Near-Infrared Spectroscopy and Transcranial Doppler Sonography for the estimation of Cerebral Autoregulation after Intra-Arterial Thrombectomy for Ischemic Stroke

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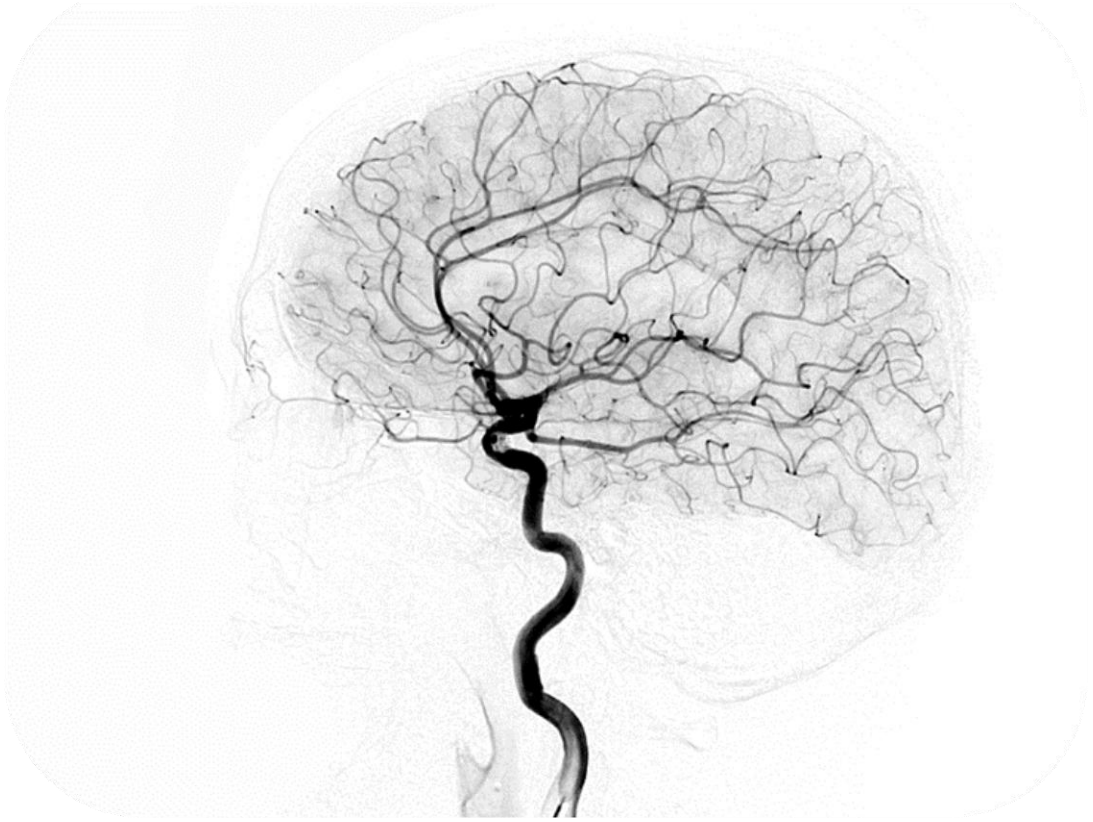

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Figure: A Cerebral Angiograph with normal vascularisation

Table of contents

Introduction

Ischemic stroke or Ischemic Cerebral Vascular Accident (CVA-i) is a major health problem in which blood flow in the cerebral vasculature is impaired. In the Netherlands, prevalence of stroke is approximately 2-3 per 1000 persons per year, with ischaemic stroke accounting for approximately 80% of the cases. Stroke is already the second most prevalent primary cause of death in women and third in men. Due to aging of the population, the prevalence of stroke is expected to rise further. [1] In ischemic stroke, the blood flow in the cerebral blood vessels is most often hampered by an embolus of cardiac or atherosclerotic origin that mechanically stops flow in a 'cork on a bottle' way.

Over the years, several treatment strategies have been developed for the treatment of ischemic stroke. Thrombolytic agents have been developed that can break down the embolus structure and allow the return of blood flow. Recently, the introduction of mechanical intra-atrial treatment options for several types of ischemic stroke has significantly improved patient outcome. In Intra-Arterial Thrombectomy (IAT) the embolus occluding the cerebral vessel(s) is mechanically removed using intra-arterial catheters and several types of balloons, stents, and suction devices.[2] IAT is currently considered a standard treatment option for infarction of the anterior, middle, and basilar cerebral circulation.[3]–[5]

Despite the fact that IAT has strongly improved long-term outcome in stroke-patients, there are still outcome differences between patients. Several factors influencing outcome have been identified. Among others, time until recanalization (vessel opening), Thrombolysis In Cerebral Infarction (TICI) and National Institutes of Health Stroke Scale (NIHSS) scores, age, and several cardiovascular comorbidities have been recognised as influencing outcome.[6], [7] Apart from the initial damage to the brain parenchyma due to the sudden decrease in perfusion, the cerebral vessels themselves may also be damaged due to a lack of perfusion. This may result in an impairment of the cerebral autoregulation, defined as the 'ability of the brain to maintain a constant blood flow despite changes in perfusion pressure'.[8]

Cerebrovascular function and cerebral autoregulation – principles and background

Although the human brain consumes approximately 20% of all glucose-derived energy in the body, energy storage in the brain is limited. Optimal cerebral perfusion is therefore crucial to allow normal brain function. Cerebral vasoregulation represents several physiological mechanisms that maintain this adequate perfusion in case of challenges like systemic blood pressure (BP) fluctuations, pH disturbances or changes in neuronal activation.[9] A major and well known component of cerebral vasoregulation is cerebral autoregulation (CA), comprising the contraction and dilation of cerebral arterioles in response to changes in BP to keep a relatively constant cerebral blood flow (CBF).[8], [10] Hence, CA is crucial for adequate cerebral perfusion.

The most used representation of Cerebral Autoregulation is the 'Lassen curve', which is shown in Figure 1. It can be seen that for a broad range of systemic BPs, CBF remains constant. The mechanism responsible for this is the active constriction and dilatation of the cerebral arterioles, which alters cerebrovascular resistance (CVR). This is depicted schematically in the top part of the Figure. However, it was found that the Lassen curve may vary between individuals. The 'CA-plateau' in which CBF remains constant may be present for different BP ranges in different individuals. [11] For an individual with a given systemic BP, it is therefore not known beforehand whether if he/she is on his/her 'CA-plateau'. This is illustrated in Figure 2, in which the BP-axis labels are unknown.

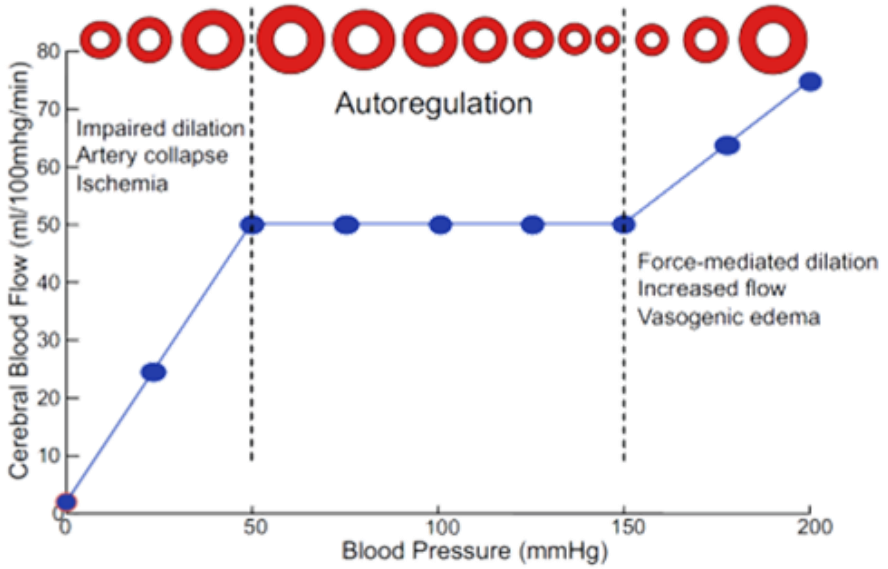


Figure 1: The classic representation of the relation between BP and CBF in the 'Lassen Curve'. For a broad range of systemic BPs, CBF remains constant, via de active constriction and dilatation of the cerebral arterioles, represented in the top of the figure. Adapted from Pires *et al. American Journal of Physiology* (2013), doi: 10.1152/ajpheart.00490.2012

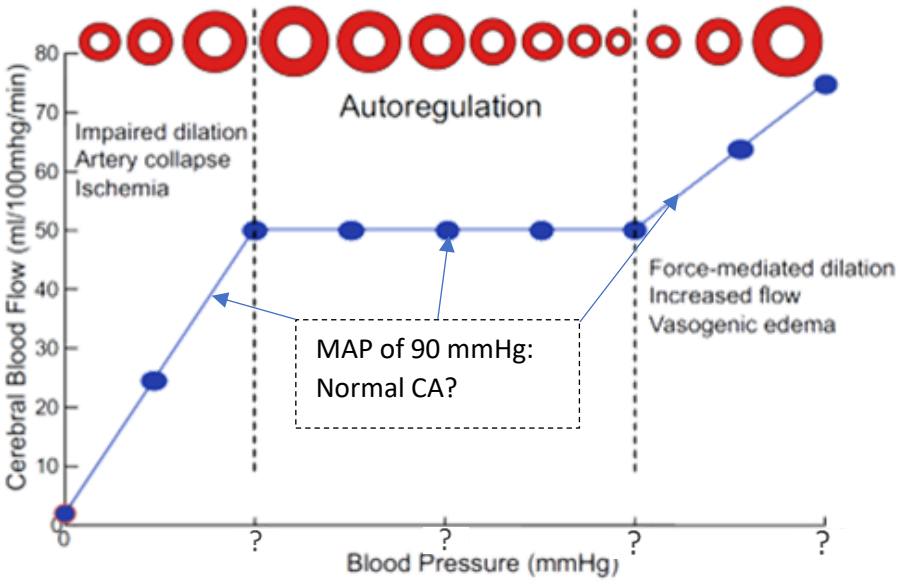


Figure 2: The classic representation of the relation between BP and CBF in the 'Lassen Curve'. In clinical practice, the blood pressures in the 'cerebral autoregulatory range' are not known and vary strongly among individuals. For a given mean arterial pressure (MAP) of 90 mmHg, it is not immediately known where the patient is on the Lassen Curve. Adapted from Pires *et al. American Journal of Physiology* (2013), doi: 10.1152/ajpheart.00490.2012

If the CA figure is to be known for a given individual, several systemic BPs would have to be induced in an individual and the CBF would be measured at each BP level. Doing so, the relation between (steady-state) BP and CBF is determined and the Lassen curve will be reproduced. This method of analysing CA is known as 'static CA', as several static BP-levels in a broad range are necessary. BP alteration is classically achieved pharmacologically or via exsanguination. These methods are unfeasible in clinical practice because of the harm the broad range of static BPs will do to the patient.[12], [13]

'Dynamic CA' represents the other group of CA analysis techniques. For dynamic CA (DCA) methods, the timing and magnitude of the response of CBF to BP changes is observed over time. DCA methods are only possible using CBF monitoring modalities with a high temporal resolution (e.g. Transcranial Doppler (TCD)), laser Doppler flowmetry (LDF) and near-infrared spectroscopy (NIRS).[14] The BP changes can either be spontaneous only[15], [16] or spontaneous and induced (e.g. using thigh cuff deflation, passive leg-raising, squat-to-stand, sit-to-stand, or Valsalva manouevres)[10], [17]–[20].

In 1995, in a classic study of Tieks *et al.,* it was found that DCA measurements estimate static CA without induction of a broad range of BPs.[21] For only a small range of dynamically changing BP values, it was possible to estimate CA-status. This is graphically shown in Figure 3, in which CA-status is shown as being 'on the CA-plateau' or 'outside of the CA-plateau'.

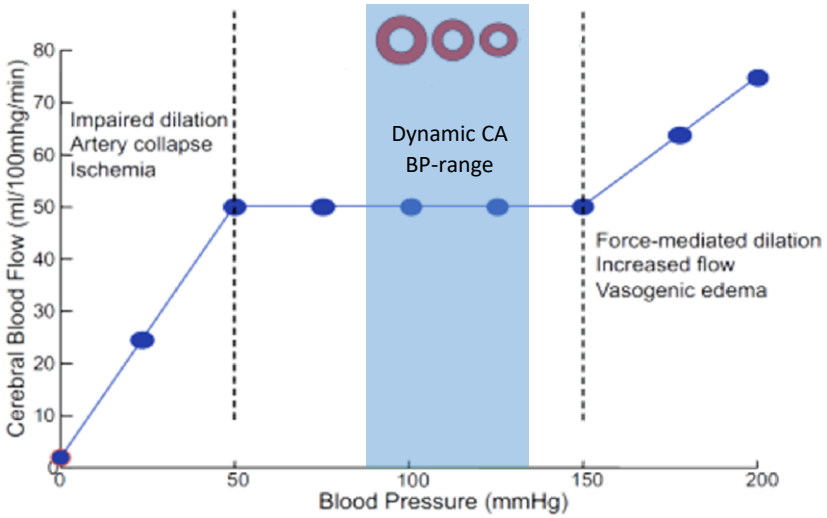


Figure 3: The classic representation of the relation between BP and CBF in the 'Lassen Curve'. With DCA, dynamic blood pressure variation over a small BP range is used to estimate CA-status. Is was shown to be possible to distinguish between functioning CA/ 'on the CA-plateau' and impaired CA/'outside the CA-plateau'. Adapted from Pires *et al. American Journal of Physiology* (2013), doi: 10.1152/ajpheart.00490.2012

The most-used type of DCA analysis is with Transfer Function Analysis (TFA), which has been described extensively by Claassen *et al.* in a White Paper of the International Cerebral Autoregulation Research Network (CARNet) [22]. TFA consists of the calculation of the gain, phase and coherence of the transfer function between BP (input) and CBFV (output). A visualization of TFA for DCA is shown in Figure 4. In general, CA is found to have the properties of a high-pass filter: high frequency oscillations (>0.20 Hz) in BP translate to similar oscillations in cerebral blood flow (CBF). Low frequency oscillations (<0.20 Hz) in BP can be counteracted by dilatation and contraction of the cerebral arterioles, leading to a relatively more constant CBF for these frequencies.[23]

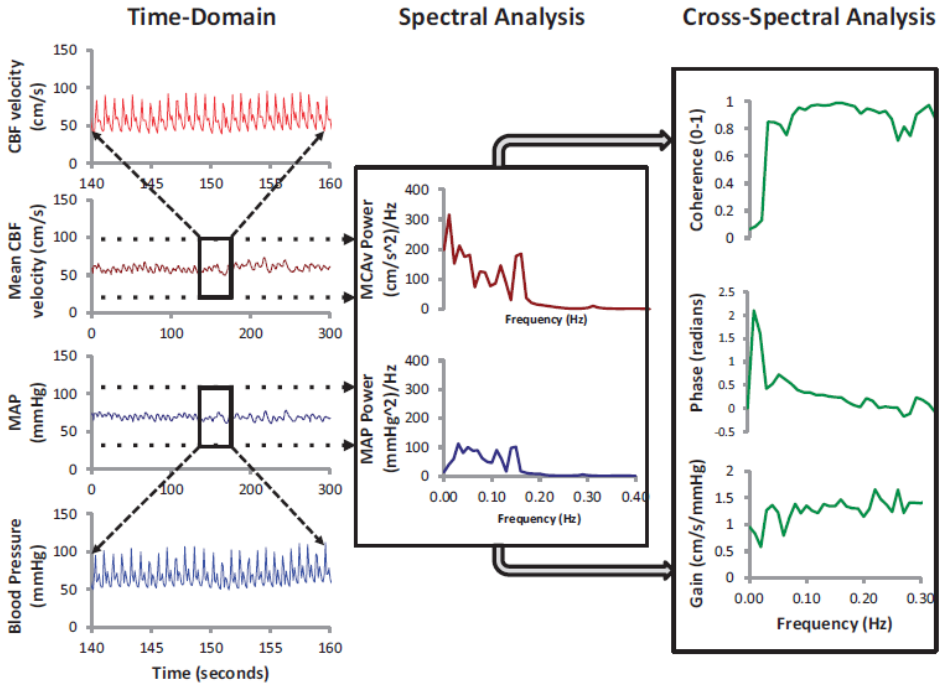


Figure 4: A example of TFA of Mean Arterial Pressure (MAP) and Cerebral Blood Flow velocity (CBFV). In the left column, the raw MAP and CBFV data is shown. The middle column graphs show the spectrogram of CBFV and MAP, obtained via the Fast Fourier Transform (FFT). In the right graphs, estimates of the coherence, phase and gain of the cross-spectrogram of MAP and CBFV are shown. Adapted from Claassen et al. (2015)

Cerebral autoregulation – toward clinical practice

CA has been shown to be altered in several cerebral diseases such as stroke, traumatic brain injury, sub-arachnoid haemorrhage, intracranial hypertension, and carotid artery disease.[24], [25] Yet, the usage of CA measurements in clinical practice remains limited. Accuracy and reproducibility are often low and depend on a centre's expertise, data analysis techniques are highly variable[26] and interpretation of results is still subject to debate, even for measurements in healthy subjects.

The clinically best established CA measurement technique is the combination of Transcranial Doppler sonography (TCD) and continuous systemic BP measurements.[13] To address the challenges described above, extensive recommendations for TCD based Transfer Function Analysis (TFA) for Dynamic CA estimation were published in 2015.[22] Still, the reproducibility of TCD-derived DCA remains low, as was shown in a large, multi-centre study[27], although some improvement be be achieved when a certain amount of blood pressure oscillations is present.[28] Furthermore, translation of CA measurements into clinical practice remains problematic, partly because of violation of the recommendations, especially when measurements are performed in the ward, intensive care unit or operating room. Finally, concrete CA-based treatment implications are sparse, although recent clinical research into CA-based BP management is onging.[29]–[31]

Near-infrared spectroscopy (NIRS) for clinical CA estimation

In 2018, a new, clinically applicable analysis protocol for CA based on near-infrared spectroscopy (NIRS) was developed at the department of Neurology, University Medical Center Groningen.[32] NIRS has several advantages over TCD when it comes to the clinical application of CA-measurements, which will be discussed in the following paragraphs.

Near-infrared spectroscopy (NIRS) is a technique that allows the determination of different concentrations of 'chromophores', materials that have distinct absorption properties of infrared light. In clinical practice, it is used to estimate local tissue hemoglobin concentrations and tissue oxygenation. Its main clinical application is the monitoring of cerebral tissue saturation during specific cardiac or cardiovascular surgeries, for which several clinical devices are available that monitor cerebral tissue oxygenation. Furthermore, NIRS is used extensively in basal neurophysiological research (cerebral NIRS), and research into sports and exercise physiology (muscle NIRS).[33], [34]

NIRS-based estimation of cerebral autoregulation are a recent development, that has been described in some studies. CA is determined using either an index of local cerebral oxygen saturation[35] or the raw concentrations of OxyHb and HHb. [36], [37] In these studies, a direct comparison of NIRS-derived and TCD/ABP-derived autoregulation estimation was, however, not yet performed.

For the clinical assessment of cerebral autoregulation, NIRS has several advantages over TCD/ABP. TCD-measurements require an experienced TCD-technician. In approximately 20% of the patients, no appropriate acoustic window can be found, making TCD-measurement unfeasible. Furthermore, the TCD-probe can be uncomfortable for the patient, especially during long-term measurements. Lastly, TCD-measurements only provide CBF values in the Middle Cerebral Artery (MCA). Information about the distal cerebral vasculature is missing. On the other hand, NIRS-measurements are relatively easy to execute and can be performed for almost all patients. The sensors are generally accepted well by patients. This allows long-term measurements, which have been shown to strongly decrease the variability of CA measurements.[22] Lastly, NIRS-measurements provide information on the capillary perfusion, be it only in a regional brain area.

Recently, a new TFA method to measure DCA using NIRS measurements on the temporal scalp was developed.[32] In this study, two NIRS-devices (Portalite, Artinis Medical Systems, Elst, The Netherlands) were placed bilaterally on the frontotemporal scalp in 15 healthy subjects. Oxygenated hemoglobin (OxyHb) and deoxygenation hemoglobin (HHb) concentrations were continuously measured. In this method, the concentrations of OxyHb and HHb were used as the respective input and output of the TFA. It was shown that this method provides an estimate of DCA that is similar to the established TFA using BP and CBFV. This was achieved by correcting the TFA phase plot for the Transit Time (TT) of blood through the capillary network and the ratio between blood flow and blood volume (BF/BV) in the brain. An example of the TFA phase plot obtained from BP and CBFV data and the 'TT-BF/BV' corrected TFA using OxyHb and HHb is shown in Figure 5.

The details of the TT-BF/BV model were extensively described in the Supplementary Material of the paper.[32] A schematic representation of the TT-BF/BV model can be found in Figure 6, adapted from the same paper. A condensed explanation of the model is given:

Changes in systemic blood pressure (BP) and the cerebral blood flow velocity (CBFV) are considered to occur simultaneously, due to the high flow of the blood in the major arteries. They are 'parallel'. Phase differences between MABP and CBFV are therefore thought to only result from active contraction of the cerebral arterioles. This phenomenon is Cerebral Autoregulation (CA).

The relation between OxyHb and HHb is different. CA still affects the relation between OxyHb and HHb, but (1) there is also a constant time delay between Oxyhb and HHb, resulting from transport of blood through the microvascular bed. This is called the 'microvascular transit time (TT)'.

In addition, (2) there may exist Blood Flow (BF) oscillations in which a change in (arterial blood rich of) OxyHb results in an opposite change in (venous blood rich of) HHb. The induces an out-of-phase, 180 degrees phase relation for OxyHb-HHb. This is better known as the 'wash-out phenomenon'.

Lastly, (3) there may be Blood Volume (BV) oscillations in which both the concentration of OxyHb and HHb increase simultaneously, resulting in a zero degrees phase relation for OxyHb-HHb.

These three phenomena would result in a phase relation between OxyHb and HHb that decreases linearly over frequency. This is shown as the grey linear trend in Figure 5. To extract the Cerebral Autoregulation part of the phase difference between OxyHb and HHb, this linear trend must be obtained and subtracted. Assuming that CA is almost absent for frequencies above 0.2 Hz, the phase differences between 0.2-0.5 Hz (HF band) could be used to estimate this linear trend. Subsequently, this trend can be subtracted from the phase difference plot, leaving a CA-only or 'TT-BF/BV corrected' phase relation between OxyHb and HHb, that is similar to the phase relation between BP and TCD.

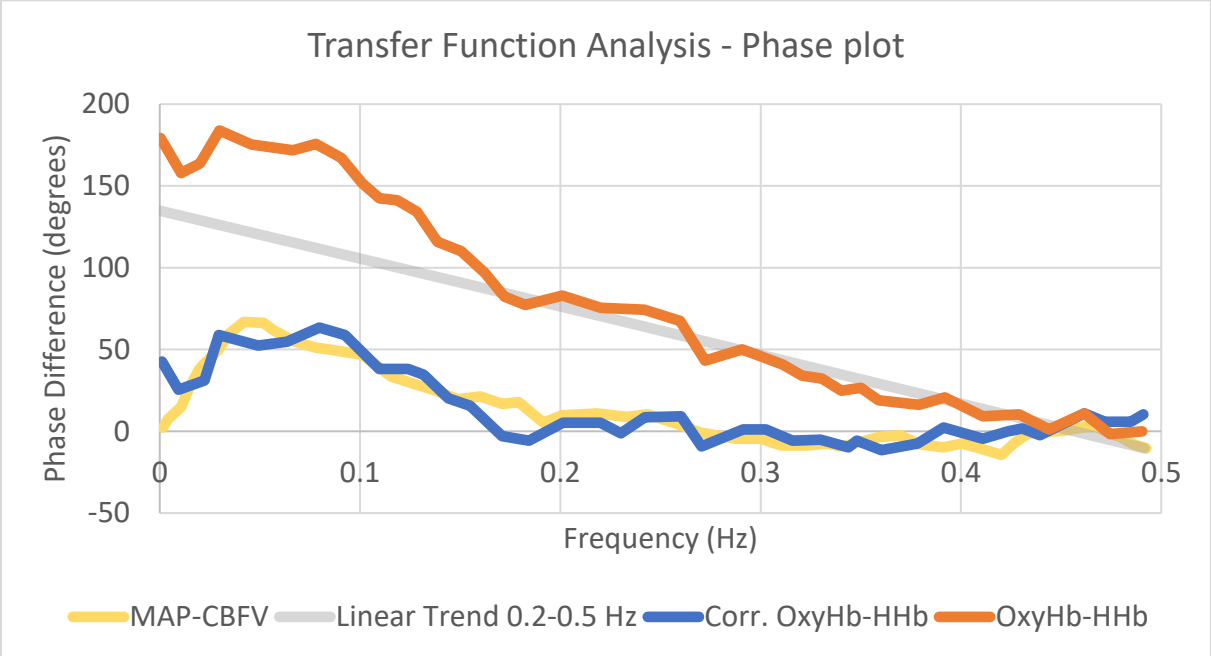


Figure 5: Average phase difference of the TFA for 15 healthy volunteers. The phase difference of the TFA for MAP-CBFV is shown in yellow and is used as the 'reference TFA'. In orange, the TFA of OxyHb-HHb is shown. In blue the TT-BF/BV corrected TFA of OxyHb-HHb is depicted, which was created by subtracting the linear trend line of TFA(OxyHb-HHb) between 0.2 and 0.5 Hz (in grey). Reproduced from Elting *et al.* (2018)

The UMCG NIRS-CA study was the first to describe a quantitative relation between NIRS- and TCD/BP- based CA, using an extensive mathematical model. Apart from measurements in rest, measurements were performed during deep breathing (hypocapnia) and deep breathing of CO2-

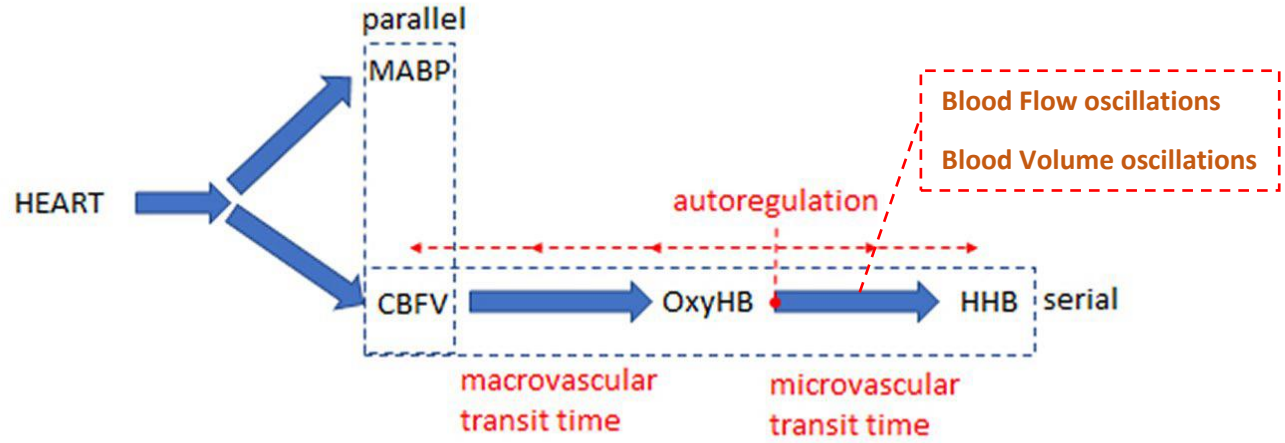


Figure 6: Schematic representation of the conduction of blood from the heart to the brain. Changes in mean/systemic arterial blood pressure (MABP) and the cerebral blood flow velocity (CBFV) are considered to occur simuntaneously, due to the high flow of blood in the major artery. They are therefore 'parallel'. Phase differences between MABP and CBFV are therefore thought to only result from active contraction of the cerebral arterioles, termed Cerebral Autoregulation (CA). For the relation between OxyHb and Hhb, three additional phenomena may be present, namely the microvascular transit time (TT), and the presence of Blood Flow (BF) and Blood Volume (BV) oscillations.

enriched air (hypercapnia). The next step in the clinical application of NIRS-based CA estimation is to test the model in a clinical(ly relevant) population.

Cerebral Autoregulation and ischemic Stroke – relevance and missing links

In 2010, is was shown in a review by Aries *et al.* that impaired CA was associated with various sub-types of ischemic stroke.[25] Furthermore, this study found that autoregulation impairment seems to be related to worse clinical outcome, but the quality of the studies included in the review was considered too low to extract firm conclusions on outcome. In the studies included in the review, autoregulation measurements were performed between 20 hours and 458 days after stroke. Measurements in the acute (<20 hours) phase were not performed in these studies. However, it is likely that cerebral autoregulation may already be impaired in the acute phase after stroke.

Knowing CA status in the acute (<20 hours) post-IAT phase may be useful, since (1) complications may already occur in this acute phase, (2) these complications may be related to impaired CA, (3) early recognition of impaired CA may facilitate treatment, mainly BP optimisation.

Aims of the current study

The aim of the current study is twofold:

1. To investigate CA-status in the acute phase(<3 hours) after ischemic Stroke
2. To compare NIRS-derived CA with TCD-derived CA in a clinical population with altered cerebrovascular physiology

Research questions

In this study, two main research question will be answered:

1. Is the CA as measured with TCD/BP and NIRS altered in the affected hemisphere in the acute stage (<3 hours) after ischemic stroke compared to the unaffected hemisphere?
2. Is NIRS-derived CA similar to TCD-derived CA in both hemispheres in the acute phase after ischemic stroke?

Methods

Design and setting

This was a prospective single centre observation study that was conducted in the stroke unit/Medium Care Unit (MCU) or Intensive Care Unit (ICU) of one Dutch university-based hospital.

Ethical approval

Examinations and measurements are either part of routine medical care (clinical data, Transcranial Doppler Sonography) or the need for informed consent was waived by the Medical Ethical Review Board UMC Groningen (NIRS measurements). Written informed consent for the study was obtained before IAT treatment by the patient or his/her legal representative.

Population

Consecutive stroke patients with a computed tomography angiography (CTA) scan proven isolated occlusion of the M1/M2 segments of the middle cerebral artery or the internal carotid artery (ICA) who underwent IAT were eligible for participation in the study. Detailed inclusion and exclusion criteria are the following.

Inclusion criteria

- Proven thrombotic occlusion in the M1 segments
- Eligible for IAT
- Age > 18 years
- Successful recanalization of the occlusion (Thrombolysis In Cerebral Infarction (TICI) score of 2b/2c/3)
- Written informed consent obtained

Exclusion criteria

- Wounds in the temporal bone region
- Impossibility to lie still for 20 minutes
- Agitated delirium

Study protocol

An extensive study protocol and measurement setup development is described in Appendix B of this thesis. In this section, the methods required for understanding of the results are provided.

Within 3 hours after recanalization through IAT, measurements are performed in the Stroke Unit/Medium Car Unit (MCU) or the Intensive Care Unit.

Two NIRS-sensors (Portalite, Artinis Medical Systems) were attached to the frontotemporal scalp with two-side adhesive tape. Concentrations of Oxygenated Hemoglobin (OxyHb) and Deoxygenated Hemoglobin (HHb) were measured continuously with a sample frequency of 50 Hz. The frontotemporal position was used to ensure the NIRS-sensors were placed over the 'anterior watershed area', a region known to be vulnerable to perfusion deficits of the middle cerebral circulation.

Concurrently, TCD-measurement were performed by a qualified technician for micro-embolus detection, as part of routine medical care. Before the measurements, patients were patient in a supine or semi-recumbent position for 15 minutes to allow BP stabilisation. Two hand-held 2 MHz probes (Delica, Shenhen, China) placed bilaterally on the frontotemporal scalp were used to determine the presence of an acoustic window. If an acoustic window was present, CBF-velocity

(CBFV) of the middle cerebral artery (MCA) was continuously measured. TCD settings were set as such that both embolus detection and CBFV calculation were possible.

During the TCD measurements, arterial blood pressure was also measured continuously via arterial volume clamping of the digital artery (Finapres, Finapres Medical Systems, Amsterdam). Furthermore, transcutaneous ($tcCO_2$ or $etCO_2$) and oxygen (tcO_2) were continuously measured (SenTec Oxivent System, SenTec AG, Switzerland). End-tidal carbon dioxide ($etCO_2$) was used for ventilated patients. Lastly, two accelerometers (built in-house with an Arduino Analog-to-Digital Converter) were attached to the patient's chest and middle forehead between the NIRS sensors, to measure breathing and whole body movements, and local movement of the NIRS-sensors respectively.

The NIRS, TCD and BP measurements were either performed simultaneously for both hemispheres for a total of 10 minutes or they were first performed for the affected hemisphere for 10 minutes and then the unaffected, contralateral hemisphere for another 10 minutes.

Data acquisition on the computer was performed with in-house built Labview data acquisition software. The software used a 'Queue structure' with which time-locking of all analogue and digital input signals was confirmed. This ensured that no time shift occurred. All data was upsampled to 250 Hz, which was the highest device sample frequency, namely for the TCD-device. This allowed continuous equally sampled data for NIRS, BP, TCD, and the accelerometer data.

Clinical outcome variable

- All-cause mortality within 48 hours post-stroke
- National Institutes of Health Stroke Scale (NIHSS) score within 48 hours post-stroke
- Occurrence of major neurological complications
    - Haemorrhagic transformation of the infarct area
    - Occurrence of cerebral edema
    - Newly developed ischemia
    - Re-occlusion of intracerebral vessels ipsilaterally from the affected hemisphere.

Covariates

- Age
- Gender
- Pre-intervention NIHSS score
- Time after Last Time Seen Well (LTSW)
- Wake-up stroke (first symptoms during sleep)
- Received intra-venous thrombolytics
- Time after recanalization
- Thrombolysis in cerebral infarction (TICI) score

Power calculation

There were insufficient data for a sample size calculation, because to the best of our knowledge TCD/ABP- and NIRS-derived DCA have not been sufficiently studied in the early period (<3 hours) post-IAT. The study was thus an exploratory pilot study. 20 patient would be measured to provide a general idea of the size and direction of changes in DCA that could be expected after reperfusion.

Data preparation and pre-processing

All measurements were performed in correspondence with the White Paper recommendations on Transfer Function Analysis for the calculation of DCA, endorsed by the international Cerebral Autoregulation Research Network (CARNet).[22]

Artefact detection

OxyHb, HHb, TCD, and BP-data was inspected for artefacts semi-automatically using a Labview-based Graphical User Interface (GUI) (Labview 2014, National Instruments, United States). For the detection of movement artefacts, the accelerometer data of the forehead was used to substantiate the decision. Artefact length and the presence of baseline drift was saved. In contrast to the White Paper guidelines, no ectopic heart-beats were classified as artefacts, because of their physiological nature.[22]

Artefact correction

Before artefact correction, TCD and BP-data were beat-averaged.This has be found to reduce the data disturbance of artefact interpolation[38] and is recommended to improved standardisation.[22] Beat averaging was performed using a semi-automatic Labview algorithm using the signal slope and hysteresis to identify individual beats. Subsequently, data from each beat was averaged. The method is equal to the one described in the Whitepaper. The data were subsequently linearly upsampled to 250 Hz to

Artefact correction differed depending on artefact length and the presence of baseline drift. For convenience, the artefact length threshold was set at < 3 seconds and not < 3 heart-beats, which is recommended.[22] Baseline drift was defined as a change in signal baseline between before and after the artefact of >2*[average per-beat amplitude]. This was estimated visually. In Table 1, the artefact correction algorithm is summarised.

Table 1: Summary of artefact classification and correction

	Artefact length < 3 seconds	**Artefact length >= 3 seconds**
Baseline drift absent	Linear interpolation	Data segment removal
Baseline drift present (>2 beat amplitude)	Data segment removal	Data segment removal

Artefact correction was performed automatically using Matlab (Matlab 2019a, The Mathworks, Inc., United States). Linear interpolation was executed using in-built Matlab functions. Data segment removal was performed by cutting the artefact out of the data and saving the remaining data as two separate data segments. To allow further analysis of the data, data segments of <100s were excluded.

Transfer Function Analysis

TFA was performed using in-house developed Labview software (Labview 2014, National Instruments, United States). Here, recommendations of the CARNet White Paper were again used.[22] The TFA was determined between OxyHb and HHb, and TCD and BP, for each hemisphere, for each patient individually. A minimum of 5 minutes of artefact-free data was used for each TFA-calculation. Power spectral and cross-spectral density estimates were performed using the Welch method (100 s epochs, 50% window overlap). If the data consisted of multiple data segments, no overlap was applied between these segments, to prevent TFA calculation of discontinuous data. For a frequency range of 0.01 to 0.5 Hz, Coherence, Gain, and Phase were calculated. If coherence for a specific frequency bin did not surpass the significance threshold, Gain and Phase estimates for this

frequency bin were excluded. The TFA algorithm is shown in Figure 7
Average Coherence, Gain, and Phase values were averaged over three frequency bands, the Very Low Frequency (VLF), Low Frequency (LF), and High Frequency (HF) bands. An overview of the frequency bands is given in Figure 8. For each measurement, an average of the gain and phase was calculated by averaging the real and imaginary parts of the Gain and Phase of each data segment separately. These were subsequently transformed back to gain and phase estimates. This was performed in Labview.

Group averages and confidence intervals were subsequently calculated using an adapted version the *CircStat* Matlab toolbox[39], which is based on the book of Zar.[40] This was needed because phase differences are of a circular data type. Using this method, confidence intervals could only be calculated below +-170 degrees, depending on the amount of samples. Larger confidence intervals are undefined using this method. The toolbox was slightly adapted so it could handle missing data.

Transfer Function Analysis of Oxygenated Hemoglobin and Deoxygenated Hemoglobin

The TFA calculation between of OxyHb and HHb is equal to that of BP and TCD. However the phase difference plot is subsequently altered by subtracting the linear trend through the phase difference values between 0.2 and 0.5 Hz. This results in the TT-BF/BV corrected phase difference.

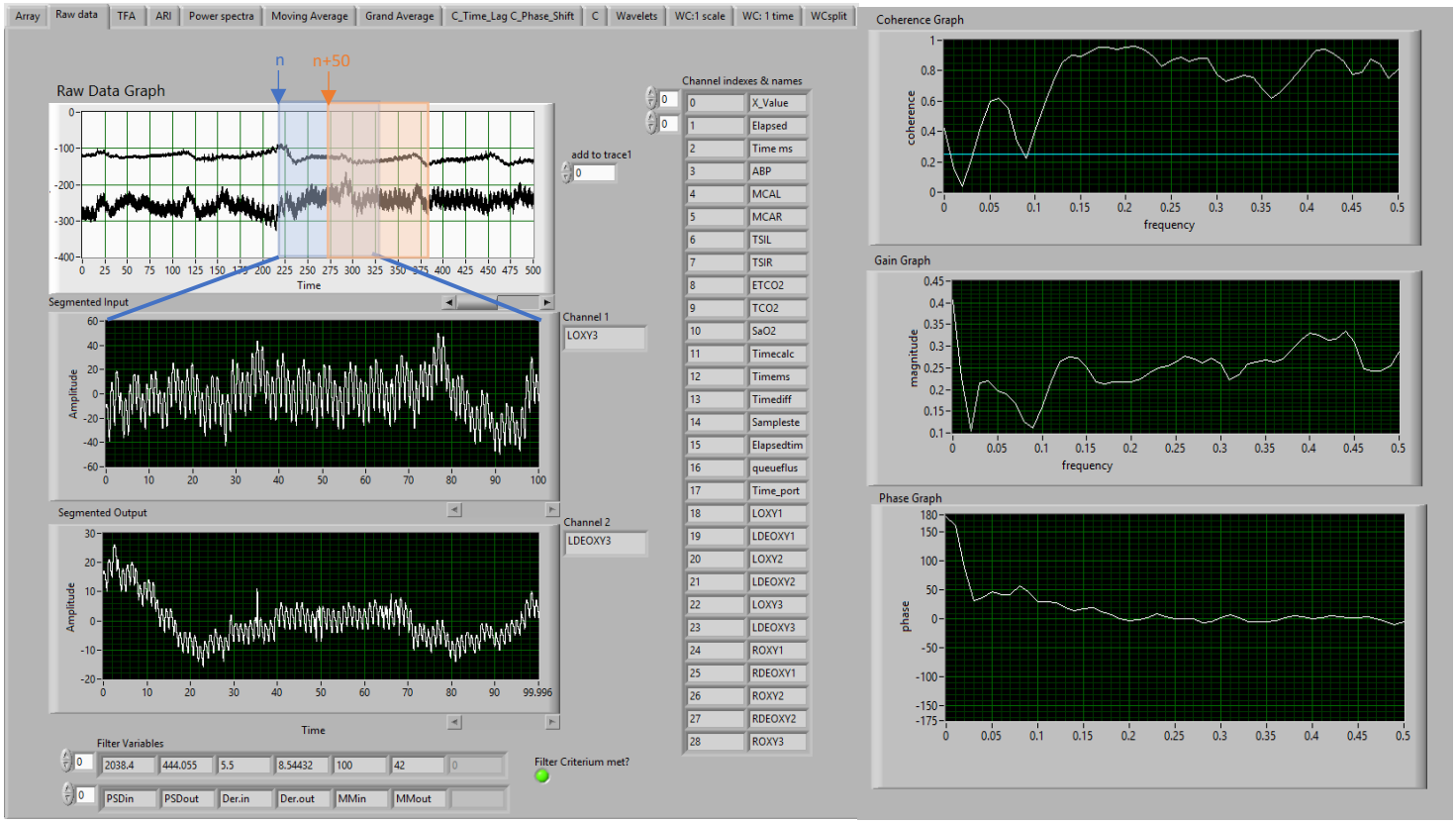


Figure 7: Screenshot of the running Transfer function analysis software implemented in Labview. In the left top quadrant in white, a data segment of both OxyHb and HHb is shown. Below that, a 100 sec segment starting at 'n sec' of data is shown for OxyHb (LOXY3) and HHb (LDEOXY3). For each 100s segment, the Transfer Function (TF) between input (here: OxyHb) and output (here: HHb) is calculated. Next, the TF is calculated for a 100 sec data segment starting a 'n+50 sec'. This is illustrated with the bars and arrows. On the right, the calculated TF parameters are shown. For the Coherence, a significance threshold is shown in light blue. Gain and Phase values for frequency bins with Coherence<Coherence$_{significance_threshold}$, will be excluded.

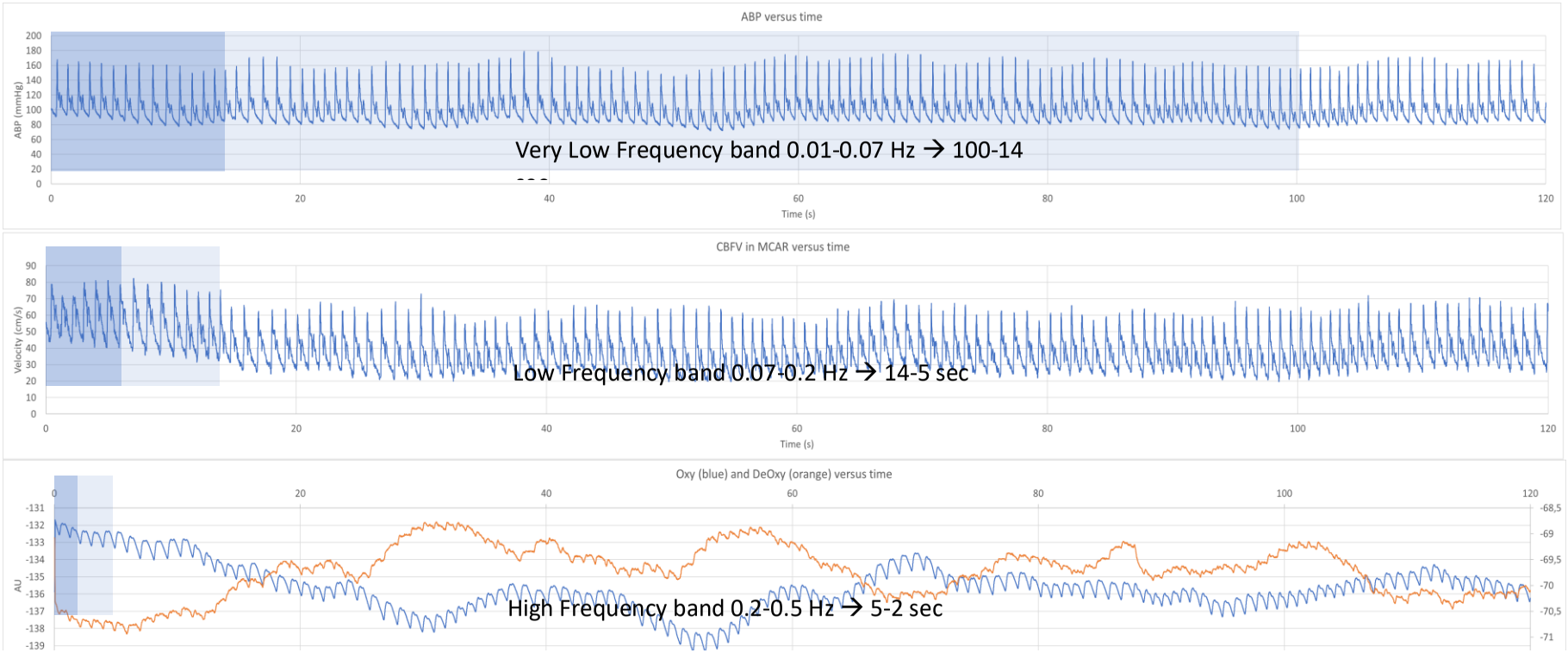


Figure 8: Overview of high-quality data. Upper graph: Systemic Arterial Blood Pressure (BP). Middle graph: Cerebral blood flow velocity measured with TCD. Lower graph: Oxygenated and DeOxyGenated Hemoglobin. In addition, the time domain period corresponding to each frequency band is highlighted in dark blue (minimal period) and light blue (maximal period).

Statistical analysis

Groups averages were visually tested for normality with histograms. If a normal distribution could be assumed, a paired T-test was performed to compare the group averages. If no normal distribution could be assumed, the Wilcoxon signed-rank test was performed. Due to the limited number of measurement, no initial correction for confounders was performed.

Results

In total, 16 patient were initially included in the study within the period between 01-05-2019 and 20-12-2019. After inspection of the data for artefacts, data from 9 patients had to be excluded due to major movement artefacts, resulting in less than 5 minutes of artefact-free data. Of the remaining 7 patients, sufficient TCD and BP data could only obtained in 4 patients. In Figure 9, the data quality of each patient is summarised.

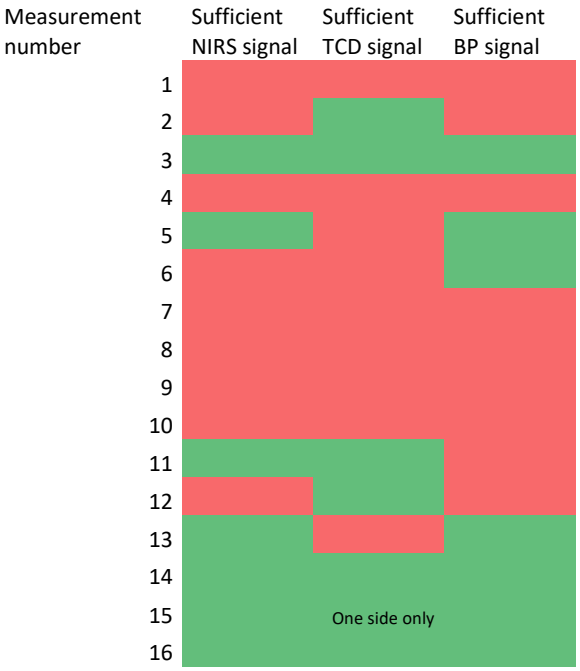


Figure 9: Description of the data quality of NIRS, TCD and BP for each measurement. For measurement 15, sufficient TCD-data was only available for one hemisphere.

The aetiology of each artefact has not been saved, but in general, artefacts could be classified into the following categories:

- Movement artefacts (majority)
- Technical failure: No Finapres BP calculation due to cold fingers, TCD-acoustic window not present, cross-talk between the NIRS-sensors.
- Software related: Data acquisition error, resulting in small segments of removed data (due to Queue Structure in Labview). Complete software crash during measurement.

In Appendices A: Per patient analysis and B: Measurement Setup development and, several artefact types are described more thoroughly.

Of the remaining 7 patients, an overview of clinical and physiological variables and the clinical outcome is provided in Table 2.

Table 2: Clinical and physiological characteristics

Characteristics		
Number of patients (n)		7
Age (SD)		72.4 (11.8)
Gender (Male)		5 (71%)
Side of occlusion (Right/Left)		4/3
Occluded vessel (MCA/ICA/both)		3/2/2
TICI 2b/2c/3		2/2/3
Time after TLSW - affected side (Hours:Minutes)		06:48 (02:22)
Time after TLSW - unaffected side (Hours:Minutes)		07:07 (02:20)
Wake-up stroke		1 (14%)
Time after Recanalization – affected side (Hours:Minutes)	(n=6)	01:25 (00:30)
Time after Recanalization – unaffected side (Hours:Minutes)	(n=6)	01:44 (00:28)
Received intra-venous thrombolytics		3 (43%)
NIHSS at admission (SD)	(n=7)	12.7 (4.5)
Occlusion/stenosis in ICA/CCA after recanalization		1 (14%)
Outcome <48 Hours		
Mortality		1 (14%)
Haemorrhagic transformation/Cerebral edema/New ischemia/Re-occlusion		2 (29%)
NIHSS closest to 48 hours (SD)	(n=6)	12.2 (6.1)

In Table 3, the overall measurement characteristics are shown. The mean TCD/BP durations are skewed, as for one patient, the TCD/BP measurements were 28 minutes long.

Table 3: Measurement characteristics

Measurement characteristics		
Number of patients (n)		7
Number of patients with TCD and NIRS measurements		4
Mean NIRS duration – affected side		08:12 (03:59)
Mean NIRS duration – unaffected side		07:30 (04:34)
Mean TCD/BP duration – affected side		11:15 (11:31)
Mean TCD/BP duration – unaffected side		13:31 (13:13)
tCO2 – affected side	n=4	5.6 (0.27); Min: 5.0; Max: 6.0
tCO2 – unaffected side	n=4	5.7 (0.17) Min: 5.4; Max: 5.9

For four patients, transcutaneous or end-tidal CO2 (tCO2) values could be calculated during the entire measurement. For the remaining three patients, tCO2 values could not be obtained due to restlessness (patient touching the sensor) (n=2) or sensor dysfunction due to membrane damage (n=1). For all patients during the entire measurement, tCO2 was between 5.0 and 6.0 kPa. An exact normal range for tCO2 is not provided by the manufacturer. For paCO2, normal physiologic values are also unknown, but they are often considered to lie between 4.6-4.8 and 6.0-6.4 kPa.[41], [42]

Comparison of the affected hemisphere and the unaffected hemisphere

After inspection of the histograms of VLF, LF, TT and %BF for NIRS, a normal distribution could not be assumed. For the VLF and LF phase differences between BP and TCD, a normal distribution also could not be assumed.

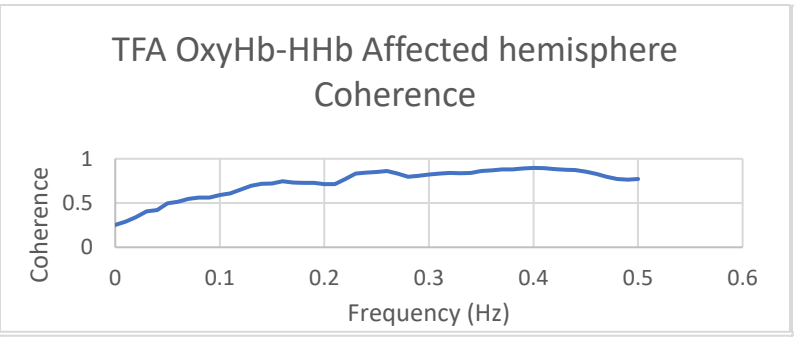
NIRS

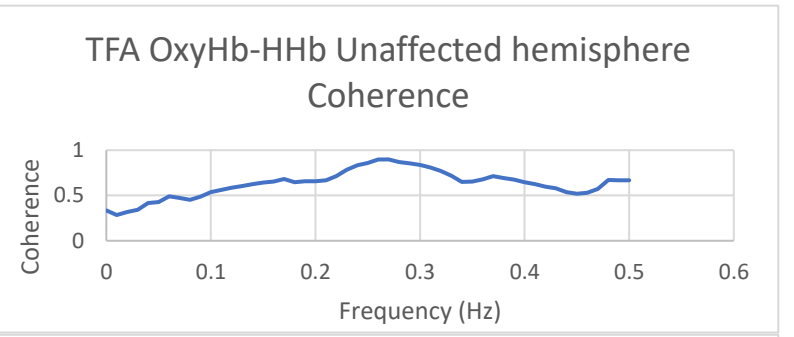
The group averaged TFA between OxyHb and HHb for the affected and unaffected hemispheres are shown in Figure 10. It can be seen that for both hemispheres, the phase difference between OxyHb and HHb is approximately zero degrees for frequencies above 0.2 Hz, but that it increases for frequencies below 0.2 Hz. As the phase difference between 0.2 and 0.5 Hz is nearly flat, the TT-BF/BV corrected phase difference is almost identical to the non-corrected phase difference.

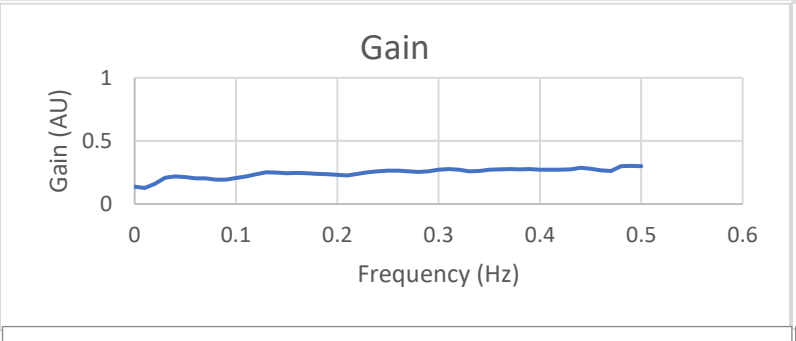
In Table 4, the Phase differences in the VLF and LF band, Microvascular Transit Time, and the %BF oscillations is statistically compared between the hemispheres. Only for the uncorrected phase difference in de LF band, a statistically significant difference is found between the affected and the unaffected hemisphere (Affected side: median: 14.8, IQR: 9.2-22.6, unaffected side (median: 70.0, IQR (21.5-79.3).

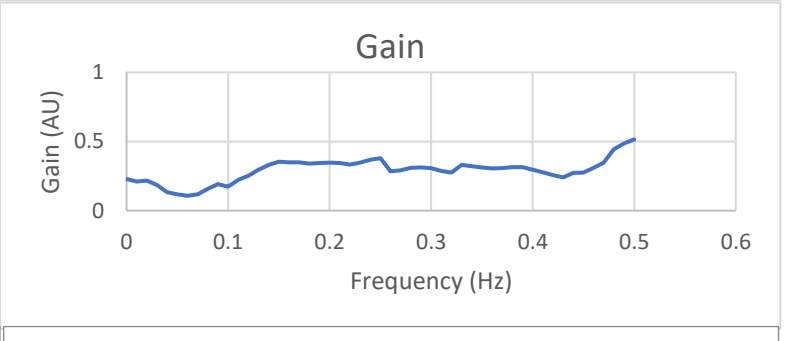
Table 4: NIRS TFA phase parameters for the affected and unaffected sides

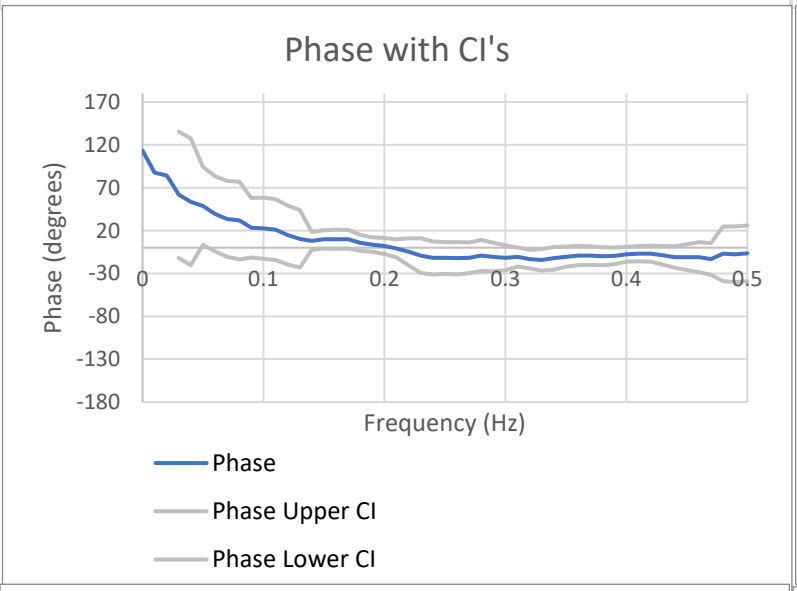
	Affected side		Affected side		Unaffected side		Unaffected side		Test statistics	
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Z	*p*
VLF	67.4	37.5	48.1	45.1-70.9	127.9	45.8	151.4	89.3-160.9	-1153	0.249
VLF corrected	72.1	41.5	53.4	41.6-106.8	116.5	54.0	146.3	80.5-153.1	-0.734	0.463
LF	14.1	13.2	14.8	9.2-22.6	63.8	51.1	70.0	21.5-79.3	-2.197	0.028
LF corrected	21.6	22.7	10.9	8.5-24.9	54.7	54.2	30.6	5.25-111.0	-1.014	0.310
Microvascular Transit Time	0.039	0.067	0.0078	-0.020 0.093	-0.014	0.67	0.080	-0.11-0.27	-0.507	0.612
%BF oscillations	-2.87	10.8	-3.12	-5.52-6.35	6.77	23.8	0.76	-7.48-21.2	-1.014	0.310

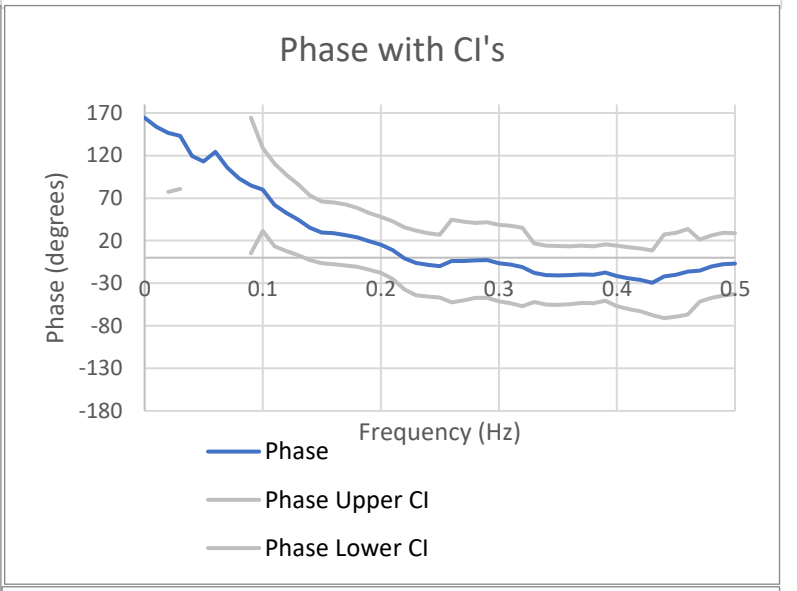


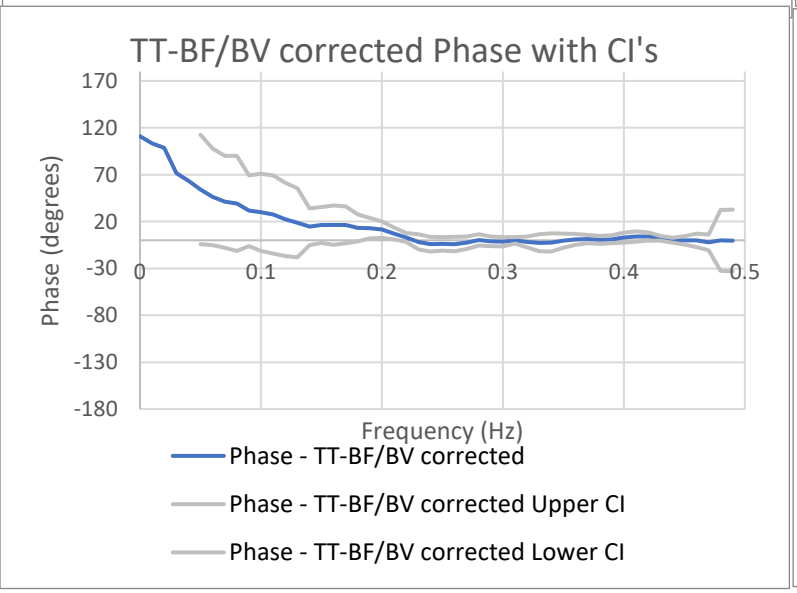












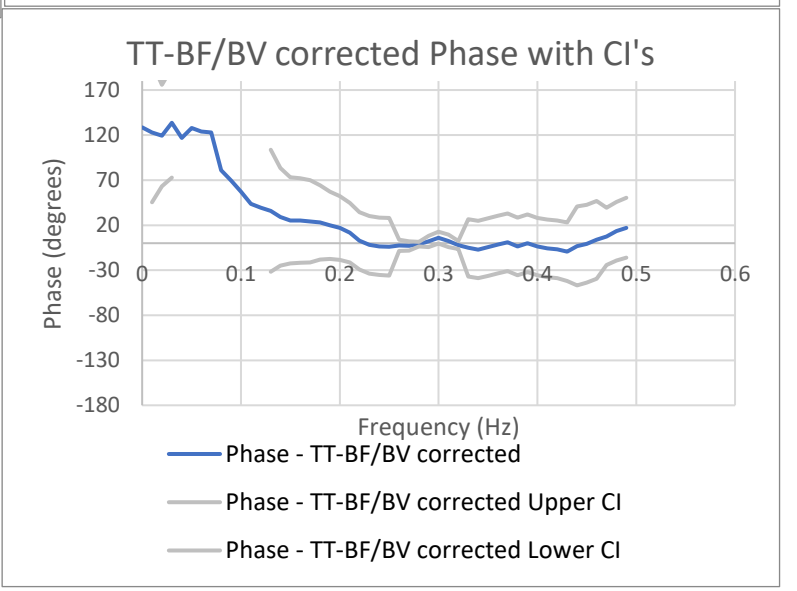


Figure 10: Transfer Function Analysis between OxyHb and HHb for the affected and unaffected hemispheres. Circular 95% Confidence Intervals (CI) are given for the phaseestimates. 95%-CI could not always be calculated with the used method. In these cases the 95%-CI can however be assumed to be large.

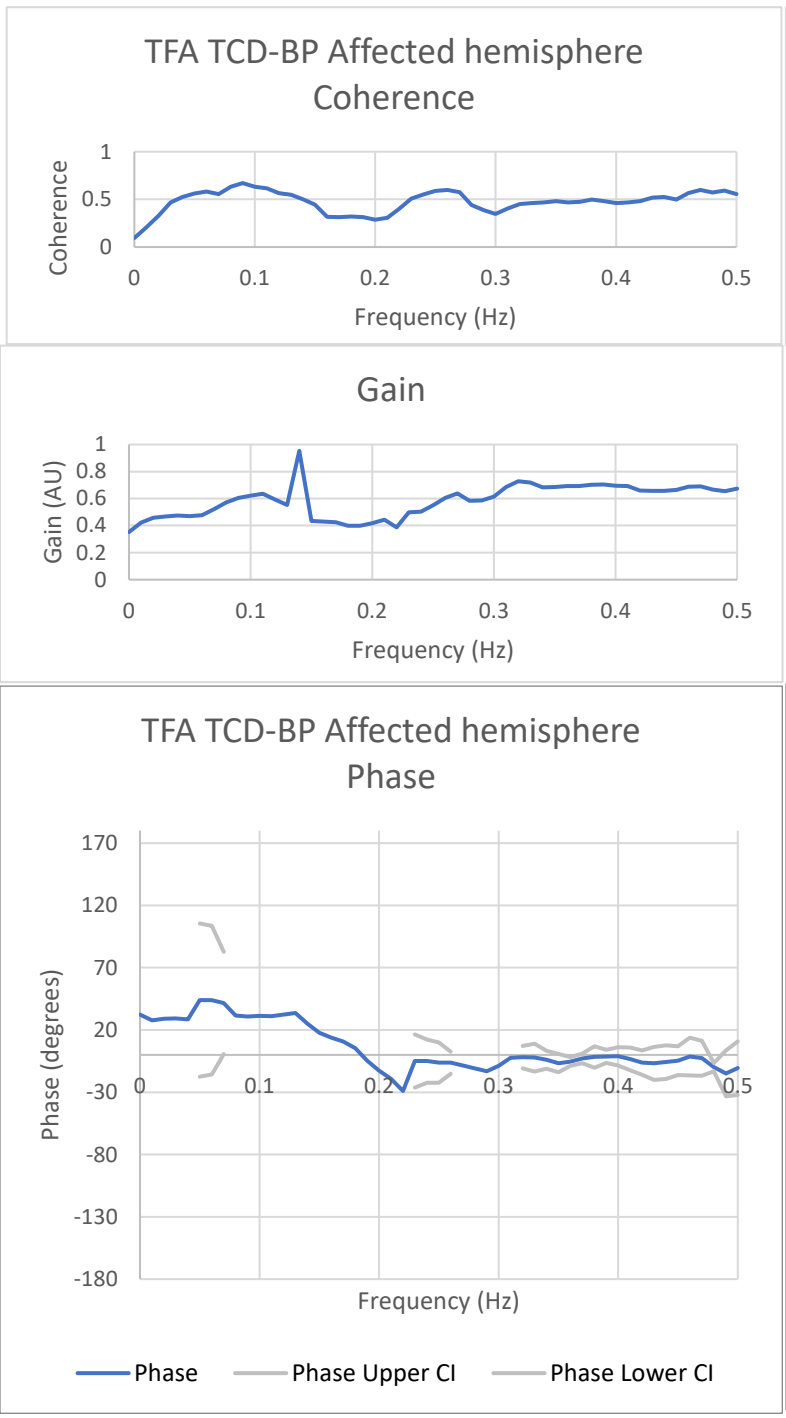
TCD/BP

The group averaged TFA between TCD and BP for the affected and unaffected hemispheres are shown in Figure 11. It can be seen that for both hemispheres, the phase difference between TCD and BP is approximately zero degrees for frequencies above 0.2 Hz, and that it increases to approximately 20 degrees below 0.2 Hz.

In Table 5, the Phase differences in the VLF, LF and HF band are statistically compared between the hemispheres. No statistically significant differences were found between the affected and the unaffected hemisphere.

Table 5: TCD/BP TFA phase parameters for the affected and unaffected sides

	Affected side		Affected side		Unaffected side		Unaffected side		Test statistics	
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Z	*p*
VLF	10.4	10.7	4.01	2.87-14.7	40.5	24.9	57.6	31.5-58.1	-1.604	0.109
LF	15.8	22.4	8.58	0.67-27.4	33.55	23.2	44.1	22.7-49.7	-1.069	0.285
HF	-1.63	3.27	0.067	-3.07-0.66	-5.88	5.65	-2.04	-7.95- -1.88	-1.604	0.109



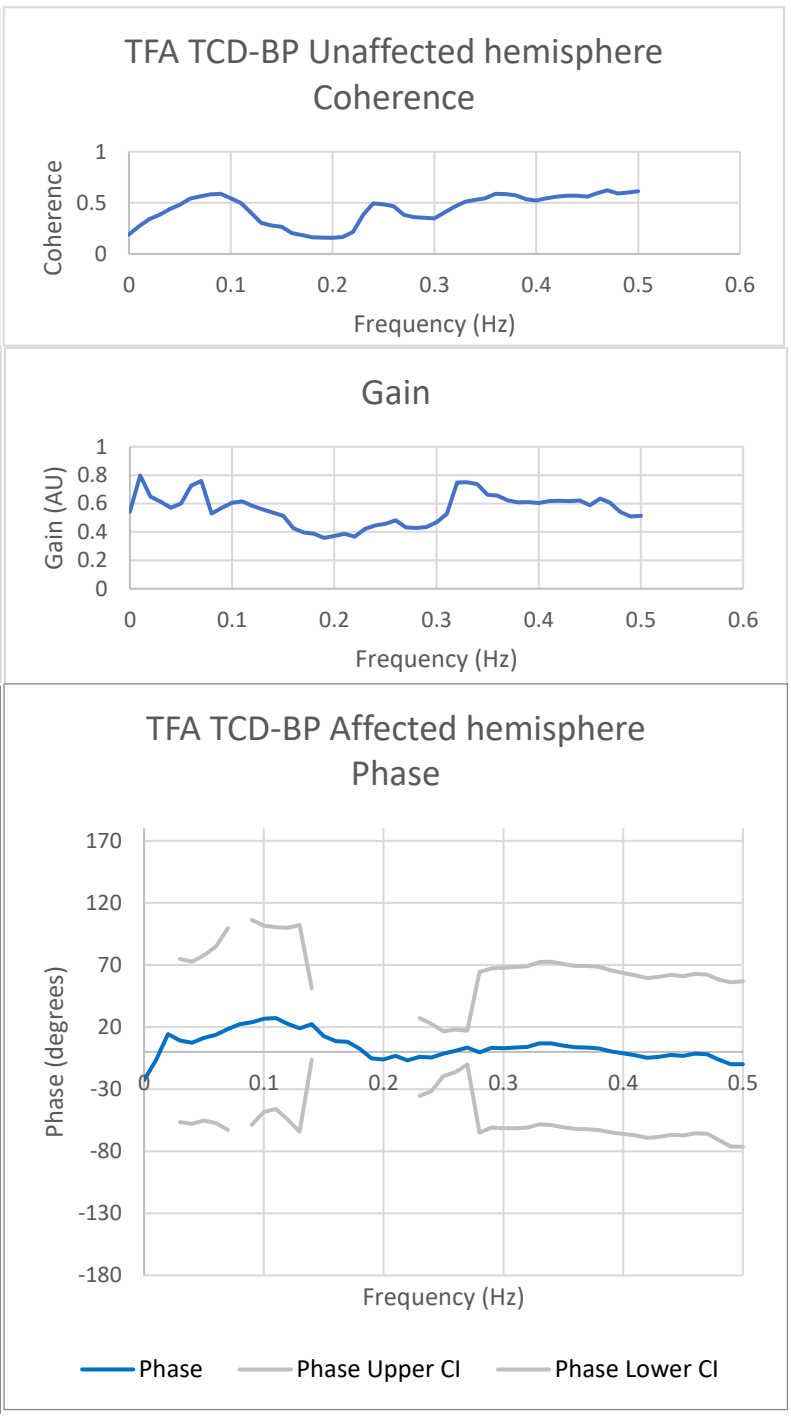


Figure 11: Transfer Function Analyse between TCD and BP for the affected and unaffected hemispheres. Circular 95% Confidence Intervals (CI) are given for the phaseestimates. 95%-CI could not always be calculated with the used method. In these cases the 95%-CI can however be assumed to be large.

Comparison between NIRS-derived and TCD/BP-derived TFA

In Figures 12 and 13, scatter plots are shown with the phase differences in the LF and VLF frequency bands, for both TCD/BP and NIRS. NIRS phase differences are shown with and without TT-BF/BV correction. TCD-data of the affected and unaffected side were available for four and three patients respectively.

For the LF phase, a statistically significant correlation of the LF phase difference for TCD/BP and NIRS without TT-BF/BV correction can be seen (R^2=0.9665; p=0.006). This can be seen in Figure 12. In addition, the phase difference for TCD/BP is lower than for NIRS without TT-BF/BV correction for all four measurements. For the other phase differences in the LF phase band, no siginifant correlations were present. It can be seen that variance between the measurements is high, which can be seen as the deviation of the point from the line of equality: $LFphase_{TCD/BP} = LFphase_{NIRS}$.

In Figure 13, a scatter plot of the phase differences in the VLF band is shown. For only two measurements, coherence in the VLF band was above the significance threshold and phase differences could be calculated. Phase differences in the VLF band were higher for NIRS than for TCD/BP for both measurements, with corresponds to the graphs in Figures 7 and 8.

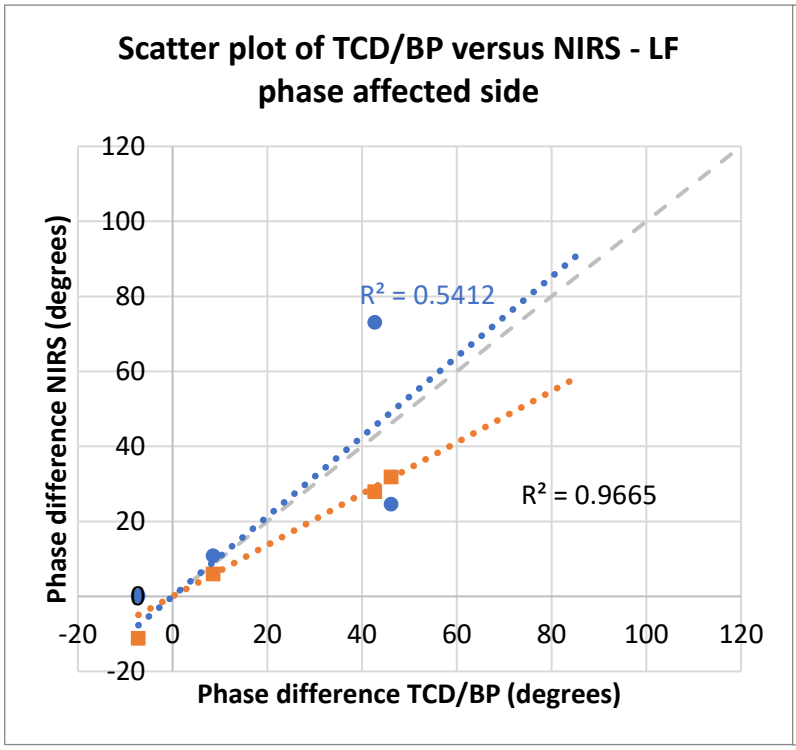
No statistically significant differences were found between the LF and VLF phase differences, as is shown in Tables 6 and 7.

Table 6: Comparison of TCD/BP and NIRS phase parameters - Affected side

	TCD				NIRS					Test statistics	
	Mean	SD	Median	IQR		Mean	SD	Median	IQR	Z	*p*
VLF	10.4	10.7	4.01	2.87-14.7	NIRS – uncorrected	58.2	14.3	48.5	48.1-63.4	-1.342	0.180
					NIRS – TT-BF/BV corrected	72.1	37.6	53.9	45.8-89.2	-1.342	0.180
LF	22.6	22.6	25.6	4.63-43.6	NIRS - uncorrected	13.6	17.4	16.9	1.67-28.9	-1.826	0.068
					NIRS – TT-BF/BV corrected	27.1	27.9	17.7	8.13-36.7	-0.730	0.465

Table 7: Comparison of TCD/BP and NIRS phase parameters - Unaffected side

	TCD				NIRS					Test statistics	
	Mean	SD	Median	IQR		Mean	SD	Median	IQR	Z	*p*
VLF	40.5	24.9	57.6	31.5-58.1	NIRS – uncorrected	151.4	9.37	151.4	146.8-156.1	-1.342	0.180
					NIRS – TT-BF/BV corrected	154.5	13.7	154.5	147.7-161.4	-1.342	0.180
LF	33.6	23.2	44.1	22.7-49.7	NIRS - uncorrected	50.9	29.1	70.0	39.9-71.5	-1.604	0.109
					NIRS – TT-BF/BV corrected	42.0	43.5	30.6	13.0-65.4	0.00	1.000



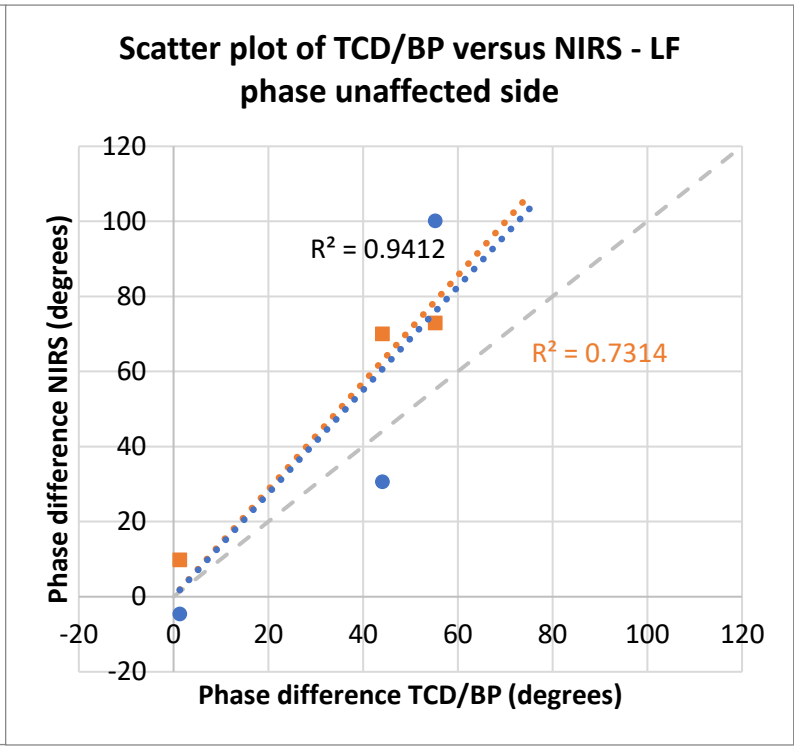
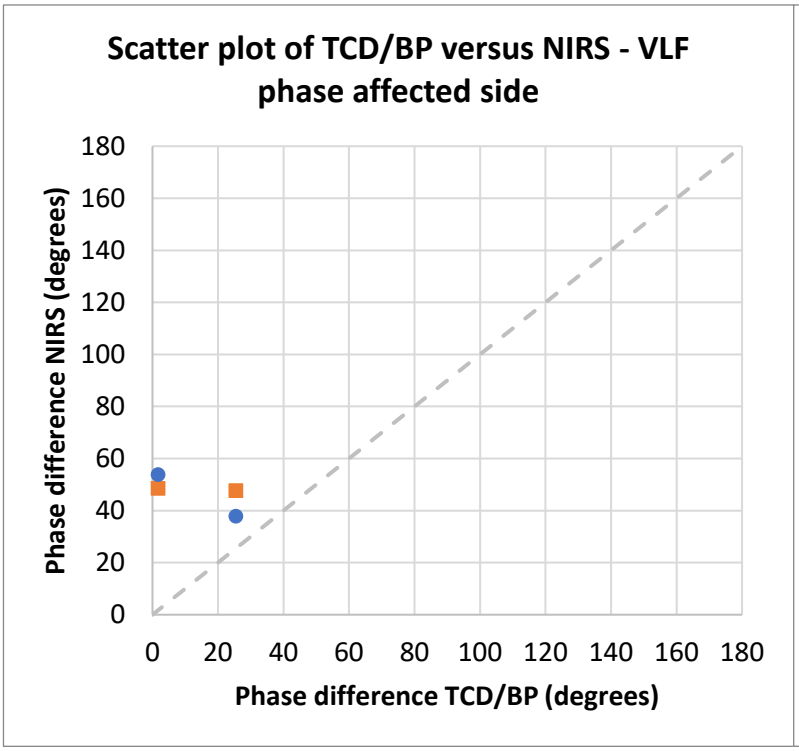


Figure 12: Scatter plot of phase differences in the LF band for TCD/BP and NIRS. In blue, the uncorrected LF phase differences between OxyHb and HHb is plotted. In orange, the TT-BF/BV corrected LF phase difference between OxyHb and HHb is also plotted against TCD/BP. The linear correlations are also shown, together with a p-value for correlation significance. The line of equality $phase_{TCD/BP}$ =$phase_{NIRS}$ is also shown in grey.



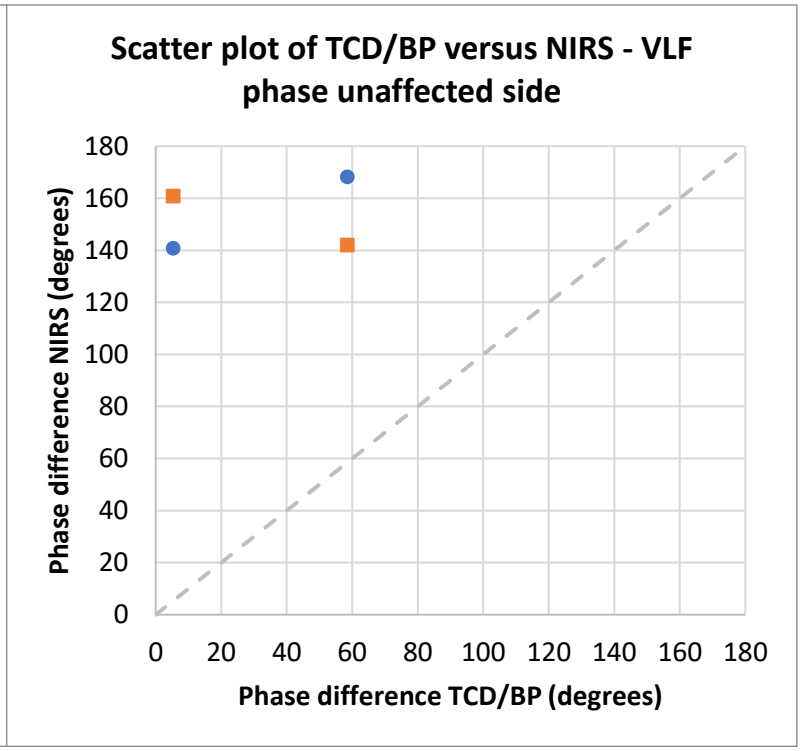


Figure 13: Scatter plot of phase differences in the LF band for TCD/BP and NIRS. In blue, the uncorrected LF phase differences between OxyHb and HHb is plotted. In orange, the TT-BF/BV corrected LF phase difference between OxyHb and HHb is also plotted against TCD/BP. The line of equality $phase_{TCD/BP}$ =$phase_{NIRS}$ is shown in grey.

Power Spectral Density for TCD/BP and NIRS

In Figure 14, the normalised Power Spectral Density (PSD) estimates are shown for NIRS and TCD/BP. PSD is calculated for 4 and 7 (all) patients for TCD/BP and NIRS respectively. For NIRS, power is high for a frequency of 0.01 Hz, the lowest frequency bin. Most power is in the VLF band (0.01 -0.07 Hz). For TCD and BP power is also highest for the VLF band, but there is relatively more power in the LF band (0.07 -0.2 Hz).

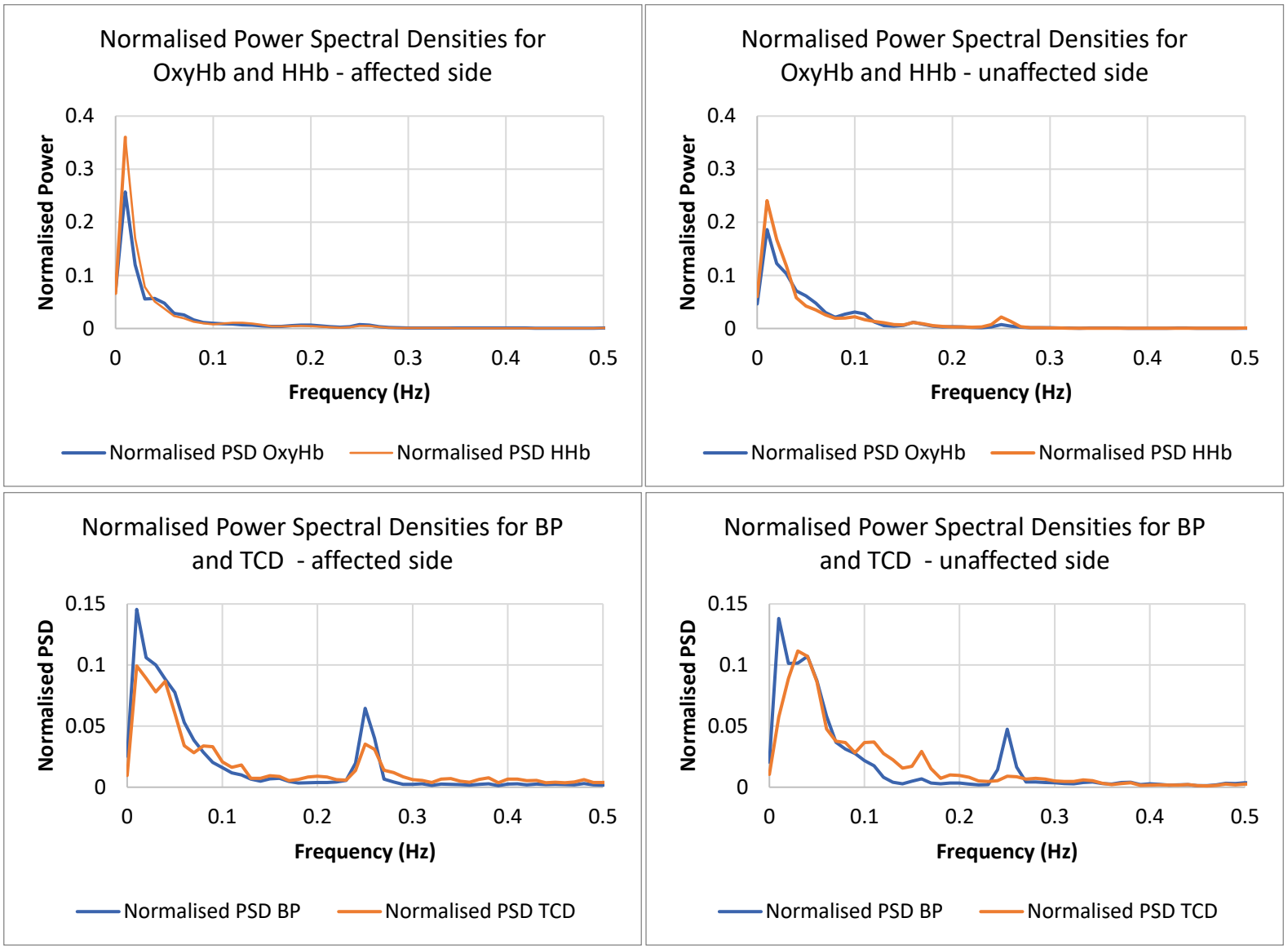


Figure 14: Power Spectral Density estimates, with total power normalised to 1. There is relatively more power in the higher VLF and LF band for TCD/BP than for NIRS.

Discussion

Main findings

In this study, NIRS and TCD/BP derived Dynamic Cerebral Autoregulation was measured in patients with an ischemic stroke who underwent intra-arterial thrombectomy. The two main objectives were to investigate TCD/BP based DCA dynamics in the acute phase of ischemic stroke in the affected and unaffected hemisphere, and to compare NIRS and TCD/BP based DCA estimates in this population. Of the 16 measurements performed, 9 measurements had to be excluded due to insufficient data quality. Of the remaining data, a statistically significant difference in LF phase was found between the affected and unaffected hemisphere, $phase_{LF,\_affected}$=14.1 degrees (SD 13.2) and $phase_{LF\_unaffected}$=63.8 degrees (SD 51.1), p=0.028. In contrast to the study of Elting *et al.*, no similarity was seen between TCD/BP derived phase difference and the NIRS derived TT-BF/BV corrected phase difference, both for the affected and the unaffected hemisphere.[32]

Data exclusion

An unexpectedly high amount of the data had to be excluded due to insufficient data quality. For each measurement modality, several reasons for data exclusion will be explained.

In general, a difficulty of TFA is the fact that segments of at least 100s of artefact-free data are necessary for the TFA calculation. In a stroke population in the acute phase, this prerequisite was found to be challenging to achieve.

TCD: In 12 patients, no sufficient TCD-data could be obtained. This was the result of patient restlessness, absence of an acoustic bone window, and varying operator experience. Although it was expected that some of the patients in our cohort would have an insufficient bone window, we hypothesized that this would be the case in <20% of the patients. It is likely that we underestimated that ischemic stroke patients are generally an older population, who are known to have the have a higher prevalence of insufficient acoustic bone windows. Patient restlessness was also underestimated, it was expected that most patients would be drowsy after the IAT-procedure. In addition, stroke related aphasia and general agitation were not expected to be this prevalent. Regarding the varying operator experience, TCD-measurements were performed by experienced TCD-technicians and the primary researcher, depending on availability. Given that TCD-measurements are difficult to perform and the measurement setup is non optimal, is would have been better if experienced TCD-operators were always available for the measurements.

BP: No sufficient BP-data could be obtained in 9 patients. This was the result of patient restlessness leading to finger movement, and cold fingers. Regarding restlessness, the discussion is equal to that previously discussed for the TCD-data. The cold fingers were unexpected, but could have been expected because of stroke patient characteristics such as high age and vascular disease.

NIRS: In 9 patients, no sufficient NIRS-data could be obtained. Artefacts in the NIRS-data were all the result of general head movement and movement of the forehead due to frowning. Although both TCD and NIRS measurements were disturbed by head movement, the underlying mechanism and eventual effect on signal quality was different. For TCD, head movement often resulted in a complete loss of the TCD-signal, but after refocussing of the probes, signal was quickly regained with little to no baseline drift. Short artefacts in TCD could therefore often be linearly interpolated. For NIRS, head movement induced large artefacts, sometimes with baseline drift due to minor sensor displacement or movement of the skin of the forehead. These artefacts could not be corrected with linear interpolation and removal of the data was performed. Correction of the baseline drift may have been performed, but this would be an invalid approach since the baseline drift may be accompanied by

subsequent drift of the signal due to slow movement of the skin on the forehead moving back to its original position. The baseline drift would not correct this slow skin movement. Furthermore, the NIRS-sensor may probe a slightly different brain area after displacement.

In Appendix B: Measurement setup development, changes in the measurement setup and suggestions are described.

Interpretation of the results

Phase correlation NIRS/TCD

The absolute NIRS phase difference values were not similar to TCD/BP phase difference. However, the correlation between NIRS and TCD/BP phase was high. It was particularly high for the uncorrected NIRS LF phase difference $R^2_{affected\_hemisphere}$=0.967, p=0. ; $R^2_{unaffected\_hemisphere}$=0.942, p=0. For the VLF band band, no correlation could be found. This indicates that there may indeed be a relation between TCD/BP and NIRS phase in the LF band, which is also the frequency range most often investigated for Cerebral Autoregulation.[22]

TT-BF/BV correction

The uncorrected NIRS phase difference showed a better correlation with TCD/BP phase difference than the TT-BF/BV corrected phase difference. Furthermore, the LF band difference between the affected and unaffected hemispheres was not present for the TT-BF/BV LF phase. An explanation can be found in the very low phase difference values in the HF band. The trendline direction is more prone to noise when all values are centred around zero. When phase difference in the HF band is approximately zero, it may be better to not perform TT-BF/BV correction. Decision thresholds for this can be the linear correction coefficient (R^2) or the mean squared error (MSE) of the trendline. These are already calculated in the Labview software.

Power spectral density

There are differences in the frequency components of the TCD/BP and NIRS signals. The NIRS data contain more VLF frequencies, in particular a frequency of 0.01 Hz, the lowest frequency bin. This is indicative of drift in the signals, which was indeed sometimes present in the data. The TCD/BP data contained more frequencies around 0.1 Hz and, interestingly, frequencies around 0.25 Hz. These likely arise from respiration or ventilation. The presence of such high VLF frequencies is indicative of either slow artefacts (drift) or physiologic variation that is not related to TCD/BP. Both would lead to a violation of the pure TCD/BP dependence of the NIRS signals.

Per patient analysis

Because only limited measurements were available and several confounding factors may have influenced the TCD/BP and NIRS signals, a more detailed look into the individual patient data was described in Appendix A. This provided a better insight into the results. The results should be interpreted with caution, as an eyeballing- or confirmation bias may be present.

In total, 7 conclusions were drawn based on the analysis of the individual patient data:

1. Differences in TFA phase can be seen between the affected and unaffected hemisphere
2. There is an inter-hemispheric variation in TCD mean flow velocity and Pulsatility Index that likely influences TFA calculation
3. Extrasystolic heart-beats were present that may influence the TFA calculation, although their exact effect is unknown

4. No similarity between the TCD/BP phase difference and OxyHb/HHb phase difference was seen in the individual patient data
5. The TCD/BP phase difference estimation could not been performed due to low coherence in a surprisingly large amount of the frequencies, which may have been the result of:
    a. Poor TCD-signal quality
    b. Large, BP-independent TCD flow velocity oscillations, that violate the TFA assumption of (mostly) BP-dependence
6. There may be a relation between clinical outcome and TCD/BP phase difference, based on the measurements of two patients

Other general conclusions:

7. For all measurements, paCO2 levels remained within the normal range of 5.1-5.8 kPa.
8. Non-invasive upper arm cuff Blood Pressure was withinin the normal to hypertensive range (70-107 mmHg)

Comparison with clinical outcome

In this study, no statistical comparison of NIRS- or TCD/BP-derived CA with clinical outcome was performed yet, due to the very limited data set with multiple potential confounders. This comparison should be performed when a larger data set is available. However, as described in Appendix A: Per patient analyse, the TCD/BP phase difference may be related with clinical outcome in two patients. These patients have either a low TCD/BP phase with poor outcome (hemorrhagic transformation) or a high TCD/BP phase with good outcome (NIHSS 3, no complications).

Future research:

Three main suggestions for future research should be given:

1. Inclusion of patients in the post-IAT study should continue, because (small) differences in the phase values between the affected and unaffected hemisphere could be found and there was a correlation between TCD/BP LF phase and NIRS LF phase. Furthermore, the measurements constitute a unique data of which the results should be open to the public. However, the measurements should be performed with the full setup. An experienced TCD-operator should therefore be present during the measurements. The measurement setup should be more controlled, preferable only in ventilated patients on the ICU.
2. To facilitate a high-quality comparison of TCD/BP and NIRS derived CA in clinical population, an additional study in the operating room in which cerebral blood flow is altered, should be performed. Carotid end-arterectomy (CEA) is a promising measurement setup, because TCD and BP measurements are already performed as part of routine clinical care. During CEA, flow to the brain is stopped in one carotid artery, which induces a large, controlled alteration in cerebral blood flow. Finally, the patient is under general anaesthesia, which limits movement.
3. As discussed in Appendix B: Measurement setup development, new devices may be needed to improve data quality. BP can be measured invasively with a intra-arterial catheter, bilateral simultaneous NIRS measurements require a different NIRS-device that prevent cross-talk. For TCD-measurements, a different TCD-head frame is needed if simultaneous NIRS+TCD are performed. Accelerometers for artefact detection are preferably wireless. End-

tidal CO_2 measurement are preferred to transcutaneous CO_2 because of the better validation and higher temporal resolution.

For the interpretation of the data, a 'broader scope' should be used. Data interpretation should be extended beyond the comparison 'TCD/BP versus NIRS for Transfer Function Analysis to estimate Cerebral Autoregulation'. Several routinely used TCD parameters could be compared with NIRS parameters and clinical outcome, such as the Pulsatility Index (PI) and mean CBFV. In the current measurements, differences in PI and mean CBFV have already been observed in the affected compared to the unaffected hemispheres. Furthermore, other measurement modalities could be used in addition to TCD/BP and NIRS to measure Cerebral Autoregulation. Intra-cranial pressure (ICP) based CA estimations exist[11] and it would be interesting to investigate NIRS-dynamics during changes in ICP or ICP-based CA.

The improvement of data quality should be twofold:

1. The suggestions for measurement setup optimisation described in Appedix B, should be implemented.

2. Artefact detection and correction should be improved. Detection of artefacts is difficult for NIRS data. No gold standard is available for normal, physiologic NIRS data. Furthermore, artefact appearance was found to be very similar to normal data, for example during ventilation movement artefacts or slow head movement. I have investigated this in my internship before the graduation project for several types of movement artefacts (unpublished findings). The gold standard for artefact detection is still visual inspection, but concurrent signals (e.g. TCD, BP, accelerometers) are necessary to distinguish artefacts from non-artefact. Very slow movements of the body or slow drift of the sensor, cannot be detected using the accelerometers, because of their limited resolution. For these movement, a strain gauge may be used that is attached to the forehead or directly on the NIRS-sensor. This sensor has been developed in the last months of my graduation in collaboration with the Robotics and Mechatronics (RaM) research group of the University of Twente. The potential for the detection of slow movement artefacts in NIRS data should be investigated.

Conclusion

In this study, a significant difference was found between the NIRS LF phase difference in the affected and unaffected. NIRS phase difference and TCD/BP phase difference were not similar, in contrast with previous research. There was however a significant correlation between TCD/BP LF phase and NIRS LF phase. Data from 9 of 16 measurements had to be excluded due to poor data quality. Several improvements for the measurement setup for future studies were suggested. The main suggestions were a more controlled measurement environment, different measurement devices and measurements only in co-operative or anaesthetised patient.

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Appendix A: Per patient analysis

For the four patients with the full measurement setup including TCD, BP and NIRS measurements of sufficient quality, an in-depth analysis of the data is performed.

Patient 004

Patient characteristics

Age	58
Gender	Male
Side of occlusion	Left
Occluded vessel	ICA
TICI-score	2b
Time after TLSW - affected side (Hours:Minutes)	05:41
Time after TLSW - unaffected side (Hours:Minutes)	05:55
Wake-up stroke	No
Time after Recanalization – affected side (Hours:Minutes)	00:57
Time after Recanalization – unaffected side (Hours:Minutes)	01:11
Received intra-venous thrombolytics	Yes
NIHSS at admission	14
Occlusion/stenosis in ICA/CCA after recanalization	No

Outcome <48 Hours

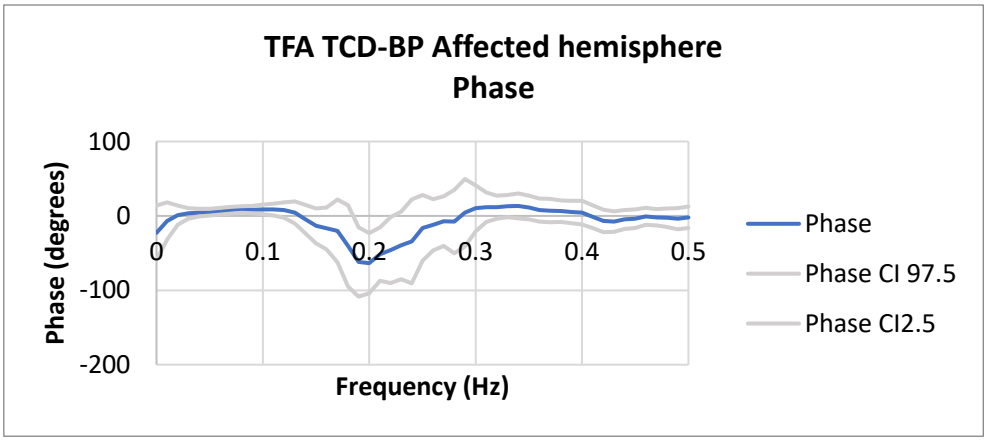
Patient deceased?	No
Haemorrhagic transformation/Cerebral edema/New ischemia/Re-occlusion	Yes
NIHSS closest to 48 hours	At least 16 (data missing)
NIHSS impairment with respect to admission	Yes

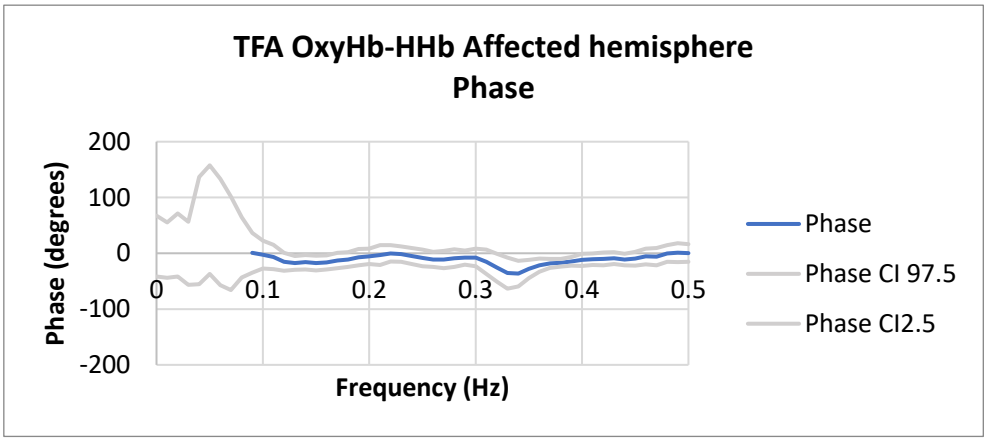
Characteristics during measurement

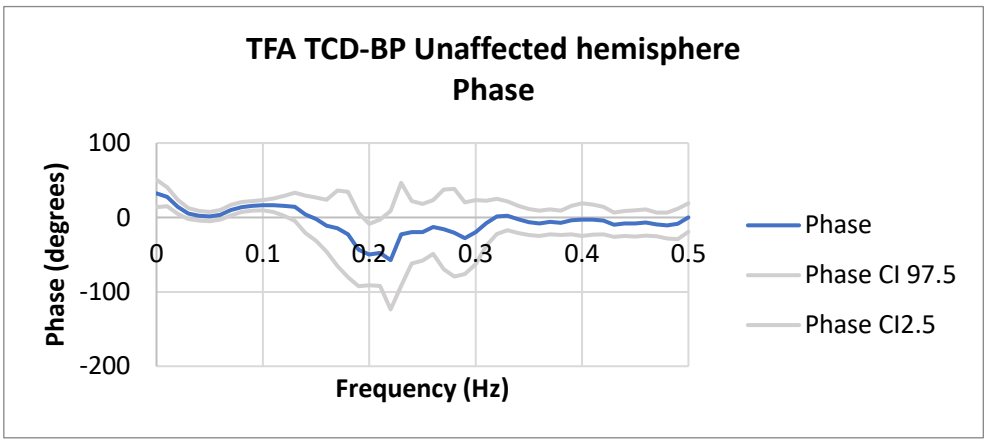
Mean arterial blood pressure (Non-invasive arm blood pressure cuff)	Unknown
paCO2 (transcutaneous)	Unknown
TCD – mean flow velocity affected (m/s)	86.1
TCD – mean flow velocity unaffected (m/s)	51.9
TCD – Pulsatility Index (PI) affected	0.74
TCD – Pulsatility Index (PI) unaffected	1

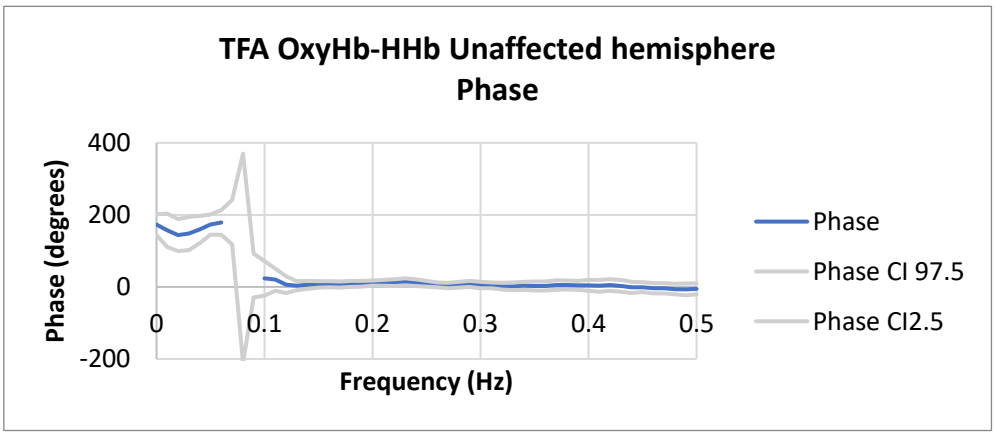
Data quality

Setting	Stroke Unit
% of good quality measurement – NIRS affected	Approximately 50%
% of good quality measurement – NIRS unaffected	Approximately 50%
% of good quality measurement –BP/TCD affected	Approximately 80%
% of good quality measurement –BP/TCD unaffected	Approximately 80%
Duration NIRS affected (mins:secs)	06:19
Duration NIRS unaffected (mins:secs)	09:54
Duration BP/TCD affected	28:50
Duration BP/TCD unaffected	30:31


TFA TCD-BP Affected hemisphere
Phase
Phase (degrees)
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Affected hemisphere
Phase
Phase (degrees)
200
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

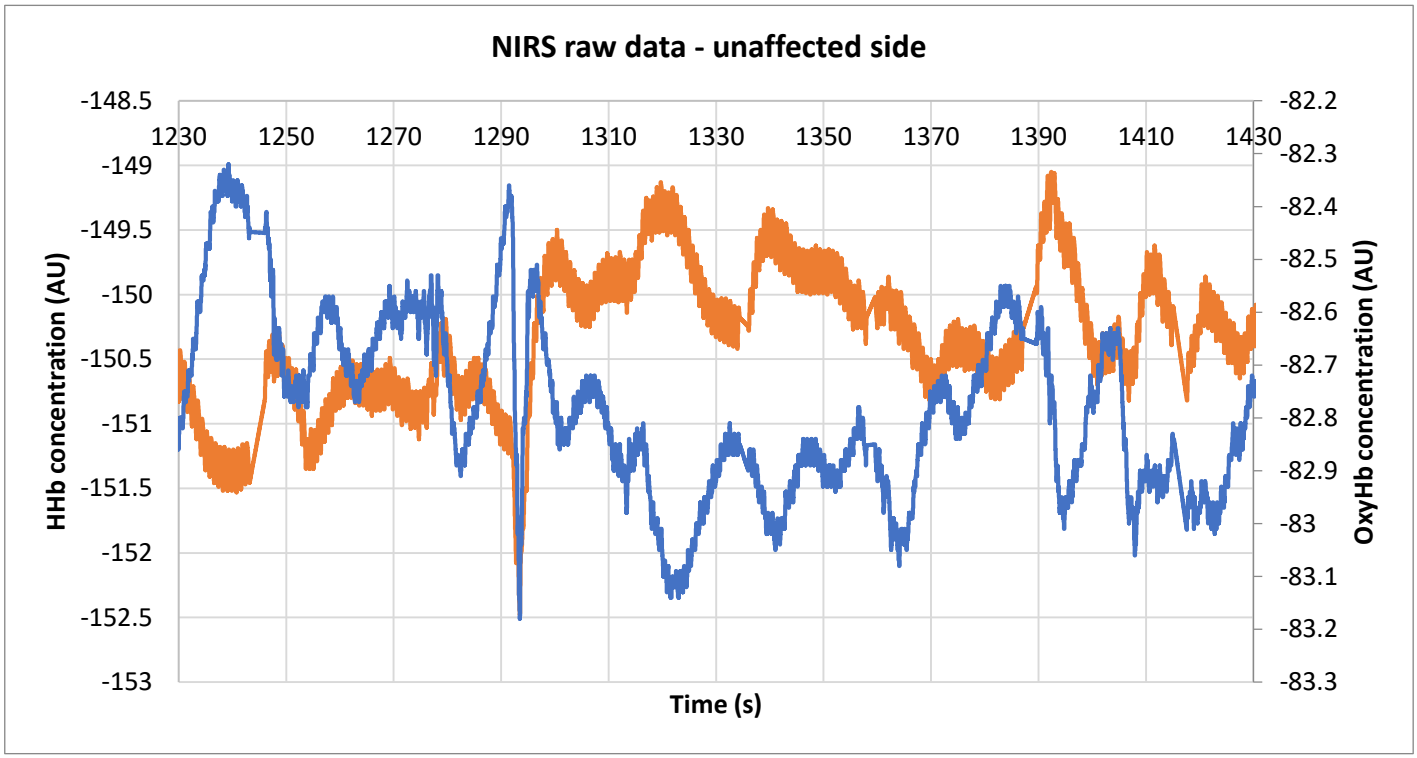

TFA TCD-BP Unaffected hemisphere
Phase
Phase (degrees)
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

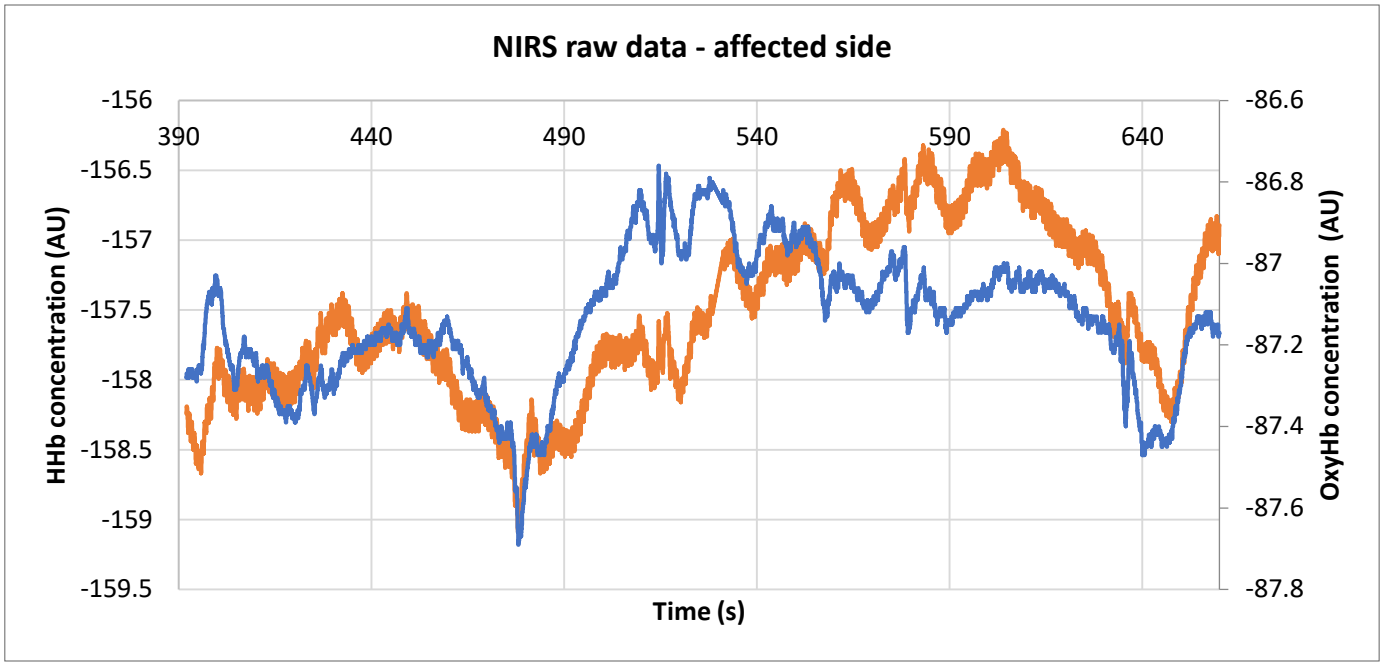

TFA OxyHb-HHb Unaffected hemisphere
Phase
Phase (degrees)
400
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

Interpretation

For this patient, approximately 50% of the NIRS data and 70% of the TCD/BP data could be used for the TFA-calculation. In the affected hemisphere, the phase difference between OxyHb and HHb was approximately zero degrees for all frequency bands above 0.1 Hz. For frequencies below 0.1 Hz, the coherence was often below the significance threshold, but still a phase difference of 180 degrees can be seen in the unaffected hemisphere. In the phase of the TT-BF/BV framework, this can be interpreted as there being almost only 'Blood Volume oscillations', except for low frequencies. This may be attributed to present Cerebral Autoregulation action for these frequencies.

Looking at the raw data, large, slow out-of-phase oscillations can be identified on the unaffected side, but not on the affected side. These oscillations have a very large amplitude relative to the faster oscillations. It might be that for this frequency, the amplitude of the oscillations is out of the 'limits of linearity', one of the assumptions of Transfer Function Analysis.





TCD/BP

For all frequencies in both hemispheres, the phase difference between TCD and BP is very low. Interestingly, for frequencies around 0.2 Hz, there is even a negative phase difference. Looking at the raw data, no explanation for this negative phase difference could be found. As the confidence limits are quite large, and it is seen on both hemispheres, the negative phase difference could be a results of noise in the data. This needs to be looked into further.

Interestingly, the autoregulation phase difference in the LF-band is not present, which might indicate absent autoregulation in both hemispheres. The mean TCD flow velocities are higher in the affected compared to the unaffected hemisphere. The pulsatility index (PI) was lower in the affected hemisphere, which might be indicative of decreased distal cerebral vascular resistance ('open vessels'). Interestingly, the patient eventually developed a haemorrhagic transformation (bleeding) in the infarct hemisphere, a well-known complication of hyperperfusion of an infarct brain area.

Comparison NIRS-derived CA and TCD/BP-derived CA

Low phase differences are present for NIRS and TCD/BP. The TT-BF/BV correction does not result in a different phase plot.

General conclusions:

1. In general low phase differences for NIRS and TCD/BP
2. For frequencies <0.1 Hz, large counter-phase oscillations are present on the unaffected side, but not on the affected side
3. For the NIRS-signals, there are strong differences in the amplitude of different frequency oscillations
4. For the TCD/BP signals, there is a small negative phase differences around 0.2 Hz
    a. CA may be absent in this patient in both hemispheres
    b. The patient had a poor outcome (haemorrhagic transformation), with may be correlated with the absent CA
5. Differences in TCD mean flow velocity and PI are seen between the hemispheres

Patient 015

Patient characteristics

Age	81
Gender	Male
Side of occlusion	Right
Occluded vessel	MCA
TICI-score	2b
Time after TLSW - affected side (Hours:Minutes)	04:29
Time after TLSW - unaffected side (Hours:Minutes)	04:48
Wake-up stroke	No
Time after Recanalization – affected side (Hours:Minutes)	01:19
Time after Recanalization – unaffected side (Hours:Minutes)	01:38
Received intra-venous thrombolytics	No
NIHSS at admission	4
Occlusion/stenosis in ICA/CCA after recanalization	No

Outcome <48 Hours

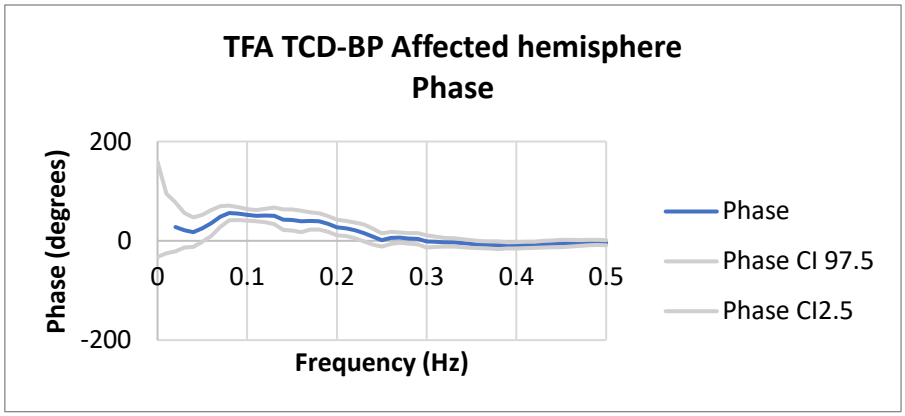
Patient deceased?	No
Haemorrhagic transformation/Cerebral edema/New ischemia/Re-occlusion	No
NIHSS closest to 48 hours	3
NIHSS impairment with respect to admission	No

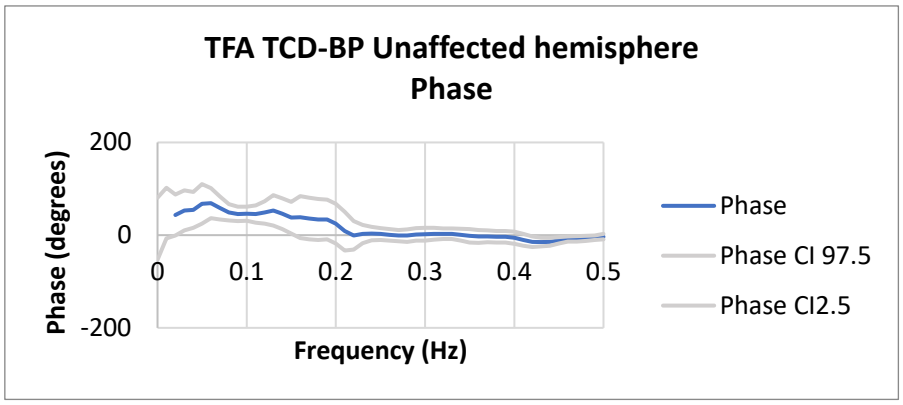
Characteristics during measurement

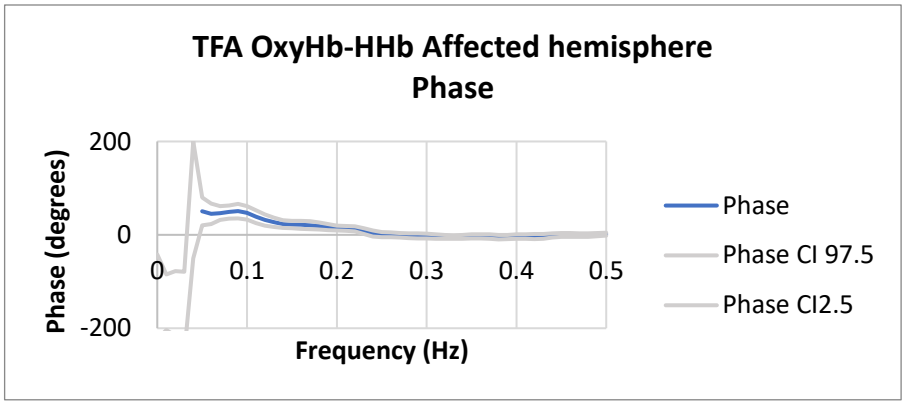
Mean arterial blood pressure (Non-invasive arm blood pressure cuff)	107.2
paCO2 (transcutaneous)	5.7
TCD – mean flow velocity affected (m/s)	48.8
TCD – mean flow velocity unaffected (m/s)	45.9
TCD – Pulsatility Index (PI) affected	1.17
TCD – Pulsatility Index (PI) unaffected	1.19

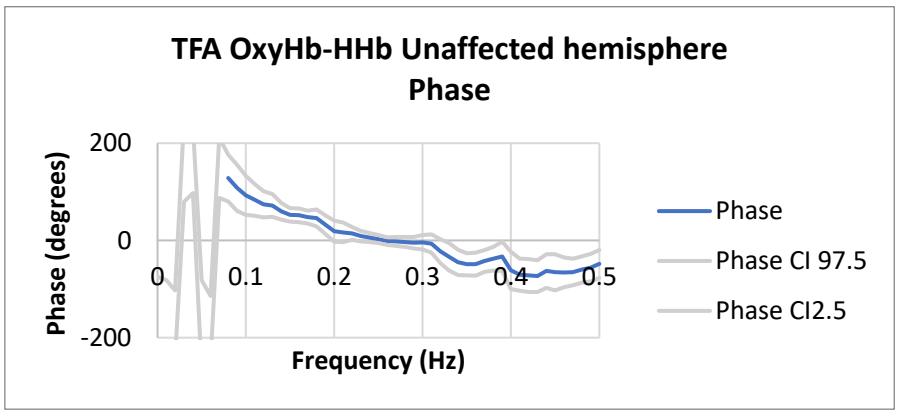
Data quality

Setting	Stroke Unit
% of good quality measurement – NIRS affected	Approximately 85%
% of good quality measurement – NIRS unaffected	Approximately 80%
% of good quality measurement –BP/TCD affected	Approximately 95%
% of good quality measurement –BP/TCD unaffected	Approximately 95%
Duration NIRS affected (mins:secs)	09:55
Duration NIRS unaffected (mins:secs)	09:10
Duration BP/TCD affected	11:11
Duration BP/TCD unaffected	11:06


TFA TCD-BP Affected hemisphere
Phase
Phase (degrees)
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA TCD-BP Unaffected hemisphere
Phase
Phase (degrees)
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Affected hemisphere
Phase
Phase (degrees)
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Unaffected hemisphere
Phase
Phase (degrees)
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

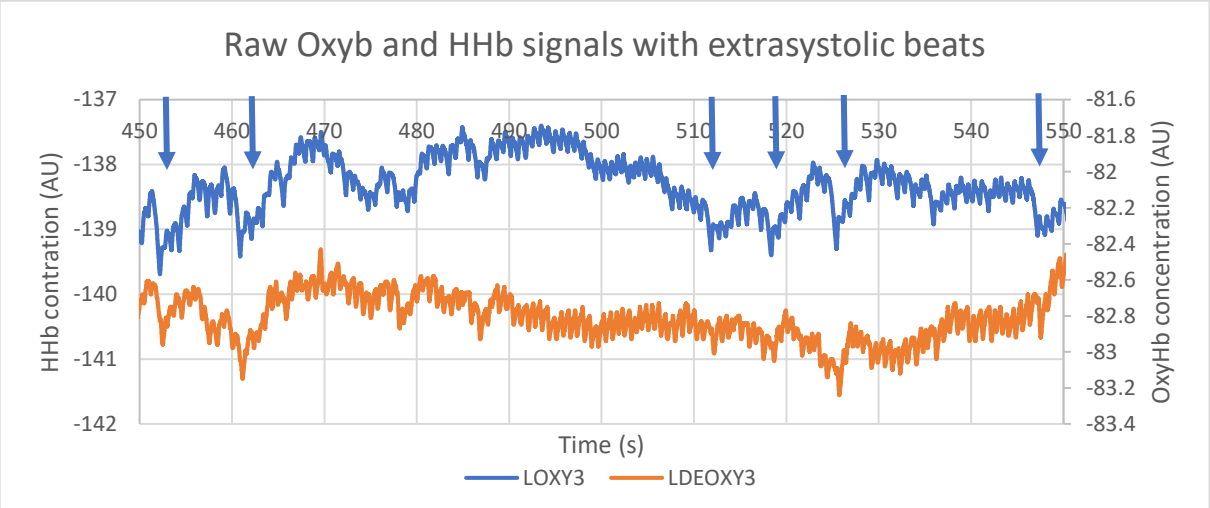
Interpretation

This measurement contained very few artefacts, approximately 80% of the NIRS data and 95% of TCD/BP data could be used.

NIRS

In the affected hemisphere, the phase difference of 50-70 degrees is present. For higher frequencies, phase is approximately zero degrees. In the unaffected hemisphere, the phase appears to linearly decrease with frequency. Interpreting this using the TT-BF/BV framework, this could indicate a microvascular Transit Time effect.

Looking into the raw NIRS data of the unaffected hemisphere, a clarification for the 'deviating' TFA phase plot of unaffected hemisphere may be seen. This patient had several extra-systolic beats during the recording on the unaffected side, which were verified online on the clinical patient



monitor and offline using the TCD and BP signals. These result in short, high amplitude OxyHb and HHb concentration changes. It is uncertain how these changes influence the TFA calculation. The high amplitude and short duration may result in non-linear dynamics, which cannot accurately be analysed using linear TFA. In the Whitepaper on TFA for CA, it is therefore advised to exclude data that contains 'considerable amounts' of extrasystolic beats.[22] On the other hand, the extrasystolic beats result in blood pressure and cerebral perfusion variation, which is an important prerequisite for analysis of CA.[27]

TCD/BP

For both hemispheres, a phase difference of 50-80 degrees in the LF band was present for frequencies below 0.2 Hz. TCD Flow velocities and PI were also similar in both hemispheres. This may indicate an intact CA. This patient had a very good neurological outcome within 48 hours, with an NIHSS of 3 and no neurological complications.

General conclusions

1. No difference in TCD/BP phase between the hemispheres
2. Differences between both hemispheres in NIRS phase. On the unaffected side, multiple extrasystolic beats during the measurement
3. TFA TCD/BP and TFA NIRS not similar on unaffected side
4. TCD/BP phase difference was 50-80 degrees, indicating intact autoregulation The patient had a good neurological outcome.

Patient 016

Patient characteristics

Age	82
Gender	Female
Side of occlusion	Right
Occluded vessel	MCA
TICI-score	2c
Time after TLSW - affected side (Hours:Minutes)	04:37
Time after TLSW - unaffected side (Hours:Minutes)	05:06
Wake-up stroke	No
Time after Recanalization – affected side (Hours:Minutes)	00:55
Time after Recanalization – unaffected side (Hours:Minutes)	01:24
Received intra-venous thrombolytics	No
NIHSS at admission	19
Occlusion/stenosis in ICA/CCA after recanalization	No

Outcome <48 Hours

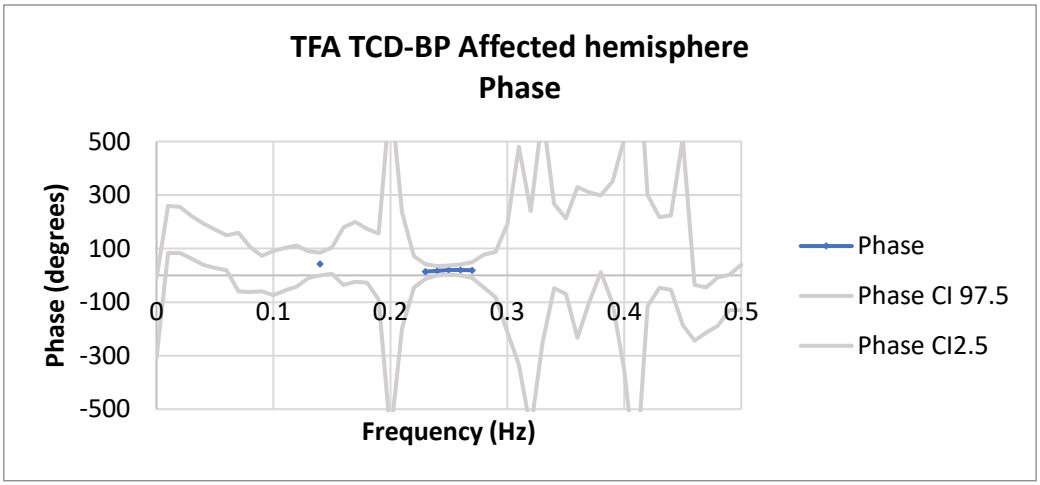
Patient deceased?	No
Haemorrhagic transformation/Cerebral edema/New ischemia/Re-occlusion	No
NIHSS closest to 48 hours	16 or 17
NIHSS impairment with respect to admission	No

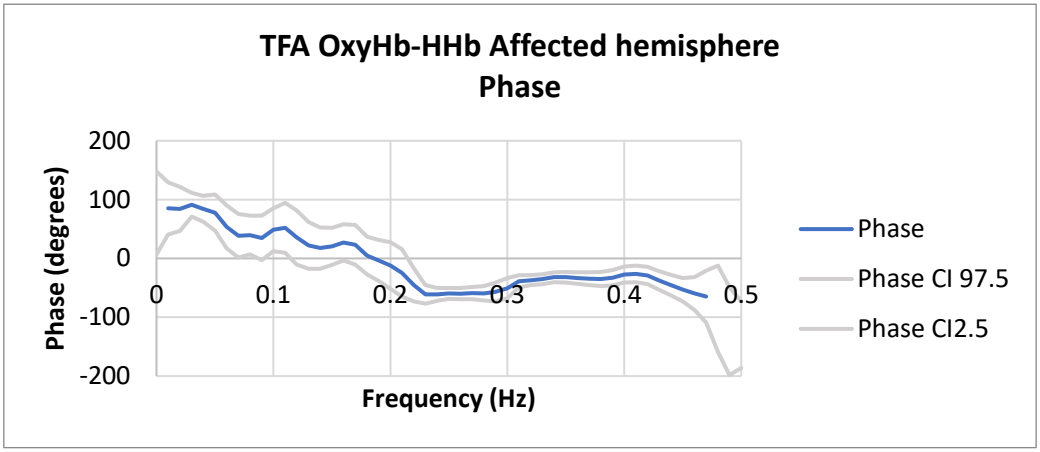
Characteristics during measurement

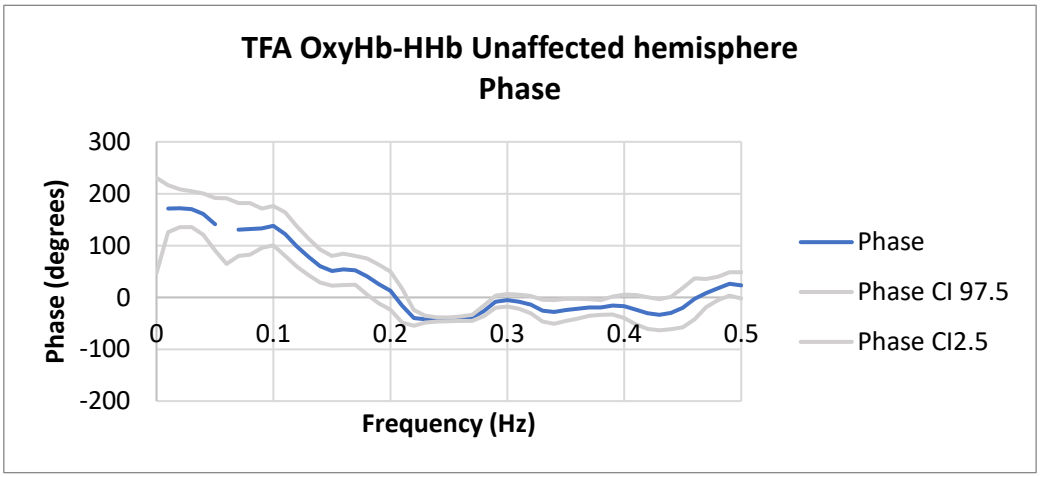
Mean arterial blood pressure (Non-invasive arm blood pressure cuff)	73.7
paCO2 (transcutaneous)	5.5
TCD – mean flow velocity affected (m/s)	31.6
TCD – mean flow velocity unaffected (m/s)	N/A
TCD – Pulsatility Index (PI) affected	1.06
TCD – Pulsatility Index (PI) unaffected	N/A

Data quality

Setting	Stroke Unit
% of good quality measurement – NIRS affected	Approximately 55%
% of good quality measurement – NIRS unaffected	Approximately 60%
% of good quality measurement –BP/TCD affected	Approximately 30%
% of good quality measurement –BP/TCD unaffected	0%
Duration NIRS affected (mins:secs)	09:32
Duration NIRS unaffected (mins:secs)	10:55
Duration BP/TCD affected	05:47
Duration BP/TCD unaffected	00:00


TFA TCD-BP Affected hemisphere
Phase
Phase (degrees)
500
300
100
-100
-300
-500
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Affected hemisphere
Phase
Phase (degrees)
200
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Unaffected hemisphere
Phase
Phase (degrees)
300
200
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

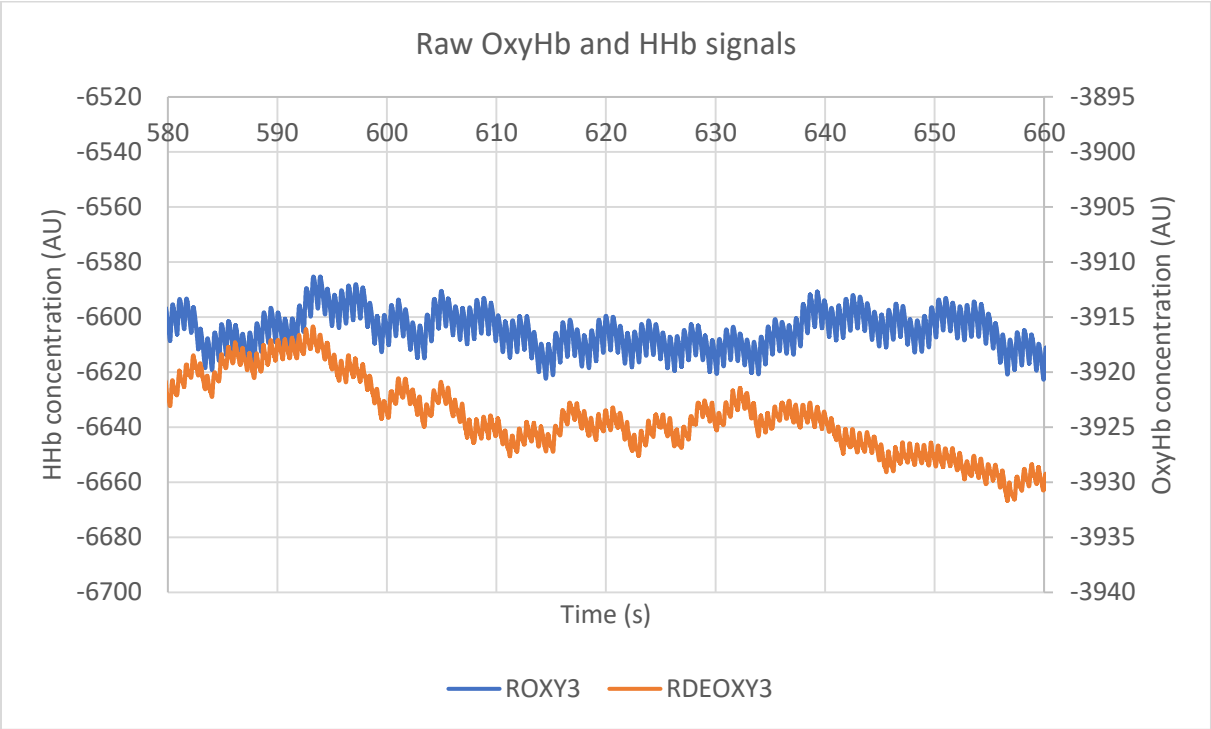
Interpretation

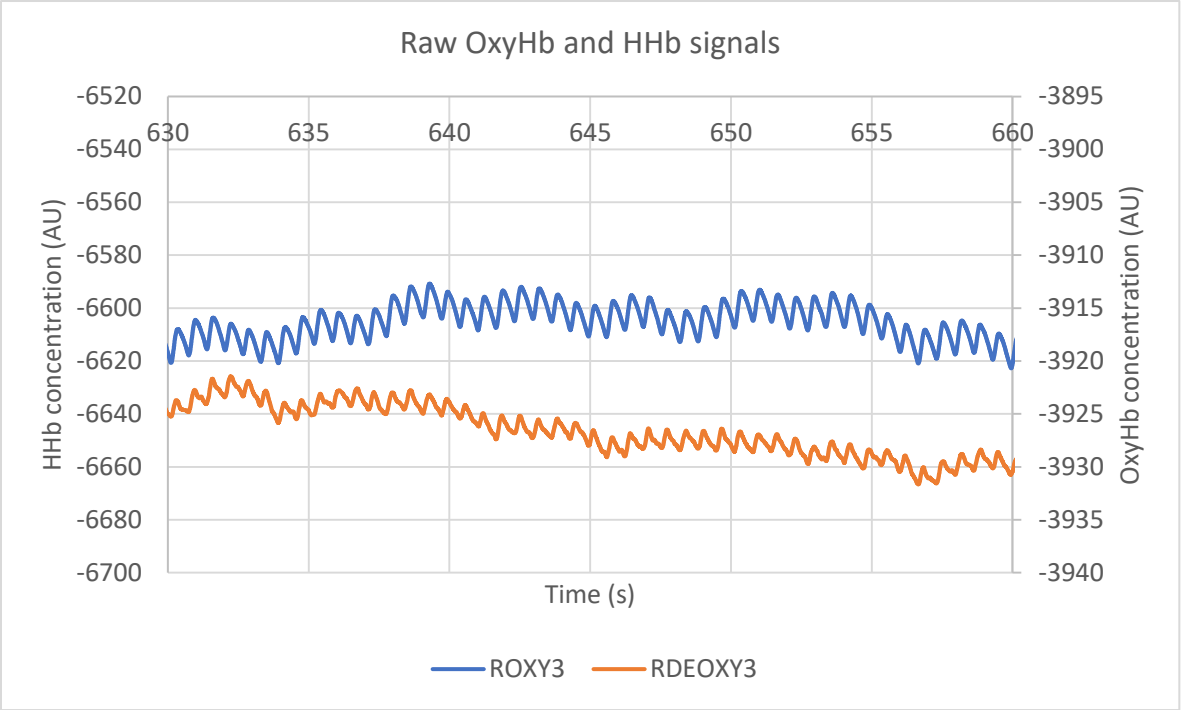
For this measurement, acquisition of the TCD-data was difficult, due to a poor acoustic bone window and patient restlessness. Only on one side, a TCD-signal was found and sufficient data could be obtained.

NIRS

For both hemispheres, there is a negative phase difference for frequencies above 0.2 Hz. For frequencies below 0.2 Hz, the phase difference is up to 95 degrees for affected hemisphere and up to 170 degrees for the unaffected hemisphere.

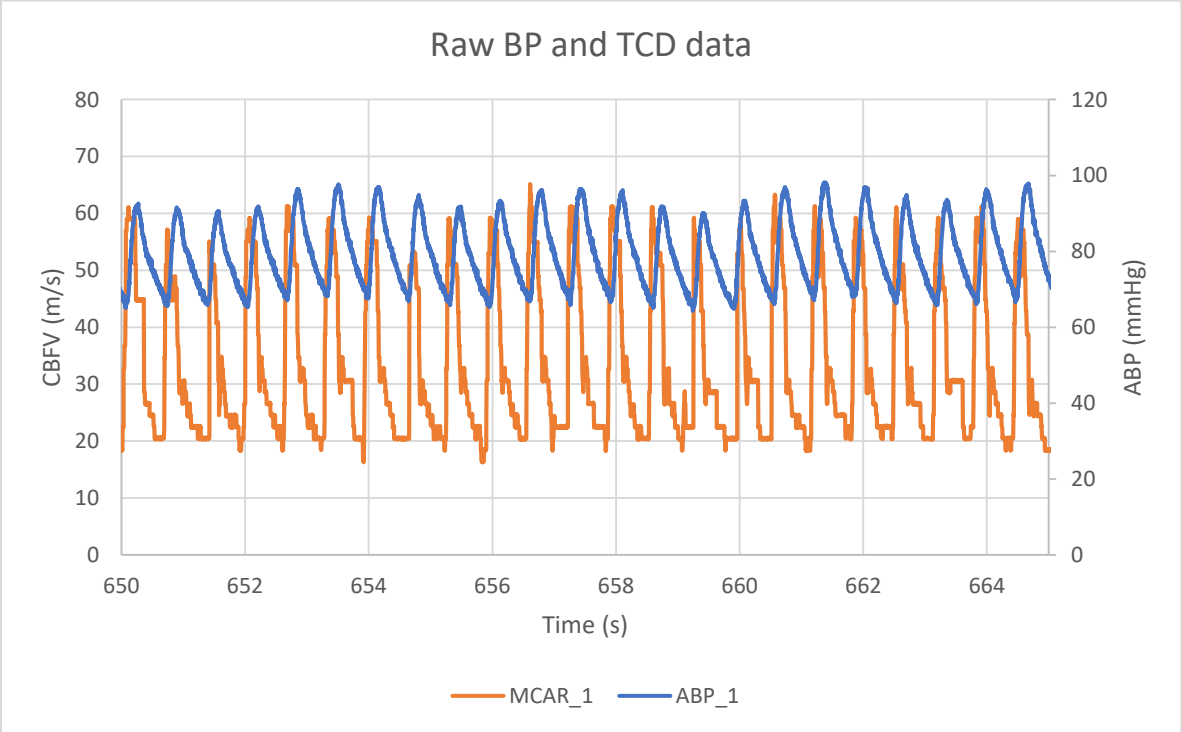
Looking into the raw data, this negative phase difference cannot clearly be recognised.





TCD

Of the data from the affected hemisphere, the TFA phase plot could only be constructed for a couple of frequency bands, as coherence was below the significance threshold for the other frequencies. In the raw TCD and BP data, the TCD-envelope is of poor quality and often data is lost. Retrospectively, the data of this measurement should be excluded.



General conclusions

1. Poor TCD-envelope results in a low TFA coherence and poor phase estimation.
2. Unexplained negative phase differences for frequencies above 0.2 Hz.

Patient 017

Patient characteristics

Age	58
Gender	Female
Side of occlusion	Left
Occluded vessel	ICA
TICI-score	2c
Time after TLSW - affected side (Hours:Minutes)	07:13
Time after TLSW - unaffected side (Hours:Minutes)	07:28
Wake-up stroke	No
Time after Recanalization – affected side (Hours:Minutes)	02:25
Time after Recanalization – unaffected side (Hours:Minutes)	02:40
Received intra-venous thrombolytics	Yes
NIHSS at admission	19
Occlusion/stenosis in ICA/CCA after recanalization	No

Outcome <48 Hours

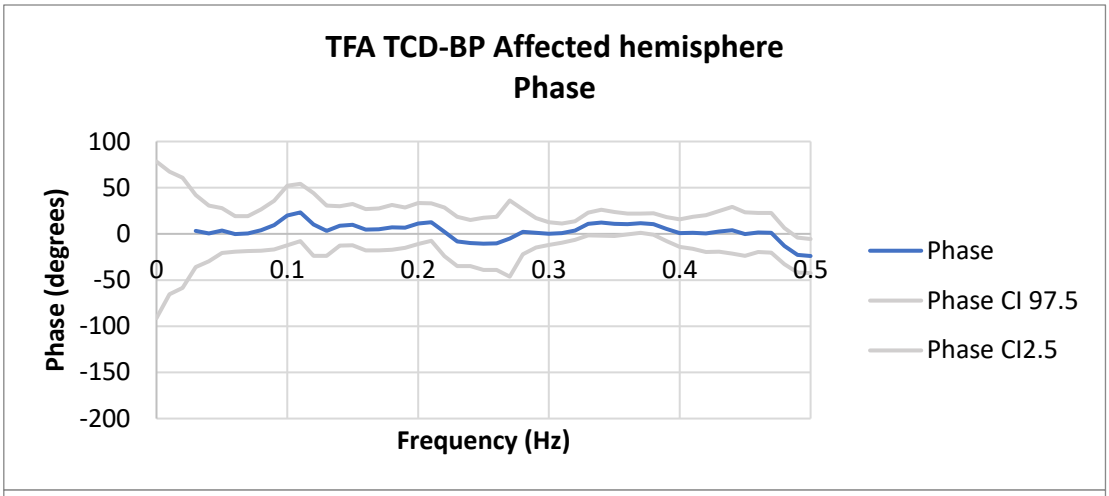
Patient deceased?	No
Haemorrhagic transformation/Cerebral edema/New ischemia/Re-occlusion	No
NIHSS closest to 48 hours	>=17
NIHSS impairment with respect to admission	?

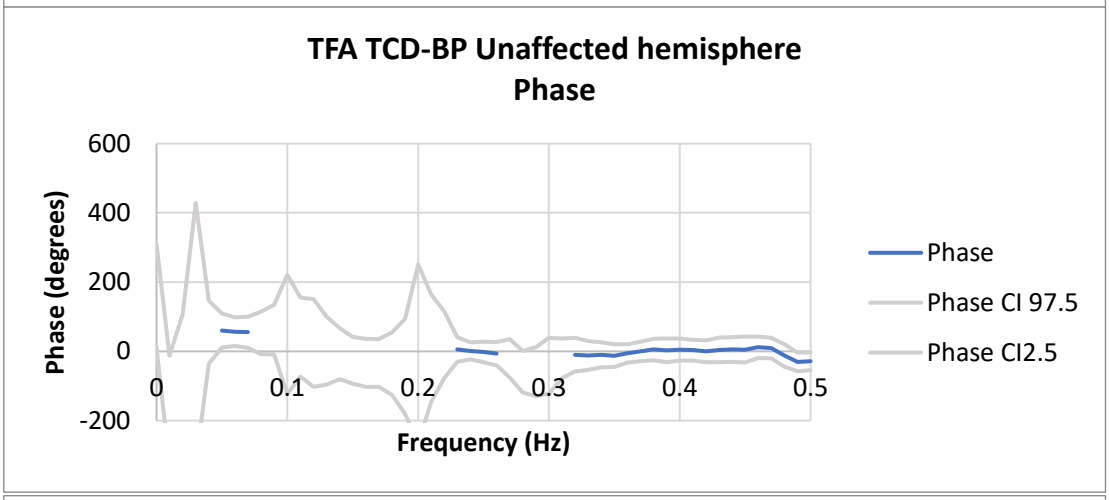
Characteristics during measurement

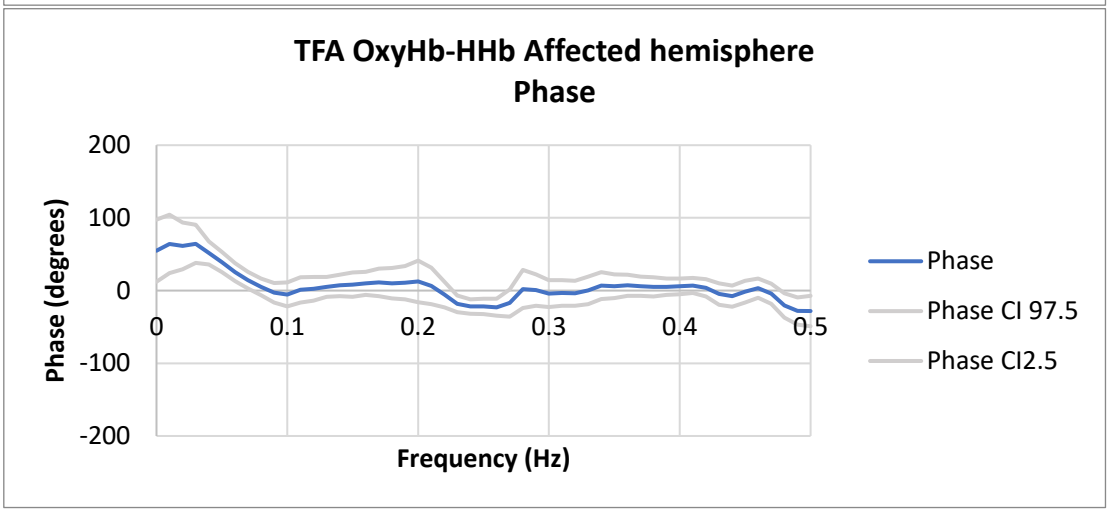
Mean arterial blood pressure (Non-invasive arm blood pressure cuff)	100.3
paCO2 (transcutaneous)	5.6
TCD – mean flow velocity affected (m/s)	30
TCD – mean flow velocity unaffected (m/s)	50.6
TCD – Pulsatility Index (PI) affected	0.45
TCD – Pulsatility Index (PI) unaffected	0.9

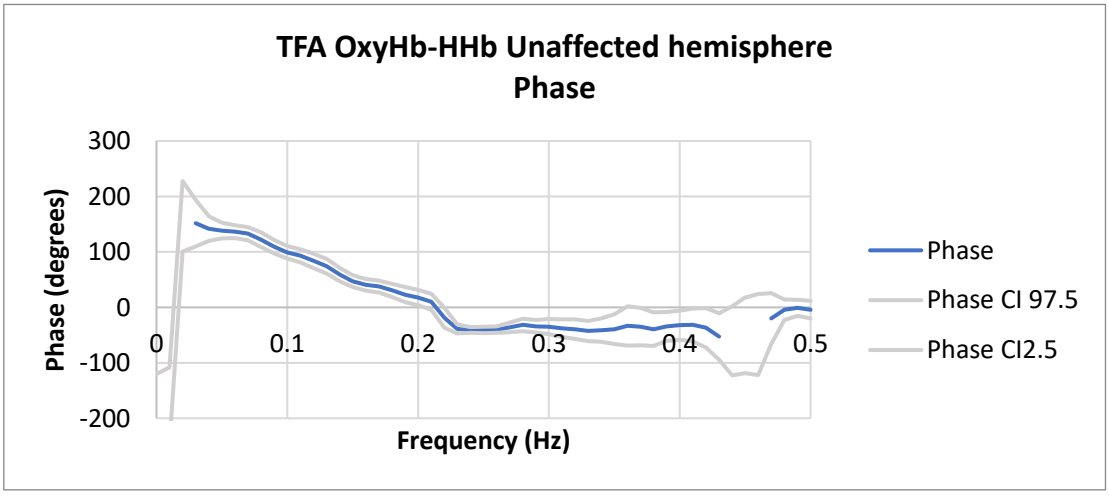
Data quality

Setting	Intensive Care Unit
% of good quality measurement – NIRS affected	Approximately 95%
% of good quality measurement – NIRS unaffected	100%
% of good quality measurement –BP/TCD affected	Approximately 90%
% of good quality measurement –BP/TCD unaffected	> 98%
Duration NIRS affected (mins:secs)	09:43
Duration NIRS unaffected (mins:secs)	08:23
Duration BP/TCD affected	09:13
Duration BP/TCD unaffected	08:14


TFA TCD-BP Affected hemisphere
Phase
Phase (degrees)
100
50
0
-50
-100
-150
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA TCD-BP Unaffected hemisphere
Phase
Phase (degrees)
600
400
200
0
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5


TFA OxyHb-HHb Affected hemisphere
Phase
Phase (degrees)
200
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

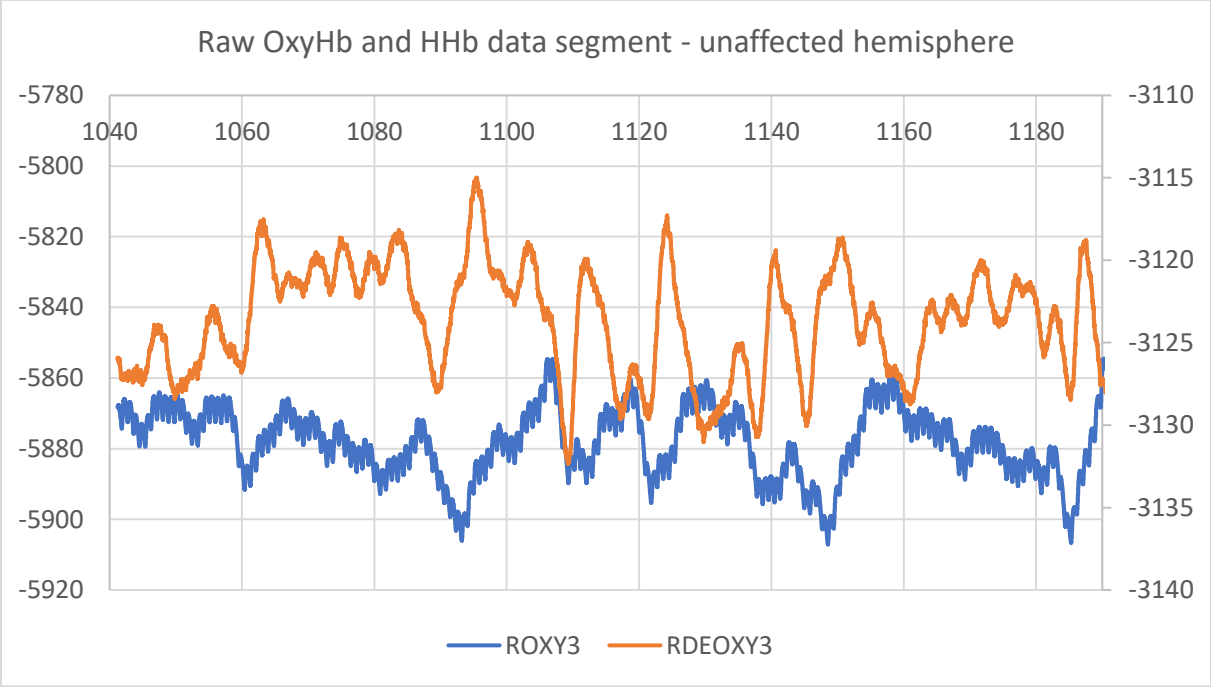

TFA OxyHb-HHb Unaffected hemisphere
Phase
Phase (degrees)
300
200
100
0
-100
-200
0
0.1
0.2
0.3
0.4
0.5
Frequency (Hz)
Phase
Phase CI 97.5
Phase CI2.5

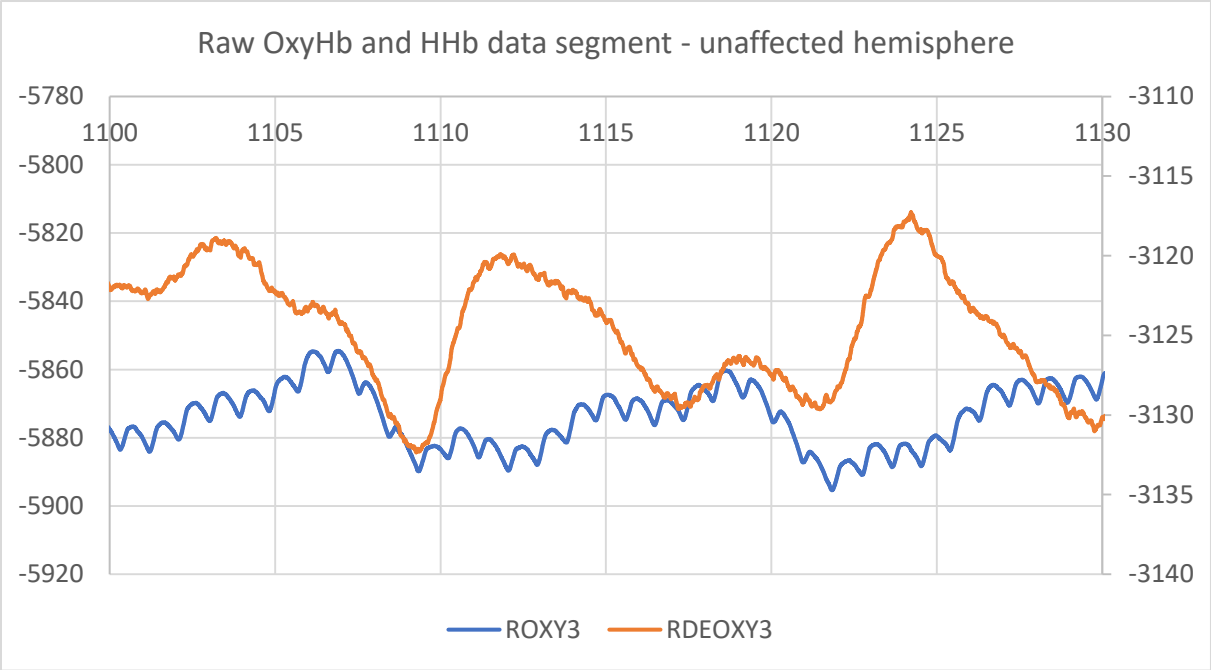
Interpretation

The data from this measurement is challenging to explain. In the affected hemisphere, phase difference is approximately zero degrees for nearly all frequencies in NIRS and TCD/BP data. Only for frequencies below 0.05 Hz, phase difference is slightly higher at approximately 50 degrees.

For the unaffected hemisphere, coherence only surpasses the significance threshold for some frequencies. Therefore, the phase calculation is only possible for some frequencies. In general, phase difference appears to increase for decreasing frequency.

The NIRS phase plot looks different, with a strong increase in phase difference for frequencies below 0.2 Hz. For frequency>0.2 Hz, phase is slightly below 0 degrees. Looking at the raw data, large low frequency counter-phase oscillations can be seen in OxyHb and HHb, which correspond to the large phase differences for frequencies below 0.2 Hz. Looking more closely at oscillations of >0.2Hz, it can be seen that the per-beat oscillations in HHb are hardly visible. This may indicate that HHb dynamics are not strongly influenced per-heartbeat changes in blood pressure. However, it can also be the result of poor signal quality, as similar patterns in HHb have been seen by the manufacturer in with poor HHb quality.

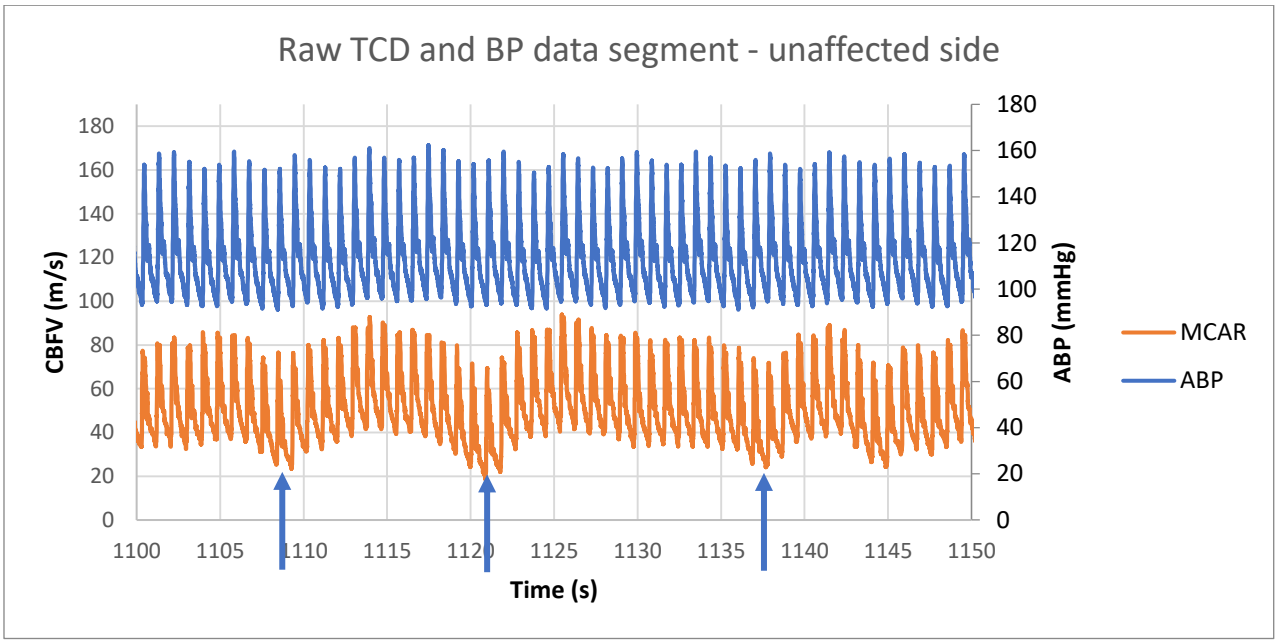




General TCD-parameters:

Comparing this with the other TCD-parameters, the TCD mean flow velocity and PI are low on the affected side, 30 m/s and 0.45 respectively. This can be classified as a 'post-stenotic' TCD-signal, indicating that there was still a partly blockage of flow proximal to the Middle Cerebral Artery. This was indeed the case, as part of the Internal Carotid Artery remained stenotic after the IAT-procedure. On the contralateral side, flow velocity and PI were higher, 50.6 m/s and 0.9 respectively. It is highly likely that these parameters influence the calculation of TFA between TCD and BP, and between the NIRS-signals. However, it is less certain how this is the case.

Low coherence between TCD/BP



An explanation for the poor coherence between TCD and BP signals for many frequencies can be found when looking at the raw data. Several slow oscillations in TCD-signals can be recognised that are not present in the BP signals. These oscillations may be the result of intracranial pressure changes or short changes in paCO2. Independent of its cause, the independent TCD-oscillations violate the TFA-assumption that TCD dynamics are nearly solely dependent on BP dynamics.

General conclusions

1. Clear difference in NIRS Transfer Function between the hemispheres
2. Clear difference between the general TCD-parameters between the hemispheres
3. Unexplained HHb dynamics, with hardly any per-beat oscillations in the unaffected hemisphere
4. Large, BP-independent oscillations in TCD flow velocity in the unaffected hemisphere, violating the TFA-assumption of sole BP-dependence.

Overall conclusions

Based on the in-depth analysis of the data of four patients who underwent all measurements, 8 conclusions can be drawn:

1. Differences in TFA phase can be seen between the affected and unaffected hemisphere
2. There is an inter-hemispheric variation in TCD mean flow velocity and Pulsatility Index that likely influences TFA calculation
3. Extrasystolic heart-beats were present that may influence the TFA calculation, although their exact effect is unknown
4. No similarity between the TCD/BP phase difference and OxyHb/HHb phase difference was seen in the individual patient data
5. The TCD/BP phase difference estimation could not been performed due to low coherence in a surprisingly large amount of the frequencies, which may have been the result of:
    c. Poor TCD-signal quality
    d. Large, BP-independent TCD flow velocity oscillations, that violate the TFA assumption of (mostly) BP-dependence
6. There may be a relation between clinical outcome and TCD/BP phase difference, based on the measurements of two patients

Other general conclusions:

7. For all measurements, paCO2 levels remained within the normal range of 5.1-5.8 kPa.
8. Non-invasive upper arm cuff Blood Pressure was withinin the normal to hypertensive range (70-107 mmHg)

Appendix B: Measurement setup development

In this appendix, the used measurement setup will be evaluated and several suggestions for future setup optimisation are given.

Measurement setup goal and requirements

The goal of the measurement setup in this study can be defined as:

'Measurement of Cerebral Autoregulation using Transcranial Doppler and systemic Blood Pressure, and Near-infrared spectroscopy in acute ischemic stroke patients'

Three main requirements of the setup can be defined:

1) Measurement quality

Measurements should meet the requirements of the CARNet guidelines.[22] Most importantly:

- High quality data of at least 5 minutes, preferably continuous
- High quality data segments of at least 100 seconds are needed
- Artefacts
    - Short artefacts (=<three beats) should be removed and replace by linear interpolation. A threshold for the occurrence of short artefacts is unknown
    - For longer artefacts, the entire 'data segment' should be excluded from analysis
- An estimate of $paCO_2$ should be obtained

For the NIRS measurements, the same criteria were used, in the absence of other data quality guidelines.
For the continuous variables, a sampling frequency of at least 50 Hz is estimated to be necessary. This is specifically to measure the high-frequency dynamics in the cardiovascular data (particularly the per-heart beat blood pressure dynamics), which contains frequencies up to 20 Hz.[14], [43]

2) Patient safety

The patient may not be harmed by the measurements and the measurements should not be uncomfortable.

3) Minimal disturbance of routine clinical care

In the acute phase after ischemic stroke (with or without IAT-treatment), treatment is intense with visits from the neurologists and family and several check-ups and care from the stroke-nurse. Therefore:

- As short as possible measurement (<30 min)
    - Possibility to have contact with patient during or between the measurements.
- In case of emergency, acute care should be possible

Measurement setup development

The measurement setup will be analyses per-device.

NIRS

Portalite NIRS devices (Artinis Medical Systems, Elst, The Netherlands) were used to measure cerebral tissue oxygenation. These NIRS devices are targeted for use in (clinical) research. Therefore, data acquisition is transparent, allowing all measured parameters to be obtained, up to individual 'photon counts' for individual transmitter-detector pairs and ambient light estimations. For the Portalite, these parameters can be obtained up to a frequency of 50 Hz.

Figure B.1: Examples of the Portalite. Figure adapted from Artinis Medical Systems, https://www.artinis.com/portalite

The Portalite was used because of its compact size and easy applicability (Req 2,3) and the fact that raw data and a Tissue Oxygenation Index (TOI) could be obtained (Req 1).

The two NIRS-sensors (Portalite, Artinis Medical Systems) were attached to the frontotemporal scalp with two-sided tape, approximately a centimetre above the eyebrow. The frontotemporal position was used to ensure the NIRS-sensors were placed over the 'anterior watershed area', a region known to be vulnerable to perfusion deficits of the middle cerebral circulation. The NIRS sensors were also placed in the frontotemporal position in the initial NIRS-CA study in healthy subjects[32], which was another reason for this position in the current study.

Observations during the study

1. During the first two measurements, it was discovered that interference took place between the two NIRS-sensors, which strongly disturbed the measurements. This phenomenon ('cross-talk') was known beforehand, but during the previous studies, it was of much lower amplitude or non-existent. Following advice of the company, both sensors would then be placed more laterally, increasing the distance between the sensors. However, in this study, cross-talk could not be avoided by increasing the sensor distance. The company would only believe this problem existed when we showed it in a meeting with researchers from Maastricht, Groningen en Artinis. It was eventually found that cross-talk would be present 3/4th of the time due to the specific firing and pausing rates of each device. It could not be solved by the company programmatically or mechanically.

   Protocol change: To prevent cross-talk, the following measurements were unilateral, performed subsequently for the affected and unaffected hemispheres.

2. In several measurements, patients were aphasic and not instructable. Several times, these patients would try to touch or remove the NIRS sensor. After a couple of minutes, the patients generally got more adjusted to the device.

Protocol change: Patients were instructed repeatedly not to touch the device.

3. Head movement and restlessness were present in several patients, more than what was expected

   Protocol change: Patients were instructed repeatedly to lie as still as possible

Further measurement optimisation

NIRS devices that can measure bilaterally and simultaneously without the occurrence of cross-talk are already available (among others at Portalite manufacturer Artinis), but these devices are large, bulky caps. A small device that can provide raw data is should be searched.
NIRS-measurements for the estimation of cerebral autoregulation should be performed in a controlled setting, with very co-operative or sedated/anesthetised patients, for example in the operation room.

TCD

TCD-measurements were performed with two 2 MHz probes (Delica, Shenhen, China) placed bilaterally on the temporal scalp, above the ear. Probes were secured in place with a head-frame from the manufacturer. On the forehead, the frame was place over the NIRS-sensor(s). An acoustic window was searched and if the window was present, CBF-velocity (CBFV) of the middle cerebral artery (MCA) was continuously measured. TCD settings were set as such that both embolus detection and CBFV calculation were possible. TCD measurements were performed by a qualified technician or a clinical neurophysiologist.

Figure B.2: A TCD head-frame with TCD-probes from Delica, similar to our device. Figure adapted from https://www.transcranialdoppler.co.uk/

Observations during the study

1. After the first two measurements, it was discovered that the TCD head-frame exaggerated the artefacts in the NIRS-signal due to movement. Head movement, frowning, yawning and movement of the body due to mechanical ventilation (in the Intensive Care Unit) all resulted in strong movement artefacts in the NIRS signals. Moreover, the head-frame was considered uncomfortable by some patients.

   Protocol change: The TCD head frame measurement was replaced by two unilateral measurement with hand-held probes above the ear.

2. In several patients, no TCD-signal could be obtained due to an insufficient temporal bone window

3. During several measurements, no TCD-technician or clinical neurophysiologist was available for the TCD-measurements.

   Protocol change: I had to perform the measurements myself. However, only in one measurement could a sufficient TCD-signal be obtained.

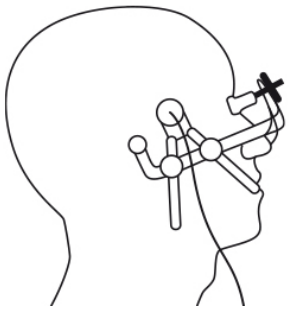


Figure B.3: Example of the LAM rack system by DWL Medical Systems. Figure adapted from https://www.dwl.de/en/products/dwl-doppler/?cn-reloaded=1

Further measurement optimisation

TCD measurements should be performed by a qualified operator in a controlled setting, mainly the operation room or the Intensive Care Unit. Handheld probes or a TCD-frame that does not touch the NIRS-sensors should be used. An example of such a frame is the LAM-rack.

Continuous BP measurements

Arterial blood pressure was measured continuously via arterial volume clamping of the digital artery for the middle or ring finger (Finapres, Finapres Medical Systems, Amsterdam). The Finapress device provides an estimate of intra-arterial blood pressure and was also on validated on intra-arterial blood pressure measurements. It is less often used for absolute measurements of blood pressure, due to possible biases and slow drifts. Therefore, absolute blood pressure was measured with an upper arm cuff BP device (Stroke Unit) or an intra-arterial BP catheter (ICU). The Finapress device was not calibrated to these absolute measurements, due to time constraints.

Figure B.4: Example of the Finapress Blood Pressure measurement device. Figure from https://www.medtach.com/finapres-products.html

Observations during the study

1. In several patients, BP measurements failed due to restlessness and movement of the hand. This could not always be prevented, as the patients were not always instructable
2. Several patients had cold fingers that could not be warmed passively with blankets. In these patients, no Finapress BP signals could be obtained. This is a known limitation of the device
3. The accuracy of Finapres measurements is not well known, especially for critically ill patients. This may have introduced additional noise in the CA calculation.

Further measurement optimisation

Finapres BP measurements does not suffice in restless or (critically) ill patients. Intra-arterial blood pressure measurements are preferred. These can be performed in the operation room or Intensive Care Unit.

Accelerometers

Two accelerometers (built in-house with an Arduino Analog-to-Digital Converter) were attached to the patient's chest and directly on the NIRS sensors, to measure breathing and whole movements, and local movement of the NIRS-sensors respectively. The accelerometers contained a tri-axial accelerometer, for which resolution and other technical specification were not known.

Observations during the study

1. The accelerometers could be clearly used to identify fast movements, such as frowning, yawming, and head turning. Slow but larger movements could also be detected, such as respiratory/ventilatory movements.
2. The accelerometers were connected with the AD converter with a rather still cable. Because one accelerometer was directly attached to the NIRS sensor, touching of the cable resulted in several minor movement artefacts.

   Protocol change: A different cableless accelerometer device (Axivity AX3, Axivity LTd, Newcastle upon Tyne, United Kingdom) was tested, but a solid connection with the existing Labview data acquisition setup could not be created. To prevent movement artefacts, the cables of the current accelerometer were attached to the patient's pillow and guided away from the researcher and patient as much as possible.

Further measurement optimisation

Cableless accelerometers should be evaluated again, because this reduces the amount of cables in the measurement system. It also facilitate long-term measurements in which only NIRS and accelerometers measurements are performed.

tCO2-measurement

Estimates of arterial CO2-concentration ($paCO_2$) were obtained with transcutaneous carbon dioxide ($tcCO_2$) measurements (SenTec Oxivent System, SenTec AG, Switzerland). The device as attached to the earlobe of the patient, which is an advised position by the manufacturer. It is known that $paCO_2$ strongly influences cerebral autoregulation (especially hypercapnia), so this should be measured.[22]

Observations during the study

1. The SenTec $tcCO_2$ device needs a 'warm-up' period of several minutes in which the ear is warmed and the proprietary algorithm can calculate $tcCO_2$ concentration. In some patients, no $tcCO_2$ value could be obtained, for which no reason could be found.

   Protocol change: In ventilated patients, the end-tidal CO_2 was used instead of $tcCO_2$. In non-ventilated patients, no CO_2 estimation could be obtained.

2. The SenTec $tcCO_2$ sensor uses infra-red light, with a comparable wavelength as the NIRS sensors. There is a possibility that there was minor cross-talk between the two sensors. This was no observed however.

3. The SenTec $tcCO_2$ sensor is poorly validated, especially in critically ill patients. Although $tcCO_2$ remained well within the normal limits for the current measurements, this may not the case in future measurements.

Further measurement optimisation

End-tidal CO_2 measurements are preferred to tCO_2 measurements, because these are better validated and provide a stable, continuous estimate of $paCO_2$. These measurements can only be performed in ventilated patients or very co-operative patients, using a $etCO_2$ cap.

Data acquisition and software

All data was obtained using a Labview data acquisition environment. A 'Queue structure' was used. This prevented a drift in data acquisition, assuring that the data from all devices was obtained at the same time. If data acquisition from one device was too slow, the queue would fill. If data acquisition continued to be slow, data would be thrown away. This resulted in missing data for several milliseconds (often >50 ms). However, it was found that this happened several time for the accelerometer data, resulting in intermittent periods of missing accelerometer data.

Moreover, the used HP Laptop was already quite old. This resulted in a general crash of the Labview software in three measurements. These measurement had to be extended to allow sufficient data acquisition. The resulted in more patient discomfort (Requirement 2) and disturbance of routine clinical care (Requirement 3).

Further measurement optimisation

To allow stable data acquisition, the acquisition software should be re-evaluated. A new laptop with a better CPU, and more RAM and storage has already been ordered. The measurement should be performed in such a way that routine care is not disturbed. Wireless measurements facilitate this in the ward/ICU and it also may be possible in the operating room.

Appendix C: Tissue Saturation Indices (TSI) in the affected and unaffected hemisphere

Introduction

Clinically used cerebral NIRS-sensors all calculate a cerebral Tissue Oxygenation Index (TOI), each with a manufacturer-specific name (e.g. for Artinis, the 'Tissue Saturation Index (TSI)'). To calculate these indices, (partly) proprietary algorithms are used. In stroke, several studies have been performed into the use of NIRS-derived TOI's during the acute and sub-acute phase of ischemic stroke. [44] There were conflicting results for interhemispheric differences of TOI's and TOI dynamics between the included studies. Both higher and lower TOI's were found on the affected hemisphere and also no difference.

The Portalite NIRS-devices used in this study calculate a TOI called the Tissue Saturation Index (TSI), which was calculated for the affected and unaffected hemispheres.

Research question: Is there is difference between the TSI measured on the fronto-temporal forehead of the affected and unaffected hemisphere, in stroke patients in the acute phase (< 3hours) after intra-arterial thrombectomy (IAT)?

Methods

The study design and measurement setup are described in the main report. In all 7 patients of the main study, TSI-values could be calculated. In the initial data preparation and preprocessing algorithm, artefact removal of the TSI-values was not performed.

In contrast, TSI preprocessing was performed by visual inspection of the data to select a high-quality data segment without movement artefacts. In addition, the TSI-Fit Factor calculated by the manufacturer was used to select high quality data. Only TSI-values with a TSI-Fit Factor of >90% were used.

For each hemisphere, a single, mean TSI value was calculated by averaging all TSI values of that measurement. In addition, the variance of the TSI values for that measurement was determined. The mean values were compared using a basic T-Test for Paired data in Excel.

Results

In Table C.1, the mean TSI values for the affected and unaffected hemispheres are shown. Mean TSI-values are almost identical and no statistically significant difference could be found between the hemispheres. In Figure C.1, the paired TSI values of the affected and unaffected hemispheres are shown in a scatter plots. No statistically significant relation between the TSI-values could be found.

Table C.1 Mean TSI values in the affected and the unaffected hemisphere

	Affected hemisphere	Unaffected hemisphere	Paired T-Test
Mean TSI (SD) (%)	63.6 (3.7)	63.8 (2.0)	p=0.97

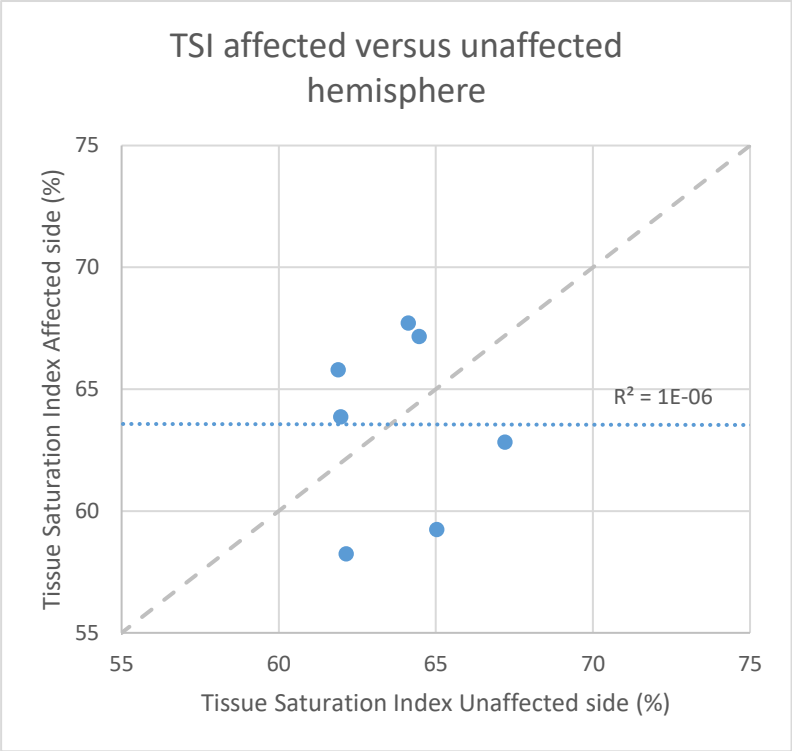


Figure C.1: Tissue Saturation Indices (TSI) measured on the Affected and Unaffected hemispheres for all (n=7) patients. No statistically significant correlation could be found (R=1E-06, p=0.4). The line of equality $TSI_{affected}$=$TSI_{unaffected}$ is also shown.

Discussion

In this preliminary analysis, no statistically significant difference was found between the TSI values of the affected and the unaffected hemispheres. The TSI values showed only a small variance between hemispheres and between patients, approximately 63% (SD 3%) for both hemispheres.

This might be explained by the fact that the anterior brain regions were less subject to oxygenation changes after infarction of the medial cerebral circulation, which affects temporal and parietal heads regions more than the anterior region. TSI/TOI measurements of the temporal or parietal hemisphere may therefore show a larger difference between the affected and unaffected hemisphere. However, this is contradicted by unpublished findings of temporal TOI measurements during the IAT-treatment in the UMCG, in which no differences between the hemispheres could be found.

Limitations

There are several limitations of the preliminary study. First, the TOI/TSI values were not compared with other literature on TOI measurements are stroke. Second, some variation in TSI values during one measurement was seen during the data selection. Investigation of the TSI-dynamics, for example during physiologic blood pressure changes may be an interesting research direction. Third, the paired T-Test may not have been validate, because the data was not tested for normality. However, the large p-value of 0.97 does provide an indication for ‘no difference between the hemispheres’.

Conclusion

No statistically significant difference between the TSI measured on the fronto-temporal forehead of the affected and unaffected hemisphere, in stroke patient in the acute phase (<3 hours) after intra-arterial thrombectomy was found.