24-hour near-infrared spectroscopy monitoring of acute ischaemic stroke patients undergoing thrombolysis or thrombectomy: a pilot study

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Abstract

Introduction

Monitoring of acute ischaemic stroke patients during thrombolysis or thrombectomy is based mostly on frequent physical examinations, since no objective measurement of cerebrovascular haemodynamics is available in routine clinical practice. Near-infrared spectroscopy (NIRS) is a bed-side, non-invasive assessment tool that could help monitor these patients and potentially guide therapeutic interventions. Our goal in this pilot study was to investigate whether NIRS is a suitable method to monitor leptomeningeal collateral circulation via changes in cortical oxygen saturation in the first 24 hours of acute ischaemic stroke.

Patients and methods

Our study included 5 patients with acute anterior circulation infarcts. All patients received thrombolytic therapy and one had thrombectomy. 24-hour continuous NIRS monitoring was performed on all participants.

Results

We aimed to give a detailed description of each NIRS recording and explain how the observed findings could correlate with changes in anterior watershed territory collateral circulation and clinical outcome.

Conclusion

Our pilot study supports the use of NIRS monitoring in acute ischaemic stroke. We believe that this technique could provide real-time information on the dynamic changes of leptomeningeal collateral circulation and help monitor the effects of thrombolysis and thrombectomy.

Keywords: near-infrared spectroscopy (NIRS), ischaemic stroke, thrombolysis, collateral circulation.

1. Introduction

Intravenous administration of recombinant tissue plasminogen activator (rt-PA) is the treatment of choice in eligible acute ischaemic stroke patients who arrive to the hospital within the therapeutic time window (1). If large vessel occlusion is present, mechanical thrombectomy should be performed as well. Monitoring of patients during these procedures is based mostly on frequent physical examinations. For the time being, no objective measurement of the patients' cerebrovascular haemodynamics is used in routine clinical practice. Near-infrared spectroscopy (NIRS) is a bed-side, non-invasive, continuous, real time assessment tool which could help monitor patients with acute ischaemic stroke. It is most commonly used during cardiac surgery and carotid endarterectomy to detect and prevent cortical desaturations which might lead to permanent neurological sequelae (2). To our knowledge, only a few observational and pilot studies have been published that investigated the potential of NIRS monitoring during acute ischaemic stroke (3-6).

NIRS utilizes a light source which emits photons in the near-infrared range (700-1100 nm). These photons can penetrate thought the skull and a few centimetres deep into the brain tissue. The emitted light is partly redirected, scattered and absorbed. The absorption spectrum of oxyhaemoglobin (Hb_{oxy}) and deoxyhaemoglobin ($Hb_{deoxy)}$ is different at various wavelengths(7). This difference allows for calculation of Hb_{oxy} and Hb_{deoxy} concentrations based on the difference in intensity of emitted and received light, using the Beer-Lambert equation:

$$A = lg\frac{I_0}{I} = \varepsilon \times c \times l$$

(A: absorption, I_0: intensity of emitted light, I: intensity of received light, ε: absorption coefficient, c: concentration, l: photon pathlenght).

Total haemoglobin (Hb_T) concentration equals the sum of Hb_{oxy} and Hb_{deoxy} concentrations and is proportional to cerebral blood volume (CBV) (8). Therefore NIRS can be used to measure cortical blood oxygenation/saturation (the fraction of Hb_{oxy} relative to Hb_T) and serve as an indicator for the balance between cerebral oxygen delivery and consumption (2, 9). Mean cortical saturation measured with NIRS comprises of approximately 70% venous and 30% arterial blood (7). It has been established that the relative change in regional O_2 saturation (rSO_2) and not the absolute rSO_2 is considered as a marker of cerebral haemodynamics, since absolute values show great interindividual variability (10, 11). Other limitations of NIRS are environmental and individual features that influence absolute rSO_2

values. These features are summarized in **Table 1** (3, 12). Combined effect of the listed factors can sometimes make the interpretation of NIRS measurements uncertain.

It has been established that collateral circulation plays a pivotal role in reducing progression of ischaemic brain damage (13). Patients with good collaterals develop smaller infarcts, respond better to mechanical thrombectomy, show better clinical outcome and have a lesser chance for haemorrhagic transformation after thrombolysis (14-16). However, real-time assessment of collateral circulation in the setting of acute ischaemic stroke is lacking. We know from multimodal MRI studies that augmented CBV, preserved cerebral blood flow (CBF) and delayed mean transit time (MTT) imply the presence of collateral flow (17). Taussky et al. showed a linear correlation between rSO_2 and CBF measured with CT perfusion (18). Therefore, since CBV and CBF correlates with rSO_2 values, our goal in this pilot study was to investigate whether NIRS is a suitable method to monitor anterior watershed territory leptomeningeal collateral circulation via changes in cortical oxygenation during thrombolysis and thrombectomy. Due to the small sample size of our pilot study, we could not draw statistical conclusions. Instead, we aimed to give detailed analysis of the 5 NIRS recordings and explain how these findings could correlate with cerebrovascular haemodynamics and clinical picture.

2. Patients and methods

The study was approved by an independent ethics committee (University of Szeged, Faculty of Medicine, Ethics Committee, ID: 211/2016-SZTE). All patients or first degree relatives gave written informed consent prior to NIRS monitoring. Our study population included 5 acute stroke patients who had left sided anterior circulation infarcts. Detailed patient characteristics are highlighted in **Table 2**. All participants received alteplase as recommended by the 2018 AHA/ASA acute ischaemic stroke guideline (1). One patient also had mechanical thrombectomy due to left M1 occlusion (Patient 3). INVOS™ 5100C Cerebral/Somatic Oximeter (Medtronic, Minneapolis, MN, USA) was used for 24-hour continuous monitoring. Application of the NIRS sensors did not delay the start of thrombolysis. The sensors were placed over bilateral frontal areas, as recommended by the manufacturer. The studied brain areas correspond to the anterior watershed territories. Baseline rSO_2 was measured before the initiation of intravenous rt-PA. rSO_2 measurements were made approximately every 30 seconds. We analysed the 5 minute average rSO_2 values registered at the start of thrombolysis

and also 1 hour, 6 hours, 12 hours, 18 hours and 24 hours after the initiation of alteplase treatment. Interhemispheric rSO_2 difference ($IH\Delta rSO_2$) was calculated as rSO_2 on the affected side minus rSO_2 measured above the contralateral side. Based on previous articles, 4% change in rSO_2 value, and 2% change in $IH\Delta rSO_2$ was considered significant (5, 19). Simultaneously, blood pressure, peripheral O_2 saturation (SpO_2), heart rate and electrocardiography were also monitored. The patients' SpO_2 was above 92% while breathing ambient air, therefore they did not receive O_2 supplementation during the study period. The only exception was Patient 3 who underwent thrombectomy. He was intubated because he could not cooperate to the procedure due to severe aphasia. The patients' clinical outcome was assessed with the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS). A mRS score of 0-2 at 90 days was considered as good functional outcome. If large vessel occlusion (LVO) was present, collateral circulation on imaging was assessed by a neuroradiologist using a 3 grade scale (good-intermediate-poor). Initially, Patients 1-3 had CT angiography (CTA) and Patients 4-5 had MR angiography – time of flight (MRA-TOF) imaging. **Figure 1** shows CT and MRI scans approximately 24 hours after thrombolysis for each patient.

3. Results

3.1. Descriptive analysis of each patients' NIRS recordings

Patient 1 suffered a left middle cerebral artery (MCA) territory stroke due to M2 occlusion. Collateral circulation was good based on CTA. During NIRS monitoring, no relevant rSO_2 difference was observed between the two hemispheres ($IH\Delta rSO_2$ was between -2% and 0%). rSO_2 values were quite stable on both sides. The patient had a good clinical outcome at 3 months.

Patient 2 had clinical signs of left hemispheric stroke. CTA revealed a left internal carotid artery (ICA) occlusion. Good collaterals were detected on CTA and rSO_2 absolute values were higher above the ipsilateral side (average $IH\Delta rSO_2$ was 3%). rSO2 levels gradually rose in the first 12 hours on both sides. This might indicate subtle increase in CBV and CBF in the leptomeningeal collaterals. The patient's NIHSS score decreased in the first few days and eventually showed good clinical outcome at 3 months.

Patient 3 had a left M1 occlusion and underwent endovascular thrombectomy after thrombolysis. Collaterals were graded as intermediate on CTA. Initially, a significant $IH\Delta rSO_2$ was observed. The affected side had a lower absolute rSO_2 value (55% vs.63%).

This difference did not change after thrombolysis (1 h post thrombolysis IHΔrSO_2 was -7%). However, after thrombectomy there was a significant increase in rSO_2 on the ipsilateral side and consequently IHΔrSO_2 substantially decreased. IHΔrSO_2 absolute values even became positive after 12 hours. These findings possibly indicate that NIRS sensors were either placed above ischaemic territory or the leptomeningeal collateral circulation was insufficient. As expected from the NIRS recording of the first 24 hours, the patient's recovery went well (mRS 1 at 90 days).

Patient 4 was the only participant who did not achieve good functional outcome at 90 days (mRS was 3). She suffered a left MCA territory infarction, MRA-TOF imaging did not show LVO. Before thrombolysis, absolute rSO_2 was significantly higher on the affected side (69% vs. 61%). After 1 hour, a marked increase of rSO_2 was observed above both hemispheres (+9%, IHΔrSO_2 remained 8%). IHΔrSO_2 then steeply decreased to -2% at 12 hours. The patient's NIHSS score worsened. Control CT scan revealed a left striatocapsular infarct. The striatocapsular territory is supplied by perforator arteries stemming from the proximal part of M1 and does not have collateral circulation (20). Since rSO_2 increased similarly above both hemispheres in the first hour, it is possible that the ischaemic insult provoked an increase in global cerebral perfusion.

Patient 5 had markedly elevated rSO_2 values above the ipsilateral hemisphere (82% vs 69%). The significantly high IHΔrSO_2 was possibly a consequence of chronic right ICA occlusion which led to long-term, effective Willisian collateralization and consequent enlargement of left ICA, MCA and anterior cerebral artery (ACA) (**Figure 1/f**). Increased blood flow in the left MCA and ACA could explains the high rSO_2 values above the ipsilateral watershed area, implying well-developed leptomeningeal collaterals. The IHΔrSO_2 value remained high throughout the 24-hour monitoring. The patient had a good functional outcome at 3 months.

Data of NIRS recordings and diagrams are found in the **Supplementary material.**

3.2. Analysis of combined results

The initial rSO_2 above the affected hemispheres showed greater variability compared to the contralateral sides. Patient 5's results might have led to bias, therefore we only examined the first 4 patients' results. Still, the difference in variability remained significant, which was most prominent in the first 12 hours. This finding probably reflects impaired autoregulation

on the affected side. Graphs demonstrating rSO_2 variability are found in the **Supplementary material.**

4. Discussion

Most of the previous studies that used NIRS in the setting of acute ischaemic stroke aimed to study the oxygenation of ischaemic brain area. Instead, we tried to investigate whether NIRS is feasible in evaluating leptomeningeal collaterals located at the anterior watershed areas. We believe, that a good example for our hypothesis is the case of Patient 5. Due to a chronic right ICA occlusion, we measured significantly higher rSO_2 values above the left hemisphere. The explanation of this finding is possibly the increased blood flow in the left ICA, MCA and ACA which provides adequate blood perfusion to both hemispheres through the circle of Willis. Long-term increased flow led to enlargement of these vessels and subsequently well-developed leptomeningeal collateral circulation in the monitored hemisphere.

Ritzenthaler et al. performed 24-hour NIRS monitoring in 17 acute stroke patients who underwent mechanical thrombectomy (4). All their patients had lower absolute rSO_2 values above the affected hemisphere. They did not find a significant relationship between initial ipsilateral rSO_2 and collateral circulation (assessed with American Society of Interventional and Therapeutic Neuroradiology Collateral Flow Grading scale, ASITN). Explanations behind their finding might be that NIRS sensors were above ischaemic territory or the leptomeningeal collateral circulation was insufficient in all participants. Since the authors reported patients with ASITN score of more than 3 (indicating good collateral flow), the latter explanation seems unlikely. In our study, Patient 3 demonstrated a similar NIRS trend to those cases published in Ritzenthaler's article. After successful recanalization, $IH\Delta rSO_2$ significantly decreased. Patient 2 had left ICA occlusion, but still had higher rSO_2 on the ipsilateral side possibly due to well-developed leptomeningeal collaterals.

In another study, NIRS monitoring was also used during thrombectomy in 43 acute ischaemic stroke patient (3). Hametner et al. reported that absolute values of median $IH\Delta rSO_2$, measured at the end of thrombectomy, were significantly lower in patients who died by 90 days. In addition, patients whose variability in rSO2 values were lower, showed significantly worse 90-day outcomes (mRS score 3-6). Due to the small sample size of our study, we could not draw significant statistical correlations related to NIRS parameters and clinical outcome. Instead, we aimed to give individual descriptions of each patients' monitoring.

Damian and Schlosser investigated patients with MCA occlusions who had consequent brain oedema (19). NIRS monitoring was performed in the subacute phase of stroke (at least 12 hours, but within 4 days after the ictus). Interestingly, 22 out of 24 patients had higher absolute rSO_2 values above the ipsilateral frontal area. These data are quite the opposite of that published by Ritzenthaler et al. We hypothesize that this difference is because the measurements were made at different time points (subacute vs. acute phase of stroke). It is possible, that the observed positive absolute IHΔrSO_2 values in Damien and Schlosser's study reflects increased compensatory leptomeningeal collateral circulation, which developed on the affected side a few days after the cerebrovascular insult. The article reported good clinical outcome (Glasgow Outcome Scale 3-4) in cases where average IHΔrSO_2 values increased over time. Outcomes were assessed between 6-24 weeks, after rehabilitation. In all 5 cases, where the initial IHΔrSO_2 decreased, the patients died. Another important finding of the study was that clinical signs of progressing brain oedema and unfavourable rSO_2 changes were reversible in some cases by hemicraniectomy, hyperventilation, hypothermia or improved systemic perfusion (19). Therefore, correct interpretation of NIRS monitoring could guide therapeutic interventions. Previous studies showed, that decrease in systemic blood pressure and/or peripheral oxygen saturation (SpO_2) correlates well with a drop in rSO_2 (3, 5). We believe, that NIRS parameters can guide clinicians in finding the target blood pressure and SpO_2 values of each individual patient. For example, some patients with acute ICA occlusion could benefit from increasing blood pressure to maintain adequate collateral circulation until thrombectomy can be performed to achieve recanalization. A preclinical study investigated this concept and found that mild induced hypertension increased cortical collateral blood flow and significantly reduced infarct volume in mice with transient distal MCA occlusion (21).

NIRS monitoring would provide additional information if more sensors were placed over the cerebral hemispheres. This way, rSO_2 could be simultaneously measured over the ischaemic territory and watershed areas. Rummel et al. used multichannel NIRS monitoring during transient balloon occlusion of cerebral arteries (8). They demonstrated that different rSO_2 changes are observed over the ischaemic core and watershed areas during transient LVOs due to haemodynamic changes in collateral flow. Moreau et al. also applied multichannel NIRS monitoring in 5 acute ischaemic stroke patient who had LVO. The sensors were placed over the frontal, parasagittal frontal, Rolandic sulcus, Broca and Wernicke areas of the brain (12). The symptom onset to monitoring time was within 9 hours. They found that, at least one region of the infarcted hemisphere showed reduced rSO_2 values compared to the unaffected,

contralateral side. One of their patient's suffered a haemorrhagic transformation a few days after the ischaemic event. Not surprisingly, rSO_2 values were significantly higher above the affected hemisphere compared to the contralateral side. This finding is probably explained by the presence of still highly oxygenated blood within the brain tissue (12).

Table 3 highlights the most important findings of previous NIRS studies.

In summary, the results of our pilot study support the use of NIRS monitoring in the setting of acute ischaemic stroke. We believe that this technique could provide valuable information on the state of leptomeningeal collaterals and help monitor the effects of thrombolysis and thrombectomy. In addition, rSO_2 values could guide individual management of patients' blood pressure and oxygen supplementation to widen the therapeutic time window for recanalization (17). However, future studies, preferably with multichannel NIRS monitoring are warranted to gain further information on the relation between leptomeningeal collaterals, ischaemic territory and rSO_2 absolute values and trends.

5. Acknowledgements

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6. Conflicts of interest

The authors declare that they have no conflict of interest.

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Tables and Figures

Table 1. Factors influencing rSO_2 values

Contamination form hair and skin
Sweating
Skull thickness
Extracranial circulation
O_2 extraction of brain tissue (e.g.: reduced O_2 extraction of infarcted or oedematous territory)
Blood pressure
Peripheral oxygen saturation
Haemoglobin concentration in blood
Level of consciousness

Table 2. Patient characteristics

	Patient 1	***Patient 2***	***Patient 3***	***Patient 4***	***Patient 5***
Sex	female	male	male	female	female
Age	80	67	63	66	78
Vessel territory	left MCA	left ICA	left MCA	left MCA	left MCA
LKW to treatment time (min)	128	97	200	245	228
Hypertension	yes	yes	yes	yes	yes
Hyperlipidaemia	no	yes	yes	yes	yes
Diabetes mellitus	no	no	no	no	no
Atrial fibrillation	no	no	no	no	no
Ischaemic heart disease	yes	no	yes	no	yes
Smoking	no	no	yes	yes	yes
Haemoglobin (g/l)	142	140	139	153	121
Large vessel occlusion	left M2	left ICA	left M1	0	right ICA (chronic)
Collateral score	good	good	intermediate	not applicable	not applicable
Stroke subtype	CE	LAA	CE	SVD (striatocapsular infarct)	CE
NIHSS baseline	14	15	17	7	9
NIHSS 24-hour	9	12	12	10	4
NIHSS discharge	4	9	8	10	1
mRS 3 months	2	2	1	3	1

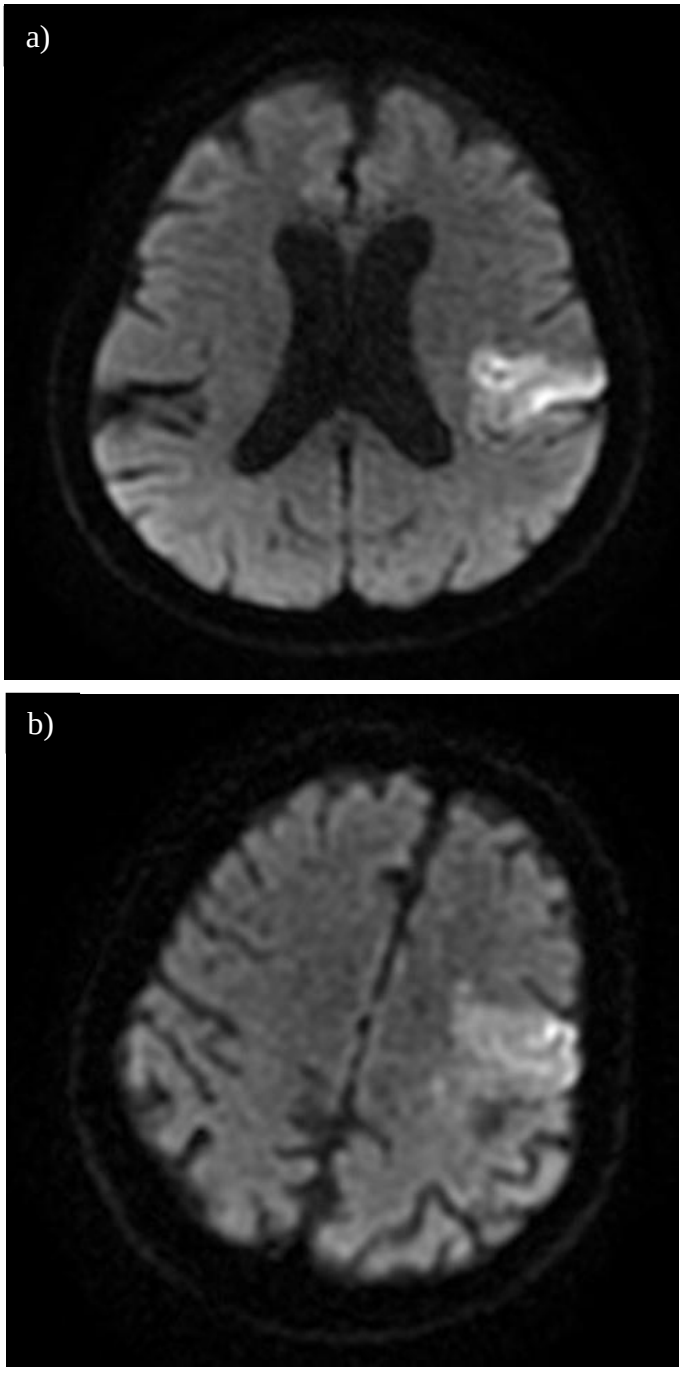
Abbreviations: CE: cardioembolic**,** ICA: internal carotid artery, LAA: large-artery atherosclerosis, LKW: last known well, MCA: middle cerebral artery, mRS: modified Rankin score, NIHSS: National Institutes of Health Stroke Scale, SVD: small vessel disease, VA: vertebral artery.

Table 3. Relevant findings of previous studies with NIRS

Study	Timing of monitoring	Findings
Ritzenthaler et al. (4)	first 24 hours, including thrombectomy	lower absolute rSO_2 values above the affected hemisphere in all patients (n=17)
		no significant relationship between initial ipsilateral rSO_2 and collateral circulation
		correlation was found between rSO_2 and MRI parameters (MTT and T_{max})
Hametner et al. (3)	during thrombectomy + 6 hours or time to extubation	median IHΔrSO_2 at the end of thrombectomy was significantly lower in patients who died by 90 days
		variability in rSO_2 were lower in patients with mRS score 3-6 at 90-days
		significant association between changes in MAP and rSO_2
Damian and Schlosser (19)	subacute phase (12 h to 4 days after stroke)	22/24 patients had higher absolute rSO_2 above the ipsilateral frontal area
		good clinical outcome when average IHΔrSO_2 values increased
		progression of brain oedema and unfavourable rSO_2 changes were reversible by therapeutic interventions (e.g.: hemicraniectomy)
Moreau et al. (multichannel monitoring) (12)	acute phase (9 hours ≥ after symptom onset)	at least one ipsilateral region showed reduced rSO_2 compared to unaffected side
		rSO_2 values were significantly higher after haemorrhagic transformation
Rummel et al. (multichannel monitoring) (8)	transient balloon occlusion of cerebral arteries	different rSO_2 changes over ischaemic core and watershed areas

Abbreviations: IHΔrSO2: interhemispheric rSO_2 difference, MAP: mean arterial pressure, MRI: magnetic resonance imaging, mRS: modified Rankin scale, MTT: mean transit time, T_{max}: time-to-maximum, rSO_2: regional oxygen saturation.

Figure 1. CT and MRI scans of patients approximately 24 hours after thrombolysis. a) Diffusion-weighted imaging (DWI) scan of Patient 1, showing left MCA territory cortical ischaemia. b) DWI scan of Patient 2 shows a similar brain infarct. c) Non-contrast CT (NCCT) scan of Patient 3 after thrombectomy. The infarct mainly involves the left basal ganglia and internal capsule. d) NCCT of Patient 4 showing slight hypodensity in the left corona radiata (striatocapsular infarct). e) DWI scan of patient 5 shows a left MCA territory infarct. f) MRA-TOF reconstruction of Patient 5 demonstrating enlarged left ICA and MCA.



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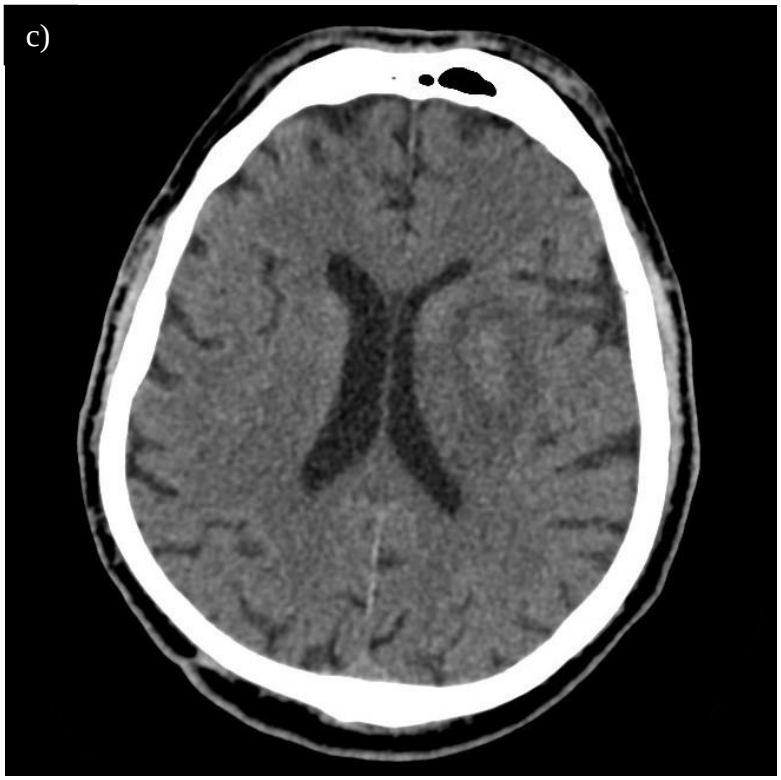

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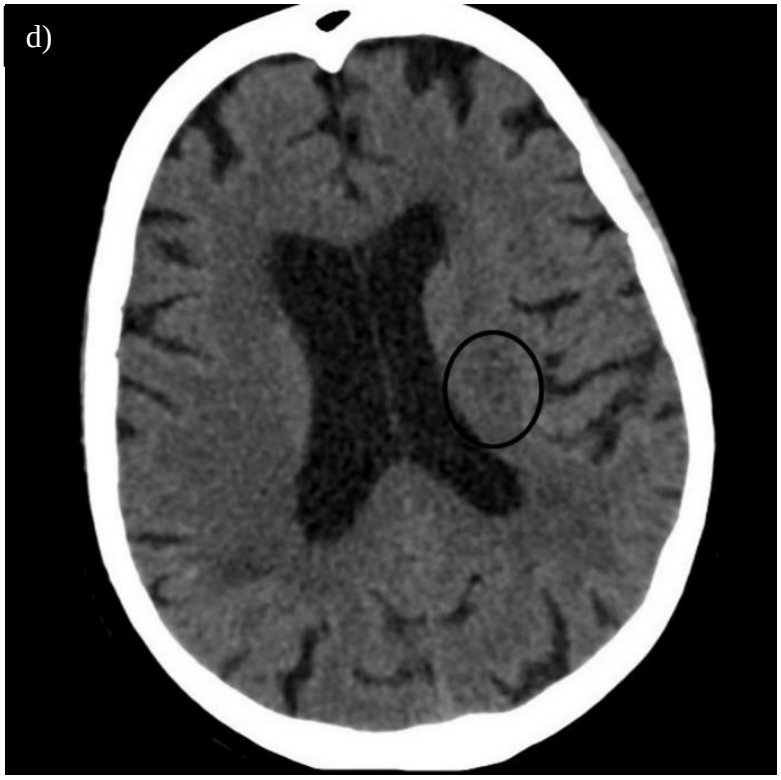

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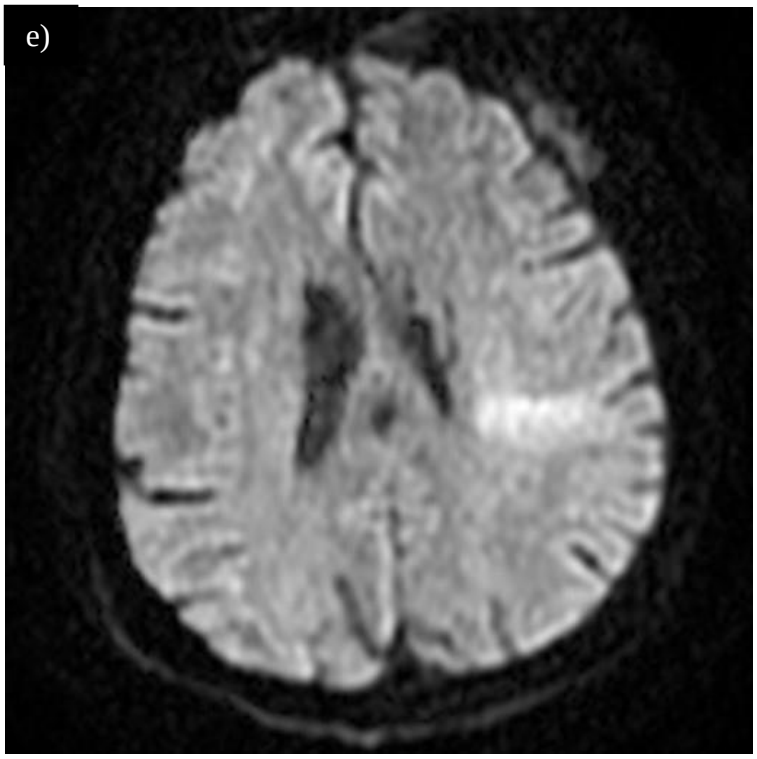

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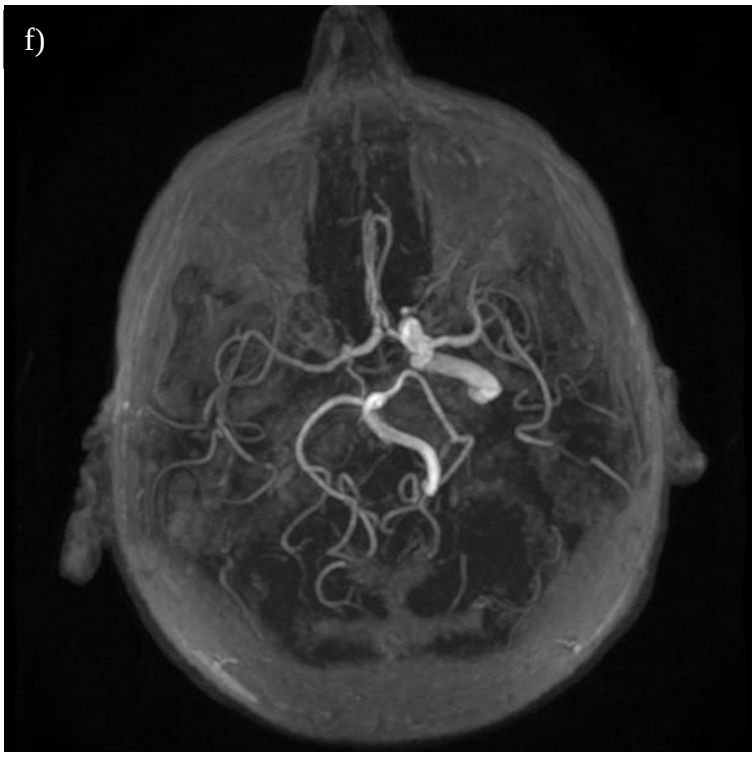
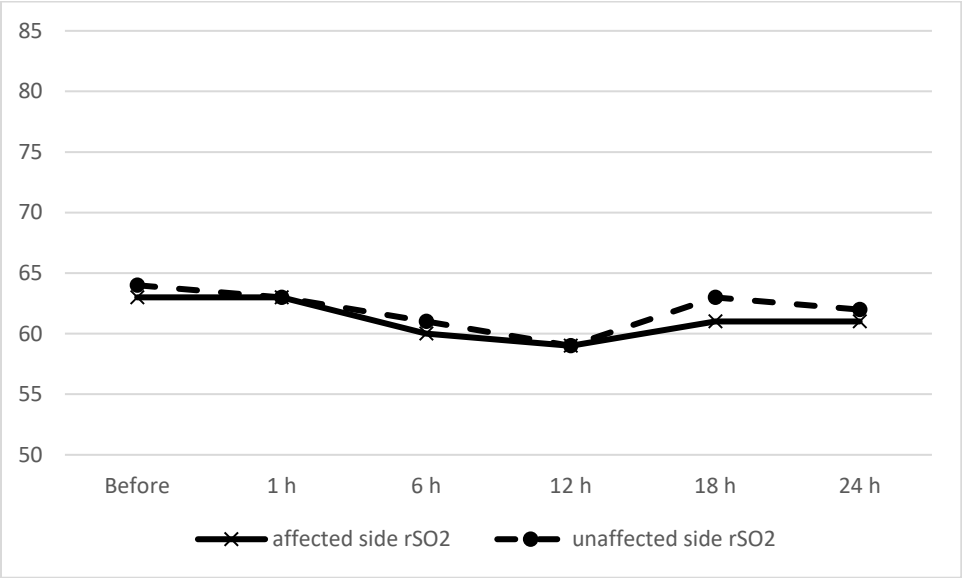


Supplementary material

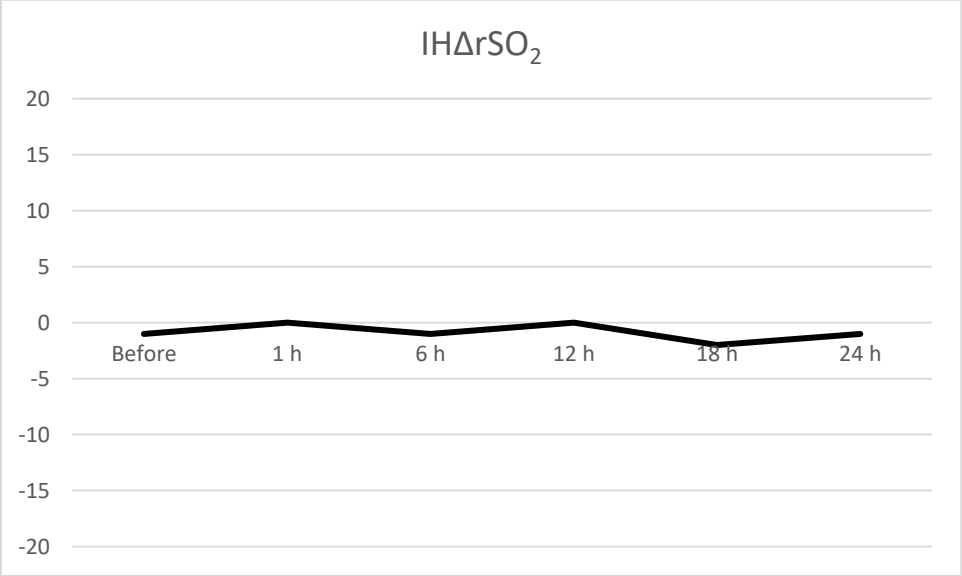
NIRS data from Patient 1.

Time	Affected side rSO_2 (%)	Unaffected side rSO_2 (%)	$IH\Delta rSO_2$ (%)
Before thrombolysis	63	64	-1
1 h post thrombolysis	63	63	0
6 h post thrombolysis	60	61	-1
12 h post thrombolysis	59	59	0
18 h post thrombolysis	61	63	-2
24 h post thrombolysis	61	62	-1
Average	60,80	61,60	-0,80

rSO_2 (%) trends of Patient 1.



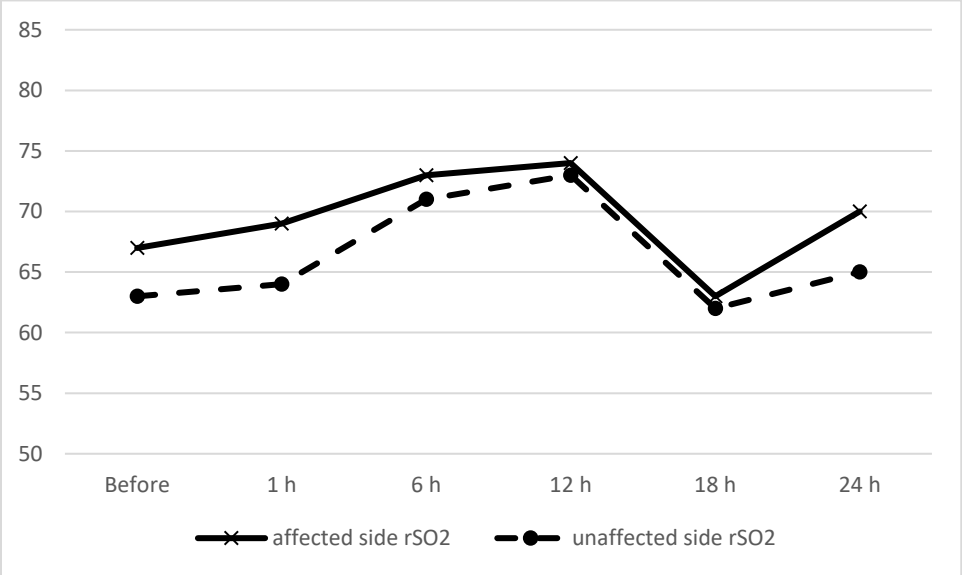
$IH\Delta rSO_2$ (%) trend of Patient 1.



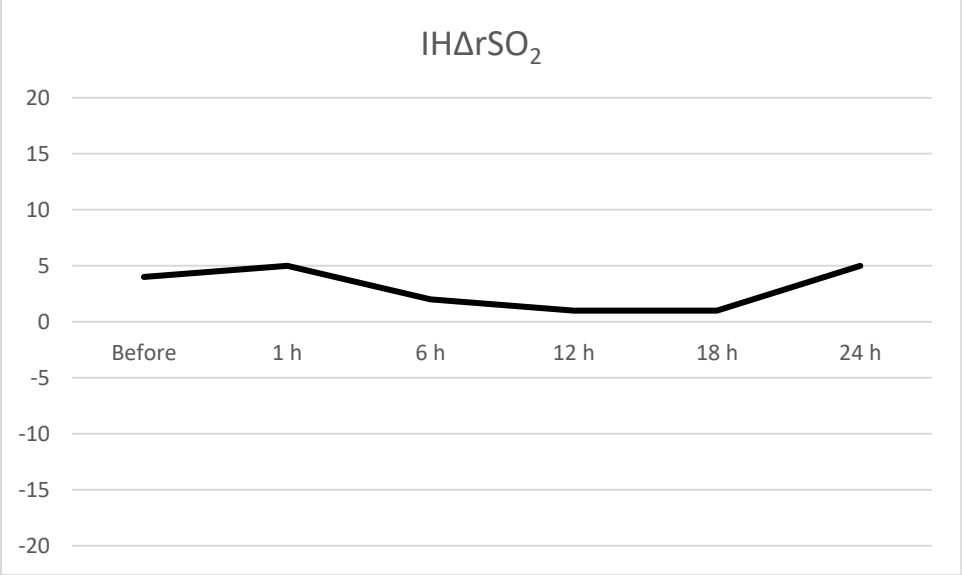
NIRS data from Patient 2.

Time	Affected side rSO_2 (%)	Unaffected side rSO_2 (%)	$IH\Delta rSO_2$ (%)
Before thrombolysis	67	63	4
1 h post thrombolysis	69	64	5
6 h post thrombolysis	73	71	2
12 h post thrombolysis	74	73	1
18 h post thrombolysis	63	62	1
24 h post thrombolysis	70	65	5
Average	69,33	66,33	3

rSO_2 (%) trends of Patient 2.



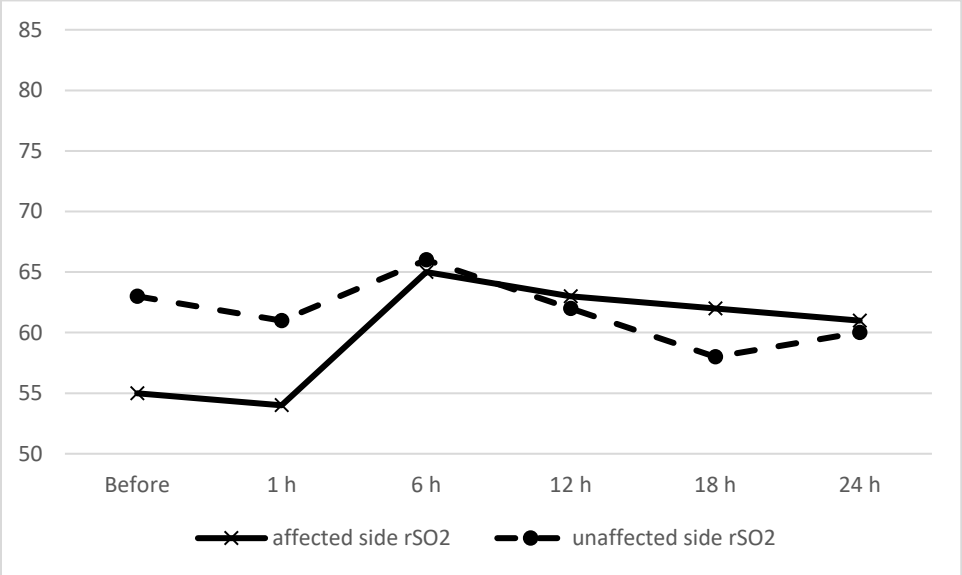
$IH\Delta rSO_2$ (%) trend of Patient 2.



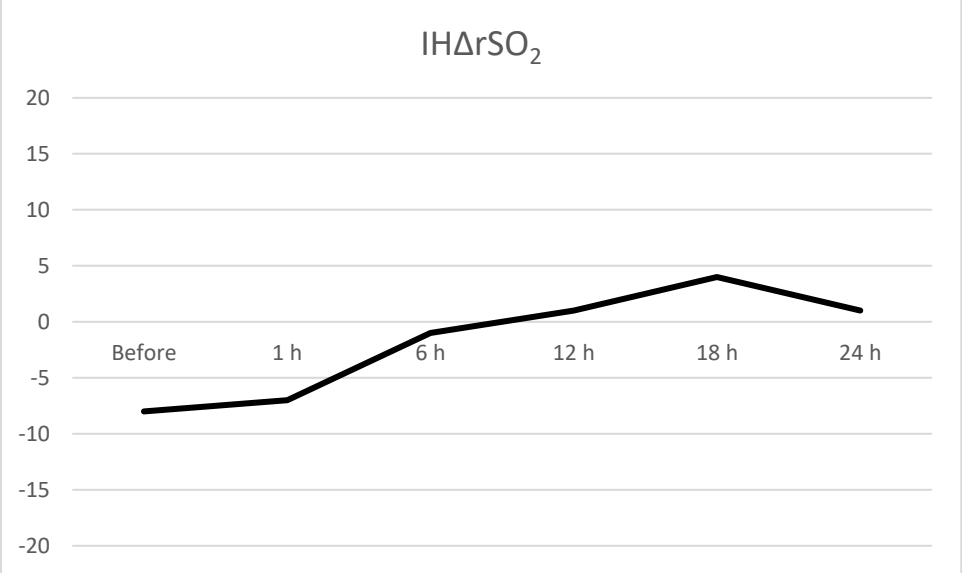
NIRS data from Patient 3.

Time	Affected side rSO_2 (%)	Unaffected side rSO_2 (%)	$IH\Delta rSO_2$ (%)
Before thrombolysis	55	63	-8
1 h post thrombolysis	54	61	-7
6 h post thrombolysis	65	66	-1
12 h post thrombolysis	63	62	1
18 h post thrombolysis	62	58	4
24 h post thrombolysis	61	60	1
Average	60,00	61,67	-1,67

rSO_2 (%) trends of Patient 3.



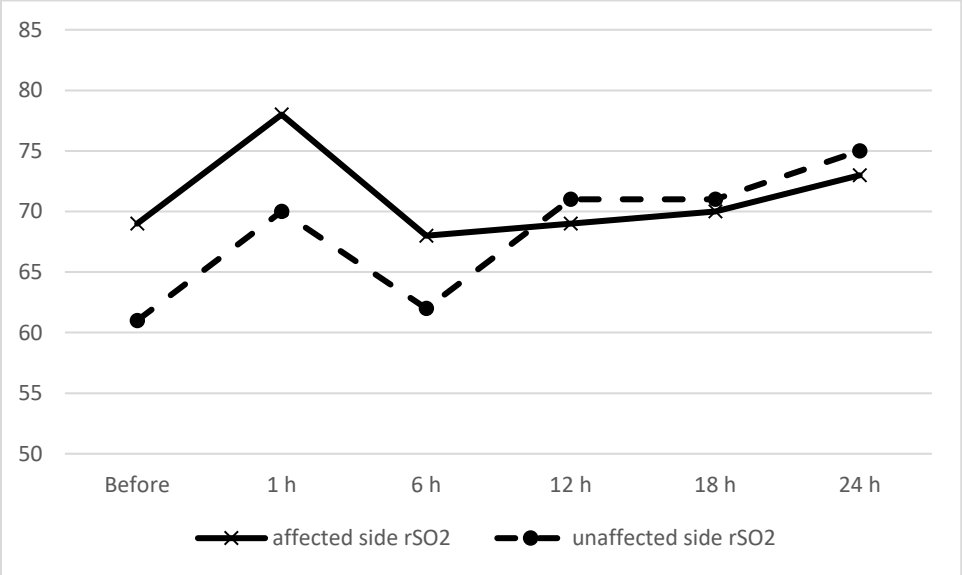
$IH\Delta rSO_2$ (%) trend of Patient 3.



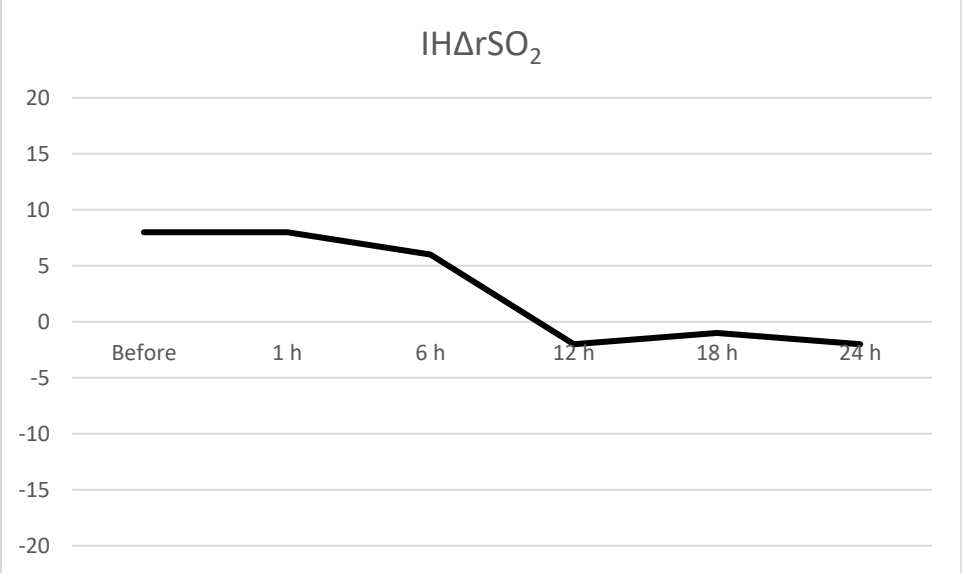
NIRS data from Patient 4.

Time	Affected side rSO_2 (%)	Unaffected side rSO_2 (%)	$IH\Delta rSO_2$ (%)
Before thrombolysis	69	61	8
1 h post thrombolysis	78	70	8
6 h post thrombolysis	68	62	6
12 h post thrombolysis	69	71	-2
18 h post thrombolysis	70	71	-1
24 h post thrombolysis	73	75	-2
Average	71,17	68,33	2,83

rSO_2 (%) trends of Patient 4.



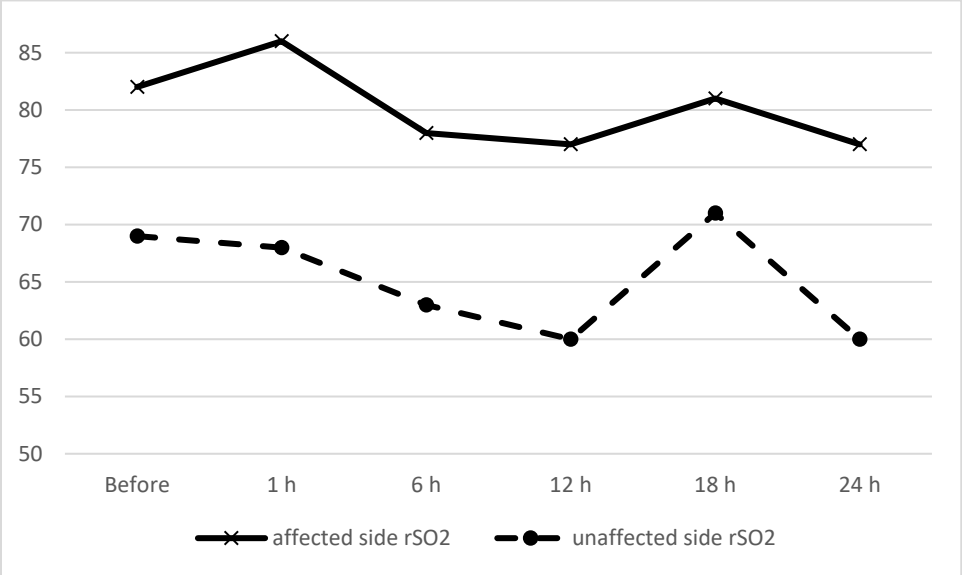
$IH\Delta rSO_2$ (%) trend of Patient 4.



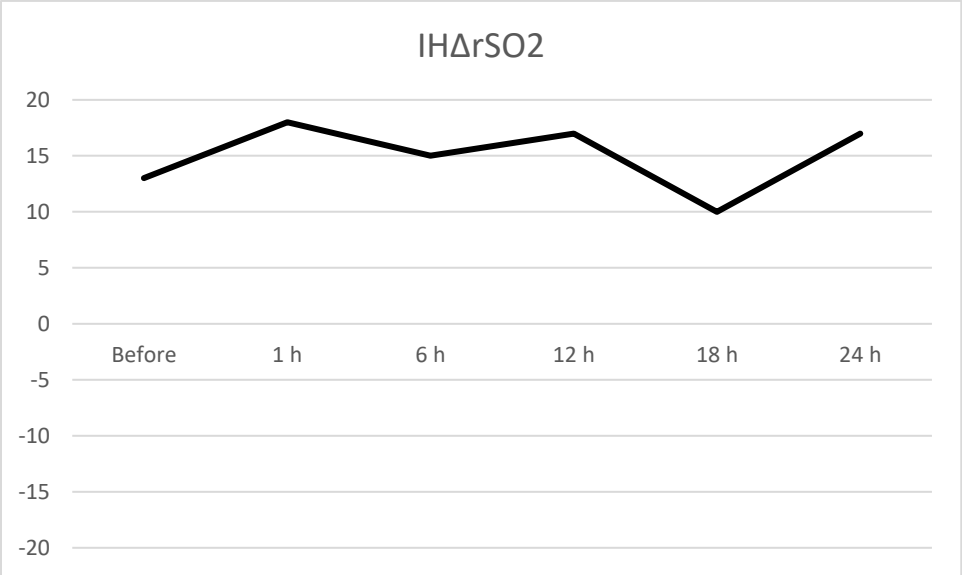
NIRS data from Patient 5.

Time	Affected side rSO_2 (%)	Unaffected side rSO_2 (%)	$IH\Delta rSO_2$ (%)
Before thrombolysis	82	69	13
1 h post thrombolysis	86	68	18
6 h post thrombolysis	78	63	15
12 h post thrombolysis	77	60	17
18 h post thrombolysis	81	71	10
24 h post thrombolysis	77	60	17
Average	80,17	65,17	15,00

rSO_2 (%) trends of Patient 5.



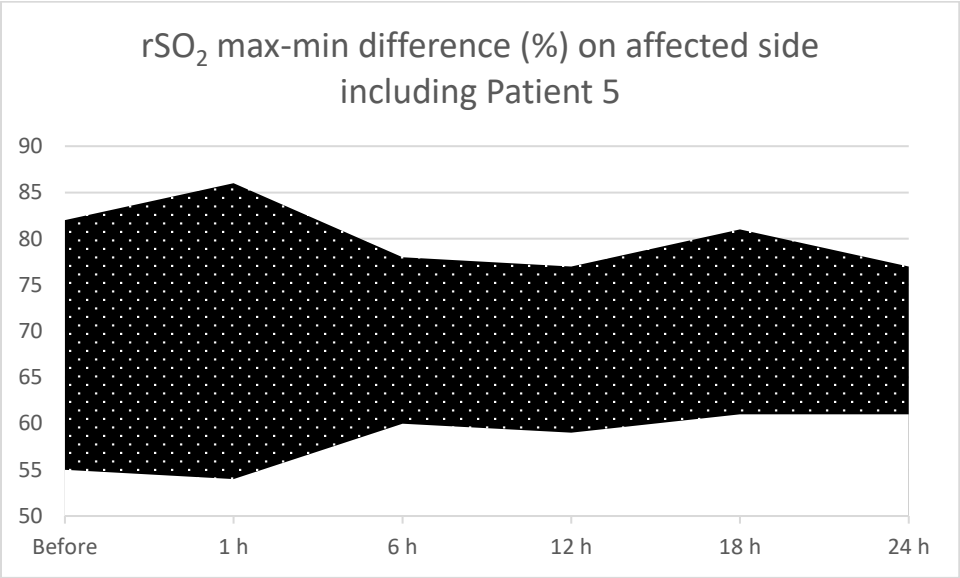
$IH\Delta rSO_2$ (%) trend of Patient 5.

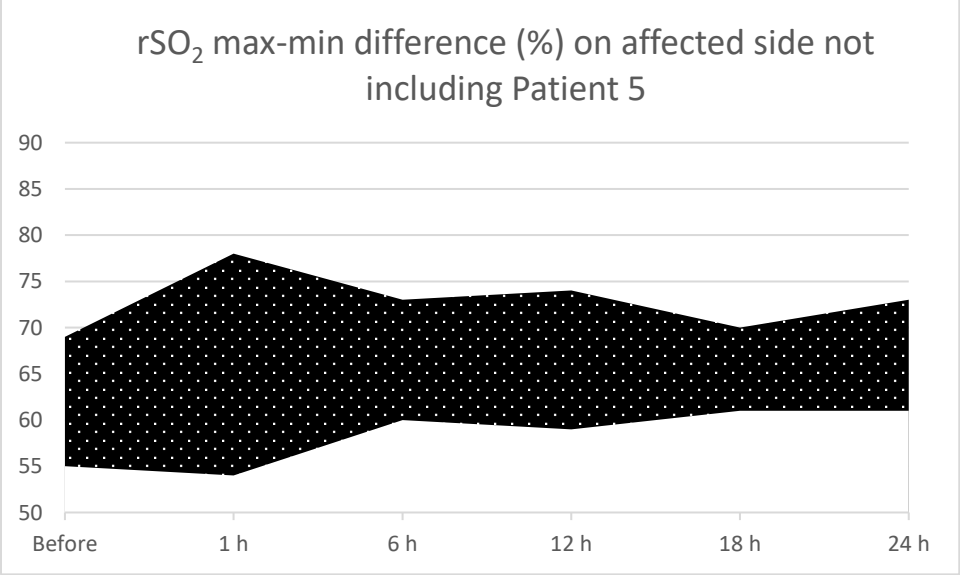


Data and graphs on rSO_2 variability

a) Ipsilateral side

Time	rSO_2 max. (%) including Patient 5	rSO_2 max. (%) not including Patient 5	rSO_2 min. (%)
Before thrombolysis	82	69	55
1 h post thrombolysis	86	78	54
6 h post thrombolysis	78	73	60
12 h post thrombolysis	77	74	59
18 h post thrombolysis	81	70	61
24 h post thrombolysis	77	73	61





b) Contralateral side

Time	rSO_2 max. (%)	rSO_2 min. (%)
Before thrombolysis	69	61
1 h post thrombolysis	70	61
6 h post thrombolysis	71	61
12 h post thrombolysis	73	60
18 h post thrombolysis	71	58
24 h post thrombolysis	75	60