 10/9/25

1 Scientific Question

By employing novel diagnostic strategies, can we establish better and individualized treatment goals and thereby improve outcomes in patients with severe cerebral vasospasm after subarachnoid hemorrhage?

2 Background

Subarachnoid hemorrhage (SAH) is the third most common cause of stroke. Survivors suffer from morbidity and reduced quality of life (1). With over 600 cases annually, SAH is the tenth most common intensive care diagnosis in Sweden (2). Despite adequate therapy, complications are common (3–5). Approximately 20-30% of patients suffer from cerebral vasospasm, a condition associated with "delayed cerebral ischemia" (DCI), which in turn is associated with poorer long-term outcomes (6).

DCI is regarded as a neurological syndrome that arises between approximately day 4 and 14 after SAH (7). The condition, which requires neurocritical care, leads to new cerebral infarctions (8). Underlying mechanisms are incompletely understood, but probable contributing factors include, among others, macro- and microvascular vasospasm, inflammation, and disturbances in cerebral autoregulation (9).

DCI is the most important cause of morbidity after SAH (10,11). Its treatment is controversial as randomized studies are few and clear benefit has been difficult to demonstrate (1,12). Differences exist between centers regarding diagnostic strategies and treatment protocols, and there is a lack of established, evidence-based guidelines and consensus regarding which methods should be applied to evaluate treatment effect (13).

In the intensive care patient, the clinical examination is often insufficient due to reduced consciousness caused by brain injury, sedation, or by a lack of patient cooperation. Therefore, multimodal neuromonitoring is warranted, employing biomarkers, invasive and non-invasive neuromonitoring, and serial radiological examinations. Individually or in combination, these can detect threatening or established injury such as DCI.

Transcranial Doppler (TCD) is, in addition to clinical examination, a well-established, validated, and easily accessible screening method for detecting vasospasm in the brain's vessels, where changes in blood flow velocities can be measured with good reliability (14). With robotic TCD for continuous measurement, the procedure can be better standardized, and measurement errors and inter- as well as intra-rater variability minimized (15).

Treatment methods for vasospasm/DCI are few and insufficiently studied. The most well-established consist of pharmacological elevation of cerebral perfusion pressure and endovascular therapy with angioplasty or endoluminal spasmolysis (ES). ES often results in an angiographically demonstrable effect, but the duration of effect and outcome on both macro- and microvascular spasm as well as DCI and clinical outcome is unknown. Previously, improved flow velocities measured with TCD have been demonstrated, but without demonstrable clinical neurological improvement (16).

Beyond oral nimodipine and neuroprotective intensive care, standardization and consensus are still lacking regarding which diagnostic and therapeutic methods should be applied. Guidelines for initiating, continuing, or terminating treatment vary both within and between centers, and subjective perceptions can become guiding factors. Long-term follow-up after endovascular treatment is lacking (17,18).

In cases of vasospasm/DCI, elevation of cerebral perfusion pressure is often recommended, provided that baseline pressure is not elevated or heart disease hinders. Recommendations are based on convincing clinical results; however, larger positive or randomized studies are lacking (14). In a randomized study comparing induced hypertension against non-hypertension, no difference in CBF between groups could be registered, as evaluated by CT-perfusion (12). It has also been shown that there is no difference in ischemic burden when comparing direct versus incremental pressure elevation (21). Retrospectively, benefit from expanded invasive monitoring with improved clinical outcomes has been demonstrated for the patient group (19, 20).

The degree of pressure elevation is up to the responsible physician to decide. Not infrequently, these patients carry cardiovascular comorbidities. Takotsubo cardiomyopathy or "cardiac stunning" is present in 5-10% of patients with SAH (22), which complicates the implementation of blood pressure elevation.

It is unclear whether the favorable effects of pressure elevation in cerebral vasospasm can solely be attributed to increased flow or transmural pressure in the brain's vessels, or if the pharmacological treatment is wholly or partially affected by other variables such as increased stroke volume or cardiac output. Effect measures before, during, and after blood pressure elevation in severe cerebral vasospasm need to be studied with continuous TCD parallel to cardiac output monitoring and multimodal intracranial monitoring to better understand the link between regional blood pressure and blood flow as well as global circulation.

For endovascular treatment in cerebral vasospasm/DCI, the support is even weaker, and it is recommended in cases where pressure elevation is considered insufficient (14). Randomized studies are lacking. Intervention consists of balloon dilation/angioplasty or endoluminal spasmolysis (ES), where consensus is lacking regarding drug choice and dosage as well as appropriate start time for treatment and treatment frequency.

A limitation of this treatment is an expected short duration of effect, but currently, it is not known how long it is, nor how it should be monitored. Usually, ES is followed up with TCD the day after treatment, but such measurement lacks the conditions to provide information regarding how long the duration of effect existed, and therefore knowledge regarding the optimal frequency of treatment is lacking.

At the transition from moderate to severe cerebral vasospasm, the flow velocity measured with TCD is a poor criterion for the degree of cerebral perfusion (23), and no specific threshold value for mean flow velocity (MFV) has been shown to accurately diagnose clinically significant angiographic vasospasm (24). Furthermore, TCD velocities quantify an associated phenomenon and possibly a surrogate marker (macrovascular vasospasm), which makes conclusions regarding the development of DCI in unconscious or sedated patients complex and likely requires expanded multimodal neuromonitoring to enable early diagnosis and treatment considerations.

In a study by Albrecht et al., a majority (71%) of conscious patients with DCI improved after endovascular intervention (median number of interventions = 1, max = 14), while in the unconscious group, 83% of patients suffered deterioration with new ischemia, despite intervention. This discrepancy could possibly be due to a lack of sensitivity, or too long intervals between examinations with manual TCD, or alternatively depend on other causes such as microcirculatory dysfunction. Interestingly, TCD MFV increased in 37% of cases with new infarctions after intervention (25). The authors called for prospective studies specifically examining subgroups of patients, such as those with poor neurological status. Weiss et al. evaluated continuous intra-arterial nimodipine as a salvage endovascular procedure and were able to demonstrate an immediate increase in PBTO2 at the start of therapy, as well as an immediate decrease at the stop of treatment, and additionally clear reductions of manual TCD MFV values (pretreatment levels 139.0±46.3 cm/s) in a cohort of conscious and unconscious patients (26).

In summary, diagnostic and therapeutic challenges in severe cerebral vasospasm and DCI after SAH are prevalent. A closer examination of the relationship between peri- and post interventional changes for continuous TCD MFV or derived indices, combined with oxygen saturation or oxygen tension, could provide a better understanding of the mechanism of action and duration of effect of pressure elevation and endoluminal spasmolysis in the most severely ill patients with cerebral vasospasm after SAH. Stronger evidence is necessary to standardize diagnostic and therapeutic strategies and to improve and individualize treatment for better outcomes in this patient group.

3 Project Description

3.1 Overall purpose and conditions

The overall purpose of the research project is to characterize and better understand the disease course and treatment effects, including measurable duration of effect and potential link to outcome in severe cerebral vasospasm after subarachnoid hemorrhage. All clinical decisions and all treatment in the study patients occur entirely within the framework of ordinary care and practice.

The patient group is usually very well-monitored. In addition to one or two ventricular drains, patients with a confirmed diagnosis of severe cerebral vasospasm often receive multiple catheters in the brain parenchyma's watershed areas, such as pressure monitors (with temperature measurement and monitors for partial pressure of oxygen or local saturation) and microdialysis catheters, often bilaterally.

In attempts to answer the research questions, we intend to apply the following measurement methods:

1. **Continuous Transcranial Doppler (TCD)** with Delica EMS 9D (CE-marked) (27).
2. **Capnodynamics**, a non-invasive capnodynamic method for determining cardiac output via the patient's ventilator, Maquet Servo-I. The method is based on a periodically altered breathing cycle in the ventilator and is CE-marked for the purpose, validated, and shows good agreement with the golden standard (28,29).

3. **Continuous EEG** with automated analysis (alpha power, alpha-variability, and alpha/delta-ratio). Automated detection algorithms and integration with other neuromonitoring appear promising (30).

Otherwise, diagnostics and monitoring will occur within the framework of the department's clinical routine, as will the application of intraparenchymal cerebral catheters. No extra catheters or invasive procedures will take place within the framework of the study. The catheters Bowman® and Luciole® (both CE-marked) have the conditions to provide information on local blood flow and perfusion. Usually, two to three, sometimes more, MRI perfusion or CT-perfusion examinations are performed during the care period, which also gives a picture of local blood flow and perfusion in affected areas.

Overall, the multimodal neuromonitoring is expanded and can provide us with new cerebral blood flow-related parameters and their relation to cardiac output. The project has the possibility to contribute to a better understanding of the condition's course and provide guidance for improved and individualized treatment of this patient group.

3.2 Study Center

The studies are conducted at the Neurontensive Care Unit, Karolinska University Hospital, Solna, Sweden.

3.3 Study Period

Patient inclusion is planned from December 2025, or as soon as the ethics application allows, and is planned to continue through December 2030.

3.4 Study Registration

The study will be registered on ClinicalTrials.gov or equivalent.

3.5 Power Analysis

The study consists of several prospective observational cohort studies intending to compare data from continuous monitoring with multiple resolutions against low-resolution information, where information regarding the natural variance is unknown. A guiding sample-size calculation assuming a normal population with severe cerebral spasm has mean flow velocities in the middle cerebral artery of 200 cm/s +/- 20 cm/s and a detectable treatment effect of approximately 5% upon pressure elevation and endoluminal spasmolysis respectively, with alpha set to 0.05 and power 90%, yields a calculated sample size of 42 individuals per treatment method. Given that some patients will be treated and studied regarding both methods, the study group does not necessarily need to be doubled. Given that many patients with risk for or established severe spasm will not develop a degree of spasm that according to clinical assessment requires endoluminal spasmolysis, over-recruitment will likely be necessary. We assess that, taking attrition into account, we need to recruit approximately 200 patients, or up to 42 completed patients per arm. This observational study with several sub-components is, however, fundamentally hypothesis-generating, as formal power analysis is problematic in a multifactorial environment. The study expects to be able to better inform future treatment RCTs.

3.6 Specific Research Questions

1. What does the flow profile in the brain's vessels look like measured with continuous TCD **during** ongoing endoluminal spasmolysis in patients with severe cerebral vasospasm? Is the flow profile dose-dependent or independent? Is it possible to demonstrate a correlation between changed blood flow velocities and radiological outcome regarding macrovascular and microvascular spasm (visual estimation, mean transit time (MTT), etc.)?
2. **Secondary questions:** Are there correlations between radiologic treatment outcome and TCD flow velocities, intraparenchymal saturation and estimated cerebral blood flow (eCBF) or ischemic burden as determined by follow-up radiology, microdialysis or serial S100?
3. What does the flow profile in the brain's vessels look like measured with continuous TCD **before, during and after** endoluminal spasmolysis in patients with severe cerebral vasospasm? How long is the duration of effect regarding changed flow velocities in the brain's vessels after intervention? Is it possible to demonstrate an attenuation of the treatment effect with TCD to inform about the appropriate time for further treatment?
4. **Secondary questions:** Is there a correlation between duration of effect or effect attenuation measured with TCD with intraparenchymal saturation measurement, serial biomarkers like microdialysis or S100? Is there a correlation between duration of effect or effect attenuation measured with TCD with other neuromonitoring such as quantitative EEG (qEEG / Alpha/Delta-ratio)?
5. What does the temporal/dynamic flow profile in the brain's vessels look like, measured with continuous TCD and intraparenchymal oxygenation/saturation measurement **during and after** elevation of the cerebral perfusion pressure in patients with severe cerebral vasospasm?
6. **Secondary questions:** Is the effect of pressure elevation attenuated or improved over time measured with continuous TCD or intraparenchymal saturation? Is there a correlation between blood pressure level and flow profile measured with TCD and intraparenchymal saturation regarding the relationship to the brain's autoregulation window, determined with Pressure Reactivity Index (PRx)?
7. What relative increase in cerebral perfusion pressure or what absolute cerebral perfusion pressures are necessary to optimize cerebral blood flow during pressure elevation in severe cerebral vasospasm, measured with continuous TCD and intraparenchymal saturation, microdialysis, and qEEG?
8. **Secondary questions:** Can threshold levels regarding pressure/flow markers be identified? Does pressure elevation correlate to other desirable or undesirable systemic effects, such as impact on cardiac output, measured with capnodynamic method? At what pressure levels can the benefit/risk ratio be considered optimal based on an overall assessment?
9. Can predictors be identified to provide guidance on individualized/optimal cerebral perfusion pressures or treatment strategies in severe cerebral vasospasm?
10. In the early stage of cerebral vasospasm, can continuous TCD describe trends regarding the acceleration of flow velocities?
11. Does the acceleration follow a linear course, and can a trend analysis be applied to guide when treatment such as pressure elevation or endoluminal spasmolysis should be considered/initiated?

12. **Secondary question:** If the acceleration trend is non-linear, are there associations between acceleration measured with continuous TCD and other physiological, pharmacological, nursing, or patient-related factors?
13. Are there correlations between dynamic flow profile in the brain's vessels, measured with continuous TCD and intraparenchymal oxygenation/saturation measurement after endoluminal spasmolysis and perfusion pressure elevation respectively?
14. Do other clinically applied diagnostic modalities such as serum biomarkers, data from invasive brain monitoring (microdialysis, cerebral autoregulation (PRx), cerebral saturation, rCBF) and/or non-invasive such as continuous quantitative EEG, quantitative pupillometry, near infrared spectroscopy (NIRS), as well as infarction development on CT scan and blood flow velocities and transit time on MRI (4D-MR) provide associations with continuous TCD?

3.7 Method

In this research project, we intend to increase the state of knowledge in severe cerebral vasospasm/DCI to better diagnose and monitor onset and progress, and to study possible outcome measures during and after treatment. We will study time series of blood flow velocities and pulsatility index in the brain's vessels with continuous and manual TCD respectively to establish effect outcome and duration of effect in connection to the established treatment methods: elevation of cerebral perfusion pressure and ES.

At pressure elevation, continuous TCD will be connected for measurement shortly before pressure elevation and measurement continues until the intended pressure level is reached and thereafter up to 12h after. If the patient has received intraparenchymal tissue saturation measurement or partial pressure measurement of oxygen, within the framework of clinical practice, these data will be included. The patient's cardiac output will be measured with a non-invasive capnodynamic method through the ventilator. A corresponding study design is also planned for planned pressure reduction.

At endoluminal spasmolysis, continuous TCD will be connected for measurement at the decision of treatment and continues during and up to 24h after treatment, to establish duration of effect regarding flow velocities according to the description in the questions above. Findings regarding blood flow velocities and duration of effect in cerebral vasospasm are primarily assessed as **a proxy** for the duration of effect regarding DCI. Additionally, we will link series of high and low-resolution information before, during, and after treatment with pressure elevation and endoluminal spasmolysis respectively, when such monitoring is established in the patient.

We intend to seek correlation in time series from continuous TCD with outcome measures with other invasive and non-invasive modalities (see above), and infarction extent on CT and infarction extent, blood flow, transit times on MRI-perfusion, possibly 4D-MR. In this way, we can enable a differentiation between duration of effect on flow velocities in vasospasm measured with TCD and possible duration of effect regarding ischemic burden, i.e., DCI. Overall, the project provides conditions to further describe the treatment modalities pressure elevation and endoluminal spasmolysis respectively and can contribute to a better understanding regarding their therapeutic potential and guide better and individualized treatment.

Primary Measurement Method:

- **Transcranial Doppler (TCD):** Measurement of blood flow velocities and derived variables in the brain's vessels. Continuous, robotized TCD is the first choice, intermittent manual TCD is the second choice. This is the mandatory measurement for all patients.

Secondary Measurement Methods (Multimodal Monitoring):

- **Neurological Monitoring:**
  - Frequent clinical neurological examinations (in awake patients)
- **Neuromonitoring data:** Available, already established invasive and non-invasive neuromonitoring data. This includes:
  - Quantitative EEG (including A/D ratio), Pupillometry, ICP, CPP, PRx, Cerebral microdialysis, Cerebral partial pressure of oxygen or local saturation, Local blood flow (rCBF).
- **Physiological monitoring data:**
  - MAP, Cardiac output with capnographic method, HRV, ECG.
- **Imaging:**
  - Angiographic data and intervention protocols (dose, location), Interventionist's subjective assessment of effect, Follow-up MRI- or CT-angiography.
- **Biomarkers (on clinical indication):**
  - **Brain injury markers:** S100b and GFAP in plasma. **Cardiac stress markers** (specifically during pressure elevation): Troponin and pro-BNP.

3.8 Project Plan

The project aims to study the effect of two clinical treatments – **endovascular spasmolysis** and **elevation of cerebral perfusion pressure** – in patients suffering from severe vasospasm or local flow disturbances after acute SAH. The goal is to, with advanced supervision (multimodal monitoring), describe the treatments' effect size and duration on the brain's blood flow, as well as their possibility to reduce the risk of DCI after SAH.

The project is a prospective observational study conducted in two steps: an initial pilot study followed by a larger cohort study with two arms. Since the treatments are acute measures often initiated during on-call hours, the project has a pragmatic approach rather than a strict, inflexible protocol. A combination of clinically available methods will be used to continuously monitor the patients before, during, and up to 12-24 hours after initiated treatment.

Project Phases

- **Pilot trial (3–5 patients):** Aims to validate the study's feasibility, test logistics regarding data collection, and get a first idea of how long after treatment TCD data needs to be collected to see if/when blood flow returns to a baseline level.
- **Subsequent prospective cohort study spasmolysis** (goal 45-50 patients, 120-150 measurement occasions). Aims to collect data from a larger patient group based on experiences from the pilot study.
- **Subsequent prospective cohort study pressure elevation** (goal 100-110 patients where the spasmolysis group is expected to be included as a subgroup).

Feasibility With the current frequency of spasmolysis at Karolinska University Hospital, and considering TCD is not anatomically possible on all patients, we estimate being able to include approx. 10-12 patients annually to the spasmolysis analysis. Each patient may undergo approximately 1–5 treatments. For the pressure elevation cohort, approx. 25 patients/year are expected to undergo pressure elevation after aSAH at the department, most with some form of invasive intracranial monitoring. Both study arms assume that patients can be included and that data can be collected even at inconvenient hours, made possible by good coverage of research-active physicians and research nurses.

3.9 Patient Selection Criteria

Inclusion Criteria

- Adult individuals, 18 years or older
- Ongoing neurocritical care after subarachnoid hemorrhage
- Source of bleeding secured surgically or endovascularly
- Suspicion of developing or established severe cerebral vasospasm

Exclusion Criteria

- Expected survival less than 5 days, according to clinician's assessment.
- Not possible to perform TCD (too dense temporal bone, unclear or unstable TCD signal)
- Pregnancy

3.10 Case Report Form – CRF

eCRF is established with pseudonymized data on a platform approved by the Region and Karolinska Institutet, REDCap, an encrypted database with authentication and two-step verification. Patient key is stored in a local safe with a code within the operation's research premises where access is pass-card protected in two steps.

- Baseline variables including age, sex, comorbidities, and medications. Time of hemorrhage, clinical condition at admission according to GCS and injury grading according to Hunt & Hess, Modified Fisher, WFNS, Vasograde, and other relevant SAH-related variables collected in the existing quality database for SAH at Karolinska University Hospital.
- Baseline variables including cardiopulmonary data including biomarkers such as troponin and NT-proBNP, ECG & echocardiography for assessment of left and right ventricular function.
- Daily ordinary laboratory analyses and patient-related data and findings in the intensive care Patient Data Monitoring System, such as, for example, drainage rate of CSF from ventricular drains, microdialysis values, blood gas analyses, end-tidal carbon dioxide, fluid balance, electrolyte levels.
- Physiological monitoring via the software ICM+, including intracranial pressure (ICP), brain oxygenation (PbtO2), brain saturation (SbtO2), estimated cerebral blood flow (eCBF), flow velocities at continuous TCD, central temperature (brain and bladder), Pressure Reactivity Index (PRx), quantitative EEG (qEEG) including alpha/delta-ratio, ECG-analysis including heart-rate variability (HRV), pulse, intra-

arterial blood pressure, saturation (SaO2), ventilator settings including fraction of oxygen.
- ICM+ annotation tools. Time-stamped changes in sedation, vasopressor or inotropic treatment, clinical or nursing intervention.
- Procedure-related information regarding endoluminal spasmolysis including time of decision for treatment, time of treatment, choice of drug, dose, potential stent treatment.
- Procedure-related information regarding endoluminal spasmolysis in the form of a questionnaire to the treating interventionist regarding treatment outcome including both subjective and objective parameters.
- Procedure-related information regarding pressure elevation and pressure reduction respectively, including time of decision for treatment, time of initiation of treatment, choice of drug for treatment, baseline value regarding cerebral perfusion pressure, target pressure and time duration to reach target pressure, causes and extent of deviation from target pressure.
- Procedure-related information and outcome at determination of cardiac output with capnodynamic method, cardiac output estimated through effective pulmonary blood flow (CO EPBF).
- Relevant drug treatment, including sedatives, beta-agonists, vasopressors, inotropic drugs, antihypertensive drugs, cardiodepressive drugs, diuretics, and electrolytes.
- Diagnostic basis for establishment and grading of cerebral vasospasm as well as associated phenomena such as cerebral salt wasting syndrome.
- Daily symptoms, clinical signs, neurological assessment.

3.11 Follow-up

Extended Glasgow Outcome Scale (GOSE) questionnaire and/or assessment at 3, 6, and 12 months respectively. When applicable; date of death.

3.12 Planned Analyses

Data will be presented descriptively as time series and by Granger causality analysis. Primary analysis will focus on describing the treatments' effect size and duration of effect. The association between treatment effect and ischemic burden (DCI) as well as relations to other collected parameters related to flow, metabolism, and injury will be evaluated. Extended analysis is expected to include dimensionality reduction of data with PCA and cluster methods, tree regressions, and other AI methods to identify composite patterns. Each patient will constitute their own cross-over control (comparisons are made before spasm, during spasm, and after treatment).

4 Ethical Considerations

Ethical application has been approved by the Swedish Ethical Review Authority, diary number 2025-05434-01. Many research subjects are unable to apprehend information or contribute to consent before inclusion. Consent with the patient is sought before inclusion when possible. In cases where the patient's condition does not allow consent, consultation occurs with the next of kin. This normally occurs before inclusion if the situation allows but shall be carried out at the latest the following day. Information regarding consent to the study is discussed at a separate meeting in a private room.

We apply a an opt-out procedure, where patients who improve during the care period and are assessed to be able to apprehend information will be informed and asked about study participation retrospectively. Patients who cannot apprehend information in such a situation shall be assessed, if possible, at outcome follow-up and then given information and a request for participation. This conversation is held by a physician or research nurse. If the patient or relative opposes participation and wishes to withdraw from the study, the research subject is excluded. Already collected data is retained within the framework of the study, but no further data is then collected. Research data is handled and saved pseudonymized in a secure environment. Research data is presented at the group level without the possibility of identifying specific patients.

This study has the conditions to add significant information regarding diagnostics and treatment of patients with severe cerebral vasospasm after subarachnoid hemorrhage. Improved and individualized treatment strategies have the possibility to limit infarction extent and secondary brain injury as well as improve functional neurological outcome. Study results have the possibility to also benefit patients with a lower degree of cerebral vasospasm as well as other cerebrovascular disease conditions.

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