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Near-infrared spectroscopy monitoring during endovascular treatment for acute ischaemic stroke

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Abstract

Introduction: The aim of endovascular treatment (EVT) for acute ischaemic stroke is to relieve the cerebral tissue hypoxia in the area supplied by the occluded artery. Near-infrared spectroscopy (NIRS) monitoring is developed to assess regional cerebral tissue oxygen haemoglobin saturation (rSO_2). We aimed to investigate whether NIRS can detect inter- and intra-hemispheric rSO_2 differences during EVT.

Patients and methods: In this prospective, observational study, patients undergoing EVT for a proximal intracranial occlusion of the anterior circulation between May 2019 and November 2020, were included. A four-wavelength NIRS monitor (O3® Regional Oximeter (Masimo, Irvine, CA)) was used to measure rSO_2 during EVT with sensors placed over the temporal lobes in 20 patients and over the frontal lobes in 13 patients. The Wilcoxon signed-rank test was used to test for inter-hemispheric rSO_2 differences after groin puncture and after recanalisation, and intra-hemispheric rSO_2 changes before and after recanalisation.

Results: In the temporal cohort, no inter-hemispheric rSO_2 differences were observed after groin puncture (median [IQR] rSO_2 affected hemisphere, 70% [67–73] and unaffected hemisphere, 70% [66–72]; $p = 0.79$) and after recanalisation. There were no intra-hemispheric rSO_2 changes over time. In the frontal cohort, no inter- and intra-hemispheric rSO_2 differences or changes were found.

Discussion and conclusion: A NIRS monitor could not detect inter- and intra-hemispheric rSO_2 differences or changes during EVT, irrespective of the sensor position. It is likely that even with temporal sensor application, a significant proportion of the received NIRS signal was influenced by oxygenation of surrounding tissues.

Keywords

Anaesthesia, endovascular procedures, ischaemic stroke, prospective studies, spectroscopy, near-infrared

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Introduction

Endovascular treatment (EVT) has become a standard part of care for patients with acute ischaemic stroke due to large vessel occlusion (LVO).[1] The aims of anaesthetic management during EVT are to facilitate the procedure and provide optimal physiological conditions to limit infarct growth.[2–4] An important goal is thus to improve oxygen delivery via the collateral circulation to the salvageable penumbra by optimising blood pressure, cerebral blood flow and arterial oxygen content. To achieve this, end-tidal CO_2, SaO_2 and invasive arterial blood pressure monitoring are recommended.[2,3,5] A monitor

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of cerebral oxygenation is also desirable since it could be used to inform decisions concerning ventilatory and haemodynamic management before and after recanalisation.

Near-infrared spectroscopy (NIRS) is a non-invasive technique used to measure regional cerebral tissue oxygen haemoglobin saturation (rSO_2). It is thought that 70% of the NIRS signal is derived from venous blood and 30% from arterial blood, and that rSO_2 values reflect the overall balance between cerebral oxygen demand and supply.[6,7] Currently, clinical use of NIRS is based on expert consensus, predominantly informed by prospective, observational studies performed during cardiothoracic, paediatric and carotid artery surgery. The evidence regarding clinical utility in these circumstances is equivocal.[8–10]

There are only limited reports of the use of NIRS during EVT, all including patients with an internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion.[11–14] These studies show conflicting outcomes, which might be due to application of the NIRS 'sensor' (i.e. the assembly containing the transmitter and receiver devices on a self-adhesive pad) on the (outer) forehead, resulting in signal interference from unaffected areas in patients with an ICA or MCA occlusion.

We aimed to determine if a four-wavelength NIRS monitor, with sensors placed over the temporal versus frontal lobes, could detect inter-hemispheric differences and intra-hemispheric changes in rSO_2 during EVT in patients with an ICA and/or MCA occlusion.

Methods

In this prospective, observational study, we included patients with acute ischaemic stroke undergoing EVT in the University Medical Centre Groningen (UMCG) between May 2019 and November 2020. Between March 2020 and August 2020, the inclusion of patients was halted due to the COVID-19 pandemic.

As this research did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO), the need for formal ethical committee approval was waived by the Institutional Ethical Review Board of the UMCG (reference number: METc 2018/464). Written informed or deferred consent was obtained from all included patients or their legal representatives.

Individual patient data will not be available to other researchers as no patient approval has been obtained to share de-identified data. The script for data processing will be made available by the corresponding author on reasonable request.

Participants

We included patients undergoing EVT for occlusion of the intracranial ICA or first segment of the MCA (M1). The diagnosis was based on computed tomography (CT) imaging and verified intra-operatively using digital subtraction angiography (DSA). EVT had to be initiated within 6 h after stroke onset (with the National Institutes of Health Stroke Scale (NIHSS) score being $\geq$2),[15,16] but could also be performed between 6 and 24 h if specific conditions were met (NIHSS score $\geq$10,[16,17] infarct core volume $<$25 mL and a CT perfusion derived mismatch ratio $>$1.8). Patients were excluded if they had a co-morbidity that could affect the NIRS measurements, such as bilateral high-grade carotid artery stenosis ($>$50%).

Initially, we aimed to investigate NIRS monitoring during EVT only with sensors placed over the temporal lobes (temporal cohort). However, during the first months of the study, we noticed that several patients had to be excluded as informed consent could not be obtained prior to EVT, for example due to patient aphasia and unavailability of a legal representative. In the temporal cohort, informed consent had to be obtained prior to EVT because the temporal sites had to be shaved to ensure optimal sensor adherence and accurate sensor readings. As of July 2019 (after approval of the Institutional Ethical Review Board of the UMCG), NIRS sensors were applied over the frontal lobes (frontal cohort) of eligible patients in whom informed consent could not be acquired before the start of the procedure. For frontal NIRS monitoring, it was permitted to obtain deferred consent as the frontal sites did not need to be shaved for sensor application, which allowed us to include more patients and increased the quality of the study because the results of both cohorts could be compared. For patients included in the frontal cohort, informed consent was attained at a later date, before the use of their data.

Study procedures

NIRS monitoring. An O3® Regional Oximeter (Massimo, Irvine, CA), a 4-wavelength continuous-wave NIRS device with two light detectors, was used to continuously monitor the rSO_2 of the affected and unaffected hemispheres.[18] On arrival of the patient in the angiography suite, NIRS sensors were applied to the scalp bilaterally. Before sensor application, we extensively prepared the sites to ensure optimal sensor adherence and accurate sensor readings. The sites were first shaved, if applicable, and subsequently degreased, wiped clean and dried. In patients from the temporal cohort, adhesive NIRS sensor were applied bilaterally to the temporal scalp 2 cm above each ear, corresponding approximately to the T3/T4 positions on an EEG 10-20-system.[19] There were no recommendations for temporal NIRS monitoring in the operator's manual.[20] The sensor location was therefore determined by the authors and was based on previously published templates regarding the flow territories of the middle cerebral artery (the closest location to the ischaemic area of interest)[21] and practical considerations (a clear anatomical landmark that allowed the sensors to be applied at the same site in each patient). In the frontal cohort, NIRS sensors

were applied bilaterally to the forehead, above the eyebrows as recommended by the operator's manual.[20]

The intention was to start NIRS monitoring before induction of anaesthesia, but due to the emergency nature of the procedure this was not always feasible. In all cases it was possible to begin monitoring before the start of EVT (defined as groin puncture). NIRS monitoring ended after endotracheal extubation or shortly before departure from the angiography suite if extubation was not feasible or not performed.

After the completion of data collection, as part of a post hoc analysis, available CT perfusion images were re-assessed (RB) to investigate the plausibility that the NIRS sensors would have been able to measure the rSO_2 in the penumbra and ischaemic core (Supplemental Figure 1).

Anaesthetic management. Patients were monitored according to the guidelines of the American Society of Anesthesiologists.[22] Continuous (physiological) data were automatically recorded by the IntelliVue MP70 Patient Monitor® (Philips Medical Systems, Best, NL).

Anaesthetic and haemodynamic management were performed in accordance with Society for Neuroscience in Anesthesiology and Critical Care and American Stroke Association guidelines.[2,3] The choice of anaesthetic technique was at the discretion of the attending anaesthesiologist, and depended on the patient's co-morbidities, clinical condition and procedure-related factors. Anaesthetic drugs were administered by target-controlled infusion using Alaris® PK Infusion Pumps (CareFusion, Hampshire, UK). Vasopressors were administered by simple infusion using Alaris® GH Infusion Pumps (CareFusion, Hampshire, UK). To ensure that the data were recorded in real-time, all monitoring equipment (including the NIRS system) and all infusion pumps were connected to a dedicated hospital computer terminal running the electronic patient record software (EPIC®, Epic Systems Corporation, Verona, WI, USA).

As per local protocol, the aim of haemodynamic management during EVT was to optimise the (collateral) cerebral perfusion. The exact blood pressure targets were again left to the discretion of the attending anaesthesiologist, however, maintenance of a systolic blood pressure between 140 and 180 mmHg was common practice.[2,3] The NIRS monitor screen was placed out of sight of the interventionist and anaesthesiologist, and treatment decisions were made independently of the rSO_2 values. Endotracheal extubation was performed as soon as possible after the EVT was finished.

EVT. EVT consisted of primary thrombus aspiration, use of a stent retriever or a combination of both techniques. In case of a secondary ipsilateral high-grade ICA stenosis or occlusion, percutaneous transluminal angioplasty could be performed with or without carotid artery stenting. The choice for the thrombectomy device and treatment technique was at the discretion of the interventionist. Successful reperfusion was defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score of $\geq$2B.[23]

The pre-procedural leptomeningeal collateral status was scored on admission by two neuro-interventionists (MU and RB) using CT angiography images. The presence of moderate to good collateral flow was defined as >50% filling of the territory of the occluded artery.[24]

Neurological outcomes were the NIHSS score within 48 h after EVT and the modified Rankin Scale (mRS) score at 90 days after EVT.[25,26] To compare our study population with other study populations and to analyse if there was a correlation with rSO_2 values, the postprocedural NIHSS score was included as an outcome parameter. We chose to analyse the NIHSS score within 48 h because the institutional guidelines required the NIHSS score to be determined within 48 h after stroke onset.

Data collection

Demographic, procedural, anaesthetic and NIRS data were retrieved from the hospital electronic patient record.

The initial primary outcomes were per-procedural rSO_2 values of the ischaemic and non-ischaemic hemisphere (before and after the induction of anaesthesia, before and after EVT and before and after the end of anaesthesia) and neurological outcomes. However, due to the emergency nature of EVT, it appeared logistically impracticable to collect NIRS data before the induction of anaesthesia and after the end of anaesthesia for a sufficiently long period of time (at least 10 min). These data were therefore omitted from further analysis.

Statistical analysis

Sample size analysis. A sample size of 10 patients was required to detect an absolute rSO_2 difference of 10%, assuming the standard deviation (SD) of the difference was 10, to achieve a significance level of 5% (two-sided) and a power of 80%. A conservative sample size of 20 patients was however chosen because of uncertainty about the SD as result of the sparse literature on NIRS monitoring during EVT and conflicting outcomes,[11–14] and to compensate for dropouts and technical failures.

Data processing. For each individual and the complete cohort, the unprocessed physiological patient data were displayed in line plots and visually inspected for data artefacts. As data for the complete cohort could not be summarised into one plot due to different durations of the EVT, data were centred around the moment of groin puncture and around the moment of recanalisation. For the rSO_2, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate and SpO_2, data artefacts were removed using locally estimated scatterplot smoothing (LOESS).

Analysis of inter-hemispheric rSO_2 differences. For assessment of inter-hemispheric rSO_2 difference at the start of the procedure, we calculated the median rSO_2 value for each hemisphere during the first 10 min after groin puncture. For assessment of inter-hemispheric rSO_2 difference after recanalisation, we calculated the median rSO_2 value for each hemisphere during the first 10 min after the final EVT attempt.

Analysis of intra-hemispheric rSO_2 changes. For assessment of intra-hemispheric rSO_2 changes associated with recanalisation, we compared the median rSO_2 during the 10 min before the first EVT attempt with the median rSO_2 during the 10 min after the final EVT attempt. We considered the 10 min before the first EVT attempt to be a more informative time period than the 10 min starting from groin puncture as this latter period is typically associated with more haemodynamic variability and higher inspired oxygenation concentrations.[27,28]

Within each cohort, the Wilcoxon signed-rank test was used to test for inter-hemispheric rSO_2 differences after groin puncture and after recanalisation, and for intra-hemispheric rSO_2 changes before and after recanalisation. We further stratified data for leptomeningeal collateral status, general anaesthesia and reperfusion status. The direction of the results was compared between both cohorts.

Statistical significance was set to $p < 0.05$. Data were analysed using R 3.4.2 software (R foundation for Statistical Computing, Vienna, Austria) with the 'tidyverse' package (Wickham H. Advanced R. 2017) and SPSS Statistics 23.0 software (IBM Corp, Armonk, NY).

Results

Participants

Between May 2019 and November 2020, 304 patients with a LVO were treated with EVT at our centre. Of the 183 patients potentially eligible for inclusion, 8 declined participation and 123 were not included due to organisational or logistical reasons (such as lack of availability of research personnel). During EVT, 19 patients were excluded for various reasons (such as thrombus migration). This left 33 patients to be included: 20 patients were monitored with temporally applied NIRS sensors and 13 patients with frontally applied NIRS sensors (Supplemental Figure 2).

Descriptive data

Patient demographics and co-morbidities

Temporal cohort. Ten out of 20 patients were female, the mean ± SD age was 71 ± 16 years, and all patients had an M1 occlusion. The median (interquartile range [IQR]) NIHSS score at baseline was 15 [7–20], and most (14/20) patients had a moderate to good collateral status (Supplemental Tables 1 and 2).

Frontal cohort. Eight out of 13 patients were female, the mean ± SD age was 65 ± 20 years, and all but one patient had an M1 occlusion. The median [IQR] NIHSS score at baseline was 18 [14–20], and 8/13 patients had a moderate to good collateral status (Supplemental Tables 1 and 2).

Physiological and procedure associated parameters

Temporal cohort. EVT was performed under local anaesthesia in 12/20 patients and under general anaesthesia in 8/20 patients. In one patient, anaesthetic management was converted from local anaesthesia to procedural sedation to manage agitation. The median [IQR] time from groin puncture to recanalisation was 43 [29–60] min. Successful reperfusion was achieved in 15/20 patients (Supplemental Tables 3 and 4). Systemic oxygenation remained within the physiological range in all patients, and all patients were haemodynamically stable during EVT (Supplemental Figures 3 and 4). The NIRS monitoring did not impede the EVT or anaesthetic monitoring. However, during DSA runs with radiation exposure, there was a temporary loss of rSO_2 signal in all patients.

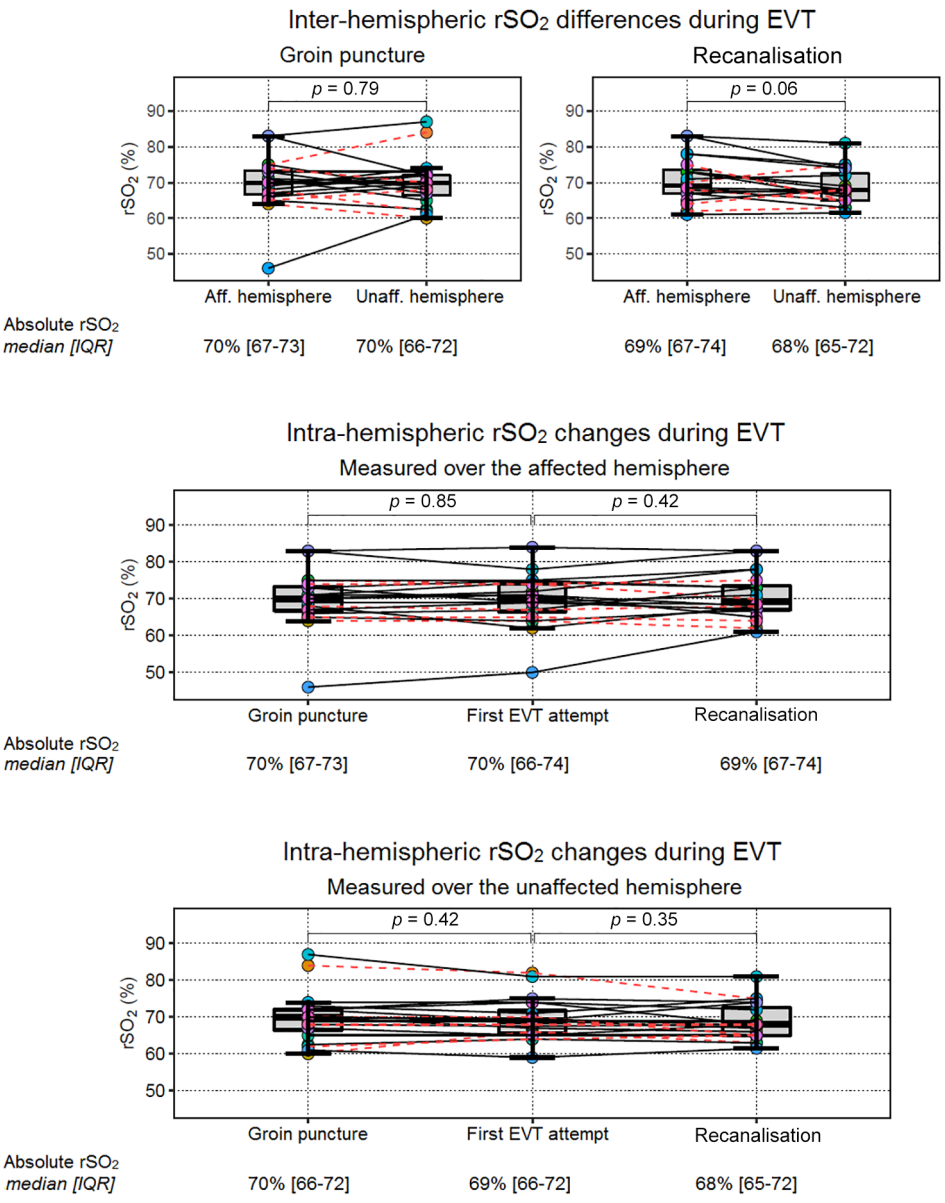
Nine patients underwent CT perfusion studies. Based on these images, near-infrared light from the ipsilateral, temporally applied sensor would have been expected to reach the penumbra in 8/9 patients and the ischaemic core in 1/9 patients. Had the sensors been placed frontally, the sensor would have been likely to detect signals from the penumbra in 4/9 patients and the ischaemic core in 1/9 patients (Supplemental Table 5).

Frontal cohort. EVT was performed under local anaesthesia in 5/13 patients and under general anaesthesia in 8/13 patients. The initial anaesthetic management plan was not altered during the procedure in any of these patients. The median [IQR] time from groin puncture to recanalisation was 32 [23–71] min. Successful reperfusion was achieved in 12/13 patients (Supplemental Tables 3 and 4). Systemic oxygenation remained within the physiological range in all patients, and all patients were haemodynamically stable during EVT (Supplemental Figures 5 and 6). As in the temporal cohort, a temporary loss of rSO_2 signal was observed in all patients during DSA runs.

Nine patients underwent CT perfusion studies. Based on these images, near-infrared light from the ipsilateral, frontally applied sensor would have been expected to reach the penumbra in 5/9 patients and the ischaemic core in 1/9 patients. The number of patients with an adequate measurement would have been higher if the sensors had been applied over the temporal lobes (penumbra, $n = 9/9$ patients and ischaemic core, $n = 4/9$ patients) (Supplemental Table 5).

NIRS measurements

Temporal cohort. No inter-hemispheric rSO_2 differences after groin puncture were observed (median [IQR] rSO_2



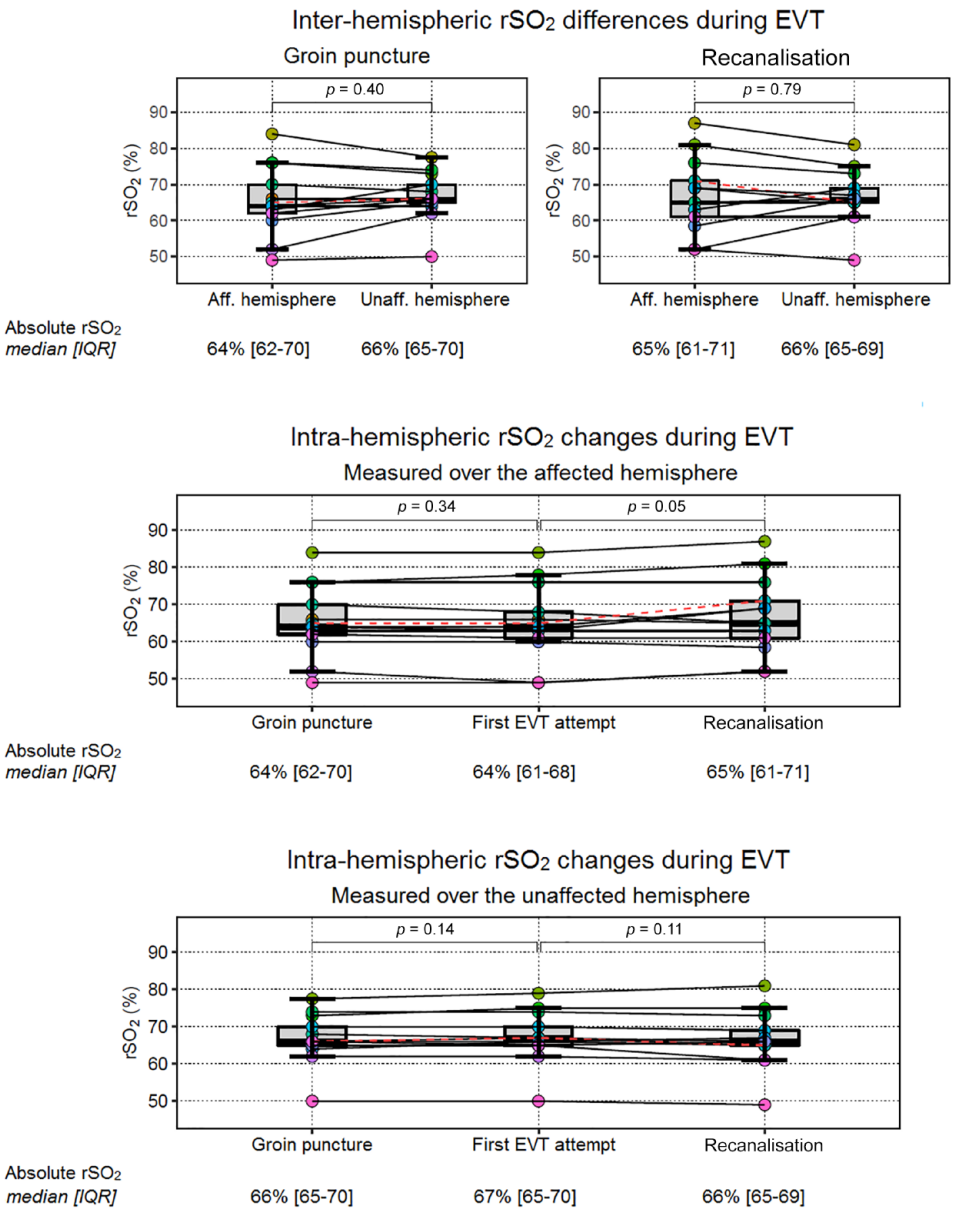
Per-procedural inter- and intra-hemispheric rSO_2 values in the temporal cohort. Solid and dotted lines indicate patients with successful and unsuccessful reperfusion, respectively.
Aff.: affected; EVT: endovascular treatment; IQR: interquartile range; rSO_2: regional cerebral tissue oxygen haemoglobin saturation; unaff.: unaffected.

affected hemisphere, 70% [67–73] and unaffected hemisphere, 70% [66–72]; $p=0.79$). Also, there were no inter-hemispheric rSO_2 differences after recanalisation and no intra-hemispheric changes over time (Figure 1). Stratification for leptomeningeal collateral status, general anaesthesia and reperfusion status did not yield significant inter- and intra-hemispheric differences or changes (data not shown). In the 15 patients in whom reperfusion was successful, the median [IQR] rSO_2 of the affected hemisphere was 71% [68–75] before the first EVT attempt and 71% [68–76] after recanalisation ($p=0.19$).

Frontal cohort. No median inter- and intra-hemispheric rSO_2 differences or changes were found during EVT (Figure 2). Stratification for leptomeningeal collateral status, general anaesthesia and reperfusion status did not yield significant results (data not shown). In the 12 patients in whom reperfusion was successful, the median [IQR] rSO_2 of the affected hemisphere was 64% [61–70] before the first EVT attempt and 65% [60–71] after recanalisation ($p=0.09$).

Neurological outcomes

Median [IQR] NIHSS scores within 48 h were 5 [2–14] in the temporal cohort and 10 [5–17] in the frontal cohort. Median [IQR] mRS scores at 90 days were 2 [0–4] in the temporal cohort and 3 [1–5] in the frontal cohort. Given that there



Per-procedural inter- and intra-hemispheric rSO_2 values in the frontal cohort. Solid and dotted lines indicate patients with successful and unsuccessful reperfusion, respectively.
Aff.: affected; EVT: endovascular treatment; IQR: interquartile range; rSO_2: regional cerebral tissue oxygen haemoglobin saturation; unaff.: unaffected.

were no inter- and intra-hemispheric rSO_2 differences or changes, we did not perform secondary analyses of correlations between the rSO_2 values and neurological outcomes.

Discussion

In this prospective, observational study in patients with acute cerebral ischaemia due to a proximal LVO of the anterior circulation, we found no inter-hemispheric rSO_2 differences. There were also no intra-hemispheric rSO_2 changes. These results applied irrespective of sensor positioning over the temporal or frontal scalp.

Our findings could be explained by one of the two scenarios: either there were no actual inter- and intra-hemispheric rSO_2 differences and changes, or there were differences that the NIRS monitor was unable to detect.

Even though two-thirds of the included patients had a moderate to good collateral status, making the first scenario plausible, our results did not change when data were stratified for collateral status. This implies that collateral status did not confound the results. Furthermore, since all study patients had neurological deficits, a characteristic of cerebral hypoxia caused by ischaemia,[29,30] we consider the first scenario to be very improbable.

Given there was a radiologically confirmed LVO, accompanied by clinical signs of ischaemia and later documented reperfusion, implies that the second scenario is more likely. If one assumes, as is likely, that ischaemia of MCA flow also causes downstream cerebral tissue hypoxia, then this implies that the monitor was unable to detect inter-hemispheric rSO_2 differences consistent with cerebral ischaemia and intra-hemispheric rSO_2 changes secondary to recanalisation. Several factors could be responsible for this.

First, the duration of rSO_2 monitoring may have been too short to detect rSO_2 differences or changes. The duration of monitoring after recanalisation was only 10 min, while it may take hours to days before any neurologic improvement is evident.[1] The period after recanalisation could therefore have been of insufficient duration. The period before recanalisation, however, should have been of more than adequate duration to detect cerebral ischaemia and hypoxia, since the LVO had usually already been present for a few hours by the time patients arrived in the angiography suite.[31]

Second, the sensor location for rSO_2 monitoring could have been suboptimal for adequate rSO_2 measurement. During re-assessment of the CT perfusion scans, we found that less than half of the frontally applied NIRS sensors were located within the ischaemic area of interest. In half of the patients in the temporal cohort, the sensors should have been close enough to the ischaemic area of interest to reliably detect changes in rSO_2.[32] Nevertheless, no clinically relevant differences were found in the temporal cohort. Targeted selection of the site for NIRS sensor application by using CT perfusion scans could improve the utility of rSO_2 measurements during EVT. This should be investigated in future studies.

Third, rSO_2 measurements may have been affected by monitor-related factors. The O3® Regional Oximeter was only validated in healthy volunteers undergoing controlled hypoxia using frontally applied NIRS sensors.[18] It is therefore unknown if the accuracy found also applied to our study in which neurologically impaired, older patients with comorbidities were monitored with temporally applied sensors. Moreover, the NIRS monitor consistently suspended signal processing during DSA runs due to radiation exposure. This was consistent with the operator's manual that warned of inaccurate rSO_2 measurements due to radio-interference.[20]

Fourth, procedure- or patient-related factors may have influenced the rSO_2 measurements. Induction of anaesthesia is associated with temporary haemodynamic fluctuations and sometimes arterial hypotension.[27,28] Our results however, did not change when data were stratified for general anaesthesia. Furthermore, although intravascular dyes, skin pigmentation, haemoglobinopathies and hyperbilirubinaemia can cause inaccurate measurements, none of these conditions applied to the included patients.[20]

Finally, oxygenation of extracranial tissues may have contaminated the rSO_2 signals. The subcutaneous and muscle tissue is thicker in temporal than frontal regions, and these tissues should be normally oxygenated in case of an ICA or M1 occlusion.[33] One could therefore hypothesise that temporal rSO_2 measurements may have been affected to a greater extent, which could be reflected by increased rSO_2 values and smaller inter- and intra-hemispheric differences or changes. We found slightly higher median rSO_2 values in the temporal than in the frontal cohort, whereas the direction of results did not differ.

Our study has some limitations. First, selection bias may have occurred due to the process of allocation. In the temporal cohort, some patients could provide informed consent themselves, whereas none of the patients in the frontal cohort were able to consent. Therefore, the overall stroke severity may have been lower in the temporal than in the frontal cohort. This might have underestimated the results of the temporal cohort and made statistical comparisons between both cohorts unreliable. In addition, 123 potentially eligible patients could not be included due to organisational or logistical reasons. This particularly involved patients who presented during out of office hours. Owing to unavailability of study personnel, the rate of wake-up strokes and subsequently stroke severity may have been higher within this group of non-included patients than among the included patients. Consequently, significant study results may have been missed. The impact on our conclusion is expected to be low, however, as the NIRS monitor could not reliably detect inter- and intra-hemispheric rSO_2 differences or changes in a majority of the patients in our study population. Second, the effect of patient- and procedure-related characteristics could not be studied in detail because the sample size did not permit this. Third, results of the temporal and frontal cohorts could not be compared statistically because the study was only powered on temporal NIRS monitoring. Finally, we were unable to perform the planned analyses of inter- and intra-hemispheric rSO_2 differences and changes before versus after induction, and before versus after the end of anaesthesia because it was logistically impractical to collect sufficient data for 10 min under stable conditions before induction and after the end of anaesthesia.

In conclusion, inter- and intra-hemispheric rSO_2 differences or changes during EVT could not be detected by a four-wavelength NIRS monitor, irrespective of sensor position over the temporal lobes or in the recommended position over the frontal lobes. It is likely that even with temporal sensor application, a significant proportion of the received NIRS signal was influenced by oxygenation of surrounding tissues.

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Author note

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Declaration of conflicting interests

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Ethical approval

Ethical approval was waived by the Institutional Ethical Review Board of the University Medical Centre Groningen (reference number: METc 2018/464) because the research did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act.

Informed consent

Written informed or deferred consent was obtained from all included patients or their legal representatives.

Guarantor

SC.

Contributorship

SC, AM, AA, JWE, MU, RB and MS designed the study. SC, AM, NE, AA, SV, JWE, MU, RB and MS acquired the data. SC, AM, NE, AA, JWE, MU, RB and MS analysed the data. All authors interpret the data, drafted and/or revised the manuscript and approved the final version.

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Trial registration

The Netherlands Trial Register: NL7323.

Supplemental material

Supplemental material for this article is available online.

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