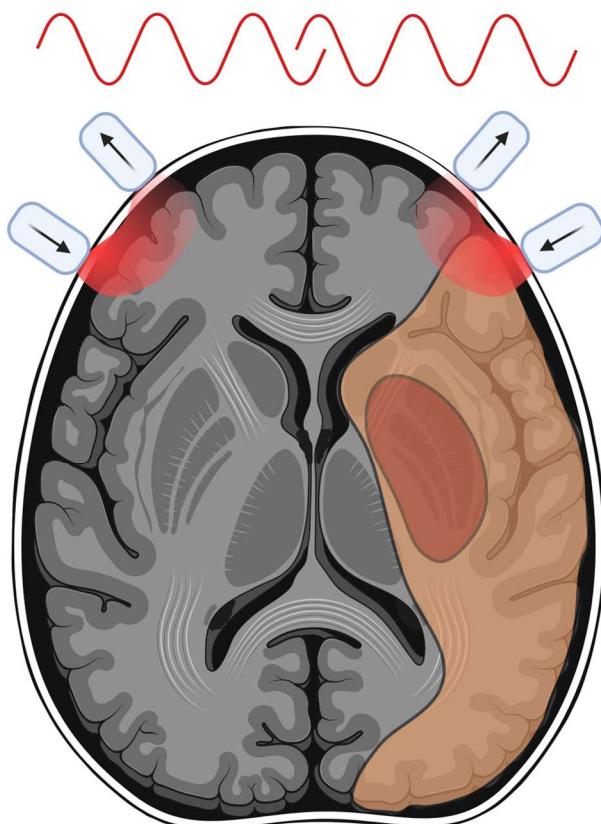


UNIVERSITY OF COPENHAGEN  
FACULTY OF HEALTH AND MEDICAL SCIENCES  
NEUROSCIENCE



## PhD Thesis

Adam Vittrup Heiberg, MD

## Near-infrared spectroscopy in acute ischemic stroke

Principal supervisor: Helle Klingenberg Iversen

June 5th, 2025

# **Near-infrared spectroscopy in acute ischemic stroke**

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## **Funding**

Novo Nordisk Foundation, Simon Fougner Hartmanns Family Foundation, Rigshospitalet Research Grant, Gangsted Foundation, Master carpenter Sophus Jacobsen and wife Astrid Jacobsen's Foundation

*Front page: Created in <https://BioRender.com>*

# Acknowledgements

*"It requires freedom to be curious."*

Jørgen Leth, Det Sidste Ord (Famous Last Words), October 2025

Most things in life start with curiosity. In research, curiosity is not only the first pedal stroke but also the engine that drives you over the mountainous obstacles along the way. My own curiosity towards research was lit back in 2015 when my principal supervisor Helle announced a pre-graduate scholarship. Since then, during our decade-long collaboration, we have had many talks not just about work but just as much about life. Thank you so much for sparking my curiosity and your thoughtful guidance but also for giving me the time and freedom to do things my way and for always having my back.

I wish to thank my co-supervisors as well. Sofie, for introducing me to the world of research. Henrik and Thomas, I really appreciate your always valuable feedback and encouragement, help and support.

In this project, we performed studies in quite challenging clinical settings. My great appreciation to everyone involved in the EVT group for their help in recruitment and project execution, and their treasured feedback. Thank you, Henrik, Goetz, Christine, and Klaus for your common curiosity and enthusiasm, and for teaching me about thrombectomy procedures and everything that goes around it. My extended thanks to all your colleagues from the radiology, anesthesiology and neurology departments, including nurses and radiographers, for their help in recruitment and our teamwork in a complicated setting. Thank you, Kirsten, for such a warm welcome during my time at your inspiring research unit, your constructive energy and well-thought suggestions.

I would not have been able to complete the project without the help of my fellow colleague Troels. A special thanks for helping me across the finish line and for your dedication to detail.

To my former and current office colleagues Pernille, Tine, Gunhild, Dewah, and Anders. I am really going to miss working with you and discussing all things in life over coffee or lunch. It has been some really productive years and an absolute pleasure.

Clinical research is impossible without the participants. My sincere gratitude especially to the patients and their relatives for the extra effort during difficult circumstances.

Last but certainly not least, I want to thank my family and friends. To my parents, their partners and my sister for so many things but certainly for inspiring me to value knowledge. Rie, I would not even know where to start. Your everlasting patience and support have been invaluable, and I simply could not have done it without you. Thank you for always making me a better version of myself. During these PhD years, we worked hard with the expansion of our “little” family. Bjørn, Elvin, Carlo, and Walter. Maybe someday you will read these words. You are everything to me, and I hope you always stay curious.

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# Publications included in the PhD thesis

- Study I    **Dynamic cerebral autoregulation during and 3 months after endovascular treatment in large-vessel occlusion stroke.<sup>1</sup>**  
*Adam Vittrup Heiberg, Troels Gil Lukassen, Thomas Clement Truelson, Henrik Gutte Borgwardt, Goetz Benndorf, Christine Sølling, Henrik Winther Schytz, Kirsten Møller, Klaus Hansen, and Helle Klingenberg Iversen.*  
Submitted to Scientific Reports (ISSN 2045-2322) on September 13<sup>th</sup>, 2025.  
Revised manuscript submitted May 26<sup>th</sup>, 2025.
- Study II    **Bilateral dynamic cerebral autoregulation assessment during endovascular treatment in large-vessel occlusion stroke.<sup>2</sup>**  
*Adam Vittrup Heiberg, Troels Gil Lukassen, Thomas Clement Truelson, Henrik Gutte Borgwardt, Goetz Benndorf, Christine Sølling, Henrik Winther Schytz, Klaus Hansen, Kirsten Møller, and Helle Klingenberg Iversen.*  
Submitted to Experimental Physiology (ISSN: 1469-445X) on June 5<sup>th</sup>, 2025.
- Study III    **Cortical hemodynamic response during cognitive Stroop test in acute stroke patients assessed by fNIRS.<sup>3</sup>**  
*Adam Vittrup Heiberg, Sofie Amalie Simonsen, Henrik Winther Schytz, and Helle Klingenberg Iversen.*  
Published in NeuroRehabilitation, 2023. 52(2): p. 199-217.



# Introduction

## Stroke

Stroke is an increasingly prevalent disease globally with major consequences for patients, families and societies being the number one source of neurologic disability<sup>4</sup> and the fifth most common cause of death<sup>5</sup>. Blood flow is disrupted which causes infarction and often results in immediate neurologic deficits (e.g., motor paresis, sensory deficit, speech disturbance, visual deficit, cognitive symptoms)<sup>6</sup>. Acute ischemic stroke (AIS) comprises about 85% of all strokes in Western societies including Denmark<sup>5, 7</sup>. The etiology of AIS is either large-artery atherosclerosis embolizing, cardiac embolism, small-vessel occlusion, arterial dissection or other less common causes while some cannot be determined due to multiple plausible etiologies or none that can be identified.

Almost 25% of AIS patients in Denmark are treated with recanalization therapies<sup>7</sup> which salvage viable tissue and improves long-term outcome especially when provided as soon as possible<sup>8, 9</sup>. Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator is an effective treatment to all AIS patients without several specific contraindications. It can be administered within 4.5 hours from onset or when onset is unknown, but no changes is seen in the fluid attenuated inversion recovery-sequences of magnetic resonance imaging<sup>10, 11</sup>. Large-vessel occlusions (LVO) affect approximately a third of AIS patients and have a more severe prognosis<sup>12</sup>. Endovascular treatment (EVT) is highly effective in LVO patients up to 24 hours after symptom onset<sup>13</sup> improving both long-term functional outcome in both anterior and posterior circulation<sup>13-15</sup>. However, less than 10% of AIS patients are treated by EVT in Denmark<sup>7</sup>. IVT can recanalize LVO if the thrombus length is less than 8 mm<sup>16</sup> and should be administered before EVT in both primary stroke centers (IVT capability) and comprehensive stroke center (IVT and EVT capability) without delaying EVT<sup>17, 18</sup>. In the context of this thesis EVT includes both mechanical thrombectomy, intraarterial thrombolysis and acute treatment of near-occlusive stenosis by balloon angioplasty and/or stenting.

Secondary prevention starts as soon as possible after the diagnosis of AIS and depends on multiple factors including recanalization therapy, stroke etiology, identified risk factors, comorbidities and concomitant medication. Prevention is comprised of pharmacological therapy (e.g., antithrombotic platelet inhibition or anticoagulant treatment, blood pressure management, lipid-lowering treatment and co-morbidity treatment of diabetes, sleep apnea etc.) and lifestyle modifications (e.g., physical activity, smoking, diet, etc.)<sup>19-22</sup>. Rehabilitation and mobilization should also commence early in the process, directed at the observed disabilities<sup>21</sup>.

## Near-infrared spectroscopy

Near-infrared spectroscopy is a non-invasive optical method able to assess continuous dynamic hemoglobin concentration in the superficial cortex<sup>23</sup>. Infrared light is placed directly on the scalp and the reflected light is measured a couple of centimeters away (usually 3 to 4 cm). The infrared light is absorbed by water, fat, and other proteins but mostly by hemoglobin and under normal circumstances only hemoglobin concentration changes significantly. Hence, the light absorption in multiple wavelengths is used in modified Beer–Lambert equations to estimate dynamic concentrations of oxygenated, deoxygenated and total hemoglobin. Exact hemoglobin concentrations are not possible with continuous wave-NIRS due to uncertainties concerning scattering and thereby the pathlength of photons<sup>23</sup>. The spatial penetration of NIRS is limited to the outer 10-15 mm of superficial cortical tissue but the temporal resolution is very high<sup>24, 25</sup>. NIRS examinations can be performed with minimal setup time and minimal experience. While recordings are not limited by portability, movement will create motion artefacts that increases noise despite several available correction methods<sup>26-29</sup>.

The photon absorption in extracerebral tissue creates contamination in the measurement of intracerebral hemoglobin concentrations. No method has been developed to isolate intracerebral signals entirely<sup>30, 31</sup>. However, short-distance channels (approximately 10 mm apart) that mainly examines extracerebral signals can be used as regressors to the long-distance channels and improve signal-to-noise ratio significantly<sup>32-34</sup>.

NIRS is most often applied as either functional imaging or cerebral oxygenation monitoring<sup>35-38</sup>. Functional NIRS (fNIRS) relies on neurovascular coupling to detect neuronal activation. The regional blood flow increase to an activated brain region far exceeds the metabolic need leading to an increase in oxygenated hemoglobin (Oxy-Hb) and a decrease in deoxygenated hemoglobin (Deoxy-Hb)<sup>39</sup>. During stroke rehabilitation fNIRS has been studied as a biomarker mainly in motor and cognitive recovery<sup>38</sup>. During the Stroop Color and Word test, several other populations have shown consistent prefrontal activation detected by fNIRS including healthy controls<sup>40-43</sup> and cerebral microangiopathy patients<sup>44</sup>. Especially the dorsolateral prefrontal cortex and the anterior cingulate cortex are activated<sup>45, 46</sup>.

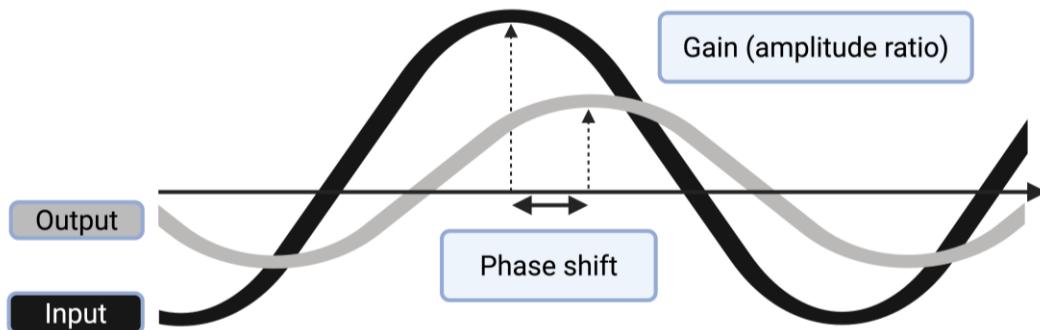
Cerebral oxygenation monitoring is often focused on the occurrence of new infarctions or cerebral hypoxia during surgery or admission<sup>36, 38, 47, 48</sup> but can also be targeted towards cerebral autoregulation assessment<sup>36, 49, 50</sup>.

## **Cerebral autoregulation**

Cerebral autoregulation is the capability of maintaining cerebral blood flow by changing the tone of vessel smooth muscle<sup>51</sup>. The concept was termed by Lassen et al. in 1959<sup>52</sup>. Cerebral autoregulation is often described by static and dynamic aspects. Static cerebral autoregulation refers to the maintenance of cerebral blood flow during steady-state perfusion pressure across minutes to hours, while dynamic cerebral autoregulation (dCA) denotes the response to more rapid or transient changes in perfusion pressure<sup>53</sup>. Different experimental paradigms are applied to investigate the two aspects although the terms probably represent parts of a continuum<sup>54</sup>.

Several approaches are used to describe dCA in either time-domain or frequency-domain analysis<sup>55-57</sup>. The transfer function analysis (TFA) is the most common frequency-domain method<sup>58</sup>. It is based on spectral transformation (e.g., Fourier transformations) of continuous recordings of arterial blood pressure (ABP) and cerebral blood flow surrogate measures including NIRS and transcranial doppler sonography (TCD) of flow velocity in major cerebral arteries. The amplitude and synchronicity between the input (ABP) and output (TCD or NIRS) measurements are compared as gain (amplitude ratio) and phase

shift in different frequency spectrums (Figure 1). While high-frequency oscillations (i.e., pulse waves, thoracic pressure changes due to respiration) are passed on passively to the cerebral circulation, both spontaneous and induced oscillations in the low-frequent ( $\sim 0.1$  Hz, LF) and very-low frequent spectrums are modified by dCA<sup>58</sup>. Thus, intact dCA is defined by gain differing from one and phase shift differing from zero although exact thresholds have never been established<sup>56</sup>. The Cerebrovascular Research Network (CARNet) have published white-paper recommendations to improve standardization of TFA execution<sup>56, 59</sup>. A modified version TFA using OxyHb in the contralateral hemisphere as input and OxyHb from the affected hemisphere as output have previously been applied in subacute stroke patients and shown interhemispheric changes<sup>60</sup>.



*Figure 1. Transfer function analysis yielding dCA measures of phase shift and gain.*

The dCA in AIS patients have been studied quite extensively. Compared to healthy people numerous studies consistently show impaired dCA of the ischemic hemisphere in LVO patients<sup>61, 62</sup>, while findings are more ambiguous in the contralateral hemisphere<sup>63, 64</sup>. Some of the ambiguity could be related to timing of examination as dCA that seem to change during the course of acute (within 2 days of onset) and subacute (2 to 7 days after onset) phases depending on the severity and etiology of the index stroke<sup>64</sup>. Mild-to-moderate ischemic stroke patients could have a different trajectory perhaps developing dCA impairment later than in LVO patients<sup>63, 64</sup>. Small-vessel disease also seem to impair dCA globally possibly dissociated from the presence of acute lacunar stroke<sup>65-67</sup>. The effect on dCA from common co-morbidities such as stenosis of supplying arteries, hypertension, diabetes, chronic kidney in AIS patient is uncertain<sup>64</sup>.

# **Objectives**

The overall aim of this PhD thesis was to investigate feasibility and possibilities of NIRS examinations mainly during acute and subacute phases following ischemic stroke.

- I. The aim of study I was to investigate dCA during and after EVT using interhemispheric TFA based on NIRS and associate dCA measures to clinical characteristics and long-term outcome.
- II. The aim of study II was to investigate unilateral dCA during and after EVT using conventional TFA based on invasive ABP and NIRS and associate phase shift to clinical characteristics and long-term outcome.

Study I and II was collectively aimed at identifying the most feasible and suitable method of investigating dCA during EVT.

- III. The aim of study III was to investigate the hemodynamic response with fNIRS during the cognitive Stroop Color and Word test in the subacute phase after ischemic stroke and thereby assess the biomarker potential.

# **Methodological considerations**

## **Ethical considerations**

All studies presented in this thesis are based on additional examinations with noninvasive NIRS. The equipment was CE-marked, commercially available for research, and approved by the Technical Department of Rigshospitalet prior to usage. Pilot examinations were performed on both healthy subjects and AIS patients prior to enrollment of the studies first participant.

The time-sensitive nature of EVT and clinical status (i.e., inability to consent) prevented patients from given informed consent prior to examinations in study I and II, but all subjects gave informed consent after the procedure. If still unable to consent, their proxy and an independent physician signed the consent form which was valid until the patient potentially regained the capacity to consent. This procedure was approved by the regional ethics committee (H-18028704) and is imperative in EVT studies to avoid selection bias. In study III, written informed consent was provided by all participants prior to enrollment (H-2-2013-091). Handling and storage of data was approved by The Danish Data Protection Agency (Study I and II, I-suite no.: 6509; Study III, I-suite no.: 2385). The studies were performed in accordance with the 1964 Declaration of Helsinki and later amendments<sup>68</sup>. All persons who qualified for authorship according to the Vancouver rules were designated as such<sup>69</sup>.

## **Design**

All studies were designed as prospective observational cohorts from everyday patients in the stroke center. Generalizability was prioritized over homogeneity leading us to design the studies with as few exclusion criteria as possible. While this choice expedites the enrollment process, the downside is the risk of primary study effects being obscured by patient heterogeneities with divergent influences.

Observational studies of the magnitude here are performed to generate new hypotheses. Therefore, it is important to investigate the cohort thoroughly and not be too limited by

preconceived notions. This includes detecting possible confounders that should be accounted for in future study design and analysis. Most findings in the studies presented here would have to be confirmed in larger multi-center studies with a more prespecified statistical plan and perhaps more narrow enrollment criteria.

Our reporting adhered to the STROBE guidelines for observational studies<sup>70</sup>.

## **Study populations**

Studies I and II are cohorts from 100 EVT patients included in the study and examined with NIRS from arrival to the angiosuite throughout procedure and 2 hours post procedure. Patients were enrolled between November 2018 and November 2020 at Rigshospitalet interrupted by paternity leaves. Rigshospitalet is a comprehensive stroke center with a catch area of approximately 2.7 million people that performed about 300 EVT yearly (2019-2020)<sup>71</sup>.

The main obstacle to enroll patient was the short period of time from decision to EVT to arrival at the angiosuite. Depending on which hospital the patient was first admitted to this period was often down to less than ten minutes. Thus, all relevant staff from the neurology, neuroradiology and neuroanesthesiology departments were encouraged to call the investigators as soon as possible. The EVT team were often given very short notice, and we supported enrollment by monitoring an electronic live listing of arriving patients during office hours. Investigators able to arrive in time enrolled patients after office hours and during weekends. A minority of patients were not enrolled due to occupied equipment (follow-up examinations), abandoned EVT without recanalization attempts or poor NIRS data quality.

The subcohorts in study I and II were primarily based on availability of steady state data at the desired time points. One patient with bilateral stroke was excluded as the interhemispheric dCA effect of the index stroke would have been incomprehensible. Three patients treated under local anesthesia were excluded due to the possible effect of anesthesia of dCA.

Study III was based on a subcohort from subacute stroke patients enrolled in a larger observational study (clinicaltrials.gov: NCT02111408)<sup>72</sup> and a group of healthy participants. The main study started in May 2015, but the setup of the fNIRS equipment and the Stroop Color and Word test was not ready until April 2016. Stroke patients were enrolled from the acute stroke unit if they had the ability to consent, had a remaining life-expectancy of more than 6 months and no other significant brain disease, and could perform all other examinations in the main study within 7 days from stroke onset. Patients were included in the subcohort if index stroke was ischemic, and they could perform the Stroop Color and Word test. Participants in the subcohort were enrolled between April 2016 and September 2016.

## **Procedures and data analysis**

### **Study I and II**

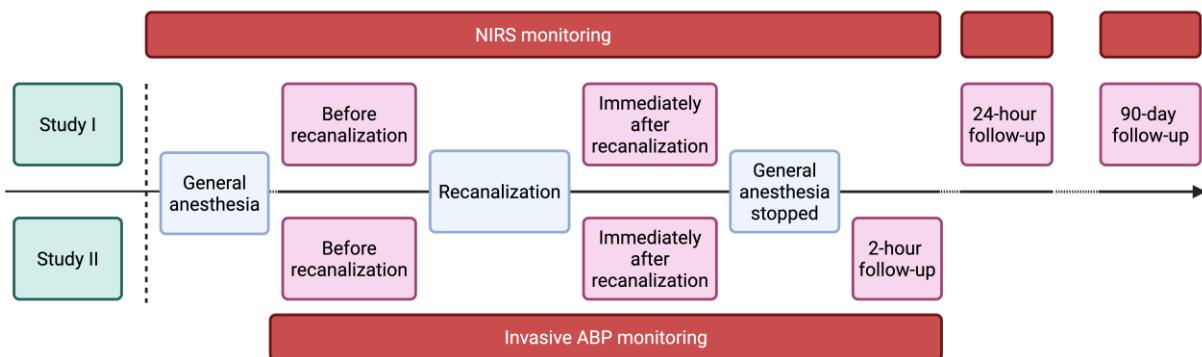
Enrolled patients had standard-of-care treatment and monitoring including invasive ABP measurement. Additional NIRS examination was performed from arrival to the angiosuite where EVT was performed and until 2 hours after the procedure. We limited our observation period this way as patients were transferred from the Post Anesthesia Care Unit to the Stroke unit at the Department of Neurology after 2 hours at which point invasive ABP measurements ended.

The prefrontal NIRS equipment (modified version of Octamon, Artinis, Elst, The Netherlands) was found to be compatible with the digital subtraction angiography used during EVT through a series of pilot examinations. NIRS data was transferred through wireless connection while other vitals and mechanical ventilator data was exported from the monitor<sup>73</sup>. The entire setup was ready in less than one minute, performed concurrently with standard-of-care arrival procedures and did not delay treatment.

Study I and II included clinical follow-up during wakefulness after 24 hours and 90 days in addition to follow-up NIRS examinations analyzed in study I (Figure 2). Many of the enrolled patients were immobilized due to their index stroke and could not be transported to Rigshospitalet at 90-day follow-up. Hence, we tried to minimize loss-to-follow-up and

the accompanying selection bias by offering follow-up examinations at patient's residence within a 2-hour transportation radius from Copenhagen. Symptom severity was evaluated by National Institutes of Health Stroke Scale (NIHSS). We used modified Rankin scale (mRS) to assess functional outcome including independency (mRS 0-2).

Both study I and II applied the TFA with recommended parameters from the Cerebrovascular Research Network to examine dCA<sup>56, 59</sup>. Five-minute steady-state segments were selected at specified time points (Figure 2) outside of anesthesia initiation and termination, changes in mechanical ventilation or medication, and recanalization attempts. NIRS and ABP data was artifact corrected by linear or spline interpolation before TFA. In study I, input and output to the TFA was oxygenated hemoglobin from contralateral hemisphere and ischemic hemisphere (interhemispheric TFA), respectively. In study II, unilateral TFAs was performed for each hemisphere with ABP as input and oxygenated hemoglobin as output (conventional TFA) which restricted dCA analysis to 2 hours post procedure (Figure 2).



*Figure 2. Monitoring of NIRS and invasive ABP during EVT and at follow-up. Time segments with applied dCA assessments in study I and II displayed in pink boxes.*

### Study III

Participants were examined with a prefrontal NIRS system (CW6, TechEn Inc., Milford, Mass., USA) while performing the Stroop color and word test. The test was designed as a block examination with three degrees of difficulty (Neutral, congruent and incongruent).

Data quality was ensured automatically and visually before correction for motion artefacts was applied using the most accurate method<sup>74</sup>. The hemodynamic response of OxyHb and DeoxyHb was analyzed for each degree of difficulty by applying a general linear model which includes short-separation regression and drift correction. Short-separation regression improves intracerebral sensitivity by filtering with NIRS channels with short distance between light source and detector that almost exclusively examines extracerebral tissue<sup>34</sup>. The hemodynamic response function was quantified by peak, time-to-peak and average slope for both OxyHb and DeoxyHb.

## Statistical considerations

Power calculations were performed during the design phase of all studies with 80% statistical power and significance level of 5%. Study I calculations were based on the findings by Phillip et al. who performed interhemispheric TFA on stroke patients with mild to moderate symptom severity<sup>60</sup>. This resulted in sample size estimations between 23 and 100 patients depending on the TFA variable. However, the cohort would surely have much wider variations in symptom severity, and we expected the effect size would increase correspondingly. Conventional TFA between ABP and V<sub>MCA</sub> was performed in stroke patients with moderate to severe symptom severity<sup>75</sup>. Detecting a similar difference in phase shift between dependent and independent patients at 3 months would have required 54 patients. Therefore, we decided to enroll 100 patients with the expectation that some patients would be excluded from analysis due to missing observations or inadequate data quality.

Sample size calculations in study III were based on a study of subjects with cerebral microangiopathy<sup>76</sup> and suggested 40 participants would be sufficient to detect a similar effect size.

All statistical analysis were performed in R Studio (R Core Team, Vienne, Austria). Descriptive statistics and 2-sample testing were applied depending on type and distribution of data as recommended<sup>77</sup>. Estimates ( $\beta$ ) are reported with 95% confidence intervals.

In study I and II, we applied linear mixed models using lme4-package which are recommended in repeated measures analysis<sup>78</sup>. The mixed models have the possibility to use both random and fixed effects. Subjects were included as a random effect as some individual variability between measured are to be expected. Fixed variables included time of measurement (i.e., before recanalization, after recanalization and follow-up examinations) and various clinical variables including index stroke characteristics, imaging, treatment and long-term outcome. The sample size did not support including several clinical variables into the mixed models. When time of measurement was included, we first examined interaction between time of measurement and the clinical variable to identify different developments in TFA results (e.g., between patient groups with dependent and independent outcome). Significant variables were subsequently used as predictors in univariate and multivariate general linear models using Stats-package or ordered logistic regression models with the MASS-package.

In study III, patients were dichotomized based on side of lesion and presence of small-vessel disease. Also, we performed an analysis to identify hemisphere lateralization of the required cognitive functions during the Stroop color and word test. Correction for multiple comparisons was done by Bonferroni by the number of fNIRS channels. Similar correction method was not necessary in study I and II as TFA-parameters were averaged across channels after analysis of individual channels showed no effect of anatomical location.

# **Study presentation**

## **Study I: Dynamic cerebral autoregulation during and 3 months after endovascular treatment in large-vessel occlusion stroke<sup>1</sup>**

### **Background and aim**

Dynamic cerebral autoregulation has never been examined during EVT. Thus, we aimed to perform consecutive dCA assessments before and after recanalization by EVT and during 24-hour and 90-day follow-up examinations using interhemispheric TFA based on NIRS. Additionally, we aimed to identify associations between dCA measures of LF gain and LF phase shift to clinical characteristics and long-term outcome.

### **Results**

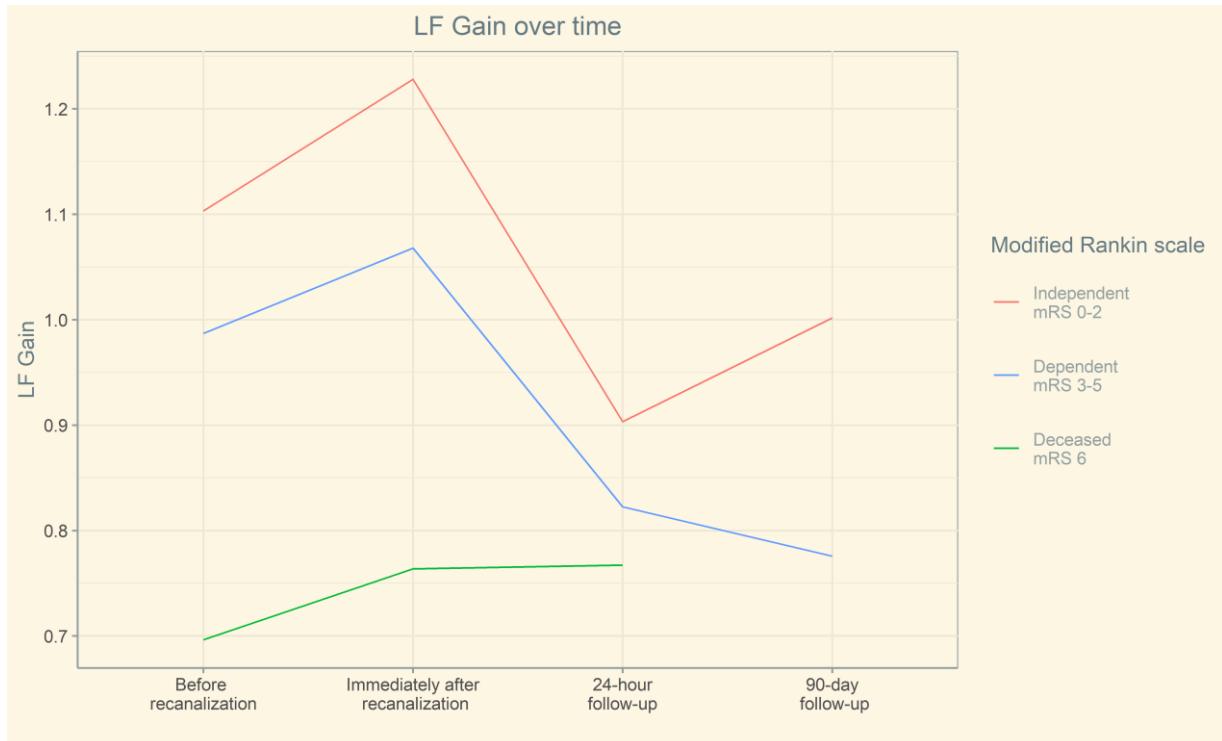
Steady-state data segments during EVT and at 24-hour follow-up were available in 77 patients (39% female sex, median age 73 years (IQR 63-80), median baseline NIHSS 16.5 (IQR 11-21.25), recanalization success 89.6%). Of these 54 patients also had a 90-day dCA assessment performed.

Interhemispheric LF phase shift remained unchanged during EVT but increased at 24-hour follow-up ( $\beta$ : +66.1%, CI: +10.5%; +149.5%, p=0.015) and returned towards baseline level at 90 days. When accounting for NIHSS, patients with mild to moderate symptoms severity (baseline NIHSS 0-10) exhibited a phase shift increase immediately after recanalization while patients with more severe symptoms ( $\geq 10$ ) had an increase in phase shift at 24-hour follow-up (p=0.01). We found no effect of age, stroke etiology, infarct size or location, sevoflurane or propofol as anesthesia, recanalization success, nor 90-day functional outcome (mRS) including mortality on interhemispheric LF phase shift.

Interhemispheric LF gain remained unchanged during EVT and at follow-up examinations but was increased in patients treated with IVT before EVT ( $\beta$ : 0.22, CI: 0.12; 0.32, p<0.001). Interhemispheric LF gain was increased in patients with better 90-day outcome including decreases in NIHSS ( $\beta$ : +1.0%, CI: +1.8%; +0.1%, p=0.029), functional outcome mRS ( $\beta$ : 0.04, CI: 0.07; 0.02, p= 0.002) and mortality (Alive,  $\beta$ : 0.2, CI: 0.35; 0.06, p=0.005). Effect of functional outcome and IVT was independent of each other. The increase in

Interhemispheric gain was due to reduction in LF amplitude in the ischemic hemisphere (Figure 3).

Interhemispheric LF gain was a significant predictor of both 90-day NIHSS, functional outcome and mortality in both univariate and multivariate models.



*Figure 3. Interhemispheric LF gain during EVT and at 24-hour and 90-day follow-up trichotomized by functional independency (mRS 0-2) and mortality. Gain did not change significantly compared to before recanalization for any group*

## Conclusion

AIS patients with mild to moderate symptom severity before EVT showed dCA changes during EVT while dCA changes in patients with more severe symptoms occurred at 24-hour follow-up. We found a strong association between dCA to both IVT administered before EVT and 90-day outcome. This association could be used to predict 90-day outcome in multivariate predictions models.

## **Strengths and limitations**

In study I, we highlighted the advantages of using NIRS to examine interhemispheric dCA during EVT. First, the possibility to perform the examination throughout the procedure requires a very fast setup which can be done with limited experience as opposed to TCD and without assuming a constant MCA diameter which can be erroneous<sup>79-81</sup>. Especially, this provided us with valuable knowledge of dCA before recanalization that cannot be examined with other current modalities. Due to the fast setup we only had to exclude 16% of examined patients due to missing steady-state time segments before recanalization attempts. This both increases the statistical power and minimizes the risk of selection bias. Second, the interhemispheric TFA approach also seems to reduce variation in gain as both input and output are of the same modality. In contrast, the conventional TFA method that have shown substantial issues in reproducing gain and is considered less reliable<sup>56, 82</sup>. Interhemispheric gain remained stable across three time segments within the first 24 hours which could indicate good reliability. Third, the interhemispheric TFA allow for an interpretation of dCA irrespective of extracerebral tissue contamination. The assumption that LF oscillations in extracerebral vasculature is well-synchronized was tested and upheld in the study. Alternative approaches to account for the extracerebral contamination includes regression methods that can filter some of the extracerebral signals before TFA is performed. No regression method has been able to perform sufficient filtering<sup>30, 31</sup> and would also risk partially removing signals of interest.

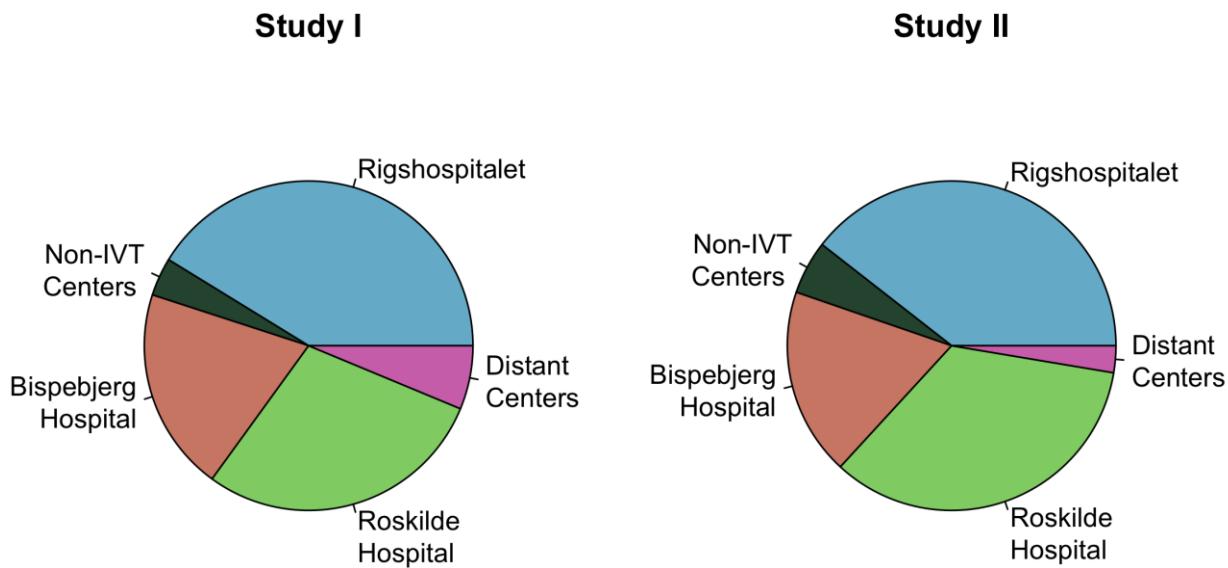
Conversely, the interhemispheric TFA approach is to some extent dependent on intact dCA in the contralateral hemisphere. Especially, phase shift has no measure of unilateral assessment and equal phase shift is near impossible to interpret as it could be the result of intact bilateral dCA or equally disturbed dCA on both hemispheres. Although a comparison to healthy control subjects would have strengthened the study, the interpretation would still be affected by this uncertainty.

Previous studies have applied other NIRS-only methods which accounts for this dependence of the contralateral hemisphere. Both methods share the advantage of enabling regional dCA assessments across superficial cortical tissue in both hemispheres but rely on NIRS data with greater concerns regarding data quality. Becker et al. proposed

to use short-distance channels as input to the TFA constituting a surrogate of systemic perfusion<sup>83</sup>. The accurate of this surrogacy is not established and short-distance channels are more prone to detector saturation. Short-distance channels also have a small intracerebral signal component and cannot be thought of as purely representative of systemic perfusion<sup>25</sup> which was also visible in our raw data with contrast artifacts appearing in some short-distance channels.

Another NIRS-only approach to examine phase shift was shown by Elting et al. who applied TFA between OxyHb and DeoxyHb from single channels measurements with spatially resolved spectroscopy-NIRS. Accounting for transit time (HF phase shift), this approach produced similar phase shift to TFA between ABP and V<sub>MCA</sub><sup>84</sup>. Whether such an approach can be reproduced with continuous wave-NIRS and in a hyperacute setting remains unanswered. Here, we choose to analyze OxyHb alone as the signal quality is superior to DeoxyHb.

Study I could also be affected by other limitations. We did not record any data on patients who were not enrolled into the study preventing any analysis on selection bias in the recruitment. For example, patients with more transportation time from primary hospital to the EVT center should have been easier to enroll due to more response time for the investigators. Such patients would be expected to have increased time from onset to puncture and worse outcome<sup>85</sup>. The largest proportion of enrolled patients (~ 41% in both Study I and II, Figure 4) were directly admitted to Rigshospitalet, but we cannot assess whether these proportions in this cohort are equivalent to the source population (i.e., screened patients).



*Figure 4. Pie chart of primary hospital in study I and II. Rigshospitalet is the comprehensive stroke center in Eastern Denmark. Bispebjerg Hospital (Capital Region) and Roskilde Hospital (Region Zealand) are primary stroke centers with IVT capability. Distant centers included hospitals with more than one hour of transportation by ambulance to Rigshospitalet.*

Likewise, we did not investigate selection bias concerning the examined patients that were excluded from analysis due to missing steady-state data segments. Most patients were excluded due to missing steady state before recanalization. They seemed to be balanced by extremely fast procedures on one hand and complicated anesthesia with difficulties establishing steady vitals on the other hand. A future study could address this issue while also using post-recanalization data segments from patients excluded from study I as a confirmation cohort to the prediction models.

In this study both NIHSS and mRS was assessed by the investigators. We performed all data analysis after these assessments and final database lock. Therefore, we consider the results unaffected by investigator bias.

Recanalization success was graded immediately after EVT by treating interventional neuroradiologist. We cannot rule out some bias in recanalization grading depending on the complexity of the procedure, collateral circulation, etc. Several patients experienced

temporary re-occlusions during the procedure and more would be expected to re-occlude early after the procedure (~6% within 48 hours)<sup>86,87</sup>. We did not perform any systematic follow-up angiography. This constrained us from performing exact assessment of futile recanalization. Undetected re-occlusions could partially explain why recanalization success, surprisingly, was not a significant predictor of outcome.

## **Study II: Bilateral dynamic cerebral autoregulation assessment during endovascular treatment in large-vessel occlusion stroke<sup>2</sup>**

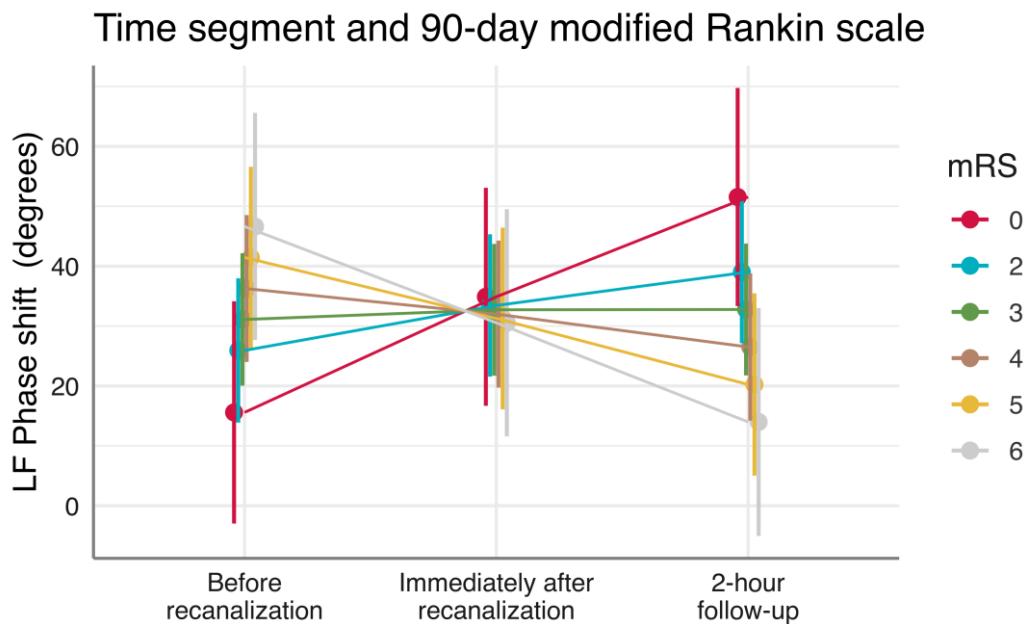
### **Background and aim**

Study I examined interhemispheric phase shift without the possibility to perform unilateral phase shift estimation. Thus, study II aimed to perform dCA assessments using the conventional TFA model based on invasive ABP and NIRS. Further, we aimed to detect associations between LF phase shift to clinical characteristics and outcome.

### **Results**

Steady-state data immediately after recanalization were available in 38 patients (34.2 % female sex, mean age 69.6 years (SD 13.9), median baseline NIHSS 16.5 (IQR 9.5-22), recanalization success 84.2%). Unilateral LF phase shift was approximately 40 degrees in the ischemic hemisphere and did not differ from the contralateral hemisphere. Sensitivity of unilateral LF phase shift to end-tidal CO<sub>2</sub> was increased in the ischemic hemisphere ( $\beta$ : -26.7 degrees per kPa, CI: -40.8; -12.6, p<0.001) compared to the contralateral hemisphere (p=0.015).

Only 11 patients were eligible for complete sequential analysis due to missing steady-state data segments before recanalization and/or at 2-hour follow-up. On the group level unilateral LF phase shift did not change between time segments, but patients had a very different progression depending on 90-day functional outcome (p=0.011, Figure 5), independency (p=0.030) and mortality (p=0.019). Patients with good outcome increased in unilateral LF phase shift from before recanalization to 2 hours after recanalization while the opposite was the case for patients with poor outcome.



*Figure 5. Unilateral LF phase shift during EVT and at 2-hour follow-up across 90-day functional outcome. Patients with good functional outcome (low mRS) had increased phase shift after recanalization and at follow-up. Poorer functional outcome (increasing mRS) gradually reversed the progression of phase shift.*

## Conclusion

Dynamic cerebral autoregulation assessed by unilateral phase shift between ABP and NIRS showed no differences between ischemic and contralateral hemisphere. The ischemic hemisphere showed increased dCA sensitivity to end-tidal CO<sub>2</sub>. Depending on 90-day outcome, dCA progressed differently during EVT and 2 hours after.

## Strengths and limitations

The conventional TFA approach applied in study II supports the interhemispheric TFA from study I by providing unilateral phase shift assessments in both hemispheres. This approach requires continuous ABP which we measured invasively as standard-of-care monitoring through an arterial line. Invasive arterial blood pressure is preferred when available and have superior reliability compared to noninvasive measurement<sup>56, 88</sup>. In the current context, the disadvantage was missing data as 20% of examined patients did not have invasive ABP measured due to difficulties in the arterial line placement which should not delay EVT. Further, a substantial proportion of patients were excluded from sequential

analysis as invasive ABP setup was not yet established in the narrow time frame before recanalization or only measured during EVT (i.e., by pressure-sensing access sheath<sup>89</sup>). Adding non-invasive ABP monitoring was a feasible although challenging alternative but only in some patients. Using noninvasive ABP interchangeably with invasive ABP in dCA analysis would be compromised by substantial reliability concerns<sup>88</sup>.

The conventional TFA approach with NIRS as output also led to the exclusion of several patient from analysis compared to the interhemispheric TFA. First, coherence between ABP and NIRS recordings was below the recommended threshold in 4% of patients. Second, the conventional TFA approach with NIRS has no intrinsic accounting for extracerebral tissue contamination. Thus, we required short-distance channels of adequate quality which were more prone to oversaturation (i.e., 8% of examined patients).

Extending general anesthesia a few minutes to record steady-state segments for dCA analysis could have increased the sample size but not without ethical, practical and economical concerns. The relatively large number of examined patients excluded from analysis increases the risk of selection bias (e.g., terminating general anesthesia quickly in young and uncomplicated patients leading to exclusion of patients without a time segment after recanalization; inability to insert arterial canula due to peripheral atherosclerosis leading to exclusion of patients without invasive ABP measurements) which could have been examined further.

Study II does not address the uncertainties concerning the phase relations between  $V_{MCA}$ , ABP and OxyHb with intact or impaired dCA. Examining healthy patients under wakefulness with NIRS, invasive ABP and possibly TCD would have aided to uncover these uncertainties.

In both study I and II we measured end-tidal CO<sub>2</sub> during EVT which remained stable for all analyzed patients. However, carbon dioxide was not measured at follow-up examinations after EVT in either study. Carbon dioxide has a substantial effect on cerebral blood flow and LF phase shift in study II. Patients were resting and were respiratory stable during recording with only minimal changes in respiratory frequency and peripheral oxygen

saturation. Therefore, the impact within follow-up dCA examinations is considered negligible. However, carbon dioxide levels could have changed after EVT and affected longitudinal analyses. End-tidal CO<sub>2</sub> during time segments during EVT in study I and II was very similar to end-tidal CO<sub>2</sub> in other post-thrombectomy studies<sup>61, 90, 91</sup> but should be measured in future studies.

## **Study III: Cortical hemodynamic response during cognitive Stroop test in acute stroke patients assessed by fNIRS<sup>3</sup>**

### **Background and aim**

A large proportion of ischemic stroke patients have impairment of cognitive function especially in the acute phase. The pathophysiology behind cognitive impairment is not always clear. Further, a biomarker could be helpful to guide rehabilitation. Therefore, the aim of study III was to investigate the prefrontal hemodynamic response of subacute ischemic stroke patients during the Stroop Color and Word test by using fNIRS and evaluate the potential of fNIRS as a rehabilitation biomarker.

### **Results**

We examined 21 AIS patients (52.4% female sex, median age 64 years (IQR 57-71) and baseline NIHSS 2 (IQR 1-5), 38.1% with cognitive impairment) and 22 healthy controls (HC) with corresponding age and gender distribution.

AIS patients performed the test with higher response time (1.85 s (SD 0.38) vs. HC 1.52 s (SD 0.38), p=0.009) and error rate (0.25 (SD 0.24) vs. HC 0.11 (SD 0.05), p=0.036).

Contrary to our expectation, both groups showed an inverse hemodynamic response with decreased OxyHb and increased DeoxyHb in the superolateral and superomedial prefrontal cortex. The hemodynamic response of AIS patients was lower than healthy controls.

The hemodynamic response did not increase with the degree of test difficulty and there was no association between hemodynamic response and test performance. The presence of small-vessel disease did not have any clear effect on hemodynamic response.

### **Conclusion**

The Stroop Color and Word test showed impaired executive function and inhibition in AIS patients. In opposition to several other studies<sup>41-44</sup>, the hemodynamic response was inverted in superomedial and superolateral prefrontal cortex and lower in AIS patients. Inverted hemodynamic response are poorly understood and the current potential for fNIRS as a rehabilitation biomarker is rather low.

## **Strengths and limitations**

The design of study III was based on previous studies examining a wide range of patients that found prefrontal activation using fNIRS including patients with cerebral microangiopathy<sup>44</sup> that have some common traits to the examined stroke patients. This study prompted us to account for small-vessel disease assessed by a MRI-based classification validated against known risk-factors<sup>92</sup> and cognitive function in elderly people<sup>93</sup>. Classification should perhaps have been adjusted to account for acute lacunas in this specific setup.

After pilot examinations we adjusted the Stroop Color and Word test compared to previous versions<sup>43</sup> to allow for an increased maximum response time and a slower hemodynamic response and relaxation time. After data analysis we discovered that the adjustment could have been even greater from a hemodynamic perspective. The test was setup with three degrees of difficulty with the difference between the two hardest constituting the Stroop effect. This allows for separate hemodynamic investigation of each condition. The downside of this test paradigm is some uncertainty whether the different difficulty levels activate the same prefrontal areas. Additionally, no validated threshold for cognitive impairment have been determined for this iteration of the Stroop Color and Word test.

The fNIRS system covered most of the prefrontal cortex but could have been designed in a denser configuration with more channels. Spatial registration of channels would have improved regional sensitivity and ensured that regions of interest were examined. We added short-separation channels to the experimental setup to account for extracerebral tissue contamination and improve motion artefact correction. Adding further auxiliary measurements such as ABP, accelerometers or multiple short-separation channels could have improved signal quality even further<sup>94-96</sup>. Concurrent measurements of activation by electroencephalogram can assist fNIRS and thereby enable assessment of optode positioning and detection of impaired neurovascular coupling. Comparing to a group of healthy control subject would often accomplish the same but not when the hemodynamic response is atypical as in this study.

The cohort consist of stroke patients with non-prefrontal lesions. They had relatively mild symptom severity as the examinations added to the standard-of-care were quite extensive and required the ability to understand and adhere to instructions. The proportion of patients classified etiologically as small-vessel occlusion were even larger than in comparable cohorts with low NIHSS (<6)<sup>97-99</sup> but otherwise similar regarding recanalization treatment and infarct location<sup>97, 99</sup>. Patients with prior stroke were not excluded from study III and the effects from prior and current stroke could not be dissociated.

Healthy control subjects with corresponding age as patients were interviewed before enrollment to exclude subjects with symptomatic vascular diseases or associated risk factor. However, no further examinations were performed, and their electronic medical records were not accessed.

# Discussion

Theoretically, NIRS is a promising method to examine the dynamics of cortical hemoglobin which could be paramount in cerebrovascular diseases. In this PhD thesis, we have investigated some of the opportunities of NIRS examinations mainly in the acute phase of ischemic stroke.

## Dynamic cerebral autoregulation in acute ischemic stroke

### Clinical findings and interpretation

#### *Gain*

Interhemispheric gain specifies the ratio of LFO amplitudes between the ischemic and contralateral hemisphere. Thus, interhemispheric gain of 1 denotes equal LFO amplitudes. Gain exceeds 1 when LFO amplitude is greater in the ischemic hemisphere, while amplitude is greater in the contralateral hemisphere if gain is lower than 1.

Interhemispheric gain was relatively stable during EVT and up until 90-day follow-up and was closely associated to 90-day functional outcome. Higher gain exceeding 1 was associated to better functional outcome and greater LFO amplitude in the ischemic hemisphere. Poor outcome patients showed linearly decreasing interhemispheric gain indicating greater LFO amplitude in the contralateral hemisphere.

The common interpretation of conventional unilateral gain between ABP and V<sub>MCA</sub> is not consistent with our findings. In this model, dCA is believed to be intact when LFOs in the systemic circulation (ABP) transmitted to the cerebral circulation (V<sub>MCA</sub>) are actively attenuated by dCA resulting in lower V<sub>MCA</sub> amplitude and lower gain. Conversely, impaired dCA results in passive transfer of LFOs to the cerebral circulation with gain approximating 1. The discordance could be explained by differences in the examined vasculature as NIRS is sensitive to all vascular compartments dominated quantitatively by the small vessel and microvasculature (diameter < 1mm)<sup>100</sup> whereas TCD measures velocity in a single large vessel with no information of diameter changes<sup>79-81</sup>.

Study I also found an association between IVT administered before EVT and higher interhemispheric gain independent from the effect of functional outcome. Previous studies suggested the effect was due to the improved recanalization induced by IVT and not a pharmacological action<sup>101, 102</sup>. In our studies, we did not show any association between dCA and recanalization to support this. This could perhaps be explained by the uncertainties regarding final recanalization (i.e., recanalization grading bias by treating interventional radiologist, no follow-up angiography). IVT is now recommended if performed without delaying EVT<sup>18</sup>. IVT can improve reperfusion both before but also after EVT by the thrombolysis of peripheral occlusions (i.e., migrated thrombi and microthrombi)<sup>103, 104</sup>. The finding indicates the need to account for IVT in future dCA studies.

#### *Phase shift*

Phase shift is another aspect of dCA determined by the delay of time between input and output in the TFA. Study I examined interhemispheric phase shift based on NIRS alone (OxyHb), while study II examined conventional and unilateral phase shift between ABP and OxyHb in both hemispheres. Both approaches found associations to clinical variables. Study I showed increased interhemispheric phase shift earlier and during EVT in patients with lower baseline NIHSS while the phase shift increase occurred later in patients with higher baseline NIHSS. This could be an indication of contralateral dCA improvement occurring differently across symptom severity which would be consistent with interhemispheric differences seen within 24 hours in other dCA studies of LVO<sup>61, 62, 75, 91</sup>. Study II did not show the same association of baseline NIHSS to unilateral phase shift of ABP and OxyHb, and we observed no phase shift difference between hemispheres during or 2 hours after EVT. However, unilateral phase shift in both hemispheres increased during and 2 hours after EVT in patients with good outcome and decreased in both hemispheres in patients with poor outcome. The association between long-term functional outcome and phase shift in the acute phase (<24 hours from onset) of ischemic stroke and especially LVO has been established in previous studies<sup>61, 62, 75, 105-107</sup> but study I and II provides insight to the early development of dCA changes. Further, study I showed an increased dCA sensitivity to ETCO<sub>2</sub> in the ischemic hemisphere compared to the contralateral hemisphere. Individual dCA changes in the hyperacute phase could possibly indicate a potential for clinical implementation.

## Clinical translation

Valid cerebral blood flow monitoring is inherently difficult to achieve continuously. No direct method has yet been developed with sufficient spatial and temporal resolution to guide perfusion<sup>108</sup> which could be paramount in cerebrovascular diseases to avoid ischemic damage due to hypoperfusion or hemorrhagic lesions due to hyperperfusion<sup>64</sup>. When using ABP as an indirect measure of cerebral perfusion, restrictions from extreme levels (>220/120 mmHg) should benefit all acute ischemic stroke patients<sup>109</sup>. Guidelines also support blood pressure reduction to <180/105 mmHg in patients during and 24 hours after recanalization therapies as recanalized tissue is vulnerable after ischemia and thus susceptible to reperfusion injuries including hemorrhagic transformation and intracerebral hemorrhage. Further narrowing the therapeutic ABP interval have been attempted in several large-scale studies but with no effect on functional outcome<sup>110</sup>. However, early neurologic deterioration is a frequent complication that is often attributable to progression of the ischemic infarction or hemorrhagic lesions and affects outcome negatively<sup>111-113</sup>.

Recent randomized trials of individualized thresholds based on arrival ABP have not shown any influence on long-term functional outcome but have been challenged by controlling ABP within the desired thresholds<sup>114, 115</sup>. The missing link between neurologic deterioration and blood pressure management could very well be dynamic cerebral autoregulation. Individualizing blood pressure limits after EVT based on dCA have shown increased associations to long-term functional outcome compared to fixed ABP thresholds<sup>116</sup>. Currently, this avenue seems to be the most achievable clinical target as no feasible measures to influence dCA directly have been identified<sup>117</sup>. The feasibility of applying dCA-guided ABP thresholds in randomized controlled trials have been shown in traumatic brain injury and cardiac surgery<sup>118, 119</sup> and the RESCUE-CA trial is registered to examine this approach in post-thrombectomy patients (Clinicaltrial.gov ID: NCT05670028). Performing similar studies in prehospital settings, before and during recanalization therapies could also have significant impact as the continued viability of penumbral tissue is dependent on adequate blood flow through collateral circulation which is also under the influence of dCA<sup>64</sup>. While feasibility of examining dCA during EVT with TFA was determined in study I and II, all previous studies examining dCA-guided thresholds were based on time-domain methods<sup>116, 118-120</sup>. Thus, several obstacles would

have to be addressed before TFA results can be applied in randomized trials. First, the translation between TFA results and individualized ABP threshold will have to be established. Second, real-time software performing TFA and individualizing ABP threshold needs to be available. Steady state is required for several minutes for TFA to produce reliable results<sup>56</sup> which hinders continuous dCA assessment in this clinical setting and dCA-guided ABP threshold would therefore be based on point estimates.

Another clinical implication of our findings was the increased CO<sub>2</sub> sensitivity in the ischemic hemisphere found in study II. Relatively intact dCA was observed in mild hypocapnia and normocapnia (4.0-5.0 kPa) and showed gradual impairment in hypercapnia. As intact dCA is a predictor for favorable long-term outcome, normocapnia or mild hypocapnia would seem desirable in the hyperacute management of LVO patients. Current guidelines do not specify how to ventilate LVO patients undergoing EVT<sup>121, 122</sup>. Observational studies are small-scale and not fully consistent. In opposition to our findings and interpretation, the trend of these studies indicates a more favorable outcome with intraprocedural hypercapnia<sup>122</sup>. The COMET-AIS trial (Clinicaltrial.gov ID: NCT05051397) are investigating both short- and long-term impact of targeting hypercapnia (50 mmHg ~ 6.7 kPa) versus normocapnia (40 mmHg ~ 5.3 kPa) during thrombectomy.

The association between interhemispheric gain and functional outcome was significant in multivariate prediction models. Such models can eventually lead to an improved selection of patient who benefit a given treatment which would have to be tested in a randomized controlled trial. This will require an early dCA assessment before EVT which could be difficult to attain in the hyperacute setting especially as the dCA assessment requires a steady state period of several minutes. Therefore, the value of this association could be prognostication of functional outcome alone.

## **Methodological findings and discussion**

Dynamic cerebral autoregulation was assessable during EVT of large-vessel occlusions when using NIRS. We used two related approaches that each has distinct advantages and limitations. The conventional TFA approach was based on invasive ABP as input and the

surrogate cerebral blood flow of OxyHb as output. The method examines each hemisphere by itself but is hampered by a large proportion of patients from an everyday cohort being excluded when using standard-of-care monitoring which does not include invasive ABP if the setup delays EVT. The interhemispheric TFA was based on OxyHb from ischemic and contralateral hemisphere and reduced the number of excluded patients, but the results can be challenging to interpret when both hemispheres could be affected by impaired dCA.

To be successful in translating dCA measures to clinical implications, studies will need an accurate, valid and reliable dCA assessment method<sup>117</sup>. Reliability of dCA methods including time-domain methods<sup>123</sup> and TFA during spontaneous oscillations have recently been questioned<sup>82</sup>. Augmentation of oscillations by certain protocols can enhance TFA reliability if CO<sub>2</sub> is not affected<sup>56, 124-126</sup> perhaps by reducing the non-linear and non-stationary components of dCA<sup>127, 128</sup>. Most of such procedures (e.g., sit-stand maneuvers, oscillatory lower-body negative pressure, passive leg raising) are not possible in this clinical setting. Paced breathing at recommended point estimate (0.1 Hz)<sup>56</sup> could be conceivable in some patients without sacrificing safety. Patients with respiratory diseases would not necessarily fall into this category and applying this protocol could therefore create a selection bias. Extending the length of recording as proposed<sup>82, 129</sup> could also enhance reliability but would have come at the cost of reduced sample size. Other white-paper recommendations to improve reliability including diurnal time of recording, exercise and dietary intake before examination<sup>56</sup> are not possible to control in this acute setting.

Reliability is an important consideration in analysis of repeated measures as performed in study I and II. Low reliability of an examination method due to measurement error or non-stationarity creates substantial intrasubject variability<sup>130</sup>. In longitudinal design this reduces the detection capability of different progressions across the repeated measurements. While the reliability of TFA using NIRS have not yet been addressed, it did not preclude study I and II from detecting differences across time segments during and after EVT.

## **Future directions of dCA within acute ischemic stroke**

A glaring limitation of study I and II are the missing comparison to control groups including age- and gender-matched healthy subjects and co-morbidity matched patients. This has yet to be performed to inform us of the presence and degree of dCA impairment in AIS patient during and after EVT. The test-retest reliability of the applied dCA examinations should be examined which could be performed in the follow-up examinations of our data set that were relatively steady. The relation between our models and the conventional ABP- $V_{MCATFA}$  model will have to be determined in future investigations.

Other data analysis only using NIRS to investigate dCA have been applied in previous studies<sup>83, 84, 131</sup> and could easily be applied to our data and compared if scripts can be made open-source available.

Different modelling of dCA with non-linear approaches is another evolving direction which will be interesting to follow<sup>128, 132-134</sup>. Processing complex and multimodal data would also be an obvious area in which artificial intelligence could be helpful<sup>135-137</sup>.

The emergence and availability of more precise optical methods including open-source oximetry<sup>138</sup>, frequency-domain NIRS, time-domain NIRS and diffuse correlation spectroscopy<sup>139</sup> could improve the sensitivity to cerebral blood flow and perhaps the validity and reliability of dCA assessments.

Many aspects of dCA within ischemic stroke are yet to be determined including the influence of etiology, small-vessel disease, regional anatomy and co-morbidities<sup>64</sup>. In future studies more exact reporting of examination time and recanalization therapy would be desirable especially in longitudinal designs.

Finally, the pathway from dCA assessments to clinical implications need further explorations at some point in the future.

## **Functional near-infrared spectroscopy in acute ischemic stroke**

In opposition to previous studies<sup>41-44</sup>, functional NIRS examination during the Stroop Color and Word test showed an inverse hemodynamic response in both subacute ischemic stroke patients and healthy control subjects especially in the superomedial and superolateral parts of the prefrontal cortex. The response was lower in stroke patients but did not correlate to test difficulty. We found no certain effect of small vessel disease nor lateralization of the inverse activational patterns.

Neurorehabilitation begins expeditiously and immediately after the hyperacute treatment of ischemic stroke<sup>140</sup>. The detection of cognitive impairment often starts with screening examination such as Montreal Cognitive Assessment. Subsequently, more specific tests such as the Stroop Color and Word test are applied. Cognitive symptoms and impairment are frequent in acute and chronic stroke patients<sup>141, 142</sup>, but the anatomical lesion does not always offer an obvious pathophysiologic explanation. Valid biomarkers to support the pathophysiologic understanding and possibly monitor such disease processes during rehabilitation could be valuable tools<sup>143</sup>. Some patients are not able to perform specific cognitive tests due to aphasia, visual deficits or upper limb motor symptoms. Tests with minor motoric requirements stimulating specific brain regions could be another situation in which biomarkers could be useful<sup>144</sup>. Theoretically, biomarkers could also be input to prediction models and support the decision making when tailoring rehabilitation efforts.

Study III did not support fNIRS as a biomarker for lesions or symptoms related to prefrontal regions that are activated during the Stroop Color and Word test. The results were surprising as previous studies applying the exact same test showed prefrontal activation<sup>43, 44, 145</sup>. Recently, aphasic stroke patients were able to comprehend and perform the Stroop Color and Word test during dense multi-channel fNIRS examination<sup>144</sup>. Healthy control subjects showed classic activational pattern in temporal cortex and some parts of the dorsolateral prefrontal cortex but atypical hemodynamic response (i.e., different from the inverse hemodynamic response observed in study III) in other parts of the dorsolateral prefrontal cortex. Stroke patients showed atypical response patterns across temporal and prefrontal regions. The study did not account for extracerebral contamination and reported no additional information concerning index stroke including time from onset to

examination<sup>144</sup>. Study III could suffer from small regional differences within the dorsolateral prefrontal cortex and emphasizes the need for dense multi-channel setups with spatial registration and short-separation regression to ensure the regions of interest are examined properly which increases sensitivity to brain activation<sup>146</sup>. Such an approach was applied by Liu et al. who examined ischemic stroke patients with executive impairment in the chronic phase during a verbal Stroop Color and Word test<sup>143</sup>. Stroke patients showed decreased activation of the left dorsolateral prefrontal cortex, the right pre-motor cortex and the primary sensorimotor cortex compared to healthy subjects. Activation in the left dorsolateral prefrontal cortex was confined to a smaller anatomical region than in healthy subjects. The study also displayed the potential of fNIRS as a biomarker. Transcranial magnetic stimulation was applied to improve executive function which was achieved in both patients and healthy subjects with a concurrent improvement in fNIRS response. Without a hemodynamic correlate the improvement in test response could easily have been discarded as a practice effect<sup>147</sup>.

## **Future direction of fNIRS within ischemic stroke**

Theoretically, the potential of fNIRS as a biomarker is tremendous as the temporal resolution is very high while the physical limitations are only marginal<sup>148</sup>. Pragmatically, this potential has been displayed especially in cognitive neuroscience<sup>39</sup> and the accuracy is improving due to advances in equipment and data analysis<sup>149</sup>. This includes the availability of multi-channel setup with dense and more widespread optode configurations, spatial registration, more advanced motion artefact corrections, and incorporation of short-separation channels and other measurements as regressors in the hemodynamic response function<sup>150, 151</sup>. Other methods such as frequency-domain NIRS, time-domain NIRS, diffuse correlation spectroscopy or electroencephalography can be used in hybrid systems to improve brain sensitivity or detection of the neurovascular coupling<sup>152-155</sup>. The development could aid researchers in explaining atypical hemodynamic responses which are not described very well<sup>156</sup> and could lead to publication bias despite efforts to reduce it by pre-registration in public domains<sup>157</sup>.

The application of fNIRS in stroke rehabilitation is not just limited to cognitive domains but have also been used in motor recovery studies<sup>158, 159</sup>. Often in combination with

electroencephalography, fNIRS has been applied in brain-computer interface and neurofeedback to enhance rehabilitation of motor symptoms and cognition<sup>158, 160-163</sup>. The rapid development of instrumentation, complex data processing and therapeutic tools emphasizes the value of collaboration between clinicians and medical engineers.

# **Conclusion**

In this thesis, some of the many opportunities to examine acute ischemic stroke patients with NIRS were performed. We have shown the feasibility of two related methods of investigating dynamic cerebral autoregulation during and after endovascular treatment of large-vessel occlusion. The conventional dCA approach can be performed unilaterally but is difficult to obtain in many patients due to the need of invasive ABP. The obtainability of interhemispheric dCA based on NIRS alone is greater but the interpretation is more complicated. Both approaches showed changes during endovascular treatment of acute ischemic stroke with associations to clinical 90-day outcome including mortality. We also applied fNIRS during subacute ischemic stroke and found an inverse hemodynamic response during the Stroop Color and Word test that could not be explained thereby diminishing the biomarker potential of fNIRS. Advances within fNIRS research could increase brain sensitivity and biomarker potential but also help to clarify the cause of atypical hemodynamic responses.

## English summary

Acute ischemic stroke is a major disease globally caused by blood flow disruption in cerebral arteries. Recanalizing occluded large arteries by endovascular treatment is an effective therapy that can salvage brain tissue if performed quickly. Dynamic cerebral autoregulation usually maintains cerebral blood flow despite rapid changes in blood pressure but is impaired in after endovascular treatment. Dynamic cerebral autoregulation has never been examined during endovascular treatment.

After the acute treatments have been performed, rehabilitation of neurologic deficits begins. This includes therapies directed at cognitive impairment which could benefit from having a valid biomarker to examine and monitor pathophysiologic processes.

Near-infrared spectroscopy is an optical examination of the dynamical hemoglobin concentrations in the cerebral cortex. Near-infrared spectroscopy have previously been applied to examine dynamic cerebral autoregulation using transfer function analysis yielding phase shift and gain (amplitude ratio) of spontaneous low-frequency oscillations in acute ischemic stroke. Functional near-infrared spectroscopy can examine the hemodynamic response during cognitive testing.

**Study I** used an interhemispheric transfer function analysis to determine dynamic cerebral autoregulation during and after endovascular treatment. In patients with mild symptoms severity the interhemispheric phase shift increased immediately after recanalization, whereas phase shift increased later in patients with greater symptoms severity. Interhemispheric gain was unaltered throughout endovascular treatment and at follow-up after 24 hours and 90 days. Higher interhemispheric gain was associated to better 90-day functional outcome including mortality and significantly predicted functional outcome in multivariate models.

**Study II** examined dynamic cerebral autoregulation unilaterally during and after endovascular treatment with invasive arterial blood pressure as transfer function input. Unilateral phase shift was not different between hemispheres, but the ischemic hemisphere

had increased sensitivity to CO<sub>2</sub>. Unilateral phase shift increased during endovascular treatment in patients with good 90-day functional outcome and decreased in patients with poor outcome including fatality.

**Study III** examined subacute ischemic stroke patients with near-infrared spectroscopy during the cognitive the Stroop Color and Word test that evaluates prefrontal executive functions. The hemodynamic response was inverted in healthy subjects and stroke patients but diminished in stroke patients. The hemodynamic response was not associated to test difficulty.

Overall, near-infrared spectroscopy in acute ischemic stroke showed feasible assessments of dynamic cerebral autoregulation during endovascular treatment with important associations to long-term clinical outcome and the clinical implications should be investigated further. The potential of near-infrared spectroscopy as a biomarker during neurorehabilitation could be dependent on recent technical and analytical advances if clinical implementation is to be made reasonable.

## Danish summary

Akut iskæmisk stroke er globalt en betydningsfuld sygdom som forårsages ved afbrydelsen af blodgennemstrømningen gennem cerebrale arterier. Rekanalisering af okkluderede store arterier med endovaskulær behandling er en effektiv behandling der redder hjernevæv hvis udført hurtigt i forløbet. Dynamisk cerebral autoregulation opretholder normalt hjernens blodgennemstrømningen til trods for hurtige ændringer i blodtryk, men denne mekanisme er beskadiget efter endovaskulær behandling. Dynamisk cerebral autoregulation er aldrig undersøgt under endovaskulær behandling.

Efter hyperakut behandling påbegyndes rehabilitering af neurologiske symptomer. Dette inkluderer behandling rettet imod kognitiv svækkelse som ville gavne af en valid biomarkør der kan undersøge og monitorere de patofysiologiske sygdomsprocesser.

Nær-infrarød spektroskopi er en optisk metode der kan undersøge dynamiske koncentrationer af hæmoglobin i den cerebrale cortex. Nær-infrarød spektroskopi er tidligere blevet brugt til at undersøge dynamisk cerebral autoregulation ved akut iskæmisk stroke ved at benytte transfer function-analyse af lav-frekvente oscillationer hvilket resulterer i målene fase skift og amplitude ratio. Funktionel nær-infrarød spektroskopi kan undersøge det hæmodynamiske respons under kognitive test.

**Studie I** benyttede en interhemisfærisk transfer function-analyse til at bestemme dynamisk cerebral autoregulation under og efter endovaskulær behandling. Interhemisfærisk fase skift steg umiddelbart efter rekanalisering hos patienter med mild sværhedsgrad af symptomer, men først senere hos patienter med sværere symptomer. Interhemisfærisk amplitude ratio var uændret under endovaskulær behandling og ved opfølgning 24 timer og 90 dage derefter. Højere interhemisfærisk amplitude ratio var associeret til bedre 90-dags funktionelt udfald hvilket inkluderer dødelighed og forudsagde udfald i multivariable modeller.

**Studie II** undersøgte dynamisk cerebral autoregulation unilateralt med blodtryk som input til transfer function-analysen. Unilateralt fase skift var ikke forskelligt mellem

hemisfærerne, men den iskæmiske hemisfære var mere følsom overfor i CO<sub>2</sub>. Unilateralt fase skift steg under endovaskulær behandling hos patienter med godt 90-dags udfald, men faldt hos patienter med dårligt udfald herunder ved dødsfald.

**Studie III** undersøgte subakutte iskæmiske stroke patienter med nær-infrarød spektroskopi under den kognitive Stroop test der vurderer præfrontale eksekutive funktioner. Det hæmodynamiske respons var omvendt hos raske forsøgspersoner og stroke patienter men mindre hos stroke patienter. Det hæmodynamiske respons var ikke associeret til testens sværhedsgrad.

Overordnet er vurdering af dynamisk cerebral autoregulation muligt under endovaskulær behandling af akut iskæmisk stroke ved brug af nær-infrarød spektroskopi og viste vigtige associationer til langsigtet klinisk udfald og de kliniske implikationer bør undersøges yderligere. Nær-infrarød spektroskopis potentiale som biomarkør under neurorehabilitering kan være afhængigt af nylige tekniske og analytiske fremskridt hvis implementering i klinikken skal give mening.

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# Appendices

## **Study I: Dynamic cerebral autoregulation during and 3 months after endovascular treatment in large-vessel occlusion stroke**

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Submitted to Scientific Reports (ISSN 2045-2322) on September 13<sup>th</sup>, 2025.

Revised manuscript submitted May 26<sup>th</sup>, 2025.

**Manuscript title**

Dynamic cerebral autoregulation during and 3 months after endovascular treatment in large vessel occlusion stroke

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**Running headline**

Dynamic cerebral autoregulation during EVT of acute ischemic stroke

**Word count**

Including introduction, results and discussion: 3755

## **Abstract**

Acute ischemic stroke caused by large vessel occlusion is effectively treated by endovascular treatment (EVT). However, treatment could be further refined by improved understanding of the pathophysiology, including dynamic cerebral autoregulation (dCA). Near-infrared spectroscopy (NIRS) requires virtually no setup time and enables dCA investigation during EVT by measuring dynamic concentration in cortical oxygenated hemoglobin (OxyHb). We aimed to investigate dCA during EVT, before and after recanalization, and at follow-up (FU) after 24 hours and 90 days. We applied interhemispheric transfer function analysis (TFA) of low-frequency (LF) oscillations (0.07-0.2 Hz) in OxyHb that yields the dCA measures, gain and phase shift. LF phase shift increased immediately after recanalization for patients with milder symptom severity and at 24-hour FU for patients with more severe symptoms, but contralateral phase shift needs further investigation. We found higher LF gain in patients with favorable outcome and in patients starting intravenous thrombolysis before EVT. Adjusted for age, infarct size before EVT, and recanalization success, average LF gain predicted independent functional outcome, symptom severity and mortality at 90-day FU. In conclusion, interhemispheric TFA based on NIRS was feasible to assess dCA during EVT and provided insights that could potentially be applied in the development of individualized treatment.

## **Clinical Trial Registration**

ClinicalTrial.gov: NCT03738644. [Https://clinicaltrials.gov/study/NCT03738644](https://clinicaltrials.gov/study/NCT03738644).

## **Keywords**

Acute ischemic stroke; Endovascular treatment; Dynamic cerebral autoregulation; Near-infrared spectroscopy; Transfer function analysis

## **Non-standard Abbreviations and Acronyms**

ACA: Anterior Cerebral Artery

AIS: Acute Ischemic Stroke

ASPECTS: Alberta Stroke Program Early CT Score

BA: Basilar artery.

CW-NIRS: Continuous Wave Near-Infrared Spectroscopy

dCA: Dynamic Cerebral Autoregulation

EVT: Endovascular Treatment

FU: Follow-up

FU<sub>24</sub>-group: All participants with sufficient data at PRE, POST and 24-hour FU.

FU<sub>90</sub>-group: All patients with sufficient data at PRE, POST, 24-hour and 90-day FU.

HF: High-frequency (0.2-0.5 Hz)

ICA: Internal carotid artery.

IVT: Intravenous thrombolysis.

LF: Low-frequency (0.07-0.2 Hz)

LFO: Low-frequency oscillations

LVO: Large vessel Occlusion

M1: First part of middle cerebral artery.

M2: Second part of middle cerebral artery.

MCA: Middle Cerebral Artery

mRS: modified Rankin Scale

mTICI: Modified Treatment In Cerebral Infarction

NIHSS: National Institutes of Health Stroke Scale

NIRS: Near-Infrared Spectroscopy

OxyHb: Oxygenated Hemoglobin Concentration

PC-ASPECTS: Posterior circulation Alberta Stroke Program Early CT Score

PCA: Posterior cerebral artery.

POST: Second time segment (after achieving final reperfusion status)

PRE: First time segment (after sedation but before any attempted revascularization)

PSD: Power spectral

STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

TFA: Transfer Function Analysis

TIA: Transient ischemic attack

VLF: Very low-frequency (0.02-0.07 Hz).

VMCA: Flow velocity in the Middle Cerebral Artery

## Introduction

Stroke remains a worldwide leading cause of disability and death despite the emergence of effective recanalization therapies<sup>1</sup>. Patients with a large vessel occlusions (LVO) face the worst prognosis and constitute up to 38% of patients with acute ischemic stroke (AIS)<sup>2</sup>. Endovascular treatment (EVT) drastically improves functional outcome after anterior circulation LVO when performed within 6 hours<sup>3</sup>, or within 24 hours in cases with mismatch between neurologic deficit and infarct core<sup>4</sup>. Posterior circulation EVT has shown similar advantages compared to best medical treatment<sup>5</sup>. However, procedure-related complications and futile recanalization still restrain the overall efficacy of EVT<sup>6,7</sup>. Impairment of cerebral autoregulation is one of the proposed mechanisms for unexplained futile recanalization<sup>7,8</sup>.

Cerebral autoregulation is the maintenance of suitable blood flow despite changes in cerebral perfusion pressure<sup>9</sup>. Dynamic cerebral autoregulation (dCA) determines how cerebral blood flow is regulated during rapid changes in perfusion pressure<sup>10</sup>. Prevailing methods indicate varying degrees of dCA impairment in patients with AIS including LVO<sup>8,11</sup> which could endanger vulnerable brain tissue by hypo- and hyperperfusion during and after EVT. Post-thrombectomy studies have shown dCA is an independent predictor of functional outcome<sup>12</sup>, and that it can be used to individualize blood pressure management<sup>13</sup>. However, dCA has never been examined before or during EVT.

Most dCA investigations rely on transcranial Doppler sonography examining blood flow velocity in the middle cerebral artery ( $V_{MCA}$ ) which requires expertise and setup time<sup>14</sup>. Assessment of dCA before EVT would compromise patient safety when every minute counts. Monitoring dCA during EVT also require modalities that do not interfere with the digital subtraction angiography. Near-infrared spectroscopy (NIRS) is an optical method which continuously measures dynamic changes in cortical hemoglobin concentrations without needing any consequential setup time or causing artifacts on the digital subtraction angiography<sup>15,16</sup>.

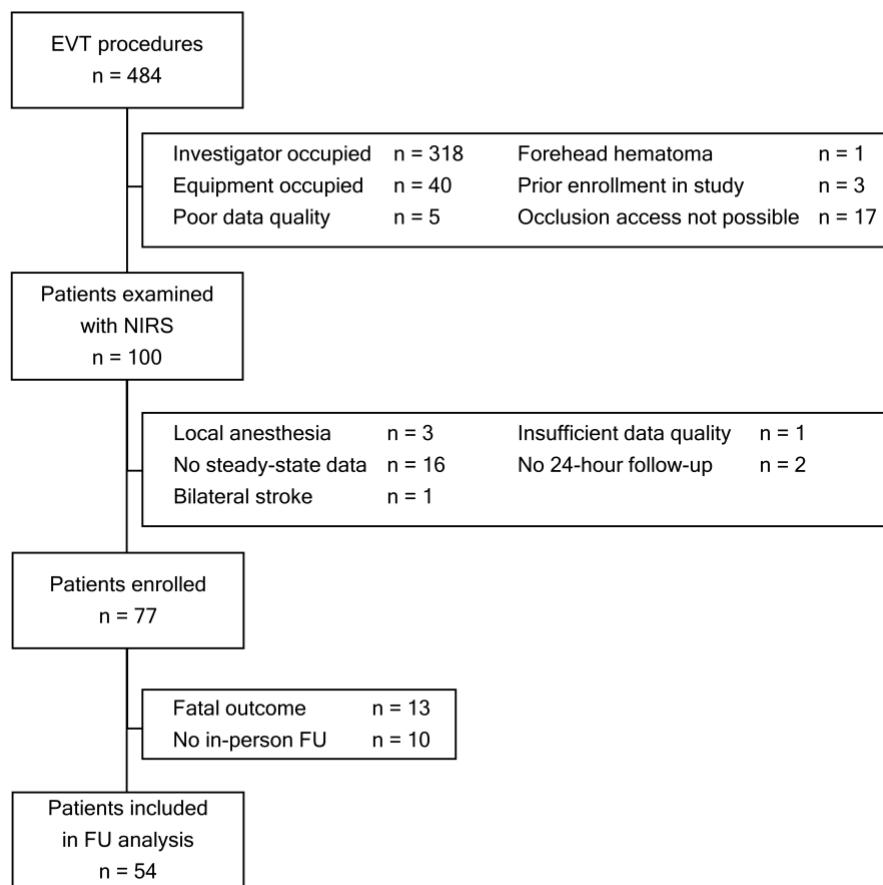
Low-frequency oscillations (LFO, approximately 0.1 Hz) are prevalent in both systemic (i.e., arterial blood pressure, ABP) and cerebral circulation (e.g.,  $V_{MCA}$ , NIRS)<sup>15,17,18</sup>. Quantifying the changes

between them in the frequency domain by transfer function analysis (TFA) is one of the most utilized and standardized methods of assessing dCA<sup>19,20</sup>. TFA quantifies dCA by phase shift and gain. Phase shift is the temporal disruption of LFOs while gain is the amplitude ratio between LFOs. Applying TFA for comparison of the NIRS signal between the unaffected and the ischemic hemisphere, we aimed to investigate dCA before, during and after EVT and associate dCA to index stroke characteristics, treatment and long-term outcome.

## Methods

This prospective observational study (ClinicalTrials.gov: NCT03738644) was conducted between November 2018 and November 2020 after approval from the Scientific Ethics Committees for the Capital Region of Denmark (H-18028704) and in accordance with the World Medical Association Declaration of Helsinki. All participants or their proxy signed written informed consent. Reporting complies with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies<sup>21</sup>. Corresponding author had full access to all the data in the study and take responsibility for data integrity and analysis. Further methodical details are provided in the supplementary information.

All AIS patients admitted to Rigshospitalet with LVO receiving EVT were screened for eligibility. The exclusion criteria are shown in the enrollment flowchart (Figure 1). Patients with bilateral infarction were excluded as no contralateral hemisphere could be defined (see interhemispheric transfer function analysis section).



**Figure 1. Enrollment and exclusion process.** NIRS: Near-infrared spectroscopy. EVT: Endovascular treatment. TFA: Transfer function analysis. FU: Follow-up.

Patients were diagnosed and treated as per standard-of-care. LVO was confirmed and Alberta Stroke Program Early CT Score (ASPECTS)<sup>22</sup> or Posterior circulation-ASPECTS (PC-ASPECTS)<sup>23</sup> were determined by staff neuroradiologists assisted by RAPID AI software (iSchemaView, Menlo Park, California, USA) and dichotomized to favorable (ASPECTS/PC-ASPECTS  $\geq 6$ ) or non-favorable (ASPECTS/PC-ASPECTS  $< 6$ ). Patients were transferred immediately to the angiosuite where symptom severity was re-assessed using the National Institutes of Health Stroke Scale (NIHSS) before EVT was performed under general anesthesia without intraarterial vasodilators. In addition to conventional monitoring<sup>24</sup>, NIRS was applied throughout the procedure (described below). Reperfusion success was assessed by the treating interventional neuroradiologist (modified Treatment In Cerebral Infarction, mTICI; Grade 0-2a unsuccessful achieving no reperfusion to reperfusion in less than half of the occluded artery territory; Grade 2b-3 successful reperfusion in

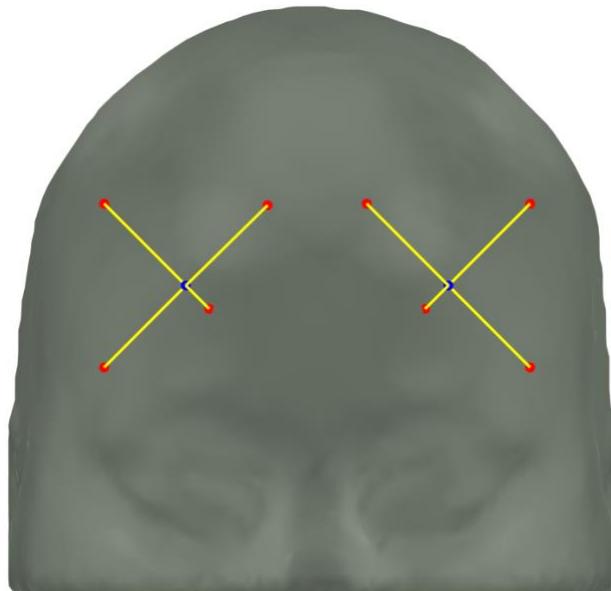
more than half of the occluded artery territory or complete reperfusion)<sup>25</sup>. Post-procedure, the patients were extubated as soon as possible and underwent dual-energy computed tomography (CT) or magnetic resonance imaging (MRI) after 24 hours to detect intracranial hemorrhage or other complications. Patients underwent further examinations as per standard-of-care. Stroke etiology was classified based on the Causative Classification System for Ischemic Stroke<sup>26</sup>.

#### *Follow-up*

Patients had two follow-up (FU) examinations during awareness with NIRS in the supine position for 20 minutes after at least 5 minutes of rest. The first FU was performed 24 hours after EVT (+/- 6 hours from end of endovascular reperfusion efforts) in addition to NIHSS assessment. The second FU was completed after 90 days (+/- 14 days) with functional outcome scored modified Rankin Scale (mRS) and independency (defined as mRS of 0-2) as well as NIHSS. Occurrence of re-hospitalizations, new vascular events (recurrent stroke, myocardial infarction, or surgery for peripheral artery disease) and all-cause mortality were registered. Patients unable to attend 90-day FU, were offered home visits within a 2-hour transportation radius. Patients who did not have in-person FU, were followed up by phone interview and using the electronic health record system.

#### *NIRS examination*

The NIRS monitoring was performed using a continuous wave-NIRS (CW-NIRS) system (Octamon, Artinis Medical Systems, Elst, the Netherlands) with three long-distance channels (35 mm) per hemisphere, examining dynamic hemoglobin concentrations in the prefrontal cortex in the border zones between territories of the middle cerebral (MCA) and the anterior cerebral arteries (ACA) (two channels) and ACA territories exclusively (one channel per side)<sup>27</sup>. A fourth channel with short diode-receiver distance (10 mm) mainly examined the extracerebral tissues on both sides (Figure 2).



*Figure 2. Placement of NIRS channels. Corresponding channels from ischemic and contralateral hemisphere were analyzed by transfer function analysis and averaged subsequently. Short distance-channels were used in separate analysis of extracerebral signals.*

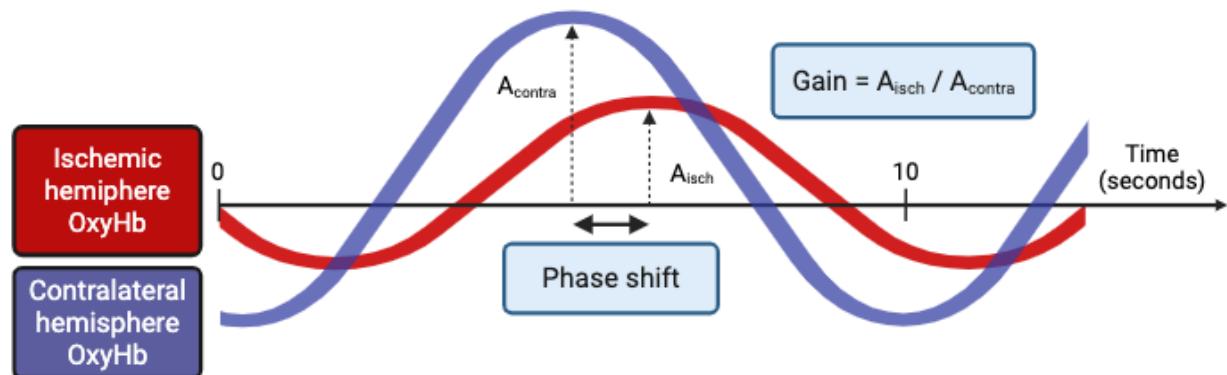
#### *Time segment selection*

Per recommendation from the Cerebrovascular Research Network only steady state data segments of five minutes were analyzed<sup>20</sup>. Thus, data segments were excluded within 5 minutes of inducing general anesthesia and within 2 minutes of changes in anesthetics, opioids, or vasopressors<sup>28</sup>. Very noisy data segments were also excluded from the analysis. Individual NIRS signal and all vitals were evaluated for steady state with an allowed variation of 10%. The first data segments free of these exclusionary criteria were chosen.

The first segment (PRE) occurred after sedation but before any attempted revascularization. The second data segment (POST) was just after the final reperfusion status was achieved, including the abandonment of reperfusion efforts. Third (24-hour) and fourth (90-day) data segments were selected based on the extent of motion artifacts. Patients who did not have complete PRE, POST and 24-hour segments were excluded from further analysis.

#### *Interhemispheric transfer function analysis*

The Cerebrovascular Research Network guidelines for TFA<sup>20</sup> were adapted with minor exceptions described throughout. TFA was only performed on oxygenated hemoglobin (OxyHb) concentrations as they are more reliable<sup>29</sup> and better reflect the arterial compartment<sup>15</sup>. Input to TFA was OxyHb from the contralateral hemisphere, while the corresponding contralateral channel from the ischemic hemisphere served as output. Fourier transformation was performed, and coherence, gain (amplitude ratio) and phase shift were then calculated in three frequency intervals (Figure 3): High-frequency (HF, 0.2-0.5 Hz), low-frequency (LF, 0.07-0.2 Hz) and very low-frequency (VLF, 0.02-0.07 Hz) and reported as recommended<sup>20</sup>. HF oscillations are transferred passively to cerebral circulation without transformation by dCA. The dCA aspects exhibited in the transformation of VLF oscillations are quite uncertain when limiting time segments to five minutes. Longer time segments were not as attainable in this clinical setting. Therefore, we restricted further analyses to the LF range. Power spectral density (PSD) specifies amplitudes ( $(\mu M \cdot mm)^2 / Hz$ ) for each hemisphere.



*Figure 3. Conceptual illustration of transfer function analysis resulting in phase shift and gain.*

Positive phase shifts denoted LFOs in the contralateral hemisphere occurring before LFOs in the ischemic hemisphere and vice versa. Because dyssynchronization of phase shifts can occur in either direction, absolute phase shift was calculated. Similarly, gain of more than 1 resulted from amplitudes in the ischemic hemisphere exceeding amplitudes in the contralateral hemisphere and vice versa. Theoretically, dCA would be deemed intact with no substantial phase shift and gain equal to one. This interpretation assumes dCA in the contralateral hemisphere is intact.

Any differences between input and output signals were assumed to result from intracerebral changes as extracerebral circulation is not under the influence of cerebral autoregulation. We tested this assumption by performing a TFA between short-distance channels from each side with the contralateral side as input and the affected side as output at 24-hour FU, under which the clinical condition was most stable and less prone to artifacts. Segment selection, data preparation and TFA methodology were equal to the processing for long-distance channels described above. Unfortunately, short-distance channels are more prone to oversaturation (i.e., by too much returned infrared light for sensors to record <changes>), reducing the number of channels with adequate data quality, especially in acute settings. Thus, incorporation of short-distance channel TFA in statistical models was not possible.

### *Statistics*

Statistical analysis was performed in two subsets of participants: 1) All participants with sufficient data at PRE, POST and 24-hour FU (FU<sub>24</sub>-group) 2) All patients with sufficient data at PRE, POST, 24-hour and 90-day FU (FU<sub>90</sub>-group) excluding patients with no in-person FU and patients who died. Baseline data from subjects without in-person FU was also analyzed to identify differences in subsets.

Normally distributed data are presented as mean and standard deviation (SD), while non-normal data are presented as median and interquartile range (IQR). Two-sample testing was performed as appropriate. False discovery rate was applied when performing multiple comparisons.

Linear mixed-effect models were fitted with LF gain or LF absolute phase shift as outcome, subjects as random effects, and fixed effects comprised of time segment in addition to and different patient characteristics (e.g., stroke etiology, age, favorable ASPECTS before EVT, anterior or posterior circulation stroke), treatment (e.g., intravenous thrombolysis (IVT), anesthesia, vasopressor, successful recanalization, and occurrence intracranial hemorrhage (ICH) regardless of symptom worsening) or outcome (e.g., NIHSS, mRS, mortality). In case of significant fixed effects, mixed-effect models were fitted with LF PSD from each hemisphere as an outcome to examine the

LFO amplitude in each hemisphere. Interaction between time segment and other fixed effects were assessed to determine different temporal developments between groups.

Significant fixed effects from mixed-effect models were used as outcome in logistic regression models with corresponding TFA parameter as univariate predictor. Two multivariate predictions were then performed. The acute prediction model was adjusted for age, recanalization success, and favorable ASPECTS/PC-ASPECTS<sup>30</sup>. NIHSS was not used as co-variate as some patients were intubated before arrival in the angiosuite and did not have a NIHSS before EVT. The 24-hour prediction was modelled with 24-hour NIHSS and age as co-variates. For dichotomous outcomes, receiver operating characteristics curves were generated, and area under the receiver operating characteristic curve (AUROC) was generated to assess the accuracy of the predictor in both univariate and multivariate models without validation subsets.

Models estimates ( $\beta$ ) are presented with 95% confidence intervals (CI). Significance level was chosen at 5%.

## Results

### *Baseline characteristics*

Baseline information and medical history of all enrolled subjects and grouped into subjects with and without in-person 90-day FU are listed in Table 1 and Supplementary Table S1. No differences between the FU and non-FU groups were detected.

*Table 1. Baseline information and medical history.*

	All enrolled (n=77)	Follow-up (n=54)	No follow-up (n=23)	P- value
Age, median (IQR)	73 (63; 80)	72 (63.3; 79.8)	75 (64.5; 80)	0.446
Female sex, n (%)	30 (39.0)	18 (33.3)	12 (52.2)	0.135
Caucasian ethnicity, n (%)	74 (96.1)	53 (98.1)	21 (91.3)	0.211
Right-handed, n (%)	66 (85.7)	47 (87.0)	19 (82.6)	0.724
BMI, median (IQR)	26 (23.0; 29.7)	26.3 (23.3; 29.7)	25.1 (22.0; 28.1)	0.223
Smoking, n (%)				0.480
Never	23 (29.9)	17 (31.5)	6 (26.1)	

Former	29 (37.7)	18 (33.3)	11 (47.8)	
Current	25 (32.5)	19 (35.2)	6 (26.1)	
Medical history, n (%)				
Prior AIS	16 (20.8)	10 (18.5)	6 (26.1)	0.545
Prior TIA	11 (13.0)	7 (13.0)	4 (17.4)	0.726
Hypertension	50 (64.9)	38 (70.4)	16 (69.6)	1.000
Diabetes	10 (13.0)	6 (11.1)	4 (17.4)	0.474
Extracranial artery stenosis ≥ 50%	33 (42.9)	25 (46.3)	8 (34.8)	0.453
Ipsilateral	30 (39)	24 (44.4)	6 (26.1)	0.201
Contralateral	27 (35.1)	16 (29.6)	2 (8.7)	0.075
Intracranial artery stenosis	9 (11.7)	5 (9.3)	4 (17.4)	0.439
Atrial fibrillation	33 (42.9)	22 (40.7)	11 (47.8)	0.620

BMI: Body-mass index. AIS: Acute ischemic stroke. TIA: Transient ischemic attack.

Index stroke characteristics, treatment and outcome are listed in Table 2 and Supplementary Table S2. Most of the living patients had in-person FU (82.8%). There were no significant differences concerning etiology, onset, occluded artery, procedural technique, complications, anesthetics, or vasopressors. Subjects who did not complete the 90 day-FU had higher NIHSS before EVT, lower proportion of successful reperfusion and longer time from last-known-well to reperfusion possibly leading to lower 24-hour ASPECTS/PC-ASPECTS as well as higher 24-hour NIHSS, 90-day mRS, and all cause-mortality. Non-FU subjects also experienced a numerically higher occurrence of complications and vascular events. Removing subjects with fatal outcome within 90 days from the non-FU group, did not alter the differences between groups.

Table 2. Index stroke, treatment, and outcome.

	All enrolled (n=77)	Follow-up (n=54)	No follow-up (n=23)	P-value
Ischemic hemisphere, right side, n (%)	44 (57.1)	32 (59.3)	12 (52.2)	0.746
Onset, n (%)				0.387
Wake-up	19 (24.7)	11 (20.4)	8 (34.8)	
Unwitnessed	10 (13.0)	7 (13.0)	3 (13.0)	
Stroke etiology, n (%)				0.397
Large-artery atherosclerosis	28 (36.4)	21 (38.9)	7 (30.4)	
Cardio-aortic embolism	27 (35.1)	18 (33.3)	9 (39.1)	
Other causes (dissection)	5 (6.5)	2 (3.7)	3 (13)	

Undetermined causes	17 (22.1)	13 (24.1)	4 (17.4)	
IVT, n (%)	35 (45.5)	28 (51.9)	7 (30.4)	0.133
Occluded artery, n (%)				
ICA	6 (7.8)	4 (7.4)	2 (8.7)	1.000
ICA-top	14 (18.2)	10 (18.5)	4 (17.4)	1.000
ICA-tandem	12 (15.6)	11 (20.4)	1 (4.3)	0.095
M1	50 (64.9)	36 (66.7)	14 (60.9)	0.795
M2	23 (29.9)	17 (31.5)	6 (26.1)	0.787
ACA	8 (10.4)	5 (9.3)	3 (13.0)	0.690
BA	5 (6.5)	2 (3.7)	3 (13.0)	0.154
PCA	3 (3.9)	3 (5.6)	1 (4.3)	1.000
ASPECTS / PC-ASPECTS, median (IQR)				
Before EVT	8 (6; 10)	9 (7; 10)	7 (6; 8.5)	0.081
24-hour	7 (5; 8)	7 (6; 8.75)	5 (3; 7)	0.002
Successful reperfusion (mTICI $\geq$ 2b), n (%)	69 (89.6)	51 (94.4)	18 (78.3)	0.047
Last-known-well to reperfusion*	294 (202; 625)	280 (178; 523)	344 (283; 887)	0.033
NIHSS, median (IQR)				
Before EVT	16.5 (11; 21.25)	15 (9.25; 20)	20 (14.25; 23.75)	0.026
24-hour	6 (3; 13.25)	5 (3; 9)	16 (8.5; 20.75)	<0.001
90-day	N/A	2 (1; 4)	N/A	
90-day mRS, median (IQR)	3 (1; 4)	2 (1; 3)	6 (4; 6)	<0.001
90-day independence <sup>t</sup> , n (%)	36 (46.8)	32 (59.2)	4 (16.7)	0.001
Vascular events <sup>#</sup> , n (%)	5 (6.5)	2 (3.7)	3 (13)	0.154
All-cause mortality, n (%)				
90-day	13 (16.9)	0 (0)	13 (56.5)	<0.001
1 year	19 (24.7)	4 (7.4)	15 (65.2)	<0.001

IVT: Intravenous thrombolysis. ICA: Internal carotid artery. M1: First part of middle cerebral artery. M2: Second part of middle cerebral artery. ACA: Anterior cerebral artery. BA: Basilar artery. PCA: Posterior cerebral artery. ASPECTS: Alberta Stroke Program Early CT Score. PC-ASPECTS: Posterior circulation ASPECTS. mTICI: Modified treatment in cerebral infarction. NIHSS: National Institutes of Health Stroke Scale. EVT: Endovascular treatment. \*: In case of mTICI 0, defined as time of abandoning EVT efforts. <sup>t</sup>: Modified Rankin Scale 0-2. #: Defined as recurrent stroke, myocardial infarction, or surgery for peripheral artery disease at 90-day FU.

Short distance channels TFA

TFA of short distance channel at 24-hour FU is shown in Supplementary Table S3. Across frequency ranges, gain did not differ from 1 and phase shift did not differ from 0. We found no side-to-side difference for mean OxyHb and PSD.

#### *Average TFA results*

The median time from last-known-well to PRE was 4.0 hours (2.5; 7.9). Mean OxyHb decreased at both POST and 24-hour FU similarly in both hemispheres. PSD increased bilaterally in both VLF and LF range after 24 hours. Overall, vitals were quite steady. TFA showed increased absolute phase difference after 24 hours in the LF range and a temporary reduction after recanalization in the VLF range normalizing after 24 hours. Mean OxyHb, vital parameters, PSD, and the results of the TFA for the FU<sub>24</sub>-group are listed in Supplementary Table S4.

In all ranges, FU subjects showed a PSD reduction between 24 hours and 90 days. Coherence and gain were stable between 24 hours and 90 days. LF and VFL absolute phase differences were reduced between 24 hours and 90 days, while quite stable in HF range. All results for the FU<sub>90</sub>-group are shown in Supplementary Table S5.

#### **Mixed-effect models**

##### *LF gain*

In the FU<sub>24</sub>-group LF gain was significantly lower in subjects with increasing mRS ( $\beta=-0.04$ , CI=[-0.07; -0.02], p=0.002), dependent outcome ( $\beta=-0.13$ , CI=[-0.24; -0.02], p=0.019), increasing NIHSS ( $\beta=-1.0\%$ , CI=[-1.8%; -0.1%], p=0.029), and in subjects with fatal 90-day outcome ( $\beta=-0.21$ , CI=[-0.35;-0.06], p=0.005) across PRE, POST and 24-hour data segments. The observed reduction in LF gain was the result of greater PSD reduction in the ischemic hemisphere. Patients treated with IVT had higher LF gain ( $\beta=0.22$  CI=[0.12; 0.32], p<0.001). Treatment with IVT is contraindicated with known onset > 4.5 hours and extensive infarction changes on CT or MRI and could confound the effect of IVT. Therefore, we accounted for time from last-known-well to arrival or ASPECTS/PC-ASPECTS but the IVT influence on LF gain remained significant (Table S6). The effect of mRS and IVT was independent of each other in multivariate model including both variables (IVT:  $\beta=0.19$ , CI=[0.09; 0.29], p=0.001; 90-day mRS:  $\beta=-0.03$ , CI=[-0.06; -0.00], p=0.041).

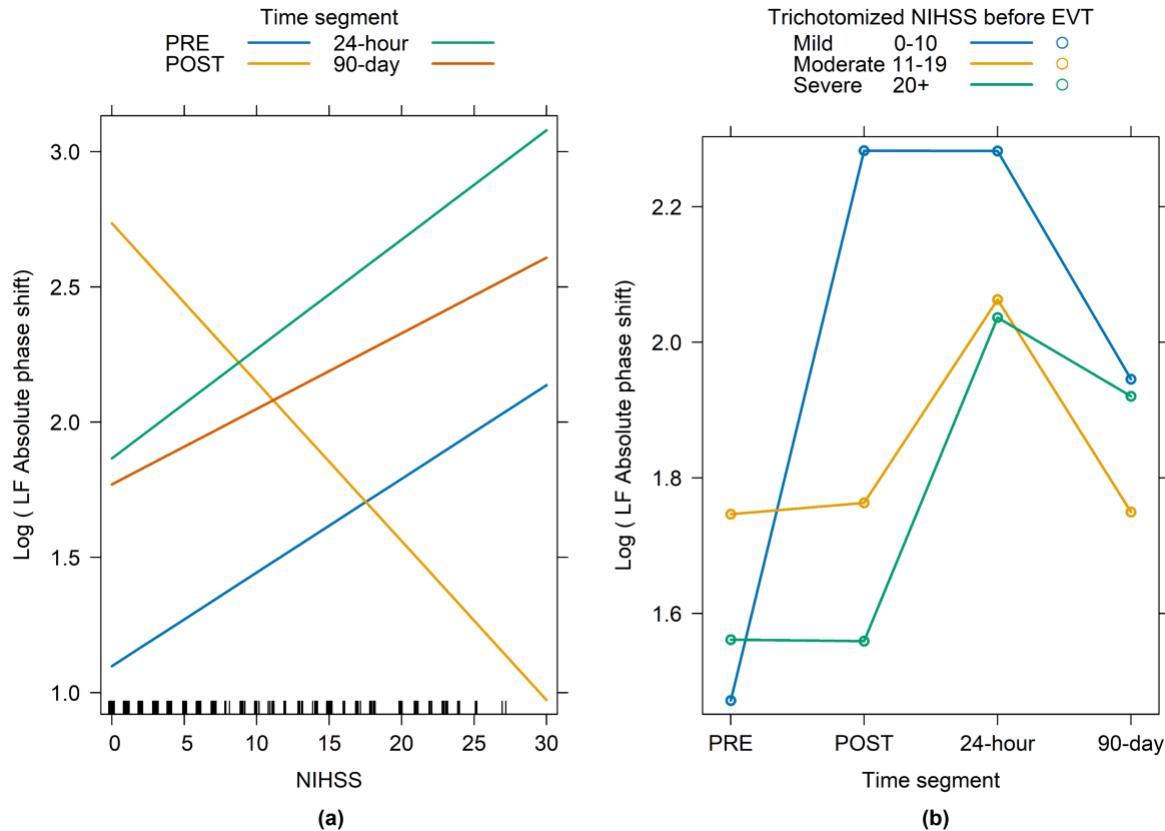
Grouping patients by anesthetics, vasopressor, stroke etiology (large-artery atherosclerosis or cardioembolic), age, occlusion complication level (simple isolated thrombus or complicated ICA-top or tandem thrombus), favorable ASPECTS/PC-ASPECTS before EVT, anterior or posterior circulation stroke, occurrence of ICH, and hypotension during recording (average mean arterial pressure (MAP) < 70 mmHg) had no effect on LF gain. Grouping patients by recanalization success (unsuccessful:  $\beta=-0.15$ , CI=[-0.33; 0.03] , p=0.105) and hypertension (MAP< 130 mmHg before recanalization or 90 mmHg after recanalization) during recording ( $\beta=0.09$ , CI=[-0.01; 0.19], p=0.082) showed no statistical change in LF gain. There was no interaction effect between the time segment and any other fixed effects. Time segment had no effect on LF gain with PRE as index.

Associations between LF gain and outcome were not prevalent in the FU<sub>90</sub> group. While LF gain was still numerically lower in subjects with worse outcomes, the difference did not reach a significance level. The association between LF gain and IVT remained in the FU<sub>90</sub> group ( $\beta=0.16$ , CI=[0.07;0.26], p=0.011). In contrast to FU<sub>24</sub>-group a significant interaction effect between favorable ASPECTS/PC-ASPECTS and the time segment was observed (p=0.035) as LF gain increased more after recanalization and declined more at 24-hour and 90-day FU in patients with non-favorable ASPECTS/PC-ASPECTS. The interaction effect is plotted in Supplementary Figure S1. LF gain was numerically lower at 24-hour and 90-day FU compared to PRE and significantly lower compared to POST.

#### *LF phase shift*

Mixed-effect models showed no effect on absolute phase shift of grouping patients by mRS, mortality, vasopressor, stroke etiology, age, occlusion complication level, favorable ASPECTS/PC-ASPECTS before EVT, anterior or posterior circulation stroke, occurrence of ICH, hypotension nor hypertension during recording. Compared to patients anesthetized with propofol, those receiving sevoflurane showed a trend towards numerically lower absolute phase shift ( $\beta=-46.0\%$ , CI=[-71.9%; +3.9%], p=0.064). We found an interaction between NIHSS and time segment as subjects with milder stroke severity had an immediate increase in absolute phase shift after recanalization,

as opposed to patients with greater stroke severity increasing in absolute phase shift between POST and 24-hour FU (Figure 4).



*Figure 4. Interaction between time segment and NIHSS in 90-day subsets. (a) Shown as continuous NIHSS (actual model). Non-parallel regression lines indicate interaction clearly seen for POST. (b) Trichotomized NIHSS before EVT (approximation model to illustrate interaction over time segments).*

Results from 24-hour and 90-day subsets was equivalent. Absolute phase shift decreased between 24-hour and 90-day FU and was not different from index (PRE) at 90-day FU.

All results from linear mixed-effect models can be found in Supplementary Tables S6-S9.

### Prediction models

LF gain showed associations to outcome and therefore, was used as co-variate in the following prediction models. LF gain was averaged across PRE, POST, and 24-hour FU because mixed-effects

models showed no effect of time segment on LF gain. Thus, average LF gain was representable for LF gain in the first 24 hours. It could theoretically still be used to predict outcome in the large proportion of enrolled subjects excluded from analysis due to missing state period (16%). The full output from multivariate models is reported in the supplementary information.

#### *Modified Rankin scale*

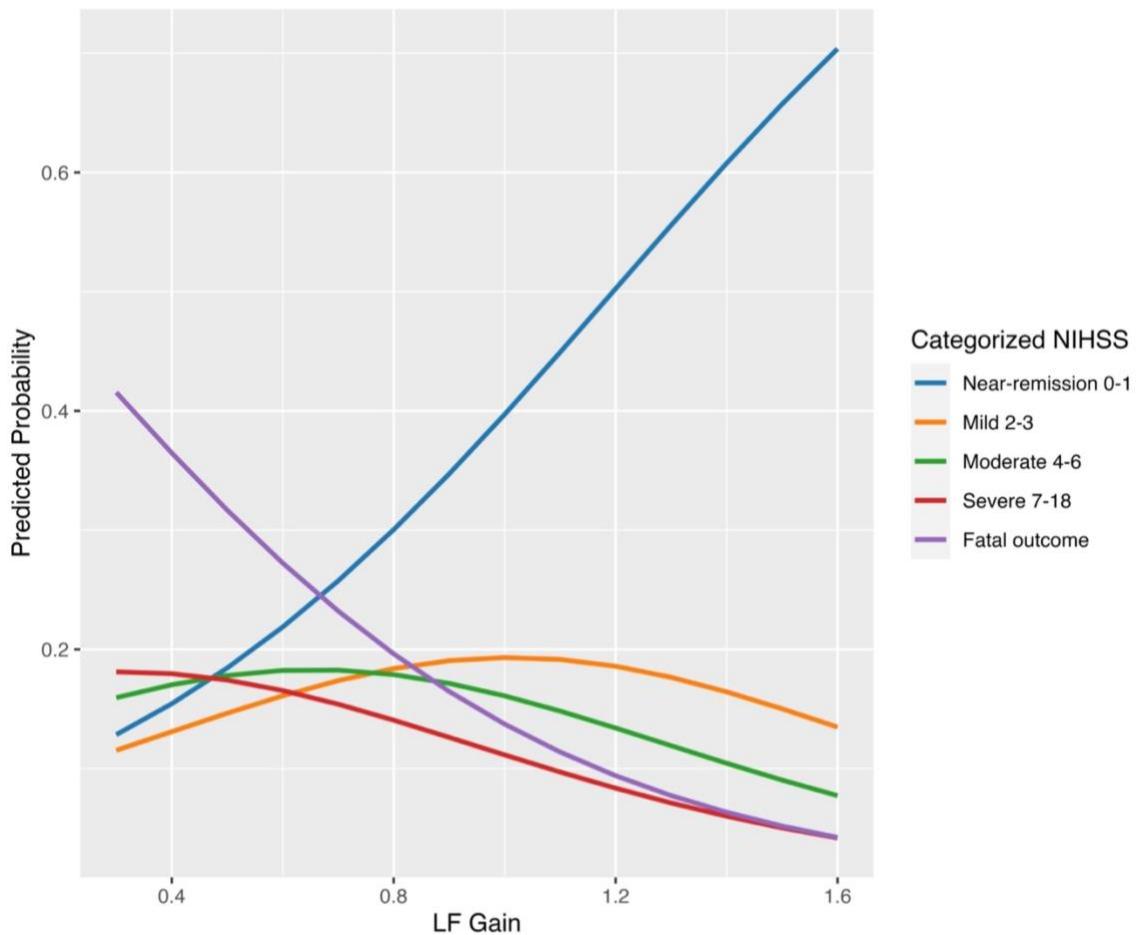
Logistic regression models were used to predict 90-day independent (mRS 0-2) or dependent (mRS > 2) functional outcome with LF gain as predicting variable. Average LF gain was significant predictor of independent outcome ( $\beta=2.36$ , CI=[0.41; 4.53], p=0.023, AUROC=0.641) with an odds ratio (OR) of 1.60 (CI=[1.07;2.41]) for a 0.2 increase in LF gain.

In the acute predictions model (adjusted for age, recanalization, and favorable ASPECTS/PC-ASPECTS before EVT), average LF gain remained a significant predictor of independent outcome ( $\beta=2.60$ , CI=[0.32; 5.22], p=0.035, AUROC=0.802, Supplementary Table S10) with an OR of 1.68 (CI=[1.04; 2.73]) for a 0.2 increase in LF gain. Age was the only other significant predictor (p=0.001).

The 24-hour model adjusted for age and trichotomized 24-hour NIHSS (0-5; 6-13; >14) and showed that LF gain ( $\beta=2.29$ , CI=[-0.14; 5.11], p=0.081, AUROC=0.876, Supplementary Table S11) had an OR of 1.58 (CI=[0.94; 2.65] for 90-day independency with a 0.2 increment. Age (p=0.002) and trichotomized 24-hour NIHSS (p=0.001) were significant predictors.

#### *NIHSS*

Predicting 1-step changes in 90-day NIHSS is of minor clinical importance prompting NIHSS categorization (Near-remission 0-1; Mild 2-3; Moderate 4-6; Severe 7-18; Fatal outcome). Ordinal logistic regression model was used to predict 90-day categorized NIHSS with average LF gain as a significant predictor ( $\beta=2.14$ , CI=[0.42; 3.94], p=0.016). With an increase of 0.2 in LF gain, the common OR was 1.53 (CI=[1.08;2.17]) for better categorical 90-day NIHSS. Predicted probabilities for the univariate model is depicted in Figure 5.



*Figure 5. Predicted probabilities of initial LF gain on categorized NIHSS.*

In multivariate acute prediction, LF gain remained a significant predictor ( $\beta=2.26$ , CI=[0.45; 4.19],  $p=0.017$ , Supplementary Table S12) with a common OR of 1.57 (CI=[1.08; 2.28]) for better categorical 90-day NIHSS. Favorable ASPECTS/PC-ASPECTS before EVT was the only other significant predictor ( $p=0.015$ ).

The 24-hour model showed average LF gain ( $\beta=3.11$ , CI=[-0.46; 3.66],  $p=0.072$ , AUROC=0.876, Supplementary Table S13) had an OR of 1.37 (CI=[0.91; 2.07] for better categorical 90-day NIHSS with a 0.2 increment. Trichotomized 24-hour NIHSS was highly predictive for 90-day NIHSS ( $p<0.001$ ).

### *Mortality*

Logistic regression models were used to predict 90-day survival. In the univariate model, average LF gain was a significant predictor of 90-day survival ( $\beta=3.73$ , CI=[1.04; 6.85],  $p=0.011$ , AUROC=0.716) with an OR of 2.11 (CI=[1.19; 3.73]) for a 0.2 increase in LF gain. In the acute model, average LF gain remained a significant predictor of 90-day survival ( $\beta=3.78$ , CI=[0.77; 7.35],  $p=0.022$ , AUROC=0.863, Supplementary Table S14) with an OR of 2.13 (CI=[1.12; 4.06]) for a 0.2 increase in LF gain. Favorable ASPECTS/PC-ASPECTS before EVT was the only other significant predictor ( $p=0.013$ ).

The 24-hour model (Supplementary Table S15) was strongly affected by collinearity between trichotomized NIHSS and LF gain.

## Discussion

Dynamic CA (dCA) in AIS is of immense interest due to its pathophysiological role and consistent association with long-term outcome<sup>8,31</sup>. Further, dCA has shown promising potential for individualized blood pressure management after thrombectomy<sup>13</sup>. In order to investigate the potential for individualizing intraprocedural treatment it is important to study dCA in the hyperacute phase of stroke and LVO before, during and after revascularization. By our account, this study is the first to examine dCA not only during EVT but also before and after recanalization and possibly the earliest dCA assessment after ischemic stroke. Here, we have shown the time course of interhemispheric TFA based on cortical OxyHb across hyperacute, acute, and chronic phases of LVO and that higher LF gain was associated with IVT prior to EVT and good 90-day functional outcome independent of each other. LF gain also exhibited predictive capabilities of 90-day symptom severity, functional outcome, and mortality.

### *Phase shift*

Studies of dCA in AIS patients have predominantly been based on transcranial Doppler sonography and TFA between ABP and V<sub>MCA</sub>. Associations between impaired dCA in the ischemic hemisphere and poor outcome have been shown in numerous studies regarding infarct size, edema, hemorrhagic transformation, symptom severity at discharge and long-term functional outcome (mRS) but mostly with LF phase shift as covariate<sup>8,32</sup>.

While we did not find associations between interhemispheric phase shift and functional outcome, our data did show an interaction between NIHSS and time segments. Absolute phase shift increased immediately after recanalization in patients with milder symptom severity whereas patients with higher NIHSS exhibited an increase at 24-hour FU. The differences in temporal development of phase shift dyssynchronization could be related to the penumbra as there were no effect of ASPECTS/PC-ASPECTS nor the recanalization success. Dichotomizing recanalization to complete (mTICI 3) or incomplete (mTICI 2a or 2b), Sheriff et al. also showed an interaction effect when examining ABP-V<sub>MCA</sub> phase shift over time<sup>33</sup>. Such interactions emphasize the importance of examination time and the need to account for clinical characteristics when studying dCA in AIS patients. Phase shift between ABP and V<sub>MCA</sub> have shown no interhemispheric difference within 6 hours of onset with moderate to severe stroke symptoms in the MCA territory<sup>34</sup>. Later, reductions compared to healthy controls and contralateral hemisphere are consistently seen from 20 hours and throughout 7 days from onset in patients with MCA occlusion<sup>12,35,36</sup>, while perhaps already normalizing after 10 days<sup>35</sup>.

Using interhemispheric TFA, we found an absolute phase shift relatively close to 0, indicating equal dCA across hemispheres. Studies of the contralateral hemisphere in LVO have shown inconsistent results concerning dCA impairment. Contralateral phase shift dyssynchronization could be the results of vasoactive substances accumulating<sup>7,8</sup> and perhaps explain why we found no association between interhemispheric phase shift and functional outcome despite consistent association reported to ABP-V<sub>MCA</sub> phase shift in the ischemic hemisphere<sup>8</sup>. Examining bilateral ABP-V<sub>MCA</sub> phase shift and interhemispheric phase shift concurrently could reveal this in the future. In this study, simultaneous interhemispheric TFA and bilateral ABP-OxyHb TFA would have diminished the sample size greatly as many patients did not have sufficient ABP segments before recanalization.

Only one study has previously used OxyHb as both TFA input and output in AIS patients<sup>37</sup>. This study was performed 1-2 days after onset and showed increased LF absolute phase shift in non-thrombolyzed patients compared to thrombolyzed patients. The thrombolyzed patients had a higher NIHSS at admission, but a higher rate of total remission and conceivably less infarction

volume, perhaps resulting in equal dCA across both hemispheres. The current study found no such difference as effect of recanalization success or IVT probably because of substantial differences concerning study design, cohort and TFA methodology.

### *Gain*

Similar to the current study, Castro et al. showed that LF gain between ABP and  $V_{MCA}$  in the affected hemisphere of moderate to severe MCA strokes within 6 hours of onset was a predictor of 90-day dependency<sup>38</sup>. Gain remained stable between hyperacute (<6 hours), acute (24 hours) and chronic (90-day) stroke stages<sup>38</sup>, while inconsistent findings are reported in the subacute stage (3 to 7 days after onset)<sup>33,39</sup>. However, gain in the ischemic hemisphere increased with outcome severity, interpreted as an increasingly impaired dCA with a diminished ability to dampen the amplitude of LFOs from systemic perfusion<sup>40</sup>. Conversely, a recent meta-analysis found lower gain and thus more intact dCA across all AIS patients compared to healthy controls<sup>11</sup>. The inconsistencies concerning ABP- $V_{MCA}$  gain could be explained by heterogeneities between stroke populations and methodical variability including scaling methods that is required when using different modalities in TFA. LF gain in patients with favorable outcome from the current cohort was close to one, indicating equal dCA between hemispheres and intact dCA in the ischemic hemisphere if intact contralateral dCA is assumed. With increasing outcome severity, LFO amplitude was relatively stable in the contralateral hemisphere while LFO amplitude in the ischemic hemisphere declined resulting in lower gain. The results indicate favorability of increased LFO amplitude and higher gain towards long-term outcome. Favorable outcome is usually associated with intact dCA which in the conventional interpretation of ABP- $V_{MCA}$  gain would be the result of reduced LFO amplitude and lower gain. Thus, direct comparisons of LF gain between conventional TFA setup (ABP- $V_{MCA}$ ) and interhemispheric TFA seems implausible perhaps due to differences in the examined vasculature. NIRS should be sensitive to all microvascular regulations, while that may not be true for  $V_{MCA}$ , which is based on upstream arteriolar resistance<sup>41</sup> and susceptible to changes in vessel diameter<sup>42-44</sup>. Multiple TFAs based on simultaneous measurements of ABP,  $V_{MCA}$  and OxyHb would be needed in the future to determine how different TFA models interact.

Therefore, we can only compare amplitude and gain directly to subacute patients that Phillip et al. examined<sup>45</sup>. Numerically amplitude in the ischemic hemisphere was higher resulting in higher gain in IVT patients while neither reached statistical significance<sup>37</sup>. This seems consistent with the current study that showed a substantial effect of IVT but also with a large study based on TCD that found better dCA in IVT patients<sup>46</sup>. The effect of IVT was independent from 90-day mRS and was not confounded by time from last-known-well nor structural damage determined by ASPECTS/PC-ASPECTS. Other possible confounders including current anticoagulant treatment, uncontrollable hypertension, co-morbidities, recent stroke or bleedings was not accounted for, but the results indicate a direct and positive effect of IVT on dCA. The influence does not seem to be a pharmacological effect of IVT but rather the effect of recanalization<sup>46,47</sup>. In LVO patients IVT can impact recanalization both before and after EVT with superior outcome compared to EVT alone<sup>48</sup>. We found no statistical effect of recanalization, but we did not discriminate between levels of successful recanalization (mTICI 2b and 3) nor account for collateral circulation and possible reocclusions after EVT in the recanalization evaluation.

LF gain was a significant predictor of 90-day categorized NIHSS, functional independency and mortality after adjusting for age, recanalization success, and favorable ASPECTS/PC-ASPECTS in the acute prediction model. The 90-day NIHSS categorization was distinguished by relatively small differences in the milder categories but could represent larger differences in lesion size which could explain the large predictive differences between categories. With the added knowledge in the 24-hour prediction model, trichotomized NIHSS seemed to confound the effect of average LF gain on predictions of independency and categorized NIHSS at 90-day FU. Average LF gain could still be impactful in the 24-hour prediction model especially when 24-hour NIHSS is unknown (e.g., due to prolonged intubation).

#### *Strengths and limitations*

In this study, we applied one of the most frequently used and standardized methods to evaluate dCA, though with the novelty adjustment of using NIRS signals as both input and output. There are certain advantages to this approach. This includes easy and fast setup in the hyperacute setting, and a very low proportion of excluded patients due to inadequate signal quality. Further, the

applied model accounts for extracerebral tissue contamination because LFO in the extracerebral tissue can reasonably be assumed to be static and without regional differences which was upheld in the short-distance channel TFA. Using NIRS we found absolute certainty of intracerebral signal component due to contrast artifacts in all long-distance channels. Thus, we are confident that any changes in LF gain or phase shift are due to intracerebral changes, i.e. dynamic autoregulation. Previous studies have attempted other TFA setups to examine dCA based on NIRS alone<sup>49-51</sup>. Such approaches benefit from the ability to perform unilateral dCA assessments but were reliant on either sufficient data quality of short-distance channels or deoxygenated hemoglobin which are more prone to poor data quality. All dCA assessments based on NIRS including the current study will be restricted by the low spatial resolution limiting assessment to the superficial parts of the cerebral cortex. Deeper parts of the brain are equally affected by LVO but whether the observed dCA changes extend into such regions cannot be determined with NIRS.

Various limitations restrict the conclusions from this study. Interhemispheric TFA examines dCA relative to the contralateral hemisphere. While amplitude can be assessed per hemisphere (PSD) phase shift cannot. This leaves uncertainty as to whether phase shift is equally impaired or equally intact in patients with LVO when not doing simultaneous TFA between ABP and OxyHb on each hemisphere. Also, we had no control group of healthy subjects to compare with.

AIS patients including those receiving EVT are inherently heterogeneous concerning stroke etiology, co-morbidities, imaging parameters, and treatment. In this study we chose to prioritize everyday generalizability and not exclude patients based on heterogeneities, but account for as many of them as possible in the statistical models instead. Examples of this approach is our analyses of posterior circulation LVO, sevoflurane anesthetics and ICH occurrence which did not influence dCA and therefore did not lead to exclusion of such patients. However, accounting for all heterogeneities is nearly impossible and requires a very large sample size especially for less common occurrences. Unidentified confounders could be affecting the clinical course and the progression of dCA between EVT and follow-up examinations. Unexamined co-morbidities, complications related to EVT or index stroke, rehabilitation efforts, and new vascular events

including reocclusions could be possible confounders which would need to be investigated in future studies.

As we considered the study to be exploratory and hypothesis generating, we did not prespecify a statistical analysis plan. Thus, the presented findings deserve confirmation in larger cohorts with prespecified analysis.

The main exclusion criteria from patients examined with NIRS was the absence of a steady state period mainly before recanalization. Reasons for this were a short procedural time to access the occlusion and attempt recanalization within exclusion period after intubation, difficulties to establish steady state, e.g. due to cardiovascular comorbidity as well as high or low sensitivity to anesthetics or vasopressors. Therefore, we believe no selection bias has been introduced by data segment selection.

We did not evaluate collateral circulation due to differences in standard-of-care imaging (CT-angiography, MRI time-of-flight angiography) and missing contralateral series from the digital subtraction angiography. Collateral circulation could certainly have an impact on both outcome and dCA<sup>52,53</sup>. However, collaterals are better developed in patients with large-artery stenosis compared to patients with cardioembolic stroke etiology and we did not find any effect of etiology.

Results from the FU<sub>90</sub>-group were affected by attrition bias as non-FU patients did not attend mainly due to very poor functional or fatal outcome and the results should therefore be interpreted with caution. Efforts were made to minimize this bias by offering FU visits at the rehabilitation center or at home visits despite COVID-19 restrictions. The exclusion of a considerable portion of patients with the worst outcome may explain why associations between LF gain and outcome were not significant in the FU<sub>90</sub>-group.

In conclusion, interhemispheric TFA based on NIRS is a feasible method for investigating dCA in AIS patients before, during and after EVT. Development of LF phase shifts depended on symptom

severity and increased immediately after recanalization in AIS patient with lower NIHSS but concurrent dCA investigations using different modalities are warranted to assess dCA in healthy subjects and in the contralateral hemisphere to understand the interplay between different dCA models. LF gain remained stable during EVT up to 90 days post-treatment and had associations to IVT treatment and long-term outcomes of symptom severity, functional outcome, and mortality. Further, LF gain significantly predicted such long-term outcomes. Future studies should confirm these exploratory findings but the study indicates a potential for individualized treatment.

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## Author contributions

A.V.H. and H.K.I. conceived and designed the study while T.C.T., H.G.B., G.B., C.S., and H.W.S. contributed. A.V.H. acquired most of the data with substantial contributions from T.G.L. as well as T.C.T., H.G.B., G.B., C.S. and K.H. A.V.H. performed data processing and analysis with contributions from T.G.L. and H.K.I. All authors participated in the interpretation of results. A.V.H. drafted the article. All authors revised the article critically and approved the final version. All persons designated as authors qualify for authorship and agree to be accountable for all aspects of the work and resolve of questions related to the accuracy or integrity of the study.

### **Data availability statement**

The processing code is open source available at <https://openfnirs.org/software/homer/> for preprocessing and at <https://www.car-net.org/tools> for TFA. NIRS data segments can be provided upon reasonable request. Individual patient data are identifiable, and availability requires approval of both centers as well as local ethics committees. All data requests can be made by contacting the corresponding author.

### **Additional Information**

The authors declare that there are no competing interests.

### **Funding**

The study was supported by Simon Fougner Hartmanns Family Foundation, Gangsted Foundation, Sophus Jacobsen Foundation and Rigshospitalet's Research Foundation.

## **Supplementary information**

### **Manuscript title**

Dynamic cerebral autoregulation during and 3 months after endovascular treatment in large vessel occlusion stroke

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### **Supplementary Methods**

#### *Medical history*

Baseline diagnosis of hypertension was based only on regular use of antihypertensive medication. Dyslipidemia diagnosis was based on regular use of cholesterol-lowering medication or Low-Density Lipoprotein > 3.0 mmol/L. Diabetes diagnosis was based on regular use of antidiabetic medication or consecutive Hemoglobin A1c measurements above 48 mmol/mol.

### *Imaging*

Alberta Stroke Program Early CT Score (ASPECTS)<sup>1</sup> or Posterior Circulation-ASPECTS (PC-ASPECTS)<sup>2</sup> were evaluated based on standard-of-care imaging using highest precision modality by the order magnetic resonance imaging (MRI), computed tomography-perfusion (CTP), and non-contrast computed tomography (NCCT).

### *Anesthesia*

Patients were put under general anesthesia maintained by propofol or sevoflurane as well as remifentanil with phenylephrine or norepinephrine as vasopressor infusion. Patients were monitored by NIRS, invasive blood pressure, peripheral pulse oximetry and 3-lead electrocardiogram (Philips IntelliVue, Philips Medical Systems, Eindhoven, The Netherlands) from arrival with vitals being exported by VSCapture.<sup>3</sup> Mechanical ventilation (Dräger, Lübeck, Germany) was adjusted by inspiratory and expiratory levels of O<sub>2</sub> and CO<sub>2</sub> as well as vitals. Ventilation parameters were exported directly to the electronic health record system at average values per minute. For dichotomizing hypotension during recording was defined as mean arterial pressure (MAP) < 70 mmHg on average,<sup>4</sup> while hypertension during recording was defined as MAP > 130 mmHg before recanalization and MAP > 90 mmHg after recanalization.<sup>4</sup> Intravenous labetalol was administered per standard of care to avoid hyperperfusion (ABP > 185/105 mmHg).<sup>5</sup>

### *NIRS examination*

The Octamon system (Artinis Medical Systems, Elst, the Netherlands) consists of dual-wavelength diodes (750 and 839 nm) paired with ambient light-protected receivers relayed to integrative computer by Bluetooth connection. The optodes were arranged in a headband and placed approximately 1 cm over the glabella with lateral projections just superior to the auricular helices. Digital spatial registration was not possible in the hyperacute setting as it would have delayed EVT. To minimize motion artefacts (MA) and avoid optode repositioning the headband was wrapped firmly with adherent gauze wrap. Bluetooth receiver was re-positioned to placement above the vertex to avoid artefacts in the preferred projections of the digital subtraction angiography (DSA). Reflected light intensity was sampled at 25 Hz using OxySoft version 3.0.103.3 (Artinis Medical Systems, Elst, the Netherlands) and exported for further processing and analysis. While not in

agreement with CARNet recommendations, the sampling frequency still complies with the Nyquist sampling theorem. Furthermore, the CARNet study showed no difference in ABP-V<sub>MCA</sub> gain and phase between sampling frequencies 50, 20 and 10 Hz in both LF range and for gain in the VLF range.<sup>6</sup> However, no similar studies have not been done using NIRS.

#### *Data preparation*

Raw light intensity was quality inspected channel-by-channel to prune any channels without clear cardiac pulse waves. Next artefacts from intracerebral contrast injection were identified to confirm an intracerebral component in the NIRS signal. Intensity was then converted to optical density (OD) before performing correction of smaller (maximum 3 heart beats in coherence with CARNet guidelines<sup>7</sup>) motion artefacts (MA) by the movement artefact reduction algorithm (MARA)<sup>8</sup> after individual identification applying the threshold of two times the average beat-to-beat amplitude in dubious cases. Automatic MA identification with identical parameters across subjects is preferred in fNIRS studies to avoid investigator bias, but the drawback is unidentified artefacts as parameters seldomly suit all recordings. Thus, manual identification was preferred in this study as even a few artefacts could alter the results of the transfer function analysis (TFA)<sup>9</sup> and all recordings were preprocessed before proceeding to TFA to avoid bias. MARA corrections are well-suited for removing baseline shifts but can sometimes be inadequate in removing spikes. Thus, after converting OD to hemoglobin concentrations by the modified Beer-Lambert law (MBLL), concentration data was run through a 3<sup>rd</sup> order median filter. Channels that could not be corrected adequately were excluded from further analysis. If two out of three corresponding channels did not pass data quality inspection, the subject was excluded. To avoid spectral leakage, the mean of each channel was subtracted from the concentration signals. OxyHb data was low-pass filtered with a third-order Butterworth filter cut off at 0.2 Hz to eliminate high-frequency components. While the majority of TFA studies of CA employ beat-to-beat-averaging and subsequent resampling, low-pass filtering is an equally well-suited method when data is free of artefacts, which is true after careful data selection, pruning of noisy channels and recordings, and MA correction.<sup>10</sup> Using the Welch' method the fast Fourier transform was applied in 100-second Hanning-windows with 50% overlap resulting in 5 windows across the data segments of 5 minutes. Triangular moving average window was applied for spectral smoothing. Coherence, gain

(amplitude ratio), and phase shift were then calculated in the HF, LF and VLF frequency intervals as is recommended when analyzing spontaneous oscillations that have some individual variation<sup>7,11,12</sup>. Coherence is used as a quality control as TFA results is rejected when coherence is lower than the threshold corresponding to the number of windows in the recording.<sup>7</sup> As input and output signals should be relatively tightly synchronized, negative phase shifts were not removed from analysis as is recommended with an expected positive phase shift (e.g. TFA between ABP and  $V_{MCA}$ )<sup>7</sup>. Preliminary analysis of differences between channels showed no effect of channel placement and included channels were therefor averaged. All data processing was performed in MATLAB version R2018b (The MathWorks Inc., Natick, Massachusetts). Preprocessing from light intensity to OxyHb was performed with HomeR package version 2.8<sup>13</sup> while TFA was performed with CARNet package.<sup>7</sup>

### *Statistics*

All statistical analysis was performed in R 4.3.3 (R Core Team 2023, Vienna, Austria).

Power calculations were aimed to detect differences in interhemispheric gain and phase shift between patient with independent and dependent 90-day outcome. Significance level was set at 0.05 and power at 0.80. The only study of interhemispheric gain was performed on subacute stroke patients having received thrombolysis or not<sup>14</sup>. Based on an equal effect size and a pooled and weighted standard deviation the required sample size was 78. The effect size was deemed conservative as the clinical difference would surely be greater in a cohort of EVT patients. Interhemispheric phase shift in large vessel occlusions was estimated from two studies. Based on the smallest effect size and the largest variance the required sample size was 50. Accounting for exclusion based on data quality and available steady state segments we aimed for a sample size of 100 patients examined with NIRS.

Testing of independent samples were performed with Welch' t-test or Wilcoxon-Mann Whitney test in case of non-normality, while dependent populations samples were tested with paired t-test or Wilcoxon signed ranks test for non-normal data. Normality was assessed visually by histograms

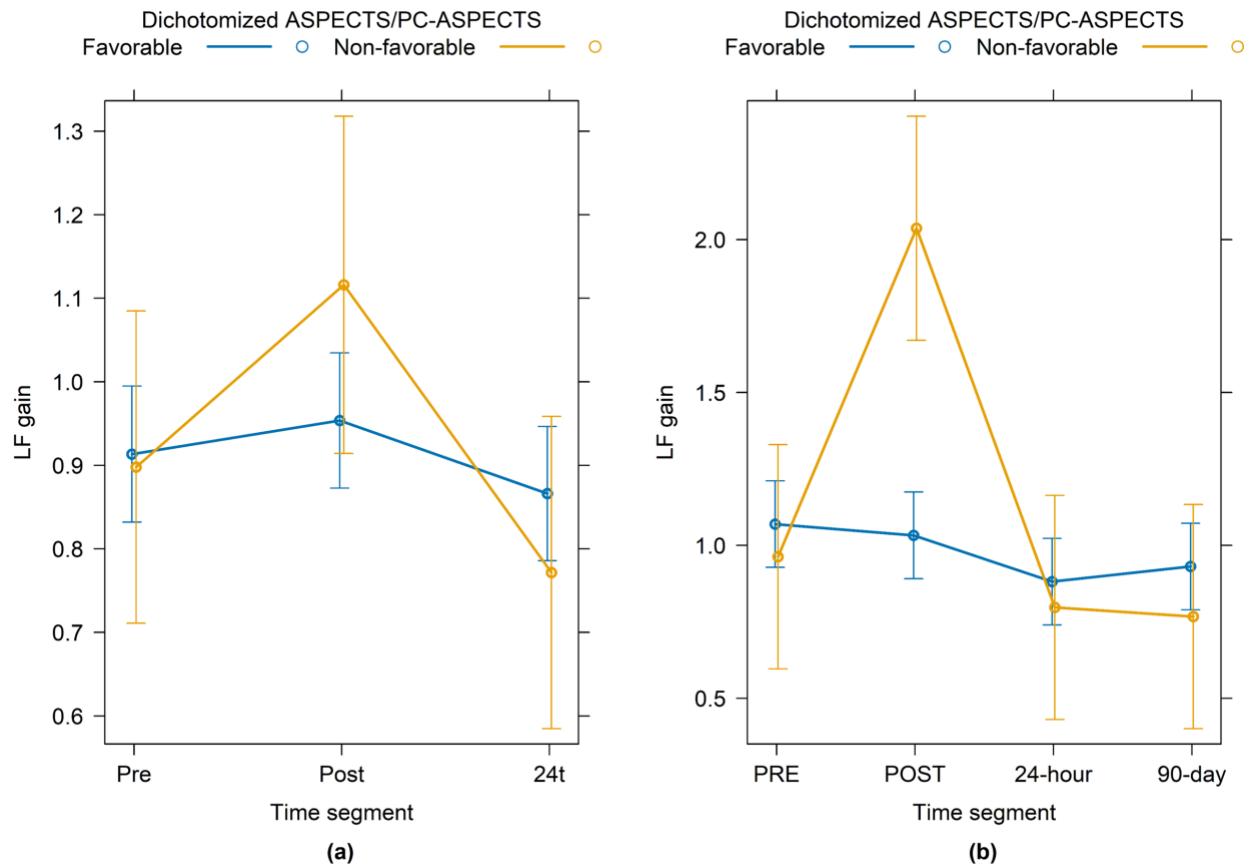
and quantile-quantile plots. Categorical proportions were tested with chi-squared test or Fisher's exact test depending on the number of categories.

In mixed-effect models, compound symmetry was chosen as correlation matrix to avoid overestimation of correlations between recordings just before and after reperfusion, while still maintaining the order of recordings.

Significant interaction between fixed effects rendered reporting of isolated fixed effects meaningless. Insignificant interactions were omitted from models before estimation of fixed effects.

## Figures

*Figure S1. Interaction effect on low-frequency (LF) gain between time segment and favorable or non-favorable ASPECTS/PC-ASPECTS in (a) FU<sub>24</sub>-group and (b) FU<sub>90</sub>-group. Alberta Stroke Program Early CT Score. PC-ASPECTS: Posterior circulation ASPECTS.*



## Tables

*Table S1. Baseline information and medical history.*

	All enrolled (n=77)	Follow-up (n=54)	No follow-up (n=23)	P- value
Alcohol, weekly consumption, median units	2 (0; 7)	3.5 (0; 7)	0 (0; 6)	0.168
Physical inactivity*, n (%)	47 (61.0)	34 (63)	13 (56.5)	0.618
Medical history, n (%)				
Dyslipidemia	74 (96.1)	53 (98.1)	21 (91.3)	0.211
Ischemic heart disease	12 (15.6)	8 (14.8)	4 (17.4)	0.742
Valvular heart disease	9 (11.7)	6 (11.1)	3 (13.0)	0.717
Heart failure	9 (11.7)	6 (11.1)	3 (13.0)	0.688
Pacemaker or ICD	5 (6.5)	4 (7.4)	1 (4.3)	1.000
Nephropathy	9 (11.7)	6 (11.1)	3 (13.0)	1.000
Venous thromboembolism	6 (7.8)	4 (7.4)	1 (4.3)	0.660
Disseminated cancer	4 (5.2)	1 (1.9)	3 (13.0)	0.084

BMI: Body-mass index. ICD: Implantable Cardioverter Defibrillator. \*: Defined as less than 1 hour weekly. No differences between subjects with and without in-person follow-up.

Table S2. Index stroke treatment and outcome.

	All enrolled (n=77)	Follow-up (n=54)	No follow-up (n=23)	P- value
Procedure, n (%)				
Aspiration only	21 (27.3)	15 (27.8)	6 (26.1)	0.540
Stent-retrieving and aspiration	52 (67.5)	35 (64.8)	17 (73.9)	0.596
PTA	17 (22.1)	15 (27.8)	2 (8.7)	0.078
Carotid stenting	7 (9.1)	7 (13.0)	0 (0)	0.097
Anesthetics, n (%)				
Propofol	69 (89.6)	50 (92.6)	19 (82.6)	0.230
Sevoflurane	6 (7.8)	3 (5.6)	3 (13)	0.356
Combination of propofol and sevoflurane	2 (2.6)	1 (1.9)	1 (4.3)	0.511
Vasopressor, n (%)				
Phenylephrine	51 (66.2)	38 (70.4)	13 (56.5)	0.295
Norepinephrine	8 (10.4)	6 (11.1)	2 (8.7)	1.000
Phenylephrine and Norepinephrine	18 (23.4)	10 (18.5)	8 (34.8)	0.147
Non-favorable ASPECTS/PC-ASPECTS before EVT (<6), n (%)	12 (15.6)	7 (13.0)	5 (20.8)	0.328
Reperfusion (mTICI), n (%)				0.014
0	4 (5.2)	2 (3.7)	2 (8.7)	
1	1 (1.3)	0 (0)	1 (4.3)	
2a	3 (3.9)	1 (1.9)	2 (8.7)	
2b	34 (44.2)	21 (38.9)	13 (56.5)	
3	35 (45.5)	30 (55.6)	5 (21.7)	
Process times (minutes), median (IQR)				
Last-known-well to imaging	140 (79; 536)	124 (75; 378)	193 (91; 721)	0.089
Imaging to artery puncture	78 (51; 108)	68 (48; 103)	92 (62; 110)	0.166
Artery puncture to reperfusion*	40 (24; 69)	36 (24; 68)	55 (31; 72)	0.280
Complications, n (%)				
New vascular territory embolization	5 (6.5)	2 (3.7)	3 (13)	0.154
Intracranial hemorrhage	6 (7.8)	2 (3.7)	4 (17.4)	0.062
Other complications†	5 (6.5)	3 (5.6)	2 (8.7)	0.632
Modified Rankin Scale, median (IQR)				
Before index stroke	0 (0; 1)	0 (0; 1)	1 (0; 1.5)	0.172
Increase at 90 days	2 (1; 3)	1 (1; 2)	4 (3; 5.5)	<0.001
Re-hospitalized within 90 days, n (%)	26 (33.8)	17 (31.5)	9 (39.1)	0.601

PTA: Percutaneous Transluminal Angioplasty. ASPECTS: Alberta Stroke Program Early CT Score. PC-ASPECTS: Posterior circulation ASPECTS. EVT: Endovascular treatment. mTICI: Modified treatment in cerebral infarction. \*: In case of mTICI 0, defined as time of abandoning EVT efforts. †: Intracerebral artery dissection, vasospasm, or equipment malfunction.

*Table S3. Median values of input and output signals, PSD in short distance channels as well as TFA gain, phase difference and coherence for all subjects at 24h follow-up.*

Short distance channels TFA, n = 55		
Average Oxy-Hb ( $\mu\text{M}^*\text{mm}$ )	Unaffected hemisphere	0.01
	Ischemic hemisphere	0.02
PSD ( $(\mu\text{M}^*\text{mm})^2 / \text{Hz}$ )	Unaffected hemisphere	0.51
	Ischemic hemisphere	0.45
Coherence	HF	0.72
	LF	0.57
	VLF	0.65
Gain	HF	0.87
	LF	0.86
	VLF	0.84
Phase shift (degrees)	HF	2.78
	LF	1.04
	VLF	-4.60

*PSD: Power spectral density. HF: High frequency spectrum (0.2-0.5 Hz). LF: Low frequency spectrum (0.07-0.2 Hz). VLF: Very-low frequency spectrum (0.02-0.07 Hz). No statistical side-to-side differences, gain different from 1 nor phase shift different from 0.*

*Table S4. Median values of input and output signals, vital parameters, PSD as well as TFA gain, phase difference and coherence for all subjects before and after reperfusion efforts and after 24 hours.*

		PRE (IQR)	POST (IQR)	24-hour (IQR)
Examination time from last-known-well (hours)		4.3 (2.7; 9.7)	5.1 (3.5; 10.4)	27.7 (25.3; 34.9)
Average Oxy-Hb, unaffected hemisphere ( $\mu\text{M}^*\text{mm}$ )		0.78 (-0.44; 14.73)	0.14* (-2.12; 6.83)	0.02 <sup>†,‡</sup> (-2.24; 0.18)
Average Oxy-Hb, ischemic hemisphere ( $\mu\text{M}^*\text{mm}$ )		2.36 (-0.30; 10.36)	0.44 (-1.69; 22.25)	0.01 <sup>†,‡</sup> (-0.96; 0.08)
PSD, unaffected hemisphere ( $(\mu\text{M}^*\text{mm})^2 / \text{Hz}$ )	HF	0.07 (0.03; 0.20)	0.05 (0.03; 0.16)	0.09 (0.03; 0.22)
	LF	0.10 (0.04; 0.22)	0.07 (0.03; 0.20)	0.22 <sup>†,‡</sup> (0.09; 0.48)
	VLF	0.16 (0.08; 0.39)	0.13* (0.04; 0.22)	1.05 <sup>†,‡</sup> (0.56; 1.92)
PSD, ischemic hemisphere ( $(\mu\text{M}^*\text{mm})^2 / \text{Hz}$ )	HF	0.07 (0.03; 0.18)	0.06 (0.03; 0.19)	0.09 (0.03; 0.33)
	LF	0.10 (0.05; 0.19)	0.06 (0.03; 0.21)	0.22 <sup>†,‡</sup> (0.08; 0.53)
	VLF	0.17 (0.08; 0.40)	0.11 (0.05; 0.32)	0.95 <sup>†,‡</sup> (0.51; 1.96)
Coherence	HF	0.70 (0.51; 0.89)	0.70 (0.53; 0.88)	0.68 (0.49; 0.80)
	LF	0.54 (0.35; 0.78)	0.55 (0.41; 0.82)	0.53 (0.32; 0.72)
	VLF	0.46 (0.27; 0.68)	0.45 (0.27; 0.71)	0.55 (0.39; 0.75)
Gain	HF	0.92 (0.76; 1.19)	1.00* (0.83; 1.37)	0.88 <sup>†</sup> (0.76; 1.06)
	LF	0.94 (0.64; 1.09)	0.97 (0.74; 1.19)	0.88 (0.72; 0.99)
	VLF	0.81 (0.59; 1.08)	0.87 (0.61; 1.06)	0.83 (0.67; 0.96)
Phase shift (degrees)	HF	-2.02 (-6.67; 4.88)	0.61 (-5.03; 4.81)	-1.34 (-8.57; 5.85)
	LF	-0.32 (-7.54; 6.53)	2.78 (-3.79; 9.22)	-1.05 (-10.64; 10.51)
	VLF	-6.19 (-16.77; 3.35)	-2.79 (-7.94; 4.91)	-1.75 (-13.56; 14.31)

Absolute phase shift (degrees)	HF	6.11 (3.18; 11.00)	5.03 (2.65; 10.29)	6.66 (3.57; 12.52)
	LF	6.56 (2.73; 12.10)	7.75 (3.34; 12.47)	10.64 <sup>‡</sup> (4.42; 19.03)
	VLF	14.84 (5.84; 25.32)	6.54* (3.73; 19.87)	14.05 <sup>†</sup> (6.92; 29.92)
HR (bpm, mean)		68.5 (SD: 13.4)	63.7* (SD: 12.3)	71.7 <sup>†,‡</sup> (SD: 12.6)
MAP (mmHg, mean)		85.9 (SD: 12.1)	82.6 (SD: 12.4)	83.3 (SD: 13.6)
SpO <sub>2</sub> (%)		100 (98.2; 100)	100 (98.4; 100)	95.4 <sup>†,‡</sup> (94; 97)
ETCO <sub>2</sub> (kPa)		4.5 (4.3; 4.76)	4.5 (4.20; 4.76)	N/A

*Normal distributed data specified (mean, SD). Oxy-Hb: Oxygenated hemoglobin. PSD: Power spectral density. HF: High frequency spectrum (0.2-0.5 Hz). LF: Low frequency spectrum (0.07-0.2 Hz). VLF: Very-low frequency spectrum (0.02-0.07 Hz). MAP: Mean arterial pressure. HR: Heart reate. SpO<sub>2</sub>: Peripheral oxygen saturation. ETCO<sub>2</sub>: End-tidal carbon dioxide. \*: Significant difference between before and after reperfusion. †: Significant difference between after reperfusion and 24 hours. ‡: Significant difference between before reperfusion and 24 hours. P-value adjusted by false discovery rate.*

*Table S5. Median values of input and output signals, vital parameters, PSD as well as TFA gain, phase difference and coherence for in-person FU subjects before and after reperfusion efforts, after 24 hours and 90 days.*

		PRE (IQR)	POST (IQR)	24-hour (IQR)	90-day (IQR)
Examination time from last-known-well (hours, h or days, d)		4.0 h (2.5; 7.9)	4.7 h (3.1; 8.8)	27.4 h (25.2; 33.5)	92.0 d (88.3; 100.8)
Average Oxy-Hb, unaffected hemisphere ( $\mu\text{M}^*\text{mm}$ )		2.92 (-0.15; 17.48)	1.30 (-0.23; 19.79)	0.01 (-2.27; 0.16)	0.02 <sup>*,†,‡</sup> (-0.44; 0.56)
Average Oxy-Hb, ischemic hemisphere ( $\mu\text{M}^*\text{mm}$ )		3.06 (-0.30; 10.36)	0.81 (-1.35; 26.00)	0.02 (-0.73; 0.13)	0.02 <sup>*,†</sup> (-0.41; 0.09)
PSD, unaffected hemisphere ( $(\mu\text{M}^*\text{mm})^2/\text{Hz}$ )	HF	0.06 (0.03; 0.20)	0.05 (0.02; 0.20)	0.11 (0.04; 0.25)	0.06 <sup>‡</sup> (0.02; 0.22)
	LF	0.10 (0.04; 0.30)	0.10 (0.03; 0.31)	0.25 (0.13; 0.70)	0.19 <sup>†,‡</sup> (0.07; 0.46)
	VLF	0.16 (0.07; 0.43)	0.13 (0.03; 0.26)	1.38 (0.70; 2.00)	0.61 (0.38; 0.91)
PSD, ischemic hemisphere ( $(\mu\text{M}^*\text{mm})^2/\text{Hz}$ )	HF	0.06 (0.03; 0.25)	0.07 (0.03; 0.28)	0.10 (0.04; 0.37)	0.05 <sup>*,†,‡</sup> (0.02; 0.16)
	LF	0.11 (0.05; 0.26)	0.07 (0.03; 0.28)	0.29 (0.12; 0.53)	0.21 <sup>‡</sup> (0.06; 0.36)
	VLF	0.20 (0.09; 0.42)	0.12 (0.05; 0.36)	1.05 (0.53; 1.96)	0.57 <sup>*,†,‡</sup> (0.40; 0.94)
Coherence	HF	0.70 (0.51; 0.89)	0.67 (0.53; 0.88)	0.69 (0.58; 0.88)	0.72 (0.52; 0.85)
	LF	0.56 (0.36; 0.79)	0.55 (0.42; 0.83)	0.63 (0.39; 0.81)	0.66 (0.53; 0.84)
	VLF	0.46 (0.25; 0.70)	0.47 (0.32; 0.71)	0.64 (0.42; 0.78)	0.66 <sup>*,†</sup> (0.51; 0.74)
Gain	HF	0.99 (0.81; 1.21)	1.10 (0.85; 1.39)	0.86 (0.72; 1.05)	0.87 <sup>†</sup> (0.79; 1.04)
	LF	0.97 (0.68; 1.13)	1.02 (0.79; 1.29)	0.91 (0.77; 0.98)	0.81 <sup>†</sup> (0.69; 0.98)
	VLF	0.93 (0.59; 1.15)	0.89 (0.68; 1.11)	0.81 (0.67; 0.95)	0.80 (0.68; 0.94)
Phase shift (degrees)	HF	-1.81 (-6.57; 5.64)	0.15 (-4.93; 4.81)	-0.08 (-6.10; 6.41)	0.92 (-4.64; 3.67)
	LF	-0.30 (-6.11; 6.23)	3.91 (-3.07; 11.05)	1.72 (-7.35; 13.89)	-3.67 <sup>†,‡</sup> (-10.20; 3.73)
	VLF	-4.83 (-15.45; 10.34)	-2.28 (-7.49; 5.22)	0.10 (-10.87; 14.20)	-0.49 (-11.19; 4.11)

Absolute phase shift (degrees)	HF	6.14 (2.87; 11.11)	4.93 (2.60; 10.29)	6.41 (3.57; 10.04)	4.51 (2.39; 8.83)
	LF	6.23 (2.64; 11.96)	7.84 (3.91; 12.56)	10.51 (4.53; 15.74)	7.66 (3.73; 11.86)
	VLF	13.87 (6.14; 20.88)	6.24 (3.80; 16.24)	12.48 (6.56; 29.31)	5.66*,‡ (2.70; 13.89)
HR (bpm, mean)		67.3 (SD: 13.1)	61.8 (SD: 10)	71.1 (SD: 12.8)	69.7 <sup>†</sup> (SD: 11.2)
MAP (mmHg, mean)		86.1 (SD: 11.8)	80.9 (SD: 9.1)	81.9 (SD: 13.3)	85.3 (SD: 11.5)
SpO <sub>2</sub> (%)		100 (98; 100)	99.8 (98; 100)	94.5 (93.3; 97)	96.5*,†,‡ (94.8; 98)
ETCO <sub>2</sub> , kPa		4.5 ()	4.48 ()	N/A	N/A

Normally distributed data specified (mean, SD). Oxy-Hb: Oxygenated hemoglobin. PSD: Power spectral density. HF: High frequency spectrum (0.2-0.5 Hz). LF: Low frequency spectrum (0.07-0.2 Hz). VLF: Very-low frequency spectrum (0.02-0.07 Hz). MAP: Mean arterial pressure. HR: Heart rate. SpO<sub>2</sub>: Peripheral oxygen saturation. ETCO<sub>2</sub>: End-tidal carbon dioxide. \*: Significant difference between before reperfusion and 90 days. †: Significant difference between after reperfusion and 90 days. ‡: Significant difference between 24 hours and 90 days. P-value adjusted by false discovery rate.

*Table S6. Mixed-effects models in FU<sub>24</sub>-group with LF gain as outcome variable, time segment and different stroke characteristics, treatment, and outcome as fixed effect with subject as random effect.*

Grouping	Interaction	Fixed effect Groups	Fixed effect Time segment	Model performance
<i>Reference: PRE</i>				
No grouping	-	-	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.44, p = 0.152)	Marginal R2 = 0.02 Conditional R2 = 0.34
			24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p = 0.178)	
90-day mRS	F(2, 145)=0.96, p=0.384	-0.04 (CI=[-0.07; -0.02], T(75)= 3.2, p= 0.002)	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.45, p=0.149)	Marginal R2 = 0.09 Conditional R2 = 0.34
		PSD Ischemic hemisphere: -0.079 (CI=[-0.156; -0.003])	24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p=0.179)	
		PSD Unaffected hemisphere: -0.041 (CI=[-0.099; 0.016])		
90-day Independence (mRS 0-2)	F(2, 145)= 0.35, p=0.706	Reference: Independence  Dependence: -0.13 (CI=[-0.24; - 0.02], T(75)=-2.41 p=0.019)	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.45, p=0.148)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p=0.178)	Marginal R2 = 0.06 Conditional R2 = 0.34
		PSD Ischemic hemisphere: -0.328 (CI=[-0.615; -0.041])		
		PSD Unaffected hemisphere: -0.148 (CI=[-0.367; 0.071])		

24-hour NIHSS recovery	$F(2, 143)=0.40, p=0.673$	-0.1% (CI=[-1.2%;+1.0%], T(74)=-0.19, p=0.854)	POST: +6.8% (CI=[-3.7%; +18.3%], T(145)=1.25, p= 0.212)  24-hour: -2.3% (CI=[-11.7%; +8.2%], T(145)=-0.44, p= 0.659)	Marginal R2 = 0.01 Conditional R2 = 0.40
NIHSS	$F(2, 142)=0.25, p=0.778$	-1.0% (CI=[-1.8%; -0.1%], T(144)=-2.21, p=0.029  PSD Ischemic hemisphere: -1.09e-2 (CI=[-0.015; 0.013]) PSD Unaffected hemisphere: -1.06e-2 (CI=[-0.0190; 0.017])	POST: +6.8% (CI=[-3.7%; +18.3%], T(145)=1.25, p= 0.215)  24-hour: -8.8% (CI=[-19.0%; +2.8%], T(145)=-1.52, p= 0.131)	Marginal R2 = 0.04 Conditional R2 = 0.39
90-day Mortality	$F(2, 145)=1.20, p= 0.304$	Reference: Alive  Dead: -0.21 (CI=[-0.35;-0.06], T(75)=-2.91, p=0.005  PSD Ischemic hemisphere: -0.271 (CI=[-0.660; 0.117]) PSD Unaffected hemisphere: -0.207 (CI=[-0.497; 0.082])	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.45, p=0.149)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.37, p=0.174)	Marginal R2 = 0.08 Conditional R2 = 0.34
Recanalization (Successful: mTICI 2b-3)	$F(2, 145)=0.96, p= 0.386$	Reference: Successful  Unsuccessful: -0.15 (CI=[-0.33; 0.03], T(75)=-1.64, p=0.105  PSD Ischemic hemisphere: -0.079 (CI=[-0.564; 0.407]) PSD Unaffected hemisphere:	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.42, p=0.157)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.36, p=0.176)	Marginal R2 = 0.04 Conditional R2 = 0.34

			0.027 (CI=[-0.336; 0.390])	
IVT	F(2, 145)=0.58, p=0.554	Reference: No IVT  IVT: 0.22 (CI=[0.12;0.32, T(75)= 4.48, p<0.001)	POST: 0.06 (CI=[-0.02; 0.15], T(147)= 1.43, p=0.154)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.36, p=0.177)	Marginal R2 = 0.14 Conditional R2 = 0.34
ICH	F(2,145)=0.30, p=0.742	Reference: No ICH  ICH: -0.08 (CI=[-0.29; 0.12]; T(75)=-0.79, p=0.432)	POST: 0.06 (CI=[-0.02; 0.15], T(147)= 1.44, p=0.151)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.36, p=0.177)	Marginal R2 = 0.03 Conditional R2 = 0.34
Anesthesia	F(2, 141)=0.12, p=0.885	Reference: Propofol  Sevoflurane: 0.01 (CI=[- 0.20;0.21], T(73)=0.05, p=0.961)	POST: 0.07 (CI=[-0.02; 0.15], T(143)=1.49, p=0.139)  24-hour: -0.05 (CI=[-0.13; 0.04], T(143)=-1.05, p=0.292)	Marginal R2 = 0.02 Conditional R2 = 0.32
Vasopressor	F(2, 110)=0.39, p=0.678	Reference: Phenylephrine  Norepinephrine: 0.04 (CI=[-0.15; 0.24], T(57)=0.45, p=0.656)	POST: 0.07 (CI=[-0.03; 0.18], T(112)=1.42, p=0.1596)  24-hour: -0.05 (CI=[-0.16; 0.05], T(112)=-1.04, p=0.301)	Marginal R2 = 0.02 Conditional R2 = 0.34
Stroke etiology: Large-artery atherosclerosis (LAA) or Cardio- embolic (CE)	F(2,105)=0.50, p= 0.609	Reference: LAA  CE: -0.03 (CI=[-0.17; 0.11], T(53)=0.812, p=0.421)	POST: 0.08 (CI=[-0.02; 0.19], T(107)=1.56, p=0.116)  24-hour: -0.09 (CI=[-0.19; 0.01], T(107)=-1.72, p=0.088)	Marginal R2 = 0.04 Conditional R2 = 0.37

Age	F(2,145)=1.05, p=0.351	-1.4e-3 (CI=[-5.6e-3; 3.5e-3], T(75)=-0.45, p=0.652)	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.44, p=0.150)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p=0.178)	Marginal R2 = 0.02 Conditional R2 = 0.34
Isolated thrombus vs complicated occlusion (ICA-Top and tandem occlusion)	F(2,133)=0.959, p=0.386	Reference: Isolated thrombus  Complicated occlusion: 0.07 (CI=[-0.06; 0.20], T(69)=1.07, p=0.289)	POST: 0.06 (CI=[-0.03; 0.16], T(135)=1.40, p=0.162)  24-hour: -0.06 (CI=[-0.15; 0.03], T(135)=-1.31, p=0.190)	Marginal R2 = 0.03 Conditional R2 = 0.33
ASPECTS/PC- ASPECTS before EVT (Favorable 7- 10 vs non- favorable 0-6)	F(2,145)=2.16, p=0.119	Reference: Favorable  Non-favorable: 0.01 (CI=[-0.15; 0.16], T(75)=0.11, p=0.914)	POST: 0.06 (CI=[-0.02; 0.15], T(147)=1.44, p=0.151)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p=0.178)	Marginal R2 = 0.02 Conditional R2 = 0.34
Anterior vs. posterior circulation stroke	F(2,143)=0.013, p=0.987	Reference: Anterior  Posterior: 0.08 (CI=[-0.13; 0.29], T(74)=0.76, p=0.449)	POST: 0.07 (CI=[-0.02; 0.16], T(145)=1.51, p=0.135)  24-hour: -0.06 (CI=[-0.15; 0.06], T(145)=-1.34, p=0.182)	Marginal R2 = 0.03 Conditional R2 = 0.34
Hypotension during EVT (MAP< 70 mmHg)	F(2,144)=0.20, p=0.817	Reference: No hypotension  Hypotension: 0.00 (CI=[-0.11; 0.11], T(146)=-0.04, p=0.969)	POST: 0.06 (CI=[-0.02; 0.15], T(146)=1.44, p=0.153)  24-hour: -0.06 (CI=[-0.15; 0.03], T(146)=-1.28, p=0.204)	Marginal R2 = 0.02 Conditional R2 = 0.34
Hypertension during EVT (MAP<	F(2,144)=0.26, p=0.769	Reference: No hypertension	POST: 0.06 (CI=[-0.03; 0.14], T(146)=1.28, p=0.203)	Marginal R2 = 0.03 Conditional R2 = 0.34

130 mmHg before recanalization or 90 mmHg after recanalization)		Hypertension: 0.09 (CI=[-0.01; 0.19], T(146)=1.75, p=0.082)  PSD Ischemic hemisphere: 0.014 (CI=[-0.221; 0.249])  PSD Unaffected hemisphere: -0.031 (CI=[-0.221; 0.160])	24-hour: -0.06 (CI=[-0.14; 0.03], T(146)=-1.24, p=0.219)	
IVT and time from LKW to arrival	IVT x Time to LKW to arrival:  F(1,72)= 2.54, p=0.116	IVT: 0.21 (CI=[0.10; 0.33]; T(74)= 3.67, p<0.001)  Time to LKW to arrival: -0.00 (CI=[-0.01; 0.01]; T(73)=-0.33, p=0.741)	POST: 0.06 (CI=[-0.03; 0.15], T(147)= 1.36, p=0.175)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.36, p=0.175)	Marginal R2 = 0.13  Conditional R2 = 0.34
IVT and ASPECTS/PC-ASPECTS before EVT	IVT x ASPECTS/PC-ASPECTS:  F(1,73)=0.10, p=0.750	IVT: 0.24 (CI=[0.13; 0.34]; T(74)= 4.51, p<0.001)  ASPECTS/PC-ASPECTS: -0.01 (CI=[-0.03; -0.01]; T(74)=-0.77, p=0.444)	POST: 0.06 (CI=[-0.02; 0.15], T(147)= 1.45, p=0.151)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.36, p=0.177)	Marginal R2 = 0.14  Conditional R2 = 0.35
IVT and 90-day mRS	IVT x 90-day mRS:  F(1,73)= 0.73, p=0.397	IVT: 0.19 (CI=[0.09; 0.29]; T(74)= 3.67, p=0.001)  90-day mRS: -0.03 (CI=[-0.06; -0.00]; T(74)=-2.08, p=0.041)	POST: 0.06 (CI=[-0.02; 0.15], T(147)= 1.44, p=0.152)  24-hour: -0.06 (CI=[-0.15; 0.03], T(147)=-1.35, p=0.178)	Marginal R2 = 0.16  Conditional R2 = 0.35

PSD: Power spectral density (unit:  $(\mu M^*mm)^2 / Hz$ ). CI: Confidence interval. mRS: Modified Rankin scale. NIHSS: National Institutes of Health Stroke Scale. mTICI: modified treatment in cerebral infarction. IVT: intravenous thrombolysis. ICH: symptomatic and non-symptomatic

*intracranial hemorrhages. ICA-top: Top of the internal carotid artery. ASPECTS: Alberta stroke program early CT score. EVT: Endovascular treatment. MAP: Mean arterial pressure. LKW: Last-known-well.*

*Table S7. Mixed-effects models in FU<sub>90</sub>-group with LF gain as outcome variable, time segment and different stroke characteristics, treatment, and outcome as fixed effect with subject as random effect.*

Grouping	Interaction	Fixed effect Groups	Fixed effect Time segment	Model performance
<i>Reference: PRE</i>				
No grouping	-	-	POST: 0.08 (CI=[-0.04; 0.19], T(159)=1.36, p = 0.184)	Marginal R2 = 0.05 Conditional R2 = 0.12
			24-hour: -0.09 (CI=[-0.20; 0.02], T(159)=-1.65, p=0.100)	
			90-day: -0.10 (CI=[-0.21; 0.01], T(159)=-1.79, p=0.076)	
90-day mRS	F(3,150)=0.16, p=0.921	-0.03 (CI=[-0.07; 0.00], T(52)= 1.85, p=0.070)	POST: 0.08 (CI=[-0.04; 0.19], T(153)=1.35, p=0.180)	Marginal R2 = 0.07 Conditional R2 = 0.21
			24-hour: -0.09 (CI=[-0.20; 0.02], T(153)=-1.65, p=0.101)	
			90-day: -0.10 (CI=[-0.21; 0.01], T(153)=-1.77, p=0.078)	
90-day Independence (mRS 0-2)	F(3,150)=0.23, p=0.874	Reference: Independence  Dependence: -0.10 (CI=[-0.20; 0.01], T(52)=-1.87, p=0.067)	POST: 0.08 (CI=[-0.04; 0.19], T(153)=1.34, p=0.180)  24-hour: -0.09 (CI=[-0.20; 0.02], T(153)=-1.65, p=0.101)	Marginal R2 = 0.07 Conditional R2 = 0.21

			90-day: -0.10 (CI=[-0.21; 0.01], T(153)=-1.77, p=0.078) POST: +5.6% (CI=[-6.5%; +19.3%], T(153)=0.89, p=0.374)	Marginal R2 = 0.02 Conditional R2 = 0.21
90-day NIHSS recovery	F(3,150)=0.08, p=0.973	+0.1% (CI=[-0.9%; +1.2%], T(52)=0.28, p=0.783)	24-hour: -6.2% (CI=[-16.8%; +5.7%], T(153)=-1.06, p=0.291)	
NIHSS	F(3,149)=0.15, p=0.932	-0.5% (CI=[-1.4%;+0.5%], T(152)=-0.96, p=0.337)	90-day: -7.2% (CI=[-17.7%; +5.8%], T(153)=-1.21, p=0.227)  POST: +5.6% (CI=[-6.5%;+19.3%], T(152)=0.89, p=0.377)	Marginal R2 = 0.03 Conditional R2 = 0.20
Recanalization (Successful: mTICI 2b-3)	F(3,150)=0.77, p=0.515	Reference: Successful  Unsuccessful: -0.17 (CI=[-0.06; 0.40], T(52)=1.47, p=0.148)	24-hour: -9.8% (CI=[-21.8%; +4.2%], T(152)=-1.41, p=0.160)  90-day: -11.9% (CI=[-25.1%; +3.6%], T(152)=-1.54, p=0.125)  POST: 0.08 (CI=[-0.04; 0.19], T(153)=1.30, p=0.195)	Marginal R2 = 0.06 Conditional R2 = 0.21
IVT	F(3,150)= 0.86, p=0.464	Reference: No IVT	24-hour: -0.09 (CI=[-0.20;0.02], T(153)=-1.66, p=0.099)  90-day: -0.10 (CI=[-0.21; 0.01], T(153)=-1.79, p=0.075)  POST: 0.07 (CI=[-0.04; 0.19], T(153)= 1.33, p=0.187)	Marginal R2 = 0.11 Conditional R2 = 0.21

		IVT: 0.16 (CI=[0.07;0.26, T(52)= 2.63, p=0.011)	24-hour: -0.09 (CI=[-0.20;0.02], T(153)=-1.65, p=0.100)	
Anesthesia	F(3,147)=0.542, p=0.654	Reference: Propofol  Sevoflurane: -0.02 (CI=[- 0.25;0.22], T(51)=-0.13, p=0.894)	POST: 0.08 (CI=[-0.04; 0.19], T(153)=1.34, p=0.184)  24-hour: -0.08 (CI=[-0.19;0.03], T(153)=-1.40, p=0.165)	Marginal R2 = 0.04  Conditional R2 = 0.20
Vasopressor	F(3, 121)=0.59, p=0.623	Reference: Phenylephrine  Norepinephrine: -0.02 (CI=[- 0.20; 0.15], T(42)=-0.28, p=0.779)	POST: 0.08 (CI=[-0.04; 0.21], T(124)=1.33, p=0.185)  24-hour: -0.09 (CI=[-0.22; 0.03], T(124)=-1.53, p=0.128)	Marginal R2 = 0.06  Conditional R2 = 0.20
Stroke etiology: Large-artery atherosclerosis (LAA) or Cardio- embolic (CE)	F(3,109)=0.17, p=0.917	Reference: LAA  CE: -0.04 (CI=[-0.18;0.10], T(37)=-0.62, p=0.538)	POST: 0.08 (CI=]-0.05; 0.21], T(112)=1.29, p=0.200)  24-hour: -0.14 (CI=[-0.27;-0.01], T(112)=-2.16, p=0.033)	Marginal R2 = 0.08  Conditional R2 = 0.29

Age	F(3,150)=0.64, p=0.587	0.00 (CI=[-0.01; 0.00], T(52)=-0.72, p=0.474)	POST: 0.08 (CI=[-0.04; 0.19], T(153)=1.35, p=0.179)  24-hour: -0.09 (CI=[-0.20; 0.02], T(153)=-1.65, p=0.101)  90-day: -0.10 (CI=[-0.21; 0.01], T(153)=-1.79, p=0.075)	Marginal R2 = 0.02 Conditional R2 = 0.21
Isolated thrombus vs complicated occlusion (ICA-Top and tandem occlusion)	F(3,147)=1.68, p=0.173	Reference: Isolated thrombus  Complicated occlusion: -11.0% (CI=[-4.0%; +28.3%], T(49)=-1.45, p=0.155)	POST: +8.6% (CI=[-6.5%; +26.2%], T(150)=1.09, p=0.277)  24-hour: -9.8% (CI=[-22.4%; +4.7%], T(150)=-1.37, p=0.174)  90-day: -7.8% (CI=[-20.6%; +7.1%], T(150)=-1.08 p=0.283)	Marginal R2 = 0.04 Conditional R2 = 0.15
ASPECTS/PC-ASPECTS before EVT (Favorable 7-10 vs non-favorable 0-6)	F(3,150)=2.95, p=0.035	Reference: Favorable  Non-favorable: -0.02 (CI=[-0.10; 0.06], T(52)=-0.55, p=0.585)	POST: 0.04 (CI=[-0.08; 0.16], T(150)=0.20, p=0.844)  24-hour: -0.08 (CI=[-0.20; 0.03], T(150)=4.17, p<0.001)  90-day: -0.09 (CI=[-0.20; 0.03], T(150)=-2.26, p=0.025)	Marginal R2 = 0.08 Conditional R2 = 0.24

Anterior vs. posterior circulation stroke	F(3,149)=1.01, p=0.391	Reference: Anterior  Posterior: 0.02 (CI=[-0.12; 0.16], T(152)=0.30, p=0.765)	POST: 0.08 (CI=[-0.04; 0.19], T(152)=1.34, p=0.181)  24-hour: -0.09 (CI=[-0.20; 0.02], T(152)=-1.64, p=0.103)  90-day: -0.10 (CI=[-0.21;0.01], T(152)=-1.78, p=0.077)	Marginal R2 = 0.05  Conditional R2 = 0.20
Hypotension during EVT (MAP< 70 mmHg)	Not evaluable	Reference: No hypotension  Hypoperfusion: -0.03 (CI=[- 0.17; 0.10], T(152)=-0.50, p= 0.621)	POST: 0.07 (CI=[-0.04; 0.19], T(149)=1.31, p=0.192)  24-hour: -0.09 (CI=[-0.20;0.02], T(149)=-1.63, p=0.105)  90-day: -0.09 (CI=[-0.21; 0.04], T(149)=-1.37, p=0.174)	Marginal R2 = 0.05  Conditional R2 = 0.21
Hypertension during EVT (MAP< 130 mmHg before recanalization or 90 mmHg after recanalization)	F(3,149)=1.43, p=0.235	Reference: No hypertension  Hypertension: 0.09 (CI=[-0.02; 0.20], T(152)=1.65, p=0.102)	POST: 0.08 (CI=[-0.03; 0.20], T(152)=1.49, p=0.138)  24-hour: -0.08 (CI=[-0.19;0.03], T(152)=-1.51, p=0.134)  90-day: -0.09 (CI=[-0.20; 0.02], T(152)=-1.61, p=0.110)	Marginal R2 = 0.06  Conditional R2 = 0.21

Power spectral density (unit:  $(\mu M^*mm)^2 / Hz$ ). CI: Confidence interval. mRS: Modified Rankin scale. NIHSS: National Institutes of Health

Stroke Scale. mTICI: modified treatment in cerebral infarction. IVT: intravenous thrombolysis. ICA-top: Top of the internal carotid artery.

ASPECTS: Alberta stroke program early CT score. EVT: Endovascular treatment. MAP: Mean arterial pressure.

*Table S8. Mixed-effects models in FU<sub>24</sub>-group with LF absolute phase shift as outcome variable, time segment and different stroke characteristics, treatment, and outcome as fixed effect with subject as random effect.*

Grouping	Interaction	Fixed effect Groups	Fixed effect Time segment	Model performance
<i>Reference: PRE</i>				
No grouping	-	-	POST: + 8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p = 0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16
90-day mRS	F(2,150)=1.09, p=0.339	0.0% (CI=[-9.0%; +9.9%], T(75)=0.00, p=0.997)	POST: +8.2% (CI=[-24.0%; +54.1%, T(152)=0.44, p=0.661)  24-hour: +56.0 (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16
90-day Independence (mRS 0-2)	F(2,150)=1.24, p=0.293	Reference: Independence  Dependence: -3.2% (CI=[- 47.3%; +27.7%], T(75)=-0.18, p=0.860)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0 (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.17

24-hour NIHSS recovery	F(2,148)=0.62, p=0.541	+0.5% (CI=[-3.6%;+4.8%], T(74)=0.24, p=0.809)	POST: +7.5% (CI=[-36.8%; +82.8%], T(148)=0.27, p=0.788)  24-hour: +89.5% (CI=[+11.4%; +222.2%], T(148)=2.38, p=0.019)	Marginal R2 = 0.03 Conditional R2 = 0.16
NIHSS	F(2,147)=3.96, p=0.021	+4.6% (CI=[0.4%; +8.9%], T(147)=2.16, p=0.032)	POST: +257.1% (CI=[+42.2%; +796.8%], T(147)=2.73, p=0.007)  24-hour: +181.7% (CI=[+28.6%; +516.8%], T(147)=2.61, p=0.010)	Marginal R2 = 0.06 Conditional R2 = 0.20
90-day Mortality	F(2,150)=0.11, p=0.894	Reference: Alive  Dead: +24.2% (CI=[-22.5; +99.0%], T(75)=0.92, p=0.363)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03 Conditional R2 = 0.16
Recanalization (Successful: mTICI 2b-3)	F(2,150)=0.80, p=0.451	Reference: Successful  Unsuccessful: +32.6% (CI=[-25.6%; +136.3%], T(75)=0.97, p=0.335)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03 Conditional R2 = 0.16

IVT	$F(2,150)=0.11, p=0.900$	Reference: No IVT  IVT: -5.5% (CI=[-33.8%; +35.0%]; T(75)=-0.32, p=0.753)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16
ICH	$F(2,150)=0.32, p=0.729$	Reference: No ICH  ICH: +16.1% (CI=[-40.1%; +125.0%]; T(75)=0.45, p=0.654)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16
Anesthesia	$F(2,146)=1.28, p=0.281$	Reference: Propofol  Sevoflurane: -46.0% (CI=[-71.9%; +3.9%], T(73)=-1.88, p=0.064)	POST: +7.0% (CI=[-25.2%; +53.2%], T(148)=0.37, p=0.709)  24-hour: +61.4% (CI=[+12.8%; +131.0%], T(148)=2.64, p=0.009)	Marginal R2 = 0.05  Conditional R2 = 0.17
Vasopressor	$F(2, 114)=1.71, p=0.186$	Reference: Phenylephrine  Norepinephrine: -3.8% (CI=[-47.8%; +77.0%], T(57)=-0.13, p=0.899)	POST: +21.5% (CI=[-21.5%; +88.1%], T(116)=0.88, p=0.378)  24-hour: +61.8% (CI=[+4.6%; +150.4%], T(116)=2.18, p=0.031)	Marginal R2 = 0.02  Conditional R2 = 0.12

Stroke etiology: Large-artery atherosclerosis (LAA) or Cardio- embolic (CE)	F(2,106)=1.36, p=0.262	Reference: LAA  CE: -16.6% (CI=[-43.6%; +23.2%], T(53)=-0.93, p=0.355)	POST: +38.3% (CI=[-9.8%; +112.1%], T(108)=1.50, p=0.136)  24-hour: +62.0% (CI=[+5.6%; +148.4%], T(108)=2.23, p=0.028)	Marginal R2 = 0.03  Conditional R2 = 0.10
Age	F(2,150)=0.04, p=0.965	-0.3% (CI=[-1.8%; +1.1%], T(75)=-0.45, p=0.653)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16
Isolated thrombus vs complicated occlusion (ICA-Top and tandem occlusion)	F(2,138)=0.027, p=0.973	Reference: Isolated thrombus  Complicated occlusion: -22.8% (CI=[-48.9%; +16.7%], T(69)= 1.25, p=0.216)	POST: +7.8% (CI=[-25.9%; +56.9%], T(140)=0.40, p=0.693)  24-hour: +51.5% (CI=[+4.1%; +120.5%], T(140)=2.19, p=0.030)	Marginal R2 = 0.03  Conditional R2 = 0.16
ASPECTS/PC- ASPECTS before EVT (Favorable 7- 10 vs non- favorable 0-6)	F(2,150)=0.40, p=0.669	Reference: Favorable  Non-favorable: +21.5% (CI=[- 25.4%; +97.8%], T(75)=0.80, p=0.428)	POST: +8.2% (CI=[-24.0%; +54.1%], T(152)=0.44, p=0.661)  24-hour: +56.0% (CI=[+9.6%; +122.2%], T(152)=2.49, p=0.014)	Marginal R2 = 0.03  Conditional R2 = 0.16

Anterior vs. posterior circulation stroke	F(2,148)=0.21, p=0.808	Reference: Anterior  Posterior: +27.8% (CI=[-34.2; +148.4%], T(74)=0.74, p=0.464)	POST: +3.8% (CI=[-27.1%; +47.8%], T(150)=0.21, p=0.833)  24-hour: +51.4% (CI=[+6.3%; +115.5%], T(150)=2.32, p=0.022)	Marginal R2 = 0.03  Conditional R2 = 0.17
Hypotension during EVT (MAP< 70 mmHg)	F(2,149)=0.32, p=0.725	Reference: No hypotension  Hypotension: +14.2% (CI=[- 25.2%; +74.5%], T(151)=0.62, p=0.536)	POST: +7.6% (CI=[-24.5%; +53.3%], T(151)=0.41, p=0.682)  24-hour: +51.3% (CI=[+4.8%; +118.4%], T(151)=2.23, p=0.027)	Marginal R2 = 0.03  Conditional R2 = 0.16
Hypertension during EVT (MAP< 130 mmHg before recanalization OR 90 mmHg after recanalization)	F(2,149)=1.09, p=0.339	Reference: No hypertension  Hyperpertension: +7.9% (CI=[- 26.6%; +58.6%], T(151)=0.39, p=0.697)	POST: +7.4% (CI=[-24.7%; +53.3%], T(151)=0.40, p=0.697)  24-hour: +56.7% (CI=[+9.9%; +123.3%], T(151)=2.50, p=0.013)	Marginal R2 = 0.03  Conditional R2 = 0.16

PSD: Power spectral density (unit:  $(\mu M^*mm)^2 / Hz$ ). CI: Confidence interval. mRS: Modified Rankin scale. NIHSS: National Institutes of Health Stroke Scale. mTICI: modified treatment in cerebral infarction. IVT: intravenous thrombolysis. ICH: symptomatic and non-symptomatic intracranial hemorrhages. ICA-top: Top of the internal carotid artery. ASPECTS: Alberta stroke program early CT score. EVT: Endovascular treatment. MAP: Mean arterial pressure.

*Table S9. Mixed-effects models in FU<sub>90</sub>-group with LF absolute phase shift as outcome variable, time segment and different stroke characteristics, treatment, and outcome as fixed effect with subject as random effect.*

Grouping	Interaction	Fixed effect Grupper	Fixed effect Time segment	Model performance
<i>Reference: PRE</i>				
No grouping	-	-	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233) 24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015) 90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)	Marginal R2 = 0.02 Conditional R2 = 0.17
90-day mRS	F(3,156)=0.82, p=0.485	-8.6% (CI=[-20.1%; +4.5%], T(52)=-1.35, p=0.183)	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233) 24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015) 90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.18, p=0.243)	Marginal R2 = 0.03 Conditional R2 = 0.17
90-day Independence (mRS 0-2)	F(3,156)=1.02, p=0.385	Reference: Independence	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233)	Marginal R2 = 0.03 Conditional R2 = 0.17

		Dependence: -9.7% (CI=[-38.9%; +33.4%], T(52)=-0.53, p=0.601)	24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)	
90-day NIHSS recovery	F(3,156)=1.51, p=0.215	-0.5% (CI=[-3.7%; +2.8%], T(52)=-0.31, p=0.756)	90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.18, p=0.243)	Marginal R2 = 0.03 Conditional R2 = 0.17
NIHSS	F(3,155)=3.82, p=0.011	+3.5% (CI=[-1.4%; +8.6%], T(155)=1.42, p=0.158)	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233)  24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)  90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)	Marginal R2 = 0.07 Conditional R2 = 0.22
Recanalization (Successful: mTICI 2b-3)	F(3,156)=1.63, p=0.186	Reference: Successful	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233)  24-hour: +115.6% (CI=[-10.0%; +416.2%], T(155)=1.74, p=0.084)  90-day: +95.8% (CI=[-15.2%; +351.9%], T(155)=1.59, p=0.115)	Marginal R2 = 0.02 Conditional R2 = 0.17

		Unsuccessful: +15.5% (CI=[-95.2%; +63.4%], T(52)=0.40, p=0.688)	24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)  90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)	
Intravenous thrombolysis (IVT)	F(3,156)=0.16, p=0.924	Reference: No IVT  IVT: +10.1% (CI=[-25.0%; +61.6%], T(52)=0.50, p=0.616)	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233)  24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)  90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)	Marginal R2 = 0.02  Conditional R2 = 0.17
Anesthesia	F(3,153)=1.16, p=0.327	Reference: Propofol  Sevoflurane: -39.1% (CI=[-73.6%; +40.2%], T(51)=-1.19, p=0.238)	POST: +26.5% (CI=[-16.4%; +91.6%], T(156)=1.12, p=0.264)  24-hour: +66.3% (CI=[+9.9%; +151.8%], T(156)=2.42, p=0.017)  90-day: +27.5% (CI=[-15.8%; +93.0%], T(156)=1.16, p=0.249)	Marginal R2 = 0.03  Conditional R2 = 0.17
Vasopressor	F(3, 126)=0.31, p=0.820	Reference: Phenylephrine  Norepinephrine: +23.4% (CI=[-34.6%; +133.0%], T(42)=0.67, p=0.508)	POST: +45.9% (CI=[-34.6%; +133.0%], T(129)=1.57, p=0.118)	Marginal R2 = 0.03  Conditional R2 = 0.16

			24-hour: +75.8% (CI=[+9.3%; +182.8%], T(129)=2.35, p=0.020)	
			90-day: +43.0% (CI=[-11.1%; +130.0%], T(129)=1.49, p=0.139)	
Stroke etiology: Large-artery atherosclerosis (LAA) vs Cardio- embolic (CE)	F(3,111)= 1.08, p=0.363	Reference: LAA  CE: -22.7% (CI=[-51.7; +23.7%], T(37)=-1.11, p=0.275)	POST: +67.6% (CI=[+4.1%; +169.8%], T(114)=2.15, p=0.034)	Marginal R2 = 0.05  Conditional R2 = 0.22
Age	F(3,156)=0.23, p=0.873	-0.1% (CI=[-1.6%;+1.5%], T(52)=-0.08, p=0.935)	24-hour: +82.8% (CI=[+13.6%; +194.2%], T(114)=2.51, p=0.014)	90-day: +50.2% (CI=[-6.7%; +141.8%], T(114)=1.69, p=0.093)
Isolated thrombus vs complicated	F(3,147)=0.32, p=0.808	Reference: Isolated thrombus	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233)	Marginal R2 = 0.02  Conditional R2 = 0.17
			24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)	90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)
			POST: +21.5% (CI=[-20.2%; +85.0%], T(150)=0.91, p=0.362)	Marginal R2 = 0.03  Conditional R2 = 0.18

occlusion (ICA-Top and tandem occlusion)		Complicated occlusion: -27.8% (CI=[-53.1%; +12.4%], T(49)=-1.47, p=0.147)	24-hour: +55.9% (CI=[+2.4%; +137.4%], T(150)=2.09, p=0.039)	
			90-day: +23.2% (CI=[-19.1%; +87.6%], T(150)= 0.98, p=0.329)	
ASPECTS/PC-ASPECTS before EVT (Favorable 7-10 vs non-favorable 0-6)	F(3,156)=0.97, p=0.408	Reference: Favorable Non-favorable: +28.6% (CI=[-27.1%; +126.9%], T(52)=0.89, p=0.378)	POST: +28.0% (CI=[-14.8%; +92.3%], T(159)=1.20, p=0.233) 24-hour: +66.1% (CI=[+10.5%; +149.5%], T(159)=2.46, p=0.015)	Marginal R2 = 0.03 Conditional R2 = 0.17
			90-day: +27.3% (CI=[-15.3%; +91.3%], T(159)=1.17, p=0.243)	
Anterior vs. posterior circulation stroke	F(3,155)= 0.22, p=0.884	Reference: Anterior Posterior: -29.1% (CI=[-57.4%; +18.1%], T(158)=-1.33, p=0.186)	POST: +26.4% (CI=[-16.0%; +90.1%], T(158)=1.13, p=0.259) 24-hour: +65.0% (CI=[+9.8%; +148.1%], T(158)=2.43, p=0.016)	Marginal R2 = 0.03 Conditional R2 = 0.17
			90-day: +27.3% (CI=[-15.3%; +91.4%], T(158)=1.17, p=0.244)	
Hypotension during EVT (MAP< 70 mmHg)	Not evaluable	Reference: No hypotension	POST: +31.2% (CI=[-12.8%; +97.4%], T(158)=1.31, p=0.191)	Marginal R2 = 0.03 Conditional R2 = 0.17

	Hypotension: +39.7% (CI=[-13.5%; +125.7%], T(158)= 1.38, p=.170)	24-hour: +66.1% (CI=[+10.6%; +149.4%], T(158)=2.46, p=0.015)	
		90-day: +12.5% (CI=[-15.3%; +91.3%], T(158)=0.52, p=0.601)	
Hypertension during EVT (MAP< 130 mmHg before recanalization OR 90 mmHg after recanalization)	F(3,155)=0.56, p=0.639	Reference: No hypertension Hypertension: -4.9% (CI=[-36.6%; +42.7%], T(158)=-0.24, p=0.807)	POST: +27.5% (CI=[-15.3%; +92.0%], T(158)=1.17, p=0.242) 24-hour: +65.4% (CI=[+9.9%; +149.1%], T(158)=2.42, p=0.016) 90-day: +26.9% (CI=[-15.8%; +91.0%], T(158)=1.15, p=0.253)

PSD: Power spectral density (unit:  $(\mu M^*mm)^2 / Hz$ ). CI: Confidence interval. mRS: Modified Rankin scale. NIHSS: National Institutes of Health Stroke Scale. mTICI: modified treatment in cerebral infarction. ICA-top: Top of the internal carotid artery. ASPECTS: Alberta stroke program early CT score. EVT: Endovascular treatment. MAP: Mean arterial pressure.

*Table S10. Acute (logistic regression) model predicting 90-day independency (mRS 0-2).*

Predictor	Estimate	SE	Z-value	P-value
LF gain	2.601	1.234	2.107	0.035
Age	-0.086	0.025	-3.430	0.001
Recanalization (successful)	0.738	1.031	0.716	0.474
ASPECTS/PC-ASPECTS (non-favorable)	-1.176	0.825	-1.426	0.154
Intercept: 90-day independency (mRS 0-2)	3.120	2.217	1.407	0.159
AIC	93.127			
Residual deviance	83.127			

*AIC: Akaike information criterion.*

*Table S11. 24-hour (logistic regression) model predicting 90-day independency (mRS 0-2).*

Predictor	Estimate	SE	Z-value	P-value
LF gain	2.294	1.316	1.744	0.081
Age	-0.087	0.029	-3.047	0.002
24-hour NIHSS: Moderate	-2.235	0.688	-3.247	0.001
24-hour NIHSS: Severe	-3.054	0.934	-3.269	0.001
Intercept: 90-day independency (mRS 0-2)	5.488	2.414		
AIC	79.958			
Residual deviance	65.958			

*AIC: Akaike information criterion.*

*Table S12. Acute (ordinal logistic regression) model predicting 90-day categorized NIHSS.*

Predictor	Estimate	SE	T-value	P-value
LF gain	2.264	0.947	2.390	0.017
Age	-0.025	0.018	-1.397	0.162
Recanalization (successful)	1.368	0.727	1.881	0.060
ASPECTS/PC-ASPECTS (non-favorable)	-1.542	0.635	-2.429	0.015
Intercepts: Categorized 90-day NIHSS	Estimate	SE		
Fatal   Severe	-0.478	1.695		
Severe   Moderate	0.366	1.701		
Moderate   Mild	1.164	1.719		
Mild   Near-remission	2.003	1.732		
AIC	231.686			
Residual deviance	215.686			

*AIC: Akaike information criterion.*

*Table S13. 24-hour (ordinal logistic regression) model predicting 90-day categorized NIHSS.*

Predictors (index)	Estimate	SE	T-value	P-value
LF gain	1.578	1.048	1.506	0.132
Age	-0.016	0.019	-0.874	0.382
24-hour NIHSS: Moderate	-2.682	0.591	-4.536	<0.001
24-hour NIHSS: Severe	-4.236	0.762	-5.562	<0.001
Intercepts: Categorized 90-day NIHSS				
Fatal   Severe	-4.000	1.919		
Severe   Moderate	-2.875	1.899		
Moderate   Mild	-1.702	1.900		
Mild   Near-remission	-0.407	1.896		
AIC	213.285			
Residual deviance	193.285			

*AIC: Akaike information criterion.*

*Table S14. Acute (logistic regression) model predicting 90-day mortality.*

Predictors (index)	Estimate	SE	Z-value	P-value
LF Gain	3.778	1.649	2.290	0.022
Age	-0.063	0.035	-1.834	0.067
ASPECTS/PC-ASPECTS (non-favorable)	-2.146	0.859	-2.498	0.013
Recanalization (successful)	0.805	1.021	0.788	0.431
Intercept: 90-day mortality	2.831	2.835	0.999	0.318
AIC		61.927		
Residual deviance		51.927		

*AIC: Akaike information criterion.*

*Table S15. 24-hour (logistic regression) model predicting 90-day mortality.*

Predictors (index)	Estimate	SE	Z-value	P-value
LF Gain	3.106	1.724	1.802	0.072
Age	-0.054	0.039	-1.383	0.167
24-hour NIHSS: Moderate	-17.463	1854.073	-0.009	0.992
24-hour NIHSS: Severe	-18.989	1854.073	-0.010	0.992
Intercept: 90-day mortality	20.62	1854.075		
AIC				
Residual deviance				

*AIC: Akaike information criterion.*

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## **Study II: Bilateral dynamic cerebral autoregulation assessment during endovascular treatment in large-vessel occlusion stroke**

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Submitted to Experimental Physiology (ISSN: 1469-445X) on June 5<sup>th</sup>, 2025.

**Manuscript title**

Bilateral dynamic cerebral autoregulation assessment during endovascular treatment in large-vessel occlusion stroke

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**Running headline**

Bilateral cerebral autoregulation during EVT of acute ischemic stroke

**Keywords**

Acute ischemic stroke; Endovascular treatment; Thrombectomy; Near-infrared spectroscopy; Cerebral circulation; Dynamic cerebral autoregulation; Large-vessel occlusion; Transfer function analysis

## **Word count and references**

5560 words (excluding title page, abbreviation list, legends, references, and additional information).

58 references.

## **New Findings**

- *What is the central question of this study?*

Dynamic cerebral autoregulation (dCA), which maintains blood flow constant despite changes in blood pressure, is impaired in acute ischemic stroke patients after endovascular treatment (EVT) but have not been examined during EVT.

- *What is the main finding and its importance?*

Assessment of dCA during EVT was feasible analyzing phase shift (PS) between near infrared spectroscopy and blood pressure. PS sensitivity to end-tidal CO<sub>2</sub> was increased in the ischemic hemisphere. PS increased during EVT for patients with good long-term outcome and vice versa. The findings could indicate a benefit of individualized intraoperative management.

## **Abstract**

Recanalization by endovascular treatment (EVT) is effective in acute ischemic stroke caused by large-vessel occlusion. Better understanding of the pathophysiology could possibly identify targets for improving peri-procedural management and thereby patient outcome. Dynamic cerebral autoregulation (dCA), which maintains cerebral blood flow despite changes in arterial blood pressure (ABP), is reportedly impaired after EVT. Blood pressure thresholds after EVT have previously been individualized by accounting for dCA, which could improve outcome. The conventional method to estimate dCA requires transcranial Doppler which is difficult to use during EVT. Instead, we investigated dCA during EVT by near-infrared spectroscopy (NIRS) which is more feasible. NIRS and ABP were measured continuously before recanalization, immediately after recanalization, and after general anesthesia termination for subsequent transfer function analysis yielding the dCA measure of phase shift (0.07-0.2 Hz). Phase shift did not differ between the ischemic and contralateral hemisphere but the sensitivity to end-tidal CO<sub>2</sub> was increased in the ischemic hemisphere immediately after recanalization. Phase shift over time interacted with 90-day functional outcome including independency and mortality. Hence, patients with good long-

term outcome showed increased phase shift during and after EVT, while phase shift decreased in poor outcome patients. In conclusion, dCA did not differ between hemispheres during EVT but was more sensitive to end-tidal CO<sub>2</sub> in the ischemic compared to the contralateral hemisphere and dCA evolved differently in patients with good and poor outcome. Our findings of individual dCA differences during EVT suggest benefit of individualized blood pressure management, which should be addressed in future studies.

#### **Non-standard Abbreviations and Acronyms**

ABP: Arterial blood pressure

ACA: Anterior Cerebral Artery

ASPECTS: Alberta Stroke Program Early CT Score

BA: Basilar artery.

β: Effect size estimate

CI: Confidence interval

dCA: Dynamic Cerebral Autoregulation

ETCO<sub>2</sub>: End-tidal carbon dioxide

EVT: Endovascular Treatment

GA: General anesthesia

HF: High-frequency (0.2-0.5 Hz)

HR: Heart rate

ICA: Internal carotid artery.

IQR: Interquartile range

IVT: Intravenous thrombolysis.

LF: Low-frequency (0.07-0.2 Hz)

LFO: Low-frequency oscillations

M1: First segment of middle cerebral artery.

M2: Second segment of middle cerebral artery.

MCA: Middle Cerebral Artery

mRS: modified Rankin Scale

mTICI: Modified Treatment In Cerebral Infarction

NIHSS: National Institutes of Health Stroke Scale

NIRS: Near-Infrared Spectroscopy

OxyHb: Oxygenated Hemoglobin Concentration

PC-ASPECTS: Posterior circulation Alberta Stroke Program Early CT Score

PCA: Posterior cerebral artery.

POST: Second time segment (after achieving final reperfusion status)

PRE: First time segment (after sedation but before any attempted revascularization)

PSD: Power spectral

SpO<sub>2</sub>: Peripheral hemoglobin saturation

TCD: transcranial doppler sonography

TFA: Transfer Function Analysis

TIA: Transient ischemic attack

VLF: Very low-frequency (0.02-0.07 Hz).

V<sub>MCA</sub>: Flow velocity in the Middle Cerebral Artery

## Introduction

Acute ischemic stroke due to large-vessel occlusion form a substantial proportion of all stroke and has the worst prognosis (Malhotra et al., 2017). However, recanalization by endovascular treatment (EVT) markedly improves the outcome of stroke patients whether performed in the anterior or posterior circulation (Baik et al., 2023; Goyal et al., 2016; Nogueira et al., 2018). While highly effective, EVT can still be improved by limiting procedure-related complications and improved understanding of mechanisms underlying futile recanalization. Cerebral autoregulation impairment has been proposed as one of the reasons for futile recanalization (Nogueira et al., 2022; Wang & Xiong, 2023) and have successfully been applied to individualize blood pressure threshold after EVT (Petersen et al., 2020).

Cerebral autoregulation is the complex mechanism of maintaining a suitable blood flow despite alterations in cerebral perfusion pressure (Paulson et al., 1990). When rapid changes in perfusion pressure occur, cerebral blood flow is maintained by dynamic cerebral autoregulation (dCA)(Claassen et al., 2021). Conventional dCA examination relies on simultaneous blood pressure

monitoring and transcranial Doppler sonography (TCD) with analysis of low-frequency oscillations (LFO, approximately 0.1 Hz) observed in both systemic (i.e., arterial blood pressure, ABP) and cerebral circulation (Andersen et al., 2018; Obrig et al., 2000; Reinhard et al., 2006). The most standardized method is the transfer function analysis (TFA) which quantifies input (ABP) and output (blood flow velocity assessment by TCD in the middle cerebral artery,  $V_{MCA}$ ) in low-frequency spectrums (Liu et al., 2020; Panerai et al., 2023). TFA estimates dCA by the attenuation (gain or amplitude ratio) and temporal displacement (phase shift) of LFOs. Thus, impaired dCA is associated with increased gain and reduced phase shift; conversely, reduced gain and increased phase shift signify enhanced dCA.

TCD requires expertise and setup time which reduces the inter-rater variability substantially (Bhuiyan et al., 2012; Nedelmann et al., 2009). Continuous TCD during EVT requires equipment that would likely interfere with the procedure of digital subtraction angiography. In contrast, near-infrared spectroscopy (NIRS) can be applied throughout the procedure as it requires almost no setup time and is compatible with digital subtraction angiography. NIRS is an optical modality that measures continuous and dynamic changes in cortical hemoglobin concentrations as a marker of regional cerebral blood flow (Andersen et al., 2018; Quaresima & Ferrari, 2019). Hence, NIRS can replace TCD in the conventional dCA examination setup (Obrig et al., 2000; Phillip et al., 2012; Reinhard et al., 2006).

Studies of dCA in large-vessel occlusion have consistently reported impaired autoregulation in the ischemic hemisphere (Intharakham et al., 2019; Nogueira et al., 2022) with ischemic or penumbral tissue vulnerable to hypo- and hyperperfusion. Further, dCA impairment in the affected hemisphere has been associated to both short-term complications (Castro, Azevedo, et al., 2017) and long-term outcome (Nogueira et al., 2022). We previously examined interhemispheric dCA during EVT, finding that the strength of autoregulation expressed by interhemispheric gain was predictive of 90-day outcome (Heiberg et al., 2024). Moreover, interhemispheric phase shift already increased during EVT in patients with milder symptom severity. The ischemic and the contralateral hemispheres were well-synchronized, indicating no or similar phase shift changes bilaterally (Heiberg et al., 2024). Finally, conventional dCA examinations (ABP- $V_{MCA}$ ) of large-vessel

occlusion showed impairment after EVT in the contralateral hemisphere in some (Meyer et al., 2020; Tian et al., 2020) but not all studies (Salinet et al., 2019).

Thus, the aim of the current study was to explore dCA during EVT in both the ischemic and the contralateral hemisphere using ABP and NIRS for TFA.

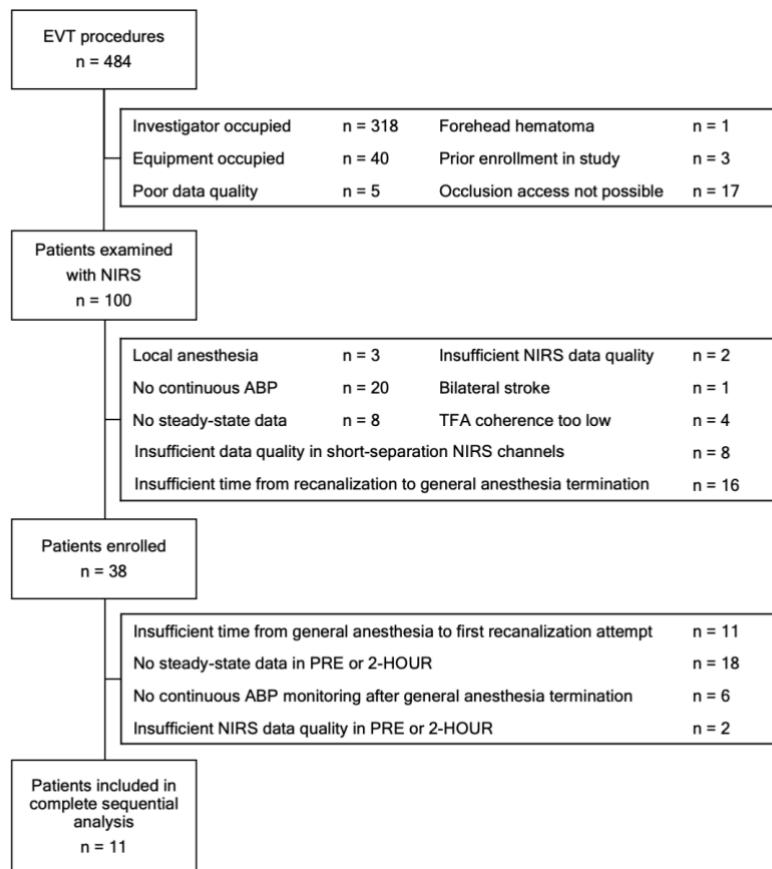
## **Methods**

### *Ethical Approval*

The study was approved by the Scientific Ethics Committees for the Capital Region of Denmark (H-18028704) and performed in accordance with the World Medical Association Declaration of Helsinki (ClinicalTrials.gov: NCT03738644). Informed consent was given in writing by all participants or their proxy. The study adhered to the policies of Experimental Physiology regarding human experiments and complied with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies (von Elm et al., 2014).

### *Enrollment*

Acute ischemic stroke patients with large-vessel occlusion admitted at a single comprehensive stroke center, Rigshospitalet, and receiving EVT were screened for eligibility between November 2018 and November 2020. Rigshospitalet covers Eastern Denmark with a population of approximately 2.7 million people. The enrollment process is shown in the Figure 1 including exclusion criteria.



*Figure 1. Enrolment flowchart including exclusion criteria.*

### *Treatment and monitoring*

Patients were diagnosed and treated as per standard-of-care (Heiberg et al., 2024). Large-vessel occlusion was confirmed prior to acute EVT which was performed under general anesthesia (GA) in all enrolled patients without intraarterial vasodilators. Alberta Stroke Program Early Computed Tomography Score (ASPECTS)(Barber et al., 2000) or Posterior circulation-ASPECTS (PC-ASPECTS)(Puetz et al., 2008) were assessed by staff neuroradiologists assisted by RAPID AI software (RRID:SCR\_027023, iSchemaView, Menlo Park, California, USA) and dichotomized to favorable (ASPECTS/PC-ASPECTS  $\geq 8$ ) or unfavorable (ASPECTS/PC-ASPECTS  $< 8$ ). Patients had symptom severity re-assessed using the National Institutes of Health Stroke Scale (NIHSS) upon arrival at the angio-suite immediately prior to EVT. Continuous standard-of-care monitoring including invasive arterial blood pressure (Philips IntelliVue, Philips Medical Systems, Eindhoven, The Netherlands) was performed from arrival to the angio suite until 2 hours after EVT and exported by VSCapture (RRID:SCR\_027024) (Karippacheril & Ho, 2013) with additional NIRS

monitoring (described below). Recanalization grading was determined by the treating interventional neuroradiologist (modified Treatment In Cerebral Infarction, mTICI (Zaidat et al., 2013); Grade 0-2a ranging from unsuccessful reperfusion to reperfusion in less than half of the occluded artery territory; Grade 2b-3 defined as successful reperfusion in more than half of the occluded artery territory or complete reperfusion). Patients were extubated as soon as possible after EVT. Dual-energy computed tomography or magnetic resonance imaging was performed 24 hours after EVT to assess infarction size (ASPECTS/PC-ASPECTS) and detect complications including intracranial hemorrhage and embolization to new vascular territory. Patients underwent stroke work up as per standard-of-care. Stroke etiology classification was performed using the Causative Classification System for Ischemic Stroke (Ay et al., 2007).

#### *Clinical follow-up*

Clinical follow-up was performed 24 hours (+/- 6 hours from end of endovascular reperfusion efforts) and 90 days (+/- 14 days) after EVT, which included NIHSS assessment and functional outcome by the modified Rankin Scale (mRS) and independency (defined as mRS of 0-2). Re-hospitalizations, new vascular events (i.e., recurrent stroke, myocardial infarction, or surgery for peripheral artery disease) and all-cause mortality were recorded at 90 days using the electronic health record system. Patients, who did not attend in-person 90-day follow-up, were interviewed over telephone or by proxy.

#### *NIRS examination*

Patients underwent dynamic cortical hemoglobin concentration measurement with NIRS using a continuous wave-system (Octamon, Artinis Medical Systems, Elst, the Netherlands) with three long-distance channels (35 mm) per hemisphere (Heiberg et al., 2024). Channels covered the prefrontal cortex both in the border zones areas (two channels) supplied by the middle cerebral artery (MCA) and the anterior cerebral arteries (ACA) and in the exclusive ACA territory (one channel)(Koenig et al., 2021). Extracerebral tissue was examined by one short-distance channel per side (10 mm).

#### *Time segment selection*

Steady state time segments of five minutes were selected as recommended by the Cerebrovascular Research Network (Panerai et al., 2023). Therefore, we did not include any data segments within 5 minutes of inducing GA and 2 minutes after the occurrence of substantial changes in anesthetics, opioids, or vasopressors (Llwyd et al., 2022). Data segments with excessive noise were also excluded. We allowed a 10 % variation of recorded vitals within the time segment.

We specified the first time segment (PRE) between the induction of GA and prior to any revascularization attempts. The second time segment (POST) was identified immediately after final reperfusion status was achieved which included abandonment in case of unsuccessful recanalization attempts and before GA termination. The third time segment was defined between GA termination and as late as possible (up to two hours from recanalization) mainly based on avoiding major motion artifacts. Due to missing steady state before recanalization attempts and setup time of invasive blood pressure measurement, the most available time segment during EVT was POST by a wide margin, and patients without valid POST segment data were excluded from analysis. A subset of patients with all available time segments (complete sequential subset) were included for analysis over time.

#### *Data analysis*

Analysis was performed as recommended in TFA guidelines from The Cerebrovascular Research Network (RRID:SCR\_027022)(Panerai et al., 2023). Raw NIRS data was converted to oxygenated hemoglobin (Oxy-Hb) by the modified Beer-Lambert law (Homer2, RRID:SCR\_009586). ABP and Oxy-Hb was corrected for noise by linear interpolation before beat-to-beat averaging and resampling at 10 Hz. Input to TFA was ABP and output was Oxy-Hb from both the ischemic and contralateral hemisphere. The Welch' method was applied which resulted in power spectral density, coherence, gain (amplitude ratio), normalized gain (accounting for different measurement ranges and units) and phase shift calculated in three frequency intervals: High-frequency (HF, 0.2-0.5 Hz), low-frequency (LF 0.07-0.2 Hz) and very low-frequency (VLF, 0.02-0.07 Hz)(Panerai et al., 2023). All data analysis was performed in Matlab (RRID:SCR\_001622).

Gain is usually interpreted as a dCA quantification given by the damping ability of oscillations in ABP relative to oscillations in Oxy-Hb. When gain equals one, dCA is suspected to be fully impaired as ABP oscillations are transferred passively to the cerebral circulation. Vice versa, increasingly intact dCA would result in a progressively lower gain (<1). Phase shift denotes the temporal displacement between signals induced by dCA (Diehl et al., 1995). A decreasing phase shift between ABP and  $V_{MCA}$  is indicative of increasingly impaired dCA (Claassen et al., 2021). When dCA is intact, LFOs in  $V_{MCA}$  precede those in ABP but the relation is conventionally determined as the phase lead by  $V_{MCA}$ , which is a positive number. Meanwhile, LFOs in OxyHb succeeds those in ABP in healthy subjects (Müller & Österreich, 2019; Phillip et al., 2012; Reinhard et al., 2006). In this paper we describe phase shift as negative number when LFOs precede ABP and positive numbers when they occur after ABP.

A common problem in TFA is phase wrap-around of 360 degrees, which we did not observe. However, a minority of single channels did exhibit an accurate 180 degree move from the remaining channels. We suspect this phenomenon could be induced by low amplitudes in the LF and VLF ranges. Therefore, we corrected single channel phase shifts by 180 degrees when other channels were consistent.

Data analysis and statistics was performed by first author unblinded to outcome.

### *Statistics*

Data are described by mean and standard deviation if normally distributed and by median and interquartile range (IQR) for non-normally distributed data. Overall results from TFA were analyzed from the side-to-side difference by appropriate paired tests. The complete sequential subset was analyzed across time segments by multiple comparisons adjusted with false discovery rate as well as side-to-side differences at each time segment.

We fitted linear mixed-effect models in with LF phase shift as outcome, subjects as random effect, and fixed effects comprised of hemisphere and different patient characteristics (e.g., stroke etiology, carotid or intracranial stenosis > 50%, patient age, baseline NIHSS, average ABP, end-tidal

carbon dioxide (ETCO<sub>2</sub>) and favorable ASPECTS/PC-ASPECTS before EVT), treatment (e.g., IVT administered before EVT, recanalization success, time from last-known-well to final recanalization status, immediate 2-hour NIHSS improvement) or 90-day outcome (e.g., NIHSS, mRS, independency, mortality).

For analysis in the complete sequential subset, time segment was added as a fixed effect and interaction between time segment and the fixed effects mentioned above were assessed to determine different progressions over time between groups. Some fixed effects did not meet statistical requirements for sample size in the complete sequential subset and were excluded.

Estimates ( $\beta$ ) are presented with 95% confidence intervals (CI). The level of significance was set at 5%. All statistical analysis was conducted with R Project for Statistical Computing (RRID:SCR\_001905).

## Results

We included 38 patients in the study of which 11 patients were eligible for complete sequential analysis. Baseline information including medical history is presented in Table 1 for all patients and comparative description of patients eligible and ineligible for the complete sequential subset. The complete sequential subset had significantly higher peripheral artery disease in their medical history.

**Table 1. Baseline information and medical history.**

	All patients (n = 38)	Complete sequential subset (n = 11)	Only POST (n = 27)	P-value
Age, mean (SD)	69.6 (13.9)	74.0 (11.0)	67.8 (14.8)	0.334
Female sex, n (%)	13 (34.2)	5 (45.5)	8 (29.6)	0.457
Caucasian ethnicity, n (%)	35 (92.1)	9 (81.8)	26 (96.3)	0.196
Right-handed, n (%)	32 (84.2)	11 (100)	21 (77.8)	0.459
BMI, mean (SD)	26.1 (6.1)	25.5 (5.6)	26.4 (6.4)	0.446
Smoking, n (%)				
Never	12 (31.6)	3 (27.3)	9 (33.3)	1.000
Former	13 (34.2)	6 (54.5)	7 (25.9)	0.136
Current	13 (34.2)	2 (18.2)	11 (40.7)	0.268

Alcohol consumption (units weekly), median	0.5 (0.0; 6.75)	0 (0; 8)	1.0 (0.0; 6.5)	0.959
Physical inactivity#, n (%)	11 (71.1)	2 (18.2)	9 (33.3)	0.452
Medical history, n (%)				
Prior ischemic stroke	5 (13.2)	3 (27.3)	2 (7.4)	0.134
Prior TIA	2 (5.3)	0 (0)	2 (7.4)	1.000
Hypertension	24 (63.2)	9 (81.8)	15 (55.6)	0.160
Diabetes	7 (18.4)	2 (18.2)	5 (18.5)	1.000
Extracranial artery stenosis ≥ 50%	11 (28.9)	5 (45.5)	6 (22.2)	0.238
Ipsilateral	10 (26.3)	5 (45.5)	5 (18.5)	0.116
Contralateral	6 (15.8)	3 (27.3)	3 (11.1)	0.328
Intracranial artery stenosis ≥ 50%	7 (18.4)	3 (27.3)	4 (14.8)	0.390
Atrial fibrillation	17 (44.7)	6 (54.5)	11 (40.7)	0.491
Dyslipidemia	36 (94.7)	9 (81.8)	27 (100)	0.078
Ischemic heart disease	2 (5.3)	1 (9.1)	1 (3.7)	0.512
Valvular heart disease	6 (15.8)	1 (9.1)	5 (18.5)	1.000
Heart failure	4 (10.5)	0 (0)	4 (14.8)	0.557
Peripheral artery disease	3 (7.9)	3 (27.3)	0 (0.0)	0.017
Nephropathy	5 (13.2)	3 (27.3)	2 (7.4)	0.134
Venous thromboembolism	3 (7.9)	1 (9.1)	2 (7.4)	1.000
Disseminated cancer	2 (5.3)	2 (18.2)	0 (0)	0.078

BMI: Body-mass index. TIA: Transient ischemic attack. #: Defined as less than 1 hour weekly.

Index stroke statistics including treatment with thrombolysis and outcome is presented in Table 2 and Table S1. The time from arterial puncture to reperfusion was numerically longer in the complete sequential subset which is expected as all these patients had available steady-state periods. However, the time from last-known-well to reperfusion was not different. Patients in the complete sequential subset had higher ASPECTS/PC-ASPECTS before EVT and 24 hours after EVT, which was not significantly associated with any clinical short-term or long-term outcome.

**Table 2. Index stroke treatment and outcome.**

	All subjects (n = 38)	Complete sequential subset (n = 11)	Only POST (n = 27)	P-value
Ischemic hemisphere, right side, n (%)	20 (52.6)	5 (45.5)	15 (55.6)	0.724

Onset, n (%)				
Wake-up	7 (18.4)	1 (9.1)	6 (22.2)	0.648
Unwitnessed	7 (18.4)	3 (27.3)	4 (14.8)	0.390
Stroke etiology, n (%)				
Large-artery atherosclerosis	15 (39.5)	5 (45.5)	10 (37.0)	0.722
Cardio-aortic embolism	14 (36.8)	3 (27.3)	11 (40.7)	0.488
Other causes (dissection)	3 (7.9)	1 (9.1)	2 (7.4)	1.000
Undetermined causes	6 (15.8)	2 (18.2)	4 (14.8)	1.000
IVT, n (%)	19 (50.0)	5 (45.5)	14 (51.9)	1.000
Occluded artery, n (%)				
ICA	2 (5.3)	1 (9.1)	0 (0.0)	0.501
ICA-top	5 (13.2)	2 (18.2)	3 (11.1)	0.615
ICA-tandem	5 (13.2)	2 (18.2)	3 (11.1)	0.615
M1	23 (60.5)	7 (63.6)	16 (59.3)	1.000
M2	15 (39.5)	5 (45.5)	10 (37.0)	0.722
ACA	4 (10.5)	1 (9.1)	3 (11.1)	1.000
BA	2 (5.3)	1 (9.1)	1 (3.7)	0.501
PCA	3 (7.9)	0 (0.0)	3 (11.1)	0.542
ASPECTS / PC-ASPECTS, median (IQR)				
Before EVT 24-hour	8 (7; 10) 7 (5; 9)	9 (8.5; 10) 8 (7; 9)	8 (7; 10) 6 (4.5; 8)	0.040 0.034
Successful reperfusion (mTICI $\geq$ 2b), n (%)	32 (84.2)	10 (90.9)	22 (81.5)	0.650
Last-known-well to reperfusion in minutes <sup>†</sup>	299 (225; 527)	311 (260; 472)	287 (173; 709)	0.459
NIHSS, median (IQR)				
Before EVT	16.5 (9.5; 22)	14 (7.5; 16)	18 (12.5; 22.5)	0.142
2 hours after EVT	11 (5.5; 13.5)	9 (4.5; 11.5)	12.5 (6; 14)	0.105
24 hours after EVT	6.5 (4; 12)	6 (5; 9)	7 (3.5; 13)	0.508
90-day	2.5 (0; 4)	1 (0; 4)	3 (0.5; 4.5)	0.898
90-day mRS, median (IQR)	3 (2; 4)	2 (2; 4.5)	3 (2; 4)	0.844
90-day independence <sup>¶</sup> , n (%)	21 (55.3)	6 (45.5)	11 (40.7)	0.491
Vascular events <sup>#</sup> , n (%)	3 (7.9)	1 (9.1)	2 (7.4)	1.000
All-cause mortality, n (%)				
90-day	6 (15.8)	2 (18.2)	4 (14.8)	1.000
1 year	7 (18.4)	2 (18.2)	5 (18.5)	1.000

IVT: Intravenous thrombolysis. ICA: Internal carotid artery. M1: First segment of the middle cerebral artery. M2: Second segment of the middle cerebral artery. ACA: Anterior cerebral artery. BA: Basilar artery. PCA: Posterior cerebral artery. ASPECTS: Alberta Stroke Program Early CT Score. PC-ASPECTS: Posterior circulation ASPECTS. EVT: Endovascular treatment. mTICI: Modified treatment in cerebral infarction. <sup>†</sup>: In case of mTICI 0, defined as time of abandoning EVT efforts. <sup>¶</sup>:

*Intracerebral artery dissection or vasospasms.* ¶: Modified Rankin Scale 0-2. #: Defined as recurrent stroke, myocardial infarction, or surgery for peripheral artery disease at 90-day follow-up.

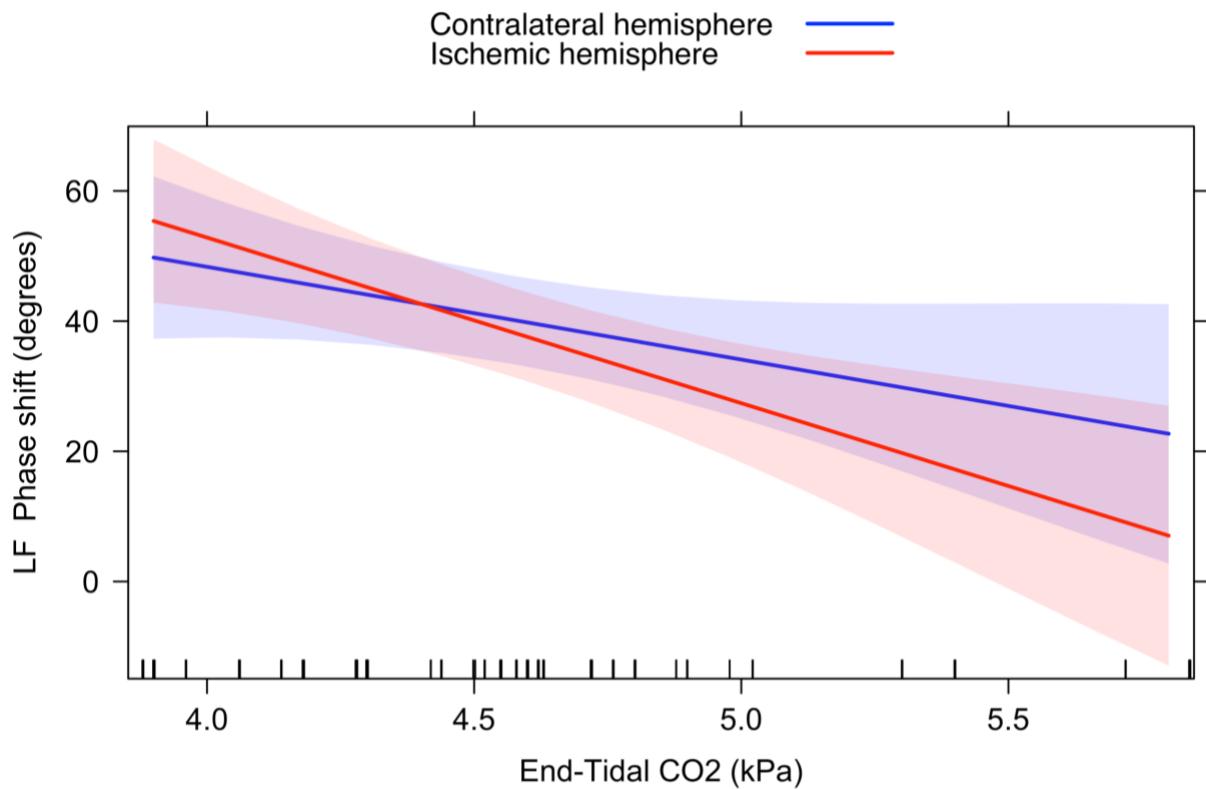
Results from the ABP-OxyHb TFA along with examination time and vitals is presented in Table 3. We found no difference between the hemispheres of any TFA measures. Phase shift for both hemispheres was approximately 40 degrees in the LF range.

**Table 3. Examination time, average vitals and TFA results.**

		Stroke hemisphere (n = 38)	Contralateral hemisphere (n = 38)
Examination time from last-known-well (hours)		5.4 (4.0; 8.9)	
HR (bpm, mean)		63.3 (12.0)	
SpO <sub>2</sub> (%)		100 (99; 100)	
ETCO <sub>2</sub> (kPa, mean)		4.59 (0.45)	
ABP (mmHg)		80.6 (75.8; 87.2)	
ABP PSD (mmHg <sup>2</sup> / Hz)	HF	1.37 (0.91; 4.18)	
	LF	1.07 (0.43; 1.83)	
	VLF	0.66 (0.31; 1.78)	
Average Oxy-Hb (μM*mm)		0.44 (-4.68; 17.82)	-0.02 (-4.84; 16.25)
Oxy-Hb PSD ((μM*mm) <sup>2</sup> / Hz)	HF	0.87 (0.29; 5.39)	2.41 (0.47; 12.80)
	LF	1.06 (0.46; 9.11)	3.12 (1.21; 14.84)
	VLF	2.41 (0.46; 15.02)	9.59 (3.32; 27.05)
Coherence	HF	0.36 (0.22; 0.62)	0.33 (0.22; 0.59)
	LF	0.55 (0.31; 0.82)	0.46 (0.26; 0.78)
	VLF	0.48 (0.24; 0.75)	0.38 (0.20; 0.73)
Normalized Gain (%/%)	HF	0.71 (0.16; 1.74)	0.66 (0.31; 1.93)
	LF	1.16 (0.41; 3.62)	1.38 (0.64; 3.12)
	VLF	1.60 (0.84; 5.35)	2.38 (1.37; 3.47)
Gain (mmHg/mm*mM) *10 <sup>8</sup>	HF	4.87 (3.64; 10.98)	5.50 (4.08; 10.25)
	LF	8.97 (5.82; 20.30)	13.29 (6.10; 25.09)
	VLF	17.29 (9.12; 30.61)	25.05 (11.33; 33.37)
Phase shift (mean, degrees)	HF	23.6 (57.0)	14.1 (57.4)
	LF	39.3 (22.1)	40.4 (20.4)
	VLF	17.2 (22.7)	11.5 (30.3)

HR: Heart rate. SpO<sub>2</sub>: Peripheral hemoglobin saturation. ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>. ABP: Arterial blood pressure. PSD: Power spectral density. Oxy-Hb: Oxygenated hemoglobin. No significant side-to-side differences.

Accounting for patient age in linear mixed-effects model showed an interaction with hemisphere ( $p=0.006$ ). Thus, LF phase shift increased with increasing age in the ischemic, but not the contralateral hemisphere. ETCO<sub>2</sub> also interacted with hemisphere ( $p=0.015$ , Figure 2), so that LF phase shift decreased with increasing ETCO<sub>2</sub> in the ischemic hemisphere ( $\beta: -26.7$ , CI: -40.8; -12.6,  $p<0.001$ ) but not in the contralateral hemisphere ( $\beta: -14.6$ , CI: -29.7; 0.5,  $p=0.058$ ). ETCO<sub>2</sub> decreased linearly with age (-0.01 kPa per year, CI: -0.02; -0.01,  $p<0.001$ ); combining both ETCO<sub>2</sub> and age in the same model resulted in preserved hemisphere interaction with ETCO<sub>2</sub> ( $p=0.012$ ) but with no certainty concerning hemisphere interaction with age ( $p=0.050$ ).



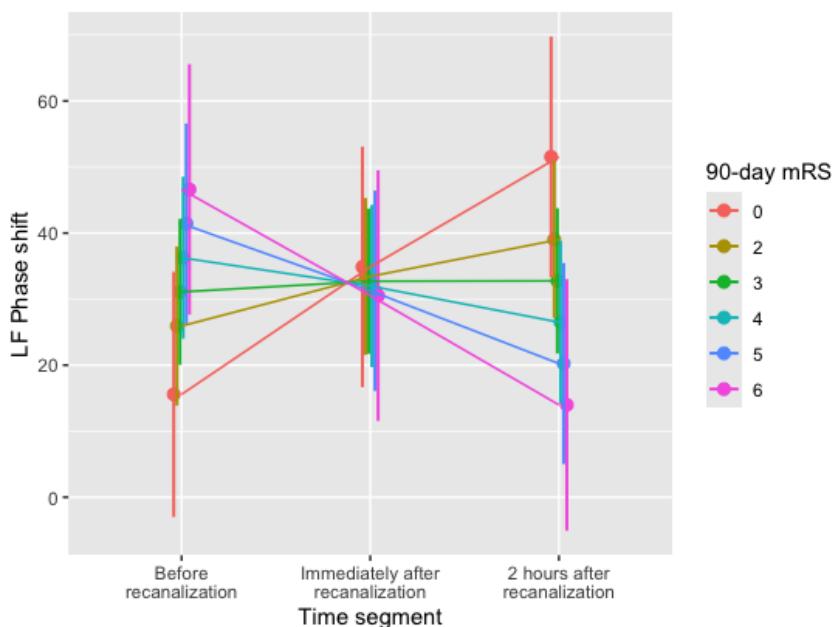
*Figure 2. Interaction between ETCO<sub>2</sub> and hemisphere on LF phase shift with accounting for patient age immediately after recanalization. The slope of the ischemic hemisphere is greater than in the contralateral hemisphere.*

LF phase shift of ABP-OxyHb was independent of stroke etiology, carotid or intracranial stenosis > 50%, favorable ASPECTS/PC-ASPECTS before EVT ( $\geq 8$ ), NIHSS before EVT, IVT administered before

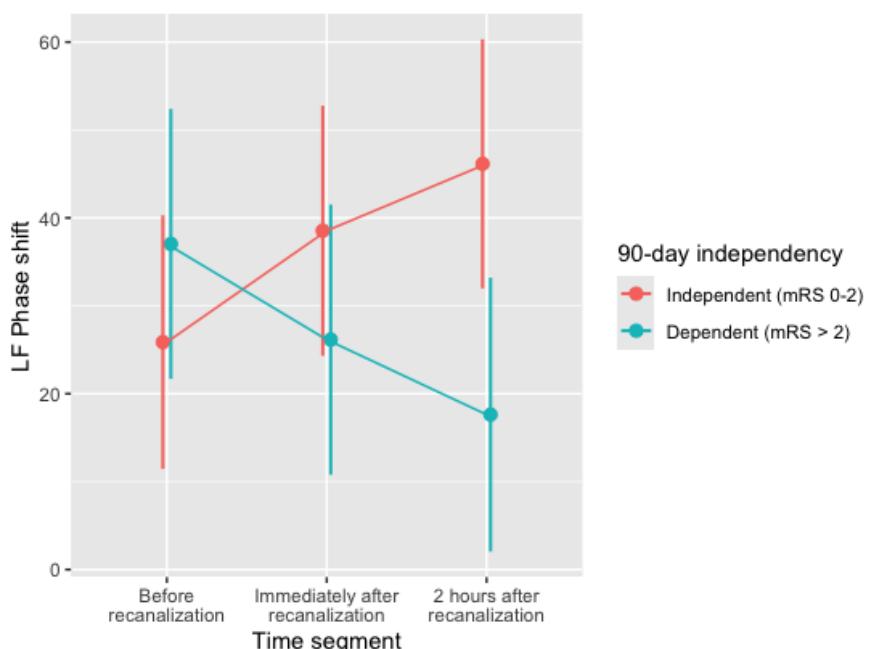
EVT, recanalization success, time from last-known-well to recanalization, treatment with antihypertensive medication, average ABP, and all 90-day outcomes including NIHSS, mRS, independency and mortality (Table S2). We found no interaction between any of the fixed effects and hemisphere.

TFA results based on the complete sequential subset is presented in Table S3. Heart rate and ABP increased after GA at the 2-hour time segment. Contrary to measurements during EVT, normalized gain showed interhemispheric difference in all frequency ranges at the 2-hour segment. Non-normalized gain increased numerically after recanalization and significantly at the 2-hour segment in the contralateral hemisphere. Our data showed no other complete sequential changes.

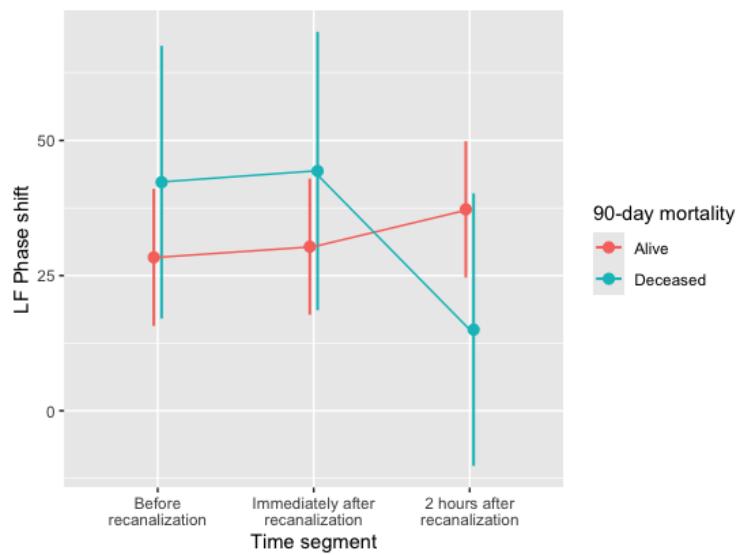
Complete sequential mixed-effect models of phase shift (Table S4) showed that time segment interacted with 90-day functional outcome measured both as categorical mRS ( $p=0.011$ , Figure 3), independency ( $p=0.030$ , figure 4) and mortality ( $p=0.019$ , figure 5). Thus, in patients with better 90-day mRS, LF phase shift was lower before recanalization and increased immediately after recanalization and at the 2-hour segment, while phase shift decreased over time in patients with higher 90-day mRS. Similar profiles were observed when dichotomizing mRS to independency or mortality. The trend was equal in both hemispheres as there were no interaction between time segment, hemisphere, and 90-day outcome.



*Figure 3. Interaction effect between 90-day modified Rankin scale and time segment on LF phase shift in the complete sequential subset. Patients with low mRS had progressive increase in phase shift whereas increasing mRS gradually inverted the progression.*



*Figure 4. Interaction effect between 90-day independency (mRS 0-2) and time segment on LF phase shift in the complete sequential subset. Independent patients exhibited progressive increase in phase shift while the inverse progression was seen in patients with dependency.*



*Figure 5. Interaction effect between 90-day mortality and time segment on LF phase shift in the complete sequential subset. Phase shift increased between recanalization and 2-hour segment in patients alive at 90-day follow-up while the inverse is seen in deceased patients.*

There was no effect of age, stroke etiology, stenosis > 50%, baseline NIHSS, time from last-known-well to recanalization, nor average ABP in the complete sequential models. We had insufficient sampling to investigate recanalization success, favorable ASPECTS/PC-ASPECTS before EVT ( $\geq 8$ ), ETCO<sub>2</sub>, antihypertensive treatment, and 90-day NIHSS. No other interaction effects were observed between fixed effects and time segment or hemisphere.

## Discussion

The current study displays the feasibility of examining dCA during EVT with NIRS in the conventional TFA setup between ABP and cerebral circulation ( $V_{MCA}$ , OxyHb). We observed no difference in dCA between hemispheres at any point in time during or after EVT. However, immediately after recanalization, dCA as measured by phase shift displayed an increased sensitivity to ETCO<sub>2</sub> changes in the ischemic hemisphere compared to the contralateral hemisphere, suggesting increased susceptibility to perturbation of cerebral blood flow with changes in ventilation.

In the complete sequential subset, we found an interaction between time segments and 90-day functional outcome including mortality. Thus, LF phase shift increased over time in patients with

good outcome, suggesting progressive stabilization of dCA, and decreased in patients with poor outcome, suggesting progressive impairment of dCA.

The focus of this study was the phase shift between ABP and OxyHb in the LF range. Gain was previously examined by interhemispheric TFA using NIRS as both input and output and produced more stable results with less variation (Heiberg et al., 2024). Unlike gain, there is no unilateral measure of phase shift when performing interhemispheric TFA. Likewise, ABP and OxyHb oscillations in the VLF range examine another interesting aspect of dCA but require longer time segments with steady-state data (Panerai et al., 2023) which was not as available in this clinical setting.

LFOs in cerebral circulation are usually examined by TCD, which has consistently shown a phase lead of  $V_{MCA}$  compared to ABP in both healthy subjects and stroke patients (Intharakham et al., 2019; Panerai et al., 2023). However, stroke patients with impaired dCA have a reduced phase lead of  $V_{MCA}$  indicating a more passive transfer of LFOs from the systemic perfusion into the cerebral circulation (Diehl et al., 1995). Conversely, OxyHb LFOs in healthy subjects follow those in ABP which has been interpreted as transit time from large vessels to the cerebral microvasculature (Müller & Österreich, 2019; Phillip et al., 2012; Reinhard et al., 2006). Spontaneous and respiratory enhanced LFOs have been estimated at 15-24 degrees in rather narrow frequency ranges (0.09-0.11 and 0.06-0.12 Hz). Parameter setting including frequency ranges explain most of the variance between TFA results from corresponding cohorts and equal settings would be preferable in comparisons between cohorts (Meel-van den Abeelen et al., 2014). Müller et al. applied a wider-ranging frequency spectrum (0.07-0.15 Hz) that better resembles the white paper guidelines and the current study (0.07-0.2 Hz) and reported a higher phase lead of 55 degrees (Müller & Österreich, 2019).

The effect of impaired dCA on ABP-OxyHb is not yet established. Presuming the relationship between  $V_{MCA}$  and OxyHb remains the same, LF phase shift of ABP-OxyHb would be expected to increase with dCA impairment. However, disruption of the  $V_{MCA}$ -OxyHb phase shift was shown despite unaltered ABP-OxyHb phase shift in carotid stenosis patients compared to healthy subjects

(Reinhard et al., 2006). Some extent of phase shift would be expected between ABP and OxyHb with intact dCA and decreasing phase shift could also be an indication of reduced autoregulatory mechanisms following the reasoning by Diehl et al (Diehl et al., 1995). The understanding of decreasing LF ABP-OxyHb phase shift with impaired dCA would seem to fit well when comparing our results to findings by Müller et al (Müller & Österreich, 2019). The observed effect of decreasing phase shift with increasing ETCO<sub>2</sub> also supports this interpretation of dCA impairment as the influence of hypercapnia has been reported in numerous studies (Johnson et al., 2025; Minhas et al., 2018; Panerai et al., 1999).

$V_{MCA}$  estimates the indirect upstream effect of dCA whereas OxyHb measures cortical hemoglobin concentration mostly in the arterial vascular compartment and could offer a more direct dCA assessment. However, as OxyHb from the capillary bed and venous compartment cannot be separated from the arterial compartment and ABP-OxyHb LF phase shift could therefore be affected by microvascular shunts as well as the venous outflow as well (Müller et al., 2020). Therefore, the relation between  $V_{MCA}$ , ABP and OxyHb require further investigations which should include the venous outflow to better guide the interpretation of NIRS-based dCA assessment.

The interpretation of our results is complicated by the possible dCA effect from anesthesia and vasopressor medications. Both propofol and sevoflurane can affect dCA but only at doses much higher than applied during EVT at our center (Claassen et al., 2021; Slupe & Kirsch, 2018). The two patients in our cohort receiving sevoflurane had similar phase shifts compared to the remaining patients (data not shown). Adding remifentanil to propofol does not affect dCA (Engelhard et al., 2001). Neither norepinephrine (Lingzhong Meng et al., 2024) nor phenylephrine (L. Meng et al., 2024) affects dCA in healthy subjects. However, the effect of the applied anesthetics, opioids and vasopressors have not been examined in acute ischemic stroke patients. In the current cohort we did not observe any difference between any dCA measures when such medications were discontinued after GA.

Previous studies of dCA in stroke patients with large-vessel occlusions have been based on TCD and only after recanalization therapy. Consistent findings across studies show impaired dCA in the

ischemic hemisphere compared to healthy subjects, while most studies also show some extent of dCA impairment in the contralateral hemisphere (Tian et al., 2020). Several TFA studies found a reduction in ABP-V<sub>MCA</sub> phase lead bilaterally, but less pronounced in the contralateral hemisphere (Castro, Serrador, et al., 2017; Ran et al., 2024; Sheriff et al., 2020; Tian et al., 2020). As the current study showed no interhemispheric difference in dCA at earlier stages, we suspect that partial remission of dCA impairment after recanalization occurs earlier in the contralateral hemisphere after recanalization which could be consistent with our previous findings showing increased interhemispheric phase shift after 24 hours (Heiberg et al., 2024).

We observed an increasing phase shift and dCA change with age in the ischemic hemisphere, but this was largely explained by decreasing levels of ETCO<sub>2</sub> with patient age. Elderly subjects are expected to have less compensatory reserve due to increasing levels of endothelial dysfunction, cerebral small-vessel disease and arterial stiffness (Beishon et al., 2021). Increasing dCA with patient age would therefore have been quite surprising and contradictory to previous studies (Beishon et al., 2021; Phillip et al., 2012) which includes conventional ABP-V<sub>MCA</sub> setups (Madureira et al., 2017; Maxwell et al., 2022) that found no effect of ageing.

Meanwhile, hypercapnia would be expected to influence dCA in both hemispheres based on previous studies of healthy subjects (Johnson et al., 2025; Minhas et al., 2018; Panerai et al., 1999). The increased sensitivity to ETCO<sub>2</sub> in the ischemic hemispheres could be an indication of dCA impairment as cerebral blood flow under such circumstances would be more dependent on other regulation mechanisms. Other unexposed confounders or effect modifiers including ICP (Czosnyka et al., 2005) could also be involved.

Numerous studies have associated LF phase shift in the ischemic hemisphere of acute stroke patients to long-term functional outcome (Nogueira et al., 2022). We did not observe this association immediately after recanalization, but the complete sequential analysis offers a potential explanation for this discrepancy. Patients with good long-term outcome (low mRS) had lower phase shift before recanalization which increase immediately after recanalization and 2-hour post-procedure, while the trend gradually reverted with increasing mRS. Although the complete

sequential analysis was based on a limited number of patients, the trend was remarkably consistent across mRS categories. All mRS categories intersected immediately after recanalization making it impossible to associate long-term mRS to LF phase shift at that time segment. Categorizing mRS to functional independency or mortality showed a similar trend although with different intersection points. Improvement in dCA would be expected in patient with better functional outcome (Nogueira et al., 2021) and could suggest that the observed increase in ABP-OxyHb LF phase shift indicates dCA restoration. Changes in dCA during and shortly after EVT could have clinical implications that need further investigations. Promising results have been shown when personalizing blood pressure limits with dCA after EVT (Petersen et al., 2020; Zhang et al., 2024) and a randomized trial is ongoing (ClinicalTrials.gov: NCT05670028). Similar studies before and during EVT could be performed using NIRS.

### **Limitations**

The current study was performed in a challenging clinical setting which merit some limitations. EVT is a time-sensitive treatment that leaves no opportunity for unnecessary delays. Thus, 20% of patients examined with NIRS were excluded due to missing continuous ABP monitoring during EVT because further attempts to place of arterial line would have delayed the procedure. Further, many patients had to be excluded because of missing steady state periods especially from the complete sequential subset. Reasons for this included recanalization attempts occurring quickly after inducing GA, and postoperative agitation due to confusion or aphasia limiting the availability of non-noisy time segments.

Another substantial limitation of this study is that we have not examined healthy controls subjects which constrains our interpretation of possible dCA impairment. Due to ethical concerns, we refrained from pursuing dCA examinations under GA. Performing dCA examinations on healthy subjects during non-vascular surgery (e.g., orthopedic) was considered but invasive ABP is often not included as standard-of-care monitoring in such settings (Nguyen & Bora, 2025). Further, such patients could perhaps be affected by pain sensation, blood loss and would need to exclude patients developing postoperative cognitive dysfunction or delirium (Chuan et al.; Longhitano et al.). While dCA examinations performed during wakefulness would also have been a possibility, an

arterial line catheter as used here for ABP measurement would be unpleasant for healthy participants. Alternatively, dCA based on non-invasive and invasive ABP measurements can be compared directly when applying certain corrections (Petersen et al., 2014) but not without considerable reliability concerns (Olsen et al., 2022; Panerai et al., 2023). Applying  $V_{MCA}$  measurements after EVT would also have been interesting and could possibly confirm the presented results.

Using NIRS is also restricted by other limitations. Spatial depth is limited to the superficial cortex impeding dCA investigations of deeper cortical and subcortical regions (Quaresima & Ferrari, 2019). While regional dCA differences in the superficial cortex can be investigated using multi-channel NIRS, we found no evidence of this in the prefrontal cortex during preliminary analysis. Further, no prevalent method has been able to filter extracerebral signals from intracerebral signals creating uncertainty concerning the extent of extracerebral contamination (Eleveld et al., 2023). To account for this issue, we performed a second TFA based on short-distance channels examining the extracerebral tissues and applied the results as a regressor in the mixed-effect models. Exploring the exact intracerebral sensitivity using this method is beyond the scope of this study.

In conclusion, NIRS can be applied during EVT to examine dCA. In our study there was no difference between dCA of the ischemic and contralateral hemisphere at any time point. However, the sensitivity of dCA to  $ETCO_2$  was increased in the ischemic hemisphere. We found dCA changes during and 2 hours after EVT with increasing phase shift in patients with good long-term functional outcome and decreasing phase shift in patients with poor outcome. Further investigations are warranted to compare the reported dCA assessment to the conventional approach based on TCD in both healthy subjects and in stroke patients. Individualizing blood pressure thresholds during EVT in patients with dCA changes based on NIRS seems plausible and could be beneficial for their clinical outcome.

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## Additional information

### Data availability statement

The processing code is open source available at <https://openfnirs.org/software/homer/> for preprocessing and at <https://www.car-net.org/tools> for TFA. NIRS data segments can be provided upon reasonable request. Individual patient data are identifiable, and availability requires approval of both centers as well as local ethics committees. All data requests can be made by contacting the corresponding author.

### Competing interest

All authors state that there are no competing interests.

### Author contributions

A.V.H. and H.K.I. conceived and designed the study while T.C.T., H.G.B., G.B., C.S., and H.W.S. contributed. A.V.H. acquired most of the data with substantial contributions from T.G.L. as well as T.C.T., H.G.B., G.B., C.S. and K.H. A.V.H. performed data processing and analysis with contributions from T.G.L. and H.K.I. All authors participated in the interpretation of results. A.V.H. drafted the article. All authors revised the article critically and approved the final version. All persons

qualifying for authorship was designated as authors and have agreed to be accountable for all aspects of the work and resolve of questions related to the integrity or accuracy of the study.

## Funding

The study was supported by Simon Fougner Hartmanns Family Foundation, Gangsted Foundation, Sophus Jacobsen Foundation and Rigshospitalet's Research Foundation.

## Supporting information

**Table S1.** Additional detail of index stroke treatment and outcome.

**Table S2.** Linear mixed-effect models of LF ABP-OxyHb phase shift immediately after recanalization.

**Table S3.** Complete sequential analysis of average vitals and TFA results.

**Table S4.** Linear mixed-effect models of LF ABP-OxyHb phase shift in complete sequential analysis.

## **Supporting information**

### **Title**

Bilateral dynamic cerebral autoregulation assessment during endovascular treatment in large-vessel occlusion stroke

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**Table S1. Additional detail of index stroke treatment and outcome.**

	All subjects (n = 38)	Complete sequential subset (n = 11)	Only POST (n = 27)	P-value
Procedure, n (%)				
Aspiration only	11 (28.9)	2 (18.2)	9 (33.3)	0.452
Stent-retrieving and aspiration	27 (71.1)	9 (81.8)	18 (66.7)	0.452
PTA	6 (15.8)	3 (27.3)	3 (11.1)	0.329
Carotid stenting	2 (5.3)	2 (18.2)	0 (0)	0.078
Anesthetics, n (%)				
Propofol	36 (94.7)	11 (100)	25 (92.6)	1.000
Sevoflurane	2 (5.3)	0 (0)	2 (7.4)	1.000
Vasopressor, n (%)				
Phenylephrine	22 (57.9)	7 (63.6)	15 (55.6)	0.729
Norepinephrine	3 (7.9)	0 (0)	3 (11.1)	0.542
Combination of Phenylephrine and Norepinephrine	13 (34.2)	4 (36.4)	9 (33.3)	1.000
Favorable ASPECTS/PC-ASPECTS before EVT ( $\geq 8$ ), n (%)	27 (71.1)	11 (100)	16 (59.3)	0.016
Process times (minutes), median (IQR)				
Last-known-well to imaging	142 (91; 411)	155 (90; 316)	140 (91; 552)	0.949
Imaging to artery puncture	92 (54; 103)	95 (74; 111)	69 (51; 103)	0.274
Artery puncture to reperfusion <sup>†</sup>	41 (19; 69)	67 (35; 77)	30 (17; 60)	0.062
Complications, n (%)				
New territory embolization	5 (13.2)	1 (9.1)	4 (11.1)	1.000
Intracranial hemorrhage	4 (10.5)	2 (18.2)	2 (7.4)	0.564
Other complications <sup>§</sup>	2 (5.3)	0 (0)	2 (7.4)	1.000
Modified Rankin Scale, median (IQR)				
Before index stroke	0 (0;1)	1 (0;1)	0 (0;0)	0.078
Increase at 90 days	2 (1; 3)	2 (0.5;3.5)	3 (1; 3)	0.395
Re-hospitalized within 90 days, n (%)	15 (39.5)	7 (63.6)	8 (29.6)	0.073

PTA: Percutaneous Transluminal Angioplasty. ASPECTS: Alberta Stroke Program Early CT Score. PC-ASPECTS: Posterior circulation ASPECTS. EVT: Endovascular treatment. mTICI: Modified treatment in cerebral infarction. <sup>†</sup>: In case of mTICI 0, defined as time of abandoning EVT efforts. <sup>§</sup>: Intracerebral artery dissection or significant groin hematoma. <sup>¶</sup>: Modified Rankin Scale 0-2. #: Defined as recurrent stroke, myocardial infarction, or surgery for peripheral artery disease at 90-day FU.

**Table S2. Linear mixed-effect models of LF ABP-OxyHb phase shift immediately after recanalization.**

Fixed effect <sup>§</sup>	Hemisphere x fixed effect interaction	Intercept	Fixed effect estimate	Hemisphere estimate <i>Index: CH</i>	SS estimate	Model fit
Hemisphere <i>Index: CH</i>	-	39.1 (CI: 30.7; 47.4)	-	-1.9 (CI: -6.2; 2.4, T(34)=-0.91, p=0.368)	0.0 (CI: -0.1; 0.2, T(34)=0.61, p=0.544)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 614.6
90-day mRS (continuous)	F(1,33)=2.04, p=0.163	39.3 (CI: 24.8; 53.8)	-0.1 (CI: -4.0; 4.0, T(35)=-0.04, p=0.966)	-1.9 (CI: -6.2; 2.4, T(34)=-0.91, p=0.368)	0.0 (CI: -0.1; 0.2, T(34)=0.62, p=0.540)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 613.5
90-day independency (mRS < 3) <i>Index: Independent</i>	F(1,33)=0.02, p=0.880	39.6 (CI: 28.4; 50.8)	Dependent: -1.1 (CI: -15.1; 13.0, T(35)=-0.15, p=0.878)	-1.9 (CI: -6.2; 2.4, T(34)=-0.92, p=0.366)	0.0 (CI: -0.1; 0.2, T(34)=-0.64, p=0.530)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 610.9
90-day mortality <i>Index: Alive</i>	F(1,33)=1.33, p=0.257	38.2 (CI: 29.0; 47.4)	4.3 (CI: -14.5; 23.1, T(35)=0.46, p=0.648)	-2.0 (CI: -6.2; 2.3, T(34)=-0.93, p=0.360)	0.0 (CI: -0.1; 0.2, T(34)=-0.68, p=0.502)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 610.9
Trichotomized baseline NIHSS <i>Index: mild (0-10)</i>	F(2,32)=0.89, p=0.421	37.5 (CI: 22.5; 52.5)	Moderate (11-19): 2.4 (CI: -15.6; 20.3, T(34)= 0.27, p=0.788)  Severe (>19): 1.7 (CI: -16.8; 20.1,	-1.9 (CI: -6.2; 2.4, T(34)=-0.92, p=0.36)	0.0 (CI: -0.1; 0.2, T(34)=0.62, p=0.540)	Marginal R2: 0.01 Conditional R2: 0.84 AIC: 606.6

			T(34)=0.19, p=0.854)			
Baseline NIHSS (continuous)	F(1,33)=3.51, p=0.070	37.4 (CI: 19.4; 55.4)	0.1 (CI: -1.3; 1.4, T(35)=0.21, p=0.833)	-1.9 (CI: -6.2; 2.4, T(34)=-0.92, p=0.367)	0.0 (CI: -0.1; 0.2, T(34)=0.62, p=0.540)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 616.1
90-day categorized NIHSS  <i>Index: Mild (0-1)</i>	F(3,31)=2.16, p=0.113	42.5 (CI: 29.8; 55.1)	Moderate (2-5): - 9.8 (CI: -26.7; 7.0, T(33)=-1.19, p=0.244)  Severe (>5): -2.0 (CI: -23.0; 19.1, T(33)=-0.19, p=0.851)  Dead: 0.0 (CI: - 20.9; 20.9, T(33)= 0.00, p=0.999)	-1.9 (CI: -6.2; 2.4, T(34)=-0.91, p=0.370)	0.0 (CI: -0.1; 0.2, T(34)=0.63, p=0.533)	Marginal R2: 0.05 Conditional R2: 0.84 AIC: 600.2
CCS  <i>Index: LAA</i>	F(2,29)=1.06, p=0.360	42.0 (CI: 30.0; 54.1)	CE: -3.4 (CI: -19.3; 12.6, T(31)=-0.43, p=0.669)  Other: Too few observations.  Undetermined: - 9.7 (CI: -30.2; 10.8, T(31)=-0.97, p=0.340)	0.4 (CI: -3.5; 4.3, T(31)=0.20, p=0.845)	0.0 (CI: -0.1; 0.1, T(31)=0.22, p=0.827)	Marginal R2: 0.03 Conditional R2: 0.88 AIC: 544.3

Carotid or intracranial stenosis (>50%) <i>Index: no stenosis</i>	F(1,32)=0.10, p=0.749	39.0 (CI: 30.4; 47.6)	Stenosis: 0.4 (CI: -7.8; 8.7, T(33)=0.11, p=0.914)	-2.0 (CI: -6.6; 2.6, T(33)=-0.88, p=0.384)	0.0 (CI: -0.1; 0.2, T(33)= 0.61, p=0.549)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 611.9
Favorable ASPECTS before EVT <i>Index: Favorable</i>	F(1,33)=0.24, p=0.630	38.0 (CI: 28.2; 47.8)	Unfavorable: 3.1 (CI: -12.0; 18.2, T(35)=0.41, p=0.681)	-1.9 (CI: -6.2; 2.3, T(34)=-0.92, p=0.362)	0.0 (CI: -0.1; 0.2, T(34)=0.66, p=0.513)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 610.6
Age (continuous) Age x IH: 0.4 (CI: 0.1; 0.7, T(33)=2.94, p=0.006)	F(1,33)=8.64, p=0.006	37.3 (CI: 0.1; 74.5)	0.0 (CI: -0.5; 0.5, T(35)=0.06, p=0.951)	-30.1 (CI: -50.0; -10.2, T(33)=-3.08, p=0.004)	0.1 (CI: -0.1; 0.2, T(33)=0.95, p=0.351)	Marginal R2: 0.05 Conditional R2: 0.87 AIC: 613.1
Recanalization <i>Index: Successful</i>	F(1,33)=0.00, p=0.990	44.6 (CI: 27.3; 61.9)	Unsuccesful: -6.8 (CI: -25.4; 11.8, T(35)=-0.74, p=0.464)	-2.0 (CI: -6.2; 2.3, T(34)=-0.93, p=0.359)	0.0 (CI: -0.1; 0.2, T(34)=0.69, p=0.496)	Marginal R2: 0.02 Conditional R2: 0.83 AIC: 609.8
IVT <i>Index: No IVT</i>	F(1,33)= 1.23, p=0.276	35.2 (CI: 23.9; 46.5)	IVT: 7.0 (CI: -6.7; 20.7, T(35)=1.04, p=0.306)	-2.0 (CI: -6.2; 2.3, T(34)=-0.93, p=0.357)	0.0 (CI: -0.1; 0.2, T(34)=0.74, p=0.462)	Marginal R2: 0.03 Conditional R2: 0.84 AIC: 609.9
Time from LKW to recanalization (continuous, hours)	F(1,34)=0.16, p=0.693	40.7 (CI: 31.4; 50.1)	-0.3 (CI: -0.9; 0.4, T(35)=-0.84, p=0.409)	-2.0 (CI: -6.3; 2.3, T(34)=-0.96, p=0.343)	0.1 (CI: -0.1; 0.2, T(34)=0.83, p=0.413)	Marginal R2: 0.02 Conditional R2: 0.83 AIC: 616.3

Treatment with antihypertensive medication  Index: No antihypertensiva	F(1,33)=0.05, p=0.834	37.4 (CI: 24.7; 50.2)	2.5 (CI: -12.2; 17.2, T(35)=0.34, p=0.733)	-1.9 (CI: -6.2; 2.4, T(34)=-0.91, p=0.370)	0.0 (CI: -0.1; 0.2, T(34)=0.58, p=0.563)	Marginal R2: 0.01 Conditional R2: 0.83 AIC: 610.7
Average ABP (continuous, mmHg)	F(1,33)=1.39, p=0.247	67.9 (CI: 9.4; 126.4)	-0.4 (-1.1; 0.4, T(35)=-1.01, p=0.319)	-2.0 (CI: -6.2; 2.4, T(34)=-0.91, p=0.368)	0.0 (CI: -0.1; 0.2, T(34)=0.61, p=0.543)	Marginal R2: 0.03 Conditional R2: 0.83 AIC: 615.8
Average ETCO <sub>2</sub> (continuous, kPa)  ETCO <sub>2</sub> x IH: -11.2 (CI: -20.1; -2.3, T(32)=-2.57, p=0.015)	F(1,32)=6.59, p=0.015	102.8 (CI: 35.6; 170.0)	-13.8 (CI: -28.3; 0.6, T(34)=-1.94, p=0.060)	49.3 (CI: 8.4; 90.3, T(32)=2.45, p=0.020)	0.0 (CI: -0.1; 0.1, T(32)=0.30, p=0.767)	Marginal R2: 0.19 Conditional R2: 0.85 AIC: 578.5
Age and ETCO <sub>2</sub>	ETCO <sub>2</sub> x hemisphere: F(1,30)=7.11, p=0.012  Age x hemisphere: F(1,30)=4.18, p=0.050  ETCO <sub>2</sub> x age: F(1,32)=0.43, p=0.516	107.2 (CI: 15.5; 198.8)	ETCO <sub>2</sub> : -14.2 (CI: -30.0; 1.5, T(33)=-1.84, p=0.075)  Age: -0.0 (CI: -0.5; 0.5, T(33)=-0.15, p=0.883)	49.3 (8.4; 90.2, T(32)=2.45, p=0.020)	0.0 (CI: -0.1; 0.1, T(32)=0.31, p=0.758)	Marginal R2: 0.19 Conditional R2: 0.85 AIC: 581.5

§: Subjects were applied as random effect and hemisphere as fixed effect in combination with other fixed effects. CH: Contralateral hemisphere, SS: Short-separation channel TFA regressor, AIC: Akaike information criterion, mRS: Modified Rankin scale, NIHSS: National

*Institutes of Health Stroke Scale, CCS: Causative Classification System for Ischemic Stroke, LAA: Large Artery Atherosclerosis, CE: Cardiac Emboli Sources, ASPECTS: Alberta Stroke Program Early CT Score, IH: Ischemic hemisphere. IVT: Intravenous thrombolysis. LKW: last-known-well. ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>.*

**Table S3. Complete sequential analysis of average vitals and TFA results.**

		PRE (IQR) (n = 11)	POST (IQR) (n = 11)	2-hour (IQR) (n = 11)
Examination time <sup>§</sup>		4.4 (3.4; 7.0)	5.6 (4.5; 7.9)	6.5 (6.0; 9.2)
HR (bpm, mean)		63.9 (16.2)	63.7 (7.3)	<b>75.1 (20.3)<sup>‡</sup></b>
SpO <sub>2</sub> (%)		99.6 (97.5; 100)	100 (99.2; 100)	99.6 (96.9; 100)
ETCO <sub>2</sub> (kPa)		4.46 (0.41)	4.48 (0.48)	N/A
ABP (mmHg)		79.6 (73.5; 82.1)	77.0 (75.2; 86.1)	<b>97.0 (88.0; 105.5) #<sup>‡</sup></b>
ABP PSD (mmHg <sup>2</sup> / Hz)	HF	2.0 (0.9; 8.7)	1.7 (1.3; 3.8)	9.8 (5.8; 12.6)
	LF	1.1 (0.4; 5.6)	1.1 (0.4; 1.9)	7.0 (4.9; 15.1)
	VLF	2.6 (0.5; 7.1)	0.4 (0.3; 0.9)	5.0 (3.4; 6.1)
Hemisphere		Ischemic	Contralateral	Ischemic
Oxy-Hb (μM*mm)		-2.6 (-17.6; 18.6)	9.1 (-4.7; 11.6)	12.5 (-0.2; 38.4)
	HF	1.0 (0.4; 2.5)	1.5 (0.7; 4.4)	0.3 (0.2; 4.0)
Oxy-Hb PSD ((μM*mm) <sup>2</sup> / Hz)	LF	2.3 (0.2; 6.7)	7.2 (1.9; 28.3)	0.6 (0.3; 3.5)
	VLF	3.4 (1.1; 6.6)	7.8 (3.8; 12.3)	1.6 (0.2; 3.3)
	HF	1.0 (0.4; 2.5)	1.5 (0.7; 4.4)	0.8 (0.4; 2.7)
Coherence	LF	2.3 (0.2; 6.7)	7.2 (1.9; 28.3)	2.4 (1.3; 3.2)
	VLF	3.4 (1.1; 6.6)	7.8 (3.8; 12.3)	8.5 (5.6; 14.0)
	HF	0.5 (0.3; 0.7)	0.5 (0.3; 0.7)	0.3 (0.2; 0.6)
Normalized Gain (%/%)	LF	0.7 (0.3; 0.9)	0.8 (0.3; 0.9)	0.5 (0.2; 0.9)
	VLF	0.6 (0.2; 0.8)	0.6 (0.1; 0.8)	0.4 (0.1; 0.8)
	HF	0.5 (0.3; 1.0)	0.6 (0.5; 0.7)	0.3 (0.1; 1.1)
Gain (mmHg/mm*mM)	LF	1.0 (0.5; 2.1)	1.3 (0.9; 1.8)	0.5 (0.3; 1.1)
*10 <sup>8</sup>	VLF	1.0 (0.7; 2.3)	1.5 (0.9; 1.6)	1.4 (0.2; 3.3)
	HF	8.3 (3.5; 13.2)	4.0 (2.1; 14.6)	9.1 (4.0; 13.0)
	LF	14.8 (5.5; 18.8)	6.3 (2.9; 15.4) <sup>‡</sup>	5.5 (3.5; 12.0)
	VLF	22.5 (13.4; 28.4)	9.5 (6.3; 18.1) <sup>‡</sup>	8.3 (6.4; 13.8)
Phase shift (mean, degrees)	HF	23.2 (31.7)	9.4 (14.2)	34.7 (21.8)
	LF	45.1 (74.7)	20.2 (33.2)	32.7 (25.7)
	VLF	34.7 (21.8)	29.6 (14.8)	20.4 (69.8)
	HF	32.6 (72.2)	16.8 (66.2)	32.6 (23.3)
	LF	31.1 (67.8)	34.6 (25.9)	32.6 (23.3)
	VLF	33.7 (27.9)	22.9 (33.3)	19.3 (34.8)
	HF	11.6 (28.7)	22.9 (33.3)	22.9 (33.3)
	LF	33.7 (27.9)	19.3 (34.8)	19.3 (34.8)
	VLF	32.6 (23.3)	22.9 (33.3)	22.9 (33.3)

§: From Last-known-well (hours). HR: Heart rate. SpO<sub>2</sub>: Peripheral hemoglobin saturation. ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>. ABP: Arterial blood pressure. PSD: Power spectral density. Oxy-Hb: Oxygenated hemoglobin. \* Significant side difference, adjusted p < 0.05. #: Difference between PRE and POST segments, adjusted p < 0.05. #: Difference between POST and 2-HOUR segments, p < 0.05. ‡: Difference between PRE and 2-HOUR, adjusted p < 0.05.

**Table S4. Linear mixed-effect models of LF ABP-OxyHb phase shift in complete sequential analysis.**

Fixed effect <sup>§</sup>	Time segment x fixed effect interaction	Time segment x hemisphere x fixed effect interaction	Intercept	Fixed effect estimate	Time segment estimate <i>Index: PRE</i>	Hemisphere estimate <i>Index: CH</i>	SS estimate	Model fit
Hemisphere <i>Index: CH</i>	-	F(2,49)=0.30, p=0.746	34.7 (CI: 22.3; 47.2)	-	POST: 2.1 (- 10.4; 14.6, T(51)=0.34, p=0.736)  2-HOUR: 2.6 (CI: -10.0; 15.2, T(51)=0.41, p=0.681)	1.4 (CI: -8.8; 11.6, T(51)=0.28, p=0.784)	-0.1 (-0.2; 0.0, T(51)= 1.50, p=0.139)	Marginal R2: 0.03 Condition al R2: 0.22 AIC: 588.4
90-day mRS (continuous)	F(2,44)=8.87, p<0.001  POST x 90- day mRS: - 5.9 (CI: - 11.4; -0.4, T(49)=-2.17, p=0.035)  2-HOUR x 90-day mRS: -11.4 (CI: - 16.8; -6.0,	F(2,44)=1.13, p=0.332	19.7 (CI: 1.2; 38.6)	5.2 (CI: -0.7; 11.0, T(9)=2.01, p=0.076)	POST: 19.3 (CI: -0.1; 38.7, T(49)=2.00, p=0.051)  2-HOUR: 36.0 (CI: 16.7, 55.2, T(49)=3.75, p<0.001)	1.4 (CI: -7.5; 10.4, T(49)=0.33, p=0.746)	-0.1 (CI: - 0.2; 0.0, T(49)=-1.75, p=0.087)	Marginal R2: 0.20 Condition al R2: 0.43 AIC: 567.6

	T(49)=-4.26, p<0.001)							
90-day independency (mRS < 3)  <i>Index:</i> <i>Independent</i>	F(2,44)=5.93, p=0.005  POST x 90- day dependent: - 23.6 (CI: - 46.3; -0.8, T(49)=-2.08, p=0.043)  2-HOUR x 90-day dependent: - 39.7 (CI: - 62.4; -16.9, T(49)=-3.50, p=0.001)	F(2,44)=0.56, p=0.575	29.0 (CI: 14.4; 43.7)	Dependent: 11.2 (CI: -12.1; 34.4, T(9)=1.09, p=0.305)	POST: 12.7 (CI: -2.7; 28.1, T(49)=1.65, p=0.105)  2-HOUR: 20.3 (CI: 4.8; 35.7, T(49)=2.64, p=0.011)	1.2 (CI: -8.0; 10.5, T(49)=0.27, p=0.789)	-0.1 (CI: - 0.2; 0.0, T(49)=-1.25, p=0.219)	Marginal R2: 0.20 Condition al R2: 0.38 AIC: 562.3
90-day mortality  <i>Index: Alive</i>	F(2,44)=3.43, p=0.041  POST x 90- day fatality: 0.1 (CI: - 31.2; 31.4, T(49)=0.01, p=0.995)	F(2,44)=0.30, p=0.739	31.7 (CI: 18.2; 45.1)	Deceased: 13.9 (CI: -17.7; 45.5, T(9)=1.00, p=0.345)	POST: 2.0 (CI: - 11.2; 15.2, T(49)=0.30, p=0.765)  2-HOUR: 8.9 (CI: -4.4; 22.2, T(49)=1.34, p=0.186)	1.3 (CI: -8.4; 11.0, T(49)=0.26, p=0.793)	-0.1 (CI: - 0.2; 0.0, T(49)=-1.24, p=0.220)	Marginal R2: 01.2 Condition al R2: 0.33 AIC: 622.1

	2-HOUR x 90-day fatal outcome: - 36.2 (CI: - 66.8; -5.5, T(49)=-2.36, p=0.022)							
Trichotomized baseline NIHSS <i>Index: mild (0-10)</i>	F(2,34)=0.12, p=0.888	F(2,34)=0.50, p=0.610	26.7 (CI: 8.3; 45.1)	Moderate (11-20): 3.3 (CI: -20.9; 27.4, T(7)=0.32, p=0.757) Severe (>20): too few observations	POST: 2.8 (CI: -10.6; 16.3, T(41)=0.43, p=0.671) 2-HOUR: 8.7 (CI: -4.8; 22.2, T(41)=1.30, p=0.200)	1.6 (CI: -9.3; 12.6, T(41)=0.30, p=0.765)	-0.0 (-0.2; 0.1, T(41)=-0.72, p=0.476)	Marginal R2: 0.03 Conditional R2: 0.33 AIC: 472.1
CCS <i>Index: LAA</i>	F(2,29)=0.18, p=0.833	F(2,29)=0.36, p=0.670	35.1 (CI: 17.3; 52.8)	CE: -8.2 (CI: -36.0; 19.5, T(6)=-0.73, p=0.495) Other and Undetermined: Too few observations	POST: -1.8 (CI: -16.1; 12.5, T(36)=-0.25, p=0.801) 2-HOUR: 4.4 (CI: -9.9; 18.7, T(36)=0.63, p=0.535)	2.3 (CI: -9.4; 13.9, T(36)=0.40, p=0.695)	-0.0 (-0.2; 0.1, T(36)=-0.61, p=0.545)	Marginal R2: 0.05 Conditional R2: 0.35 AIC: 417.1
Carotid or intracranial stenosis (>50%) <i>Index: No stenosis</i>	F(2,43)=1.79, p=0.179	F(2,43)=0.69, p=0.505	32.6 (CI: 19.8; 45.3)	Stenosis: 9.5 (CI: -5.0; 23.9, T(48)=1.31, p=0.195)	POST: 2.2 (CI: -10.2; 14.6, T(50)=0.36, p=0.724) 2-HOUR: 2.8 (CI: -9.8; 15.4,	-1.9 (CI: -13.3; 9.4, T(50)=-0.34, p=0.733)	-0.1 (-0.2; 0.0, T(48)=-1.71, p=0.094)	Marginal R2: 0.07 Conditional R2: 0.24 AIC: 582.9

					T(50)=0.45, p=0.653)			
Age (continuous)	F(2,44)=0.57, p=0.570	F(2,44)=0.49, p=0.615	28.6 (CI: - 31.1; 88.2)	0.1 (CI: -0.8; 1.0, T(9)=0.21, p=0.839)	POST: 2.1 (CI: - 10.4; 14.6, T(51)=0.34, p=0.738)  2-HOUR: 2.6 (CI: -10.1, 15.2, T(51)=0.41, p=0.686)	1.4 (CI: -8.8; 11.6, T(51)=0.27, p=0.787)	-0.1 (CI: - 0.2; 0.0, T(51)=-1.45, p=0.153)	Marginal R2: 0.03 Condition al R2: 0.24 AIC: 590.4
Time from LKW to recanalization (continuous, hours)	F(2,44)=0.44, p=0.649	F(2,44)=0.15, p=0.859	34.1 (CI: 14.7; 53.5)	0.1 (CI: -2.5; 2.7, T(9)=0.07, p=0.944)	POST: 2.1 (CI: - 10.4; 14.6, T(51)=0.34, p=0.737)  2-HOUR: 2.6 (CI: -10.1, 15.2, T(51)=0.41, p=0.686)	1.4 (CI: -8.8; 11.6, T(51)=0.27, p=0.786)	-0.1 (CI: - 0.2; 0.0, T(51)=-1.43, p=0.158)	Marginal R2: 0.03 Condition al R2: 0.24 AIC: 588.3
Average ABP (continuous, mmHg)	F(2,43)=1.69, p=0.197	F(2,43)=0.02, p=0.980	-1.0 (CI: - 40.6; 38.6)	0.4 (CI: -0.0; 0.9, T(50)=1.90, p=0.063)	POST: 2.1 (CI: - 10.1; 14.2, T(50)=0.34, p=0.734)  2-HOUR: -5.1 (CI: -19.9, 9.7, T(50)=-0.69, p=0.491)	1.4 (CI: -8.5; 11.4, T(50)= 0.28, p=0.778)	-0.1 (CI: - 0.2; 0.0, T(50)=-1.55, p=0.127)	Marginal R2: 0.10 Condition al R2: 0.28 AIC: 587.9

*§: Subjects were applied as random effect and hemisphere as fixed effect in combination with other fixed effects. CH: Contralateral hemisphere, SS: Short-separation channel TFA regressor, AIC: Akaike information criterion, mRS: Modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, CCS: Causative Classification System for Ischemic Stroke, LAA: Large Artery Atherosclerosis, CE: Cardiac Emboli Sources, ASPECTS: Alberta Stroke Program Early CT Score, LKW: last-known-well.*

## **Study III: Cortical hemodynamic response during cognitive Stroop test in acute stroke patients assessed by fNIRS**

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Published in NeuroRehabilitation, 2023. 52(2): p. 199-217.

# Cortical hemodynamic response during cognitive Stroop test in acute stroke patients assessed by fNIRS

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Received 21 July 2022

Accepted 12 December 2022

## Abstract.

**BACKGROUND:** Following acute ischemic stroke (AIS) many patients experience cognitive impairment which interferes neurorehabilitation. Understanding and monitoring pathophysiologic processes behind cognitive symptoms requires accessible methods during testing and training. Functional near-infrared spectroscopy (fNIRS) can assess activational hemodynamic responses in the prefrontal cortex (PFC) and feasibly be used as a biomarker to support stroke rehabilitation.

**OBJECTIVE:** Exploring the feasibility of fNIRS as a biomarker during the Stroop Color and Word Test (SCWT) assessing executive function in AIS patients.

**METHODS:** Observational study of 21 patients with mild to moderate AIS and 22 healthy age- and sex-matched controls (HC) examined with fNIRS of PFC during the SCWT. Hemodynamic responses were analyzed with general linear modeling.

**RESULTS:** The SCWT was performed worse by AIS patients than HC. Neither patients nor HC showed PFC activation, but an inverse activation pattern primarily in superolateral and superomedial PFC significantly lower in AIS. Hemodynamic responses were incoherent to test difficulty and performance. No other group differences or lateralization were found.

**CONCLUSIONS:** AIS patients had impaired executive function assessed by the SCWT, while both groups showed an inverse hemodynamic response significantly larger in HC. Investigations assessing the physiology behind inverse hemodynamic responses are warranted before deeming clinical implementation reasonable.

Keywords: Acute stroke, hemodynamics, near-infrared spectroscopy, stroop test, executive function, cognitive impairment

## 1. Introduction

Ischemic stroke is one the major causes of death and disability across the world (Krishnamurthi, Ikeda, & Feigin, 2020; Tsao et al., 2022) and a main cause of acquired neurologic deficits including cognitive symptoms (e.g., impaired memory, language, attention, or executive function). While

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not as apparent, cognitive symptoms can be equally impairing as other stroke sequelae (Mellon et al., 2015; Tatemichi et al., 1994). Cognitive impairment (CI) is highly prevalent in both the acute (around 75%) (Blackburn, Bafadhel, Randall, & Harkness, 2013; Demeyere et al., 2016; Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009) and chronic stages (up to 53%) (Barbay, Diouf, Roussel, & Godefroy, 2018) of the disease, while around 25% of stroke patients with CI progresses to dementia (Sachdev et al., 2009). Furthermore, independent associations to long-term functional outcome and mortality have been shown (Obaid, Flach, Marshall, C, & Douiri, 2020; Zietemann et al., 2018). CI often interferes with rehabilitation of other stroke symptoms emphasizing the importance to diagnose and treat CI. Understanding and possibly monitoring the pathophysiology during rehabilitation efforts would therefore be highly beneficial specifically during actual testing and training.

The most frequently used tests to assess CI in stroke rehabilitation are multi-domain screening tools such as Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) (Saa et al., 2019). Another widely performed examination focusing on executive function is the Stroop Color and Word Test (SCWT) (Stroop, 1935). The SCWT challenges patients' ability to distinguish descriptive color words (e.g., red, green, blue) from font color of the text by way of inhibition and selective attention, while also testing attention retention and processing speed (MacLeod, 1991). The Stroop effect (interference) is the prolonged response time and increased error percentage between descriptive color words written in congruent text color and descriptive color words written in incongruent text color.

The prefrontal cortex (PFC) is the main area activated during the SCWT according to both lesional studies (Demakis, 2004; Gläscher et al., 2012) and functional examinations using magnetic resonance imaging (MRI) and positron emission tomography (Hung, Gaillard, Yarmak, & Arsalidou, 2018; Nee, Wager, & Jonides, 2007; Xu, Xu, & Yang, 2016) as well as near-infrared spectroscopy (NIRS) (Ehlis, Herrmann, Wagener, & Fallgatter, 2005; Lague-Beauvais, Brunet, Gagnon, Lesage, & Bherer, 2013; Leon-Carrion et al., 2008; Matthias L. Schroeter, Zysset, Kruggel, & von Cramon, 2003). Activated subregions in the PFC mainly include the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Lateralization of activation has not been well established but seems to depend partly on the

test response being verbal or non-verbal (Xu et al., 2016). Other brain regions also seem to be involved during SCWT including the supplementary motor area, thalamus and cerebellum (Ravnkilde, Videbech, Rosenberg, Gjedde, & Gade, 2002) coherent with stroke studies showing reduced performance regardless of frontal lobe or non-frontal lesion (Leskelä et al., 1999) as well as cerebellar lesions (Shin, Park, & Shin, 2017). While the exact anatomical lesion of ischemic stroke is a central component in developing cognitive impairment, the accumulation of small vessel disease seems equally important (Nannoni et al., 2022; Zhi et al., 2021). Small vessel disease could possibly explain why cognitive decline often precedes the ischemic stroke by several years (Heshmatollah et al., 2021) and partially why accounting for age is important in lesional SCWT studies (Cipolotti et al., 2015).

NIRS non-invasively examines the dynamic concentration of oxygenated (Oxy-Hb) and deoxygenated (Deoxy-Hb) hemoglobin in superficial parts of the cerebral cortex. Infrared light passing through tissue is partially absorbed by several chromophores, but the degree of light passing through only changes significantly with hemoglobin changes. The hemodynamic increment due to activation far exceeds the increased consumption giving way to the activational pattern of increased Oxy-Hb and decreased Deoxy-Hb. Such patterns during SCWTs have been witnessed in healthy young and elderly people as well as in several clinical conditions such as migraine (Schytz, Ciftci, Akin, Ashina, & Bolay, 2010), cerebral microangiopathy (M. L. Schroeter, Cutini, Wahl, Scheid, & Yves von Cramon, 2007), depression (Ikeda, Shiozaki, Ikeda, Suzuki, & Hirayasu, 2013) and partially in traumatic brain injury (Plenger et al., 2016). While the spatial resolution of NIRS is quite limited compared to imaging modalities such as PET or MRI, the promise in neurorehabilitation settings is immense due to excellent temporal resolution, accessible equipment and easily performed examinations that can be performed by anyone with almost no physical restrictions.

The functional hemodynamic response during the SCWT have never been examined with fNIRS in stroke patients and the aim of this study was to explore hemodynamic responses of subacute stroke patients from an everyday cohort with fNIRS. We hypothesized that stroke patients had an impaired hemodynamic response reflective of their performance in the SCWT amplified with higher degrees of small vessel disease.

## 2. Material and methods

### 2.1. Design

This was a sub-study of a prospective observational study conducted at the Stroke Unit, Department of Neurology, Rigshospitalet, which is described elsewhere ([clinicaltrials.gov: NCT02111408](#)). Subjects in this sub-study were enrolled from April 2016 to September 2016 after written informed consent. The study was approved by The Regional Ethics Committee in The Capital Region of Denmark on September 29, 2015 (H-2-2013-091), the Danish Data-Protecting Agency (GLO-2013-18; IT suite nr. 02385) and in accordance with the Declaration of Helsinki of 1964 and its later amendments. We report in compliance with STROBE guidelines for observational studies (von Elm et al., 2007).

### 2.2. Participants

Patients were enrolled during weekdays after being diagnosed clinically with stroke following computed tomography (CT) or magnetic resonance imaging (MRI) to exclude patients with intracranial hemorrhage. Patients were excluded if they did not have the ability to consent, had other significant brain disease, short remaining life-expectancy (months), could not perform the SCWT due to colorblindness or other deficits. Patients were only included if the complete NIRS examination and all other procedures in main study could be performed within 7 days of their index stroke.

A group of healthy sex- and age-matched control subjects (HC) were recruited and examined with NIRS after the same protocol as stroke patients. Only diseases relevant for cerebrovascular disease were viewed as exclusion criteria (diagnosed or initiated treatment of atherosclerotic disease, hypertension, hypercholesterolemia, diabetes, etc.), while diseases in non-relevant organs were allowed (allergies, skin disease, osteoporosis, etc.).

### 2.3. Examinations

Patients received standard-of-care stroke treatment and examinations during admission including patient history (current and former diagnosed or treated diseases, medications, physical activity, consumption of alcohol and tobacco), neurological examination, blood pressure, body mass index (BMI), CT or MRI of the brain, chest x-ray, ECG, carotid ultrasound

and/or CT-angiography, routine blood samples, and at least 48-hour cardiac telemetry. Selected patients also underwent echocardiography and extended blood examination when deemed appropriate.

Outside of the standard examinations, patients underwent the following examinations and classifications:

- Index stroke classified according to the Causative Classification of Stroke system (CCS) (Ay et al., 2007).
- Stroke severity according to the National Institute of Health Stroke Scale (NIHSS).
- Functional status according to the modified Rankin Scale (mRS).
- Cerebral magnetic resonance imaging (MRI) with a Siemens Avanto 1.5 tesla scanner with a standard protocol including sagital T2, axial T2, axial fluid attenuation inversion recovery, 3D T1, susceptibility weighted imaging and diffusion weighted imaging. Total small-vessel disease score (SVD) from 0–4 was rated by the presence of non-acute lacuna, white matter hyperintensities (Fazekas score 2–3), microbleeds and enlarged perivascular spaces (Staals, Makin, Doubal, Dennis, & Wardlaw, 2014). Stroke patients were subcategorized by hemispherical location of infarction (left and right) and by SVD (none (0) and moderate-severe (2–4)). Images were assessed by a neuroradiologist. Patients with MRI-negative stroke or contraindications to MRI, were classified according to location based on their clinical presentation. Patients with contraindication to MRI were not SVD scored and excluded from sub-group analysis.
- Cognition assessed by the Montreal Cognitive Assessment (MoCA) and the trail making test (TMT). Cognitive impairment was defined as a total MoCA score <25 (Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012), TMT-A > 78 seconds or TMT-B > 273 seconds (Ciolek & Lee, 2020). Compound CI was defined as CI in either MoCA, TMT-A or TMT-B.
- Near-infrared spectroscopy during the SCWT (described below).

### 2.4. The stroop color and word test

Participants were placed comfortably and upright positioned in a chair in a silent room with dimmed lights. A 15.4-inch laptop computer placed approximately 70 cm from the participants eyes was then

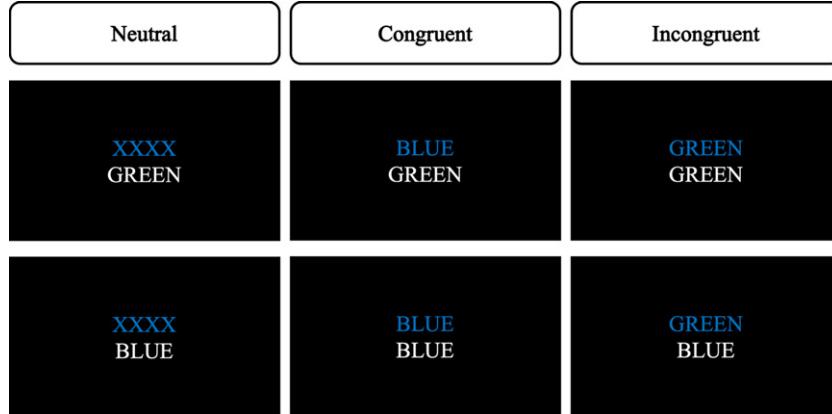


Fig. 1. The Stroop Color and Word Test applied with screengrabs showing incorrect (top row) and correct stimuli (bottom row).

presented showing only a white crosshair on black background for a resting period of five min. Before performing the Stroop task, participants received instructions and did a trial block of each degree of difficulty.

The SWCT was constructed in a block design with three degrees of difficulty (Fig. 1): Neutral, congruent (text and descriptive color-word matching) and incongruent (text and descriptive color-word not matching). Each block was composed by 6 consecutive stimuli of the same degree of difficulty. Stimuli was constituted by two words displayed on separate rows on the black background screen. The top row was written in colored letters whereas the bottom row was written in white letters. The bottom row either correctly or incorrectly denoted the color of the letters in the top row, which participants were instructed to assess by clicking either the left mouse button in the case of correct denotation or right mouse button in case of incorrect denotation (Fig. 1). Participants were asked to answer as quickly and accurately as possible. The maximum response time of five seconds was increased from original test (Schytz et al., 2010) to fit the cognitive abilities of the current cohort. Distribution of correct and incorrect stimuli was 50% of each across the entire test. The top row was presented 100 milliseconds before the bottom row to maintain focus on the colored letters (MacLeod, 1991). In neutral blocks the top row letters were XXXX in contrast to the other blocks that either congruently or incongruently wrote a color-word (GREEN, YELLOW, BLUE, or RED) with the colored letters (Fig. 1).

The inter-block period was 15 seconds minus the response time from the last stimulus from the former block creating varying inter-stimulus periods as recommended (Herold, Wiegel, Scholkmann, & Müller,

2018). During the inter-block period the laptop again presented the crosshair. The order of blocks was the same for every participant with 5 blocks for each degree of difficulty.

## 2.5. NIRS examination

Relative changes in Oxy-Hb and Deoxy-Hb were measured with using continuous wave NIRS (CW6, TechEn Inc., Milford, Massachusetts, USA) at a sampling rate of 200 Hz. Infrared light sources of two wavelengths (690 nm and 830 nm) were placed laterally and medially on each side of the forehead with detectors distanced 3.5 cm in between the light sources together comprising a rhomb over each pre-frontal cortex while carefully avoiding the midline sinus. Sensitivity mapping of the probe configuration on the average head size in the current cohort (Fig. 2) was generated in AtlasViewer (Aasted et al., 2015). Channels were named accordingly (superomedial, superolateral, inferomedial and inferolateral PFC). To enable short-separation regression by filtering out extracerebral signals and thus increasing brain sensitivity, four detector optodes were placed in close proximity to the light sources (eight mm). Both light sources and detectors were arranged in an elastic band tightened firmly around the participants head to avoid movement of optodes and ensure the best possible signal.

## 2.6. Data analysis

Data was preprocessed using the HOMER3 toolbox (Huppert, Diamond, Franceschini, & Boas, 2009) in MATLAB R2018b (Mathworks, Massachusetts, USA). Channels were pruned automatically with a

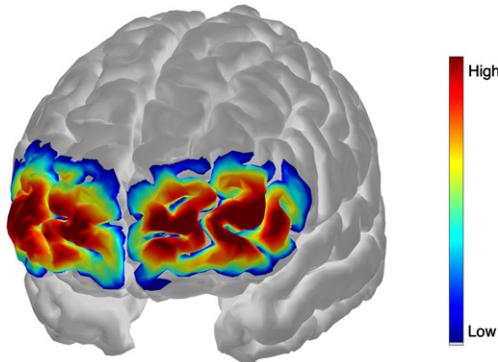


Fig. 2. Sensitivity map of participant with head size average to all participants.

signal-to-noise threshold of five (enPruneChannels function) and manually thorough visual quality control. Raw intensity signals were downsampled to 20 Hz before conversion to optical density (hmriIntensity2OD function). Motion artefacts (MA) was then detected channel by channel with a standard deviation threshold of 10 (within tMotion = 0.5 seconds and marking the neighboring period as MA, tMask = 1 seconds), which fitted most accurately to investigators visual assessment of MA across all subjects. Both Spline interpolation ( $p=0.99$ ), targeted principal component analysis (tPCA, nSV = 0.97 and maximum iterations of 5) and wavelet transformation (iqr = 1.5) was employed separately and compared. No smoothing filters were applied. Correlation-Based Signal Improvement-method was disregarded beforehand as it relies on the assumption of a constant relationship between Oxy-Hb and Deoxy-Hb, which is not always met under cerebral pathology as in the current study population (Obrig & Steinbrink, 2011). Hybrid methods of more than one MA correction were deemed too invasive. After correction MA detection was processed once again to assess efficiency of correction methods and to reject any stimuli in the vicinity of the remaining MA (-2 to 15 seconds). MA correction with tPCA resulted in the fewest stimuli rejections and was chosen going forward. All subjects had at least 3 blocks of each stimulus. Targeted PCA performs a principal component analysis in the areas defined as MA and thus ignores the most extreme signal outliers. Optical density was then converted to concentrations of oxygenated (Oxy-Hb) and deoxygenated (Deoxy-Hb) hemoglobin with partial pathlength factor of 1 to indicate the uncertainty of travelled light distance and instead report hemoglobin changes in units of micro-

molar x mm. Lastly, the general linear model (GLM) was calculated using the hmrDeconvHRF\_DriftSS function with a time frame of -2 to 20 seconds around stimulus start. The function applies short-separation regression using the channel with the greatest correlation and a 3rd order polynomial drift correction. The temporal basis function was a consecutive sequence of Gaussian functions defined by a width of 1.5 seconds and temporal spacing of 1.5 seconds to give the GLM temporal flexibility without giving outlying responses excessive influence. The least squares method was used to solve the GLM (Barker, Aarabi, & Huppert, 2013).

Hemodynamic response function (HRF) was then exported to MATLAB and analyzed individually channel by channel. Peak was defined as maximum increase or decrease from baseline with the corresponding time from stimulus onset defining time-to-peak and the average slope was calculated as ratio between peak and time-to-peak.

To examine the hemodynamic Stroop effect, the difference between the parameters of hemodynamic response (peak, average slope) from incongruent and congruent stimuli (I-C) was analyzed. Lateralization was assessed by the difference in peak during incongruent stimuli between contralateral channels.

## 2.7. Statistical analysis

Power calculations based on results from the most comparable study (M. L. Schroeter et al., 2005) revealed that a sample size of 40 participants would be sufficient to show group differences in almost every PFC channel.

Categorical data are reported as numbers and percentages. Continuous data of non-normal distribution are reported as median and interquartile range (IQR) and as mean and standard deviation (SD) in case of normal distribution. Group differences were tested with Fisher's exact test or Chi-square test for categorical data and Welch unpaired *t*-test for normally distributed continuous data. In cases of ordinal or non-normal continuous data the Wilcoxon-Mann-Whitney test or Kruskal-Wallis test was applied depending on the number of independent variables. Associations were assessed by Spearman's rank rho correlation when data was non-normally distributed.

All statistical analyses were performed using RStudio version 1.4.1106 (Boston, MA, USA). Overall statistical significance level of 0.05 was chosen with Bonferroni correction for multiple comparisons by the number of channels for fNIRS data.

Table 1  
Subject characteristics at enrollment

	Stroke patients (n = 21)	HC (n = 22)	P-value
Age, median (IQR)	64 (57–71)	64.5 (58.5–69)	0.862 <sup>†</sup>
Female sex, n (%)	11 (52.4)	12 (54.5)	1.000 <sup>‡</sup>
Caucasian ethnicity, n (%)	21 (100)	21 (100)	1.000 <sup>‡</sup>
Right-handed, n (%)	16 (76.2)	18 (81.8)	0.721 <sup>‡</sup>
BMI, median (IQR)	26.8 (23.7–29.0)	25.1 (22.2–26.3)	<b>0.032*</b>
Daily physical activity (0 = never, 1 = few times a year, 2 = few times a month, 3 = once a week, 4 = few times per week, 5 = daily), median (IQR)	2 (0–4)	4 (3.25–5)	<b>0.007<sup>¶*</sup></b>
Smoking			
Currently, n (%)	10 (47.6)	3 (13.7)	
Previously, n (%)	8 (38.1)	7 (31.8)	<b>0.010<sup>#*</sup></b>
Never, n (%)	3 (14.3)	12 (54.5)	
Smoking years, median (IQR)	25.5 (6–42)	0 (0–11.2)	<b>0.003*</b>
Weekly alcohol consumption, median units (IQR)	2 (0–10)	7 (1.25–13.75)	0.393

<sup>†</sup> Welch unpaired t-test. <sup>‡</sup> Fisher's exact test. <sup>#</sup> Chi-square test. <sup>¶</sup> Kruskal-Wallis test. Wilcoxon Mann-Whitney test. \*Significant difference with statistical level of 0.05.

### 3. Results

#### 3.1. Baseline characteristics

The baseline characteristics of both stroke patients and HC disclosed no significant group differences concerning age and sex (Table 1). Patients showed higher BMI, less physical activity and more smoking than the HC group.

The stroke patients' disease characteristics concerning medical history and index stroke are presented in Table 2. Patients experienced mild to moderate stroke symptoms according to NIHSS and mRS at enrollment and most patients had hemispherical infarction in either MCA or PCA territory with a slight shift towards left hemispherical infarction (57.1%). All patients were examined median 4 days, IQR 3–5 days after their index stroke. CCS etiology classification showed most patients experienced their stroke due to small-artery occlusion. Stroke patients were dichotomized to almost equal groups with SVD scores of 0 (47.4%) and 2–4 (42.1%). Only 4 patients (19.0%) were treated with rTPA. Incidence of cognitive impairment (Table 3) ranged from 9.5% to 23.8% depending on the test, while accumulated impairment across cognitive tests was higher (38.1%).

#### 3.2. Stroop task performance

Stroke patients had longer response time and higher error percentage in all stimuli conditions except during neutral stimuli (Table 4).

The SCWT was successful in showing the Stroop effect with greater response time and error percentage in the incongruent tasks. While the congruent tasks were significantly harder than the neutral tasks for all subjects regarding response time, the error percentage did not increase.

Performance in Stroop task with stroke patients dichotomized to a SVD score of  $\geq 2$  or 0 are displayed in Table 5. Patients with higher SVD burden performed equally to stroke patients without small vessel disease.

#### 3.3. Activational hemodynamic response

Peak values of all channels and chromophores of stroke patients and HC are shown in Table 6. Stroke patient tended towards activation in right inferomedial PFC during congruent stimuli as opposed to HC, but no channel exhibited the classic activational pattern on the group level. However, superolateral PFC channels in both hemispheres show significant increase in Deoxy-Hb especially for congruent and incongruent stimuli in healthy subjects. Stroke patients showed a corresponding response, which did not reach significance level after Bonferroni correction. Healthy subjects exhibited a similar pattern in superomedial channels. Mean Oxy-Hb peaks in the corresponding channels were negative values though not significantly differing from zero.

The average slope values of stroke patients and HC (Table 7) showed that stroke patients exhibited classic activation pattern in the right inferomedial PFC

Table 2  
Stroke patient's disease characteristics at enrollment

Medical history, n (%)	
Prior stroke	4 (19.0)
Prior TIA	1 (4.8)
Hypertension	11 (52.4)
Dyslipidemia	16 (69.2)
Diabetes	3 (14.3)
Ischemic heart disease	3 (14.3)
Atrial fibrillation	1 (4.8)
Valvular heart disease	2 (9.5)
Carotid artery disease	3 (14.3)
Symptomatic hemisphere, left, n (%)	12 (57.1)
Infarction location, n (%)	
ACA territory	0 (0)
MCA territory	14 (66.7)
PCA territory	4 (19.0)
Brainstem	3 (14.3)
Cerebellum	0 (0)
Stroke etiology (CCS), n (%)	
Large artery atherosclerosis	2 (9.5)
Cardioaortic embolism	2 (9.5)
Small-artery occlusion	11 (52.4)
Other causes	1 (4.8)
Undetermined	5 (23.8)
Small vessel disease score, n (%)	
0	19 (90.5)
1	9 (47.4)
2	2 (10.5)
3	3 (15.8)
4	3 (15.8)
	2 (10.5)
Treatment with intravenous rTPA, n (%)	4 (19.0)
Day of examination from index stroke, median (IQR)	4 (3–5)
NIHSS, median (IQR)	2 (1–5)
Modified Rankin Scale, median (IQR)	2 (1–3)

TIA: Transient Ischemic Attack. ACA: Anterior cerebral artery. MCA: Middle cerebral artery. PCA: Posterior cerebral artery. CCS: The Causative Classification of Stroke system. rTPA: Recombinant tissue plasminogen activator. NIHSS: National Institutes of Health Stroke Scale.

Table 3  
Stroke patient's cognitive performance

MoCA	
Total score, median (IQR)	26 (25–27)
CI, n (%)	5 (23.8)
TMT-A	
Time (s), median (IQR)	49 (40–62)
CI, n (%)	3 (14.3)
TMT-B	
Time (s), median (IQR)	119 (97–152)
CI, n (%)	2 (9.5)
Compound CI across tests, n (%)	8 (38.1)

MoCA: Montreal Cognitive Assessment. TMT: Trail Making Test (part A and B). CI: Cognitive impairment.

channels during congruent stimuli, while no other channel in any groups or conditions did. The pattern from Table 6 was otherwise largely repeated.

Spearman's rank correlations showed no associations between hemoglobin peaks and response time

during congruent and incongruent stimuli (Table 8) outside of a positive association in left inferolateral PFC between Deoxy-Hb and response time during congruent stimuli, but only in stroke patients.

#### 3.4. Group comparisons of activational response

The increase in Deoxy-Hb peak values was significantly less in stroke patients than HC especially in right superomedial PFC during neutral and congruent stimuli and in right inferomedial PFC during neutral stimuli, while the same tendency did not reach significance level after Bonferroni correction in right superolateral and left superomedial PFC during neutral stimuli.

Average Deoxy-Hb slope were lower for stroke patients than HC in right superolateral channels during neutral stimuli, but not significantly so in more difficult conditions. No other group differences

Table 4  
Stroop task performance for stroke patients and HC

	Stroke (n = 21)	HC (n = 22)	P-value
Response time, mean (SD)			
Neutral	1.39 (0.35)	1.22 (0.27)	0.073
Congruent	1.58 (0.35)	1.37 (0.28)	0.046
Incongruent	1.85 (0.38)	1.52 (0.38)	0.009
<i>P</i> -value, response time			
NS vs. CS	<0.001	<0.001	
NS vs. IS	<0.001	<0.001	
CS vs. IS	<0.001	0.002	
Error percentage, median (IQR)			
Neutral	3.8 (5.8)	2.6 (3.5)	0.409
Congruent	5.1 (7.9)	1.7 (2.2)	0.034
Incongruent	24.9 (23.7)	11.2 (5.0)	0.036
<i>P</i> -value, error percentage			
NS vs. CS	0.097	0.300	
NS vs. IS	<0.001	0.017	
CS vs. IS	<0.001	0.010	

Group comparisons tested with Welch's *t*-test, while differences within group were tested with paired *t*-tests. NS: Neutral stimuli. CS: Congruent stimuli. IS: Incongruent stimuli.

Table 5  
Stroop task performance for stroke patients dichotomized according to small vessel disease score (SVD) of either 0 or 2–4 and HC

	SVD (n = 11)	No SVD (n = 10)	HC (n = 22)
Response time, mean (SD)			
Neutral	1.52 (0.41)	1.31 (0.26)	1.22 (0.27)
Congruent	1.73 (0.41)	1.41 (0.18)	1.37 (0.28)*
Incongruent	1.92 (0.35)	1.79 (0.42)	1.52 (0.38)*
Error percentage, mean (IQR)			
Neutral	3.0 (2.9)	2.7 (2.8)	2.6 (3.5)
Congruent	4.7 (5.7)	2.7 (3.7)	1.7 (2.2)
Incongruent	27.3 (20.3)	16.0 (8.3)	11.2 (5.0)*

Group comparisons tested with Welch's *t*-test. \*Statistically significant difference from stroke patients with SVD ≥2.

reached significance level, but Deoxy-Hb slope in right superomedial PFC showed the same pattern across all conditions.

PFC between stroke patients with SVD score of ≥2 to HC and stroke patients with SVD score of 0, indicated that accounting for SVD score could be desirable in future studies.

### 3.5. Group comparisons of hemodynamic Stroop effect

Further group comparisons of hemodynamic Stroop effect were limited to channels exhibiting significant changes in activation analysis (excluding inferolateral channels). Group comparisons of differences between peak and average slope corresponding to the Stroop effect (response during congruent stimuli subtracted from response during incongruent stimuli) are presented in Tables 9–11. No hemodynamic Stroop effect and no group differences was shown in any channel.

Comparing Deoxy-Hb incongruent to congruent peak difference in superolateral and superomedial

### 3.6. Lateralization of hemodynamic response

We found no lateralization in any channels of any group analysis during incongruent stimuli. Analysis did not show any group differences between stroke patients and HC nor when accounting for the affected hemisphere (Table 12).

## 4. Discussion

The cognitive deficits are quite heterogenous in the general stroke population especially due to anatomical differences in stroke lesion as well as the extent

Table 6  
Peak value of oxygenated and deoxygenated hemoglobin in stroke patients and HC during SWCT

Peak, $\mu\text{M}^*\text{mm(SD)}$	Hemis-sphere	Stroke patients						HC					
		Neutral		Congruent		Incongruent		Neutral		Congruent		Incongruent	
Condition	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb
Chromophore													
Superolateral PFC	Right	7.0 (79.2)	<b>-2.3*</b> <b>(26.3)</b>	-4.2 (102.5)	<b>14.8*</b> <b>(29.7)</b>	-11.0 (112.3)	11.5 (47.6)	9.9 (56.0)	<b>16.8*</b> <b>(28.9)</b>	-13.5 (62.6)	<b>28.4***</b> <b>(32.2)</b>	-1.5 (72.7)	<b>19.6***</b> <b>(29.8)</b>
	Left	-3.3 (71.8)	0.5 (41.2)	-2.7 (79.0)	<b>18.3*</b> <b>(33.2)</b>	-25.1 (84.6)	18.5 (34.5)	-23.0 (70.0)	<b>20.1*</b> <b>(35.6)</b>	-5.7 (47.8)	<b>30.4***</b> <b>(32.9)</b>	-0.1 (72.8)	<b>17.1*</b> <b>(42.8)</b>
Inferolateral PFC	Right	-5.1 (66.9)	-5.3 (24.2)	39.8 (84.0)	-3.3 (27.7)	23.0 (78.5)	0.8 (40.2)	12.5 (35.8)	7.1 (25.1)	5.5 (51.6)	8.2 (23.2)	8.6 (59.4)	8.1 (23.2)
	Left	13.9 (60.9)	-3.3 (28.4)	14.5 (83.5)	-13.4 (43.5)	-4.3 (90.6)	-5.2 (33.6)	2.5 (67.5)	2.2 (42.0)	15.7 (55.1)	10.9 (46.8)	4.3 (43.0)	9.9 (38.7)
Superomedial PFC	Right	-12.3 (44.0)	-3.3 (25.3)	-6.5 (69.6)	-0.9 (31.2)	-13.4 (56.6)	3.0 (36.0)	-6.2 (64.0)	<b>36.6**</b> <b>(55.1)</b>	-33.0 (80.5)	<b>45.1***</b> <b>(64.1)</b>	3.2 (83.9)	24.5 (64.4)
	Left	7.2 (52.6)	-3.4 (37.4)	-19.1 (56.7)	10.6 (45.7)	3.2 (59.8)	12.1 (50.3)	1.8 (40.2)	<b>21.2*</b> <b>(41.6)</b>	-16.1 (52.8)	<b>32.7***</b> <b>(39.4)</b>	-11.3 (49.3)	9.0 (40.7)
Inferomedial PFC	Right	14.3 (50.4)	-10.8 (21.8)	<b>38.1*</b> <b>(47.4)</b>	7.1 (26.1)	28.7 (76.6)	-7.8 (46.8)	18.6 (37.3)	<b>17.1*</b> <b>(32.4)</b>	-1.9 (49.6)	<b>24.6*</b> <b>(45.0)</b>	15.6 (69.3)	14.0 (38.8)
	Left	4.1 (51.9)	-5.4 (26.2)	6.6 (59.7)	8.0 (35.1)	7.4 (66.0)	12.2 (42.0)	<b>18.5*</b> <b>(33.1)</b>	4.1 (27.1)	-1.2 (37.1)	11.4 (39.0)	24.0 (74.0)	-0.4 (40.4)

PFC: Prefrontal cortex. HC: Healthy control subjects. \*Unadjusted  $p$ -value  $<0.05$ . \*\*Unadjusted  $p$ -value  $<0.01$ . \*\*\*Adjusted  $p$ -value with Bonferroni correction for multiple comparisons  $<0.05$ .  
 $H_0$ : Peak = 0. Unadjusted  $p$ -value  $<0.05$ . Unadjusted  $p$ -value  $<0.01$ . Adjusted  $p$ -value with Bonferroni correction for multiple comparisons  $<0.05$ .  $H_0$ : Peak equal in stroke patients and HC.

Table 7  
Average slope values of oxygenated and deoxygenated hemoglobin in stroke patients and HC during SWCT

Slope, $\mu\text{M}^*\text{mm/s}$ (SD)	Hemis-sphere	Stroke patients						HC					
		Neutral		Congruent		Incongruent		Neutral		Congruent		Incongruent	
Condition		Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb
Chromo-phore													
Supero-lateral PFC	Right	2.49 (17.80)	-2.29 (6.35)	0.38 (16.71)	1.45 (5.09)	-0.90 (25.22)	0.06 (6.95)	1.43 (9.51)	<b>3.58**</b> <b>(5.71)</b>	-2.71 (9.29)	<b>4.98***</b> <b>(5.48)</b>	-0.69 (8.94)	2.47 (6.34)
	Left	-0.90 (15.35)	-0.28 (7.85)	1.98 (16.05)	2.78 (6.83)	-1.43 (11.29)	1.22 (4.13)	-2.68 (9.80)	2.98 (7.06)	0.14 (12.54)	<b>5.60***</b> <b>(6.39)</b>	0.04 (9.10)	2.36 (8.10)
Infero-lateral PFC	Right	-1.07 (10.47)	-0.82 (4.66)	<b>8.13*</b> <b>(14.40)</b>	-1.60 (6.77)	1.92 (12.72)	-0.35 (5.56)	2.25 (6.88)	1.87 (5.09)	0.47 (8.36)	2.20 (5.12)	0.92 (8.25)	1.75 (4.81)
	Left	-2.91 (9.36)	-0.40 (5.60)	1.29 (16.08)	-2.43 (8.47)	-2.07 (15.48)	-2.00 (7.75)	1.39 (21.78)	0.54 (10.54)	4.01 (14.87)	1.46 (9.47)	2.15 (17.14)	2.12 (7.10)
Supero-medial PFC	Right	-1.97 (7.11)	-0.21 (6.32)	-2.24 (10.31)	0.33 (5.92)	-1.26 (10.16)	-0.83 (5.98)	-0.48 (10.40)	<b>5.90**</b> <b>(9.09)</b>	-4.25 (12.63)	<b>8.12***</b> <b>(10.78)</b>	0.39 (9.98)	<b>4.75*</b> <b>(9.29)</b>
	Left	1.02 (8.79)	-1.51 (6.98)	<b>-5.27*</b> <b>(10.94)</b>	2.24 (8.62)	0.38 (9.28)	1.08 (5.51)	0.72 (7.38)	<b>4.13***</b> <b>(6.05)</b>	-2.47 (7.95)	<b>5.43***</b> <b>(6.90)</b>	-1.43 (7.85)	1.19 (6.42)
Infero-medial PFC	Right	2.10 (10.32)	-1.44 (5.46)	<b>7.23***</b> <b>(7.86)</b>	1.07 (5.68)	3.87 (12.58)	-3.22 (8.74)	<b>2.70*</b> <b>(5.65)</b>	<b>3.29*</b> <b>(6.89)</b>	0.62 (9.06)	<b>4.36*</b> <b>(8.71)</b>	2.88 (8.81)	<b>2.77*</b> <b>(5.79)</b>
	Left	-0.70 (10.08)	-1.77 (5.14)	2.32 (11.94)	0.89 (6.31)	-0.51 (12.49)	0.71 (6.83)	<b>2.97*</b> <b>(5.47)</b>	1.33 (5.72)	-0.20 (6.99)	1.84 (6.14)	3.22 (9.90)	0.18 (6.39)

PFC: Prefrontal cortex. HC: Healthy control subjects. \*Unadjusted  $p$ -value  $<0.05$ . \*\*Unadjusted  $p$ -value  $<0.01$  \*\*\*Adjusted  $p$ -value with Bonferroni correction for multiple comparisons  $<0.05$ .

$H_0$ : Peak = 0. Unadjusted  $p$ -value  $<0.05$ . Unadjusted  $p$ -value  $<0.01$  Adjusted  $p$ -value with Bonferroni correction for multiple comparisons  $<0.05$ .  $H_0$ : Average slope equal in stroke patients and HC.

Table 8  
Spearman's rank correlation rho between hemoglobin peaks and response time in stroke patients and HC during SWCT

Spearman's rank correlation rho	Hemisphere	Stroke patients				HC		
		Congruent		Incongruent		Congruent		Incongruent
Condition	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb	Oxy-Hb	Deoxy-Hb
Chromophore	Right	0.22	0.03	0.20	0.30	0.24	-0.12	-0.14
	Left	0.38	0.35	0.15	0.33	0.11	-0.29	0.18
Inferolateral PFC	Right	-0.01	0.08	0.26	-0.01	-0.07	-0.07	-0.05
	Left	0.31	<b>0.59*</b>	-0.13	0.32	-0.15	0.01	0.38
Superomedial PFC	Right	-0.06	0.06	-0.34	0.21	0.30	-0.31	0.23
	Left	0.16	0.03	0.18	0.08	0.01	-0.31	-0.01
Inferomedial PFC	Right	-0.25	0.10	0.04	-0.07	0.30	-0.09	0.12
	Left	0.20	0.14	-0.10	-0.11	-0.15	-0.30	0.09
PFC: Prefrontal cortex. HC: Healthy control subjects. *P-value <0.05. H <sub>0</sub> : Spearman's rank correlation rho = 0.								

Table 9  
Average group differences in Peak I-C and slope I-C values of superolateral PFC channel

Superolateral PFC	Comparison	Chromo-phore	Left hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)	Right hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)
Peak I-C	Stroke vs. HC	Oxy-Hb	-28.1 (-81.2–25.1)	-18.9 (-107.3–69.5)
		Deoxy-Hb	13.6 (-17.8–45.0)	5.5 (-22.2–33.3)
		Oxy-Hb	-19.0 (-89.5–51.5)	-21.7 (-76.7–12.5)
		Deoxy-Hb	4.0 (-40.2–48.2)	9.1 (-34.4–52.7)
	HI vs. HC	Oxy-Hb	-52.7 (-125.7–20.1)	-88.3 (-205.7–29.1)
		Deoxy-Hb	23.1 (-24.4–70.7)	<b>29.1 (1.1–57.2)*</b>
	SVD vs. HC	Oxy-Hb	-23.7 (-96.4–49.0)	-137.6 (-345.9–70.8)
		Deoxy-Hb	24.3 (-30.6–79.1)	<b>56.2 (6.7–105.7)*</b>
	SVD vs. non-SVD	Oxy-Hb	-3.31 (-13.13–6.51)	-3.29 (-19.38–12.79)
		Deoxy-Hb	1.68 (-4.72–8.08)	1.12 (-3.76–5.99)
		Oxy-Hb	-2.91 (-17.54–11.71)	0.78 (-13.61–15.16)
		Deoxy-Hb	0.28 (-8.86–9.43)	0.70 (-8.41–9.81)
	Slope I-C	Oxy-Hb	-9.92 (-28.13–8.27)	-16.92 (-46.64–12.80)
		Deoxy-Hb	4.79 (-3.04–12.62)	3.33 (-0.82–7.48)
	SVD vs. non-SVD	Oxy-Hb	-10.50 (-28.39–7.39)	-27.05 (-64.97–10.86)
		Deoxy-Hb	7.10 (-4.37–18.57)	8.00 (-0.38–16.38)

HI: Hemisphere with infarction. SVD: Small vessel disease score 2–4. No-SVD: Small vessel disease score 0. I-C: Difference between incongruent and congruent stimuli. CFI: Confidence interval. PFC: Prefrontal cortex. \*Unadjusted p-value <0.05.  
\*\*Unadjusted p-value <0.01. ‡Adjusted p-value with Bonferroni correction for multiple comparisons <0.05. H<sub>0</sub>: Difference between group estimates = 0.

and location of small vessel disease and pre-stroke cognitive ability. Cognitive neurorehabilitation is individualized based on thorough testing to detect deficits. The SCWT is a highly utilized part of testing in stroke patients to assess specific domains of executive function (primarily selective attention and inhibition). While direct retraining of specific cognitive skills is part of current clinical practice in cognitive stroke rehabilitation, the evidence for adaptive or compensatory strategies within the daily living of patients the latter is stronger (Quinn et al., 2021) including metacognitive strategy training (Cicerone et al., 2019). Although testing is the more prevalent method to detect cognitive issues in clinical practice, behavioral scales of executive dysfunction such as DEX-R (Simblett, Ring, & Bateman, 2017)

could perhaps reflect the issues of daily living better and be more sensitive in monitoring progress that are important to the individual stroke patient. Both progress monitoring and evaluation of the better method could benefit greatly from a biomarker. In the current study, we examined the feasibility of using fNIRS as a method for monitoring cortical hemodynamic response of the PFC during cognitive neurorehabilitation after stroke. While the results were not as expected, we made several interesting observations.

#### 4.1. Stroop task performance

Although the SCWT is very commonly applied in stroke populations, there are significant differences

Table 10  
Average group differences in Peak I-C and slope I-C values of superomedial PFC channel

Superomedial PFC	Comparison	Chromo-phore	Left hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)	Right hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)
Peak I-C	Stroke vs. HC	Oxy-Hb	17.3 (-17.5–52.3)	-43.1 (-92.5–6.3)
		Deoxy-Hb	25.2 (-1.0–51.3)	24.5 (-0.4–49.4)
	HI vs. HC	Oxy-Hb	24.4 (-17.3–66.1)	-55.7 (-125.2–13.8)
		Deoxy-Hb	16.0 (-17.5–49.6)	<b>40.5 (6.7–74.2)*</b>
	SVD vs. HC	Oxy-Hb	-4.4 (-71.5–62.7)	-30.4 (-110.4–49.7)
		Deoxy-Hb	<b>40.5 (10.9–70.2)*</b>	<b>32.4 (0.4–64.5)*</b>
	SVD vs. non-SVD	Oxy-Hb	-34.9 (-115.1–45.4)	33.6 (-47.6–115.0)
		Deoxy-Hb	<b>40.8 (1.0–80.5)*</b>	13.7 (-28.5–56.0)
	Slope I-C	Oxy-Hb	4.61 (-1.86–11.07)	-3.65 (-11.66–4.35)
		Deoxy-Hb	3.08 (-1.70–7.85)	2.22 (-2.31–6.74)
	HI vs. HC	Oxy-Hb	5.30 (-2.94–13.54)	-6.31 (-16.6–3.98)
		Deoxy-Hb	1.71 (-5.14–8.56)	<b>5.71 (1.66–9.76)**</b>
	SVD vs. HC	Oxy-Hb	2.04 (-11.96–16.05)	1.82 (-10.64–14.27)
		Deoxy-Hb	<b>5.28 (0.43–10.14)*</b>	3.23 (-2.94–9.42)
	SVD vs. non-SVD	Oxy-Hb	-5.53 (-21.03–9.97)	9.89 (-2.97–22.76)
		Deoxy-Hb	5.95 (-1.26–13.16)	2.18 (-7.21–11.57)

HI: Hemisphere with infarction. SVD: Small vessel disease score 2–4. No-SVD: Small vessel disease score 0. I-C: Difference between incongruent and congruent stimuli. CFI: Confidence interval. PFC: Prefrontal cortex. \*Unadjusted  $p$ -value  $<0.05$ . \*\*Unadjusted  $p$ -value  $<0.01$ . ‡Adjusted  $p$ -value with Bonferroni correction for multiple comparisons  $<0.05$ .  $H_0$ : Difference between group estimates = 0.

Table 11  
Average group differences in Peak I-C and slope I-C values of inferomedial PFC channel

Inferomedial PFC	Comparison	Chromo-phore	Left hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)	Right hemisphere difference, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)
Peak I-C	Stroke vs. HC	Oxy-Hb	-24.5 (-71.6–22.5)	-26.8 (-77.2–23.6)
		Deoxy-Hb	16.0 (-8.3–40.3)	-4.2 (-29.1–20.5)
	HI vs. HC	Oxy-Hb	-24.7 (-79.2–29.7)	-33.5 (-78.4–11.3)
		Deoxy-Hb	20.4 (-15.5–56.2)	-0.7 (-26.1–24.6)
	SVD vs. HC	Oxy-Hb	10.4 (-59.3–80.1)	11.7 (-50.3–73.7)
		Deoxy-Hb	30.7 (-14.4–75.8)	-15.4 (-60.1–29.2)
	SVD vs. non-SVD	Oxy-Hb	63.8 (-8.8–136.5)	84.5 (-5.4–174.5)
		Deoxy-Hb	23.0 (-25.4–71.4)	-18.6 (-72.2–35.0)
	Slope I-C	Stroke vs. HC	-6.25 (-13.69–1.19)	-5.62 (-13.29–2.04)
		Deoxy-Hb	1.47 (-2.08–5.03)	2.22 (-2.31–6.74)
	HI vs. HC	Oxy-Hb	-5.71 (-13.80–2.39)	-5.57 (-12.95–1.80)
		Deoxy-Hb	2.53 (-2.54–7.59)	0.22 (-4.65–5.09)
	SVD vs. HC	Oxy-Hb	-4.16 (-15.37–7.04)	0.04 (-11.38–11.45)
		Deoxy-Hb	3.99 (-2.71–10.70)	-4.15 (-13.19–4.89)
	SVD vs. non-SVD	Oxy-Hb	2.05 (-9.85–13.95)	13.41 (-0.86–27.67)
		Deoxy-Hb	4.45 (-2.54–11.45)	-1.01 (-10.75–8.73)

HI: Hemisphere with infarction. SVD: Small vessel disease score 2–4. No-SVD: Small vessel disease score 0. I-C: Difference between incongruent and congruent stimuli. CFI: Confidence interval. PFC: Prefrontal cortex. No group differences found.

in the execution of the test. Many SCWTs are performed with a certain time limit and the result being the number of correct answers. This limits our understanding of behavior and physiology between each test condition and as such the Stroop effect.

The SCWT applied in this study showed the Stroop effect as both response time and error percentage showed increments with greater difficulty, though

response time was slightly more reliable in line with a previous study (Shao et al., 2020).

Stroke patients in the subacute phase performed the SCWT significantly worse than HC with respect to both response time and error percentage, despite suffering from stroke with heterogeneous anatomical lesions and relatively low NIHSS. Response time and error percentage was slightly greater in this study

Table 12

Lateralization analysis of oxygenated and deoxygenated hemoglobin (left vs. right hemisphere) in stroke patients and HC as well as in stroke hemisphere vs. healthy hemisphere during incongruent stimuli

Peak lateralization	Chromo-phore	Stroke patients, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)	HC, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)	Stroke hemisphere, mean, $\mu\text{M}^*\text{mm}$ (95% CFI)
Superolateral PFC	Oxy-Hb	-1.7 (-44.9–41.4)	2.6 (-32.6–37.8)	27.1 (-13.6–67.8)
	Deoxy-Hb	1.2 (-19.7–22.2)	-4.4 (-27.6–18.8)	-7.9 (-28.4–12.7)
Inferolateral PFC	Oxy-Hb	-17.6 (-70.1–34.9)	-5.4 (-31.4–20.5)	15.8 (-36.9–68.5)
	Deoxy-Hb	3.5 (-24.6–31.6)	1.1 (-16.7–19.0)	0.6 (-27.5–28.8)
Superomedial PFC	Oxy-Hb	18.0 (-22.2–58.3)	-14.7 (-57.0–27.7)	2.5 (-38.6–43.7)
	Deoxy-Hb	6.9 (-12.5–26.4)	-14.8 (-43.5–13.9)	-2.2 (-21.9–17.4)
Inferomedial PFC	Oxy-Hb	-19.0 (-69.7–31.6)	12.3 (-21.8–46.5)	17.4 (-33.4–68.3)
	Deoxy-Hb	27.7 (-15.2–70.6)	-14.3 (-40.9–12.3)	28.3 (-14.4–71.1)

CFI: Confidence interval. PFC: Prefrontal cortex. No significant lateralization, nor any group differences observed.

compared to the findings in chronic stroke patients who had more time to recover (5–20 weeks) (Morein-Zamir, Henik, Balas, & Soroker, 2005). While the incidence of CI (assessed by other cognitive tests) was comparable to other acute stroke studies (Blackburn et al., 2013; Jaillard et al., 2009), no cut-off for CI have been established for the applied SCWT.

To explore the importance of small vessel disease in our stroke population, we dichotomized patients according to SVD score quite similar to Schroeter et al. who found significantly increased response time and error percentage in cerebral microangiopathy patients with moderate to severe microangiopathy scored by lacunar infarctions and periventricular white matter lesions (M. L. Schroeter et al., 2007). Our study could not replicate this finding as stroke patients with moderate to severe SVD score (2–4) showed equal response time and error percentage compared to stroke patients with SVD score of 0. A drawback of the SVD scoring system in the current setting is the omission of acute lacunar infarctions in calculation of the SVD score, despite being a clear imaging sign of small vessel disease, which could possibly explain the incoherence between the two studies.

#### 4.2. Activational analysis of fNIRS response

Stroke patients had significant activation of their right inferomedial PFC during congruent stimuli, but not during neutral and incongruent stimuli although their mean average response of Oxy-Hb was positive and Deoxy-Hb close to zero, which could be consistent with this finding. However, neither HC nor left inferomedial PFC showed a similar response pattern which could indicate a type 1 error despite Bonferroni correction.

Absence of classic activation in the PFC is contradictory to previous studies of both healthy young (Ehlis et al., 2005; Lague-Beauvais et al., 2013; Leon-Carrion et al., 2008; Matthias L. Schroeter et al., 2003) and elderly people (Lague-Beauvais et al., 2013; Matthias L. Schroeter et al., 2003) as well as in patients with migraine (Schytz et al., 2010), cerebral microangiopathy (M. L. Schroeter et al., 2007), depression (Ikeda et al., 2013) and traumatic brain injury (Plenger et al., 2016). However, fNIRS studies of both subjects with obsessive compulsive disorder and attention deficit hyperactivity disorder did not find any PFC activation (Okada, Ota, Iida, Kishimoto, & Kishimoto, 2013; Ueda et al., 2018).

Possible reasons for type 2 errors in fNIRS studies include inadequate stimuli, adaptation and fatigue during prolonged testing, poorly positioned optodes, untimely examination window, excessive MA correction and contamination by changes in systemic and extracerebral perfusion (Tachtsidis & Scholkemann, 2016). While the applied SCWT in our study is quite similar or even identical to other studies (Lague-Beauvais et al., 2013; M. L. Schroeter et al., 2007; Matthias L. Schroeter et al., 2003; Schytz et al., 2010), we believe the inter-block period was insufficient as the HRF for some subjects did not return baseline within 20 seconds. This could potentially diminish the hemodynamic response in the subsequent stimuli block. Furthermore, most fNIRS studies observe functional hemodynamic responses within 5–10 seconds from stimuli onset (Paola Pinti et al., 2020) including Stroop studies (Ikeda et al., 2013; Leon-Carrion et al., 2008; M. L. Schroeter et al., 2007; Matthias L. Schroeter et al., 2003; Schytz et al., 2010), but others have observed activation within a prolonged observation window (Ehlis et al., 2005; Jahani, Hemmati, Rahimpour, & Setarehdan, 2015).

The configuration of optodes applied in this study was constructed to examine most of the superficial PFC, while deeper cortical tissue cannot be examined with fNIRS. Both DLPFC and ACC were areas of interest and examined with superolateral and superomedial channels according to sensitivity mapping of average optode positioning (Fig. 1). However, not all subjects matched the average subject, and thus we suspect optodes were not optimally positioned in some cases to possibly account for some of the large variations observed. Future studies could benefit from digitized optode positioning to account for individual anatomical differences.

In contrast to most other fNIRS studies examining the SCWT, we did apply short-separation regression. This was performed to improve signal quality and brain sensitivity, but also to minimize the possibility of sympathetic nervous activation increasing extracerebral blood flow and mimicking a functional cerebral activation (Tachtsidis & Scholkmann, 2016). However, running the GLM without short-separation regression did not alter our findings (data not shown).

In the processing of data, we examined several MA correction methods and eventually applied a relatively conservative method and then removed all other stimuli blocks with MA to avoid excessive MA correction. Results did not change significantly when other MA correction methods were applied (data not shown).

The inverse activational response observed in superolateral and superomedial PFC was quite consistent especially in healthy subjects. Inverse activational patterns are often attributed to pathologic conditions in the brain with disruption of the neurovascular coupling (Lindauer et al., 2010). Thus, blood flow remains constant, and the increased neuronal metabolism leads to a reduction in Oxy-Hb and an increase in Deoxy-Hb. While this could be true for stroke patients, it should not be the case in our group of HC. Inverse activational pattern have also been observed in fNIRS studies of some subject performing motor tasks (Sato et al., 2005) as well as in motor imagery studies in which inhibition of motion have been proposed to account for the inverse pattern in frontal and prefrontal cortex (Holper, Shalom, Wolf, & Sigman, 2011). While subjects in the current study only performed slight motor tasks in clicking the mouse, a significant proportion found the response actions (left mouse click for correct stimuli and right mouse click for incorrect stimuli) counterintuitive

and conceivably had to employ some level of motor inhibition.

Cases of slight optode misplacement (i.e. to activated parts of DLPFC and ACC) could also lead to such an inverse activational pattern due to a steal phenomenon, as have been observed in multichannel fNIRS setups in healthy subjects (Amiri et al., 2014; P. Pinti, Siddiqui, Levy, Jones, & Tachtsidis, 2021) and in cerebrovascular patients (Akiyama et al., 2005; Murata, Sakatani, Katayama, & Fukaya, 2002). Nearby activation adjacent to the examined cortical area can cause regional increases in the activated area and reductions to blood flow in the examined area and thus diminished Oxy-Hb and greater Deoxy-Hb concentration. A denser and more widespread optode configuration would be preferable in future studies to assess this possibility.

Partial volume effect (i.e., when sampling from activated and non-activated tissues) is another possible explanation for the observed response (Boas et al., 2001; Kleinschmidt et al., 1996; Strangman, Culver, Thompson, & Boas, 2002), but that is impossible to assess in one-modality studies. Systemic perfusion noise has also been attributed to inverse fNIRS responses (Caldwell et al., 2016), which is unlikely in our study due to short-separation regression.

As no definitive physiological explanation of the inverted hemodynamic response have been identified, we conclude that fNIRS have significant path ahead before implementation into a clinical neurorehabilitation setting is feasible. The need for simultaneous and multi-modal examinations (i.e., together with MRI or PET) to investigate inverted hemodynamics is apparent.

Stroke patients exhibited associations between Deoxy-Hb peaks and response time in left inferolateral PFC, but not in right inferolateral PFC nor in any other channels including all HC channels, which could indicate a type 1 error. The lack of associations between hemoglobin peaks and response time conceivably speaks to the heterogeneity in the stroke patient's disease characteristics, shortcomings in optode positioning and examination protocol as covered above and the complex nature of regional blood flow. Such factors could have created too much noise for any associations to be detected. Instead, this finding emphasizes the need for using any individual as its own control condition whenever it is possible as accounting for the functional response during congruent stimuli when analyzing the functional response during incongruent stimuli.

#### 4.3. Group differences

Regardless of the physiological explanation for the inverse activational patterns observed, HC had significant higher Deoxy-Hb increments than stroke patients in superomedial PFC across conditions and to a lesser extent in superolateral and inferomedial PFC. These findings indicate possible differences in cortical hemodynamics or neuronal activation due to ischemic stroke, though further interpretation of the pathophysiology is incomprehensible.

While group differences were observed in raw hemodynamic response, there was no coherence between hemodynamic response and test performance during incongruent stimuli when accounting for subjects' response during congruent stimuli. Although rational from a test performance logic, the congruent and incongruent stimuli in the SCWT are quite different in nature and could very well activate neural pathways differently, thus not proving logical in neural activational nor hemodynamic patterns. To our knowledge, there are no comparable studies, but one study of subacute TIA patients showed the same increment in prefrontal perfusion as in HC after physical activity during a one-block SCWT (36 consecutive stimuli). The hemodynamic change was not related to the improvement in test performance in accordance with our findings (Faulkner et al., 2017).

We dichotomized stroke patients to either no small vessel disease or moderate to severe small vessel disease, which indicated higher Deoxy-Hb in superomedial and superolateral PFC during Stroop test in patients with small vessel disease, although these findings were non-significant after Bonferroni correction. Nonetheless, we believe examining and accounting for small vessel disease is crucial in stroke patients when performing hemodynamic or cognitive investigations as most stroke patients have some degree of small vessel disease regardless of stroke etiology (Simonsen et al., 2022; Staals et al., 2014) that can affect blood flow regulation (Kim et al., 2021; Liu et al., 2022) and cognitive performance (Rost et al., 2022). Stroke patients conform an inherently heterogenous population with different lesions and symptoms, cognitive performance, medical history, stroke etiology and anatomy, medication, stroke-related complications, etc. It is beyond the scope of this study to do further investigations across such heterogeneities.

Although activational response seemed more pronounced in the right hemisphere, lateralization

analysis showed no significant findings in either group or between groups, even when accounting for infarction hemisphere.

#### 4.4. Strengths and limitations

The NIRS examinations in this study were of high quality with short-separation regression to filter out extracerebral contamination, but with no digitization of optode placement creating uncertainty of the examined area in the individual subject and with insufficient inter-stimulus resting periods in some subjects.

The enrollment criteria for stroke subjects were designed to reflect the common heterogeneity among stroke patients in the everyday clinical setting. Patients were for instance not excluded if the index stroke was a recurrent stroke, nor if their stroke lesion was not within the examined cortical area. While this choice favors the generalizability, it also generates the possibility of multiple cofounders for which it is not possible to account for in such as limited sized population. A very large-scale study would be required to incorporate precise anatomical lesion as well as stroke etiology, domains of executive dysfunction and other important variables into the statistical model beyond the scope and nature of this exploratory study. The stroke patients in our study had to be excluded if their symptoms were too severe for them to perform the Stroop test resulting in a population with only mild to moderate stroke patients. While we recruited HC with sex and age matched to stroke patients, we did not control for educational level which could be a possible confounder.

The large variations in hemodynamic response were greater than anticipated. Thus, the sample size in this study conceivably led to inadequate statistical power as several findings did not survive Bonferroni correction. While it is interesting to examine the entire PFC rather than certain regions of interest, this tendency is also aggravated in multi-channel fNIRS setups. However, increasing the sample size and statistical power would probably not have changed the main conclusions from this study.

Implementation of fNIRS as a biomarker during stroke rehabilitation would require a better understanding of inverted functional responses. Future studies should focus on this as well as examining functional hemodynamic responses during other domains of cognitive and executive function perhaps leaning on lessons learned in the current study.

## 5. Conclusions

In this study, we investigated the hemodynamic response of acute ischemic stroke patients during the SCWT to examine the feasibility of fNIRS as a biomarker for the hemodynamic pathophysiology behind cognitive symptoms in stroke rehabilitation. While stroke patients showed partial executive dysfunction performing the SCWT worse than HC matched in age and sex, both groups exhibited an inverted hemodynamic response in the superolateral and superomedial prefrontal cortex. The inverse hemodynamic response was lower in stroke patients compared to HC but did not increase with test difficulty and showed no coherence to test performance. No further group differences were proven including lateralization, but accounting for SVD score could be valuable in future studies. Further investigations are warranted to assess the physiology behind inverse activational responses seen in fNIRS examinations possibly with a multi-modal setup and preferably with a dense and more widespread optode configuration. At the moment fNIRS have significant challenges ahead before implantation in clinical stroke rehabilitation would be viable.

## Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Funding

This work was supported by the Novo Nordisk Foundation, Copenhagen, Denmark (Grant number 17948).

## Data availability statement

Clinical data will not be made available, while the fNIRS data can be obtained from the corresponding author upon reasonable request. HRF analysis is accessible at <https://github.com/adamheiberg/SWCT-Stroke.git>.

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