CZECH TECHNICAL UNIVERSITY IN PRAGUE

FACULTY OF BIOMEDICAL ENGINEERING

Department of Biomedical Technology

Pilot study for comparison of cerebral and somatic NIRS in septic patients.

Bachelor Thesis

Study program: Biomedical and Clinical Technology
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BACHELOR'S THESIS ASSIGNMENT

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II. BACHELOR'S THESIS DETAILS

Bachelor's thesis title in English:

Comparison of cerebral and somatic NIRS in septic patients

Bachelor's thesis title in Czech:

Porovnání cerebrální a somatické NIRS u septických pacientů

Guidelines:

Analyze signals from Near-infrared Spectroscopy (NIRS) in critically ill patients in sepsis. Compare cerebral and somatic NIRS signals during septic shock. Analyze somatic NIRS signals from different somatic locations, propose suitable somatic NIRS probe placement for this group of patients.

Bibliography / sources:

[1] Webster, J.G., Encyclopedia of Medical Devices and Instrumentation, ed. 6, Wiley, 2006, ISBN 978-0-471-26358-6
[2] Desmond, F.A., Namachivayam, S., Does near-infrared spectroscopy play role in paediatric intensive care, BJA Education, ročník 16, číslo 8, 2016, 281-285 s.

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Assignment valid until: **19.09.2021**

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DECLARATION

I hereby declare that I have completed this thesis having the topic “Comparison of cerebral and somatic NIRS in septic patients” independently, and that I have attached an exhaustive list of citations of the employed sources.

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In Kladno 2020 …..……..……...

Yahya Beqqali

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ABSTRACT

Pilot study for comparison of cerebral and somatic NIRS in septic patients

As sepsis disease is the third leading death cause in the world, one of the leading research questions is the early prediction of sepsis to reduce the death rates. To find a new predictor of sepsis, a comparison between cerebral and somatic NIRS (near-infrared spectroscopy) values was done in septic patients. The data collection was done using the INVOS system 5100, where the recording of the NIRS signals from the patients was taken from 4 different locations and recorded simultaneously. The comparison was performed by analyzing the signals using MATLAB software and by the correlation coefficient calculation. The results obtained in this pilot study recommend the use of the hands and left forearm somatic sites as suitable locations for the measurement of the regional oximetry values, as their correlation with the cerebral sites is high, thus further studies with a bigger number of samples are required to assess the use of NIRS as a sepsis early predictor.

Key words
Sepsis, NIRS, Somatic oximetry, Cerebral oximetry

ABSTRACT

Pilotní studie porovnání cerebrální a somatické NIRS u septických pacientů

Sepse je třetí nejčastější příčinou smrti ve světě, a proto jednou z hlavních výzkumných otázek je její včasná predikce za účelem snížení počtu obětí. K ověření nového přístupu k predikci sepse bylo použito porovnání cerebrální a somatické oximetrie pomocí NIRS (near infrared spectroscopy). Sběr dat byl proveden pomocí přístroje INVOS system 5100, díky němuž byly signály NIRS zaznamenány simultánně ze 4 různých tělesných částí pacientů. Porovnání signálů bylo provedeno pomocí softwaru MATLAB, byl stanoven korelační koeficient mezi jednotlivými signály. Výsledky této pilotní studie mohou doporučit ruku a levé předloktí jako vhodné místo pro umístění senzoru pro somatickou oxymetrii, jelikož tyto signály dobře korelují s cerebrální oximetrií, přestože budou třeba další studie s větším množstvím vzorků k ověření možnosti použití NIRS jako včasného prediktoru sepse.

Key words

sepse, NIRS, somatická oximetrie, cerebrální oximetrie

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List of symbols

Symbol	Unit	Importance
$crSO_2$	%	Cerebral regional oxygen saturation
HR	bpm	Heart rate
RR	bpm	Respiratory rate
rSO_2	%	Regional oxygen saturation
SpO_2	%	peripheral capillary oxygen saturation
StO_2	%	Tissue oxygen saturation
SvO_2	%	Venous oxygen saturation
T	C°	Temperature

List of abbreviations

Abbreviation	Meaning
AI	Artificial Intelligence
BMI	Body mass index
CBF	Cerebral blood flow
CCD	Charge couple device
CPB	Cardiopulmonary bypass
CSOR	cerebro-splanchnic oxygenation ratio
CW	Continuous wave
ED	Emergency department
FcTOE	Fractional cerebral tissue oxygen extraction
FD	Frequency domain
FsTOE	Fractional somatic tissue oxygen extraction
InGaAs	Indium Gallium Arsenide
MRI	Magnetic resonance imaging
NIR	Near Infrared
NIRS	Near Infrared Spectroscopy
SBP	Systolic blood pressure
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
TD	Time domain

1 Introduction

In the intensive care field, the evolution of the equipment especially medical devices and their new methods for the usage is improving. In addition to the help of artificial intelligence (AI), new devices are to create and new methods are to be used. Today we will be discussing an important topic that has an impact and its result could be a big effect on the medical field.

The early detection of the life-threatening disease of sepsis is meant to be a complicated subject where medical doctors find it very hard and difficult to recognize, even the use of different methods to detect it and prevent it from happening, the success rate to achieve the wanted goal is low, that means that with all the new inventions and the improvised ways that are available in the medical field today, still, it is an issue that we face. (1)

Early identification and timely supportive care, coupled with antibiotic therapy and source control, resulting in improved outcomes. As a result, current international consensus guidelines recommend aggressive, invasive approach for the resuscitation of patients with severe sepsis and septic shock. Unfortunately, central monitoring is not always available that is what pushed us to look for new ways and methods to achieve our purpose, detecting the disease earlier using non-invasive specific parameters, that could make the medical doctors work easier and can set a clear path for the recovery of the patients. One of the best-used devices currently that works based on non-invasive diagnosis are Near-infrared Spectroscopies (NIRS), there is a growing interest as to whether it could help us detect septic situation on critically ill patients.

The objective of this study was to test the hypothesis that NIRS-derived tissue oxygen saturation (StO_2) measurements can identify patients who have sepsis by collecting the signals from multiple somatic locations and cerebral ones. There is a small body of literature suggesting that cerebral regional oxygen saturation ($crSO_2$) monitoring added value in assessment management of intensive care unit (ICU) patients, and that is what motivated us to analyze somatic locations too, those obtained signals will undergo analyses where the comparison will be made and see what they share and don’t, the final step is the proposal of some suitable somatic NIRS probe

placement for this group of patients.

We are motivated to have a positive feedback and finding a way to the solution for this disease that has been affecting many lives in those past few years. With getting the result wanted, a step forward will be set to minimize the percentage of this disease occurring, and it will be monitored easily using NIRS, plus the suggested location that will benefit the cause.

2 Overview of the current state of the art

2.1 Sepsis

Sepsis is a dangerous disease that is mortal, it is an overreaction from our immune system against an infection that is introduced to our body, and that leads up to multiple injuries to skin tissues and organs, it is mainly caused by an inflammatory immune response influenced by an infection.(2)

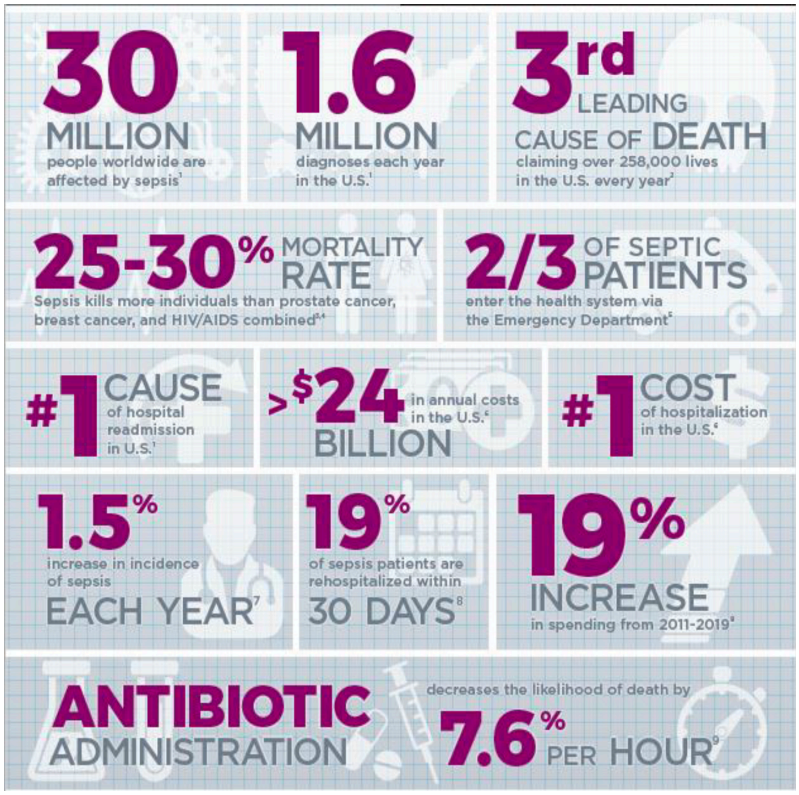


Figure 2.1: general stats for sepsis. (2)

2.1.1 Sepsis stages

To identify a patient with sepsis, they have to go through different stages and show some specific symptoms, as it is necessary for the selection of the cohorts. The initial symptoms of the first stage of sepsis are considered to be one of the components of the systemic inflammatory response syndrome (SIRS):

1) respiratory rate (RR) ≥ 20 breaths per minute.
2) Temperature (T) > 38.3 C°, or < 36 C°.
3) heart rate (HR) >90 beats per minute.
4) white cell count <4 or >12 g/l.

Additional symptoms may include Shivering, paleness, or shortness of breath, Confusion, or difficulty waking up, and Extreme pain. (3) Then the development of the inflammation proceeds and can reach its second stage when it becomes sepsis, and that is the presence of two components of the SIRS plus a confirmer or a suspected inflammation. The third stage of the disease is the severe sepsis, where the patient already is suffering from sepsis has any sign of end-organ damage plus hypotension where the systolic blood pressure (SBP) is lower than 90, it is similar to the septic shock, the only main difference is that this last one is persistent.

Mainly, for this research, the focus will be on the problem of the perfusion of the tissue that was caused by the sepsis, and that leads us to the use of the medical device NIRS to analyze it.

2.2 NIRS

Generally speaking, NIRS is a diagnostic method, that uses a non-invasive approach to analyze different materials, the device electromagnetic spectrum used is in the near-infrared region, (from 780 nm to 2500 nm) and its application can include the analysis of food products, pharmaceuticals, combustion products, and a major branch of astronomical spectroscopy.

2.2.1 NIRS the medical device

In the medical field, NIRS is a sensor device considered as a portable technology to monitor the oxygenation in the brain, muscle, and other organs. The goal of it is to measure the capillary-venous oxygen saturation in the tissue directly beneath the sensor, and those measurements allow us to detect the changes happening in the tissue oxygenations in real-time.

The device was mainly used for the measurements of cerebral oxygenation in medicine, but now its use has evolved to evaluate oxygenation of tissues other than the brain. These other somatic sites include over the liver, abdomen, kidney, or muscle such as the thigh. The sensor can simply be placed on the body part of interest.

The device uses infrared light (700-900 nm) as those lights can pass easily through the skin and bone, which gives us the values for the mixed vascular oxygen saturation as those photons are absorbed by the hemoglobin with the Beer-Lambert law of tissue (2.1), where other components like adipose tissue and fat are absorbed in a very low extent, those lights are reflected in a lower arterial percent and a higher venous percent saturation, as the type of the device and probes plays the bigger role in the percentage reflected. As most of the measured blood in tissues is venous, NIRS should reflect a value similar to but slightly higher than the venous oxygen saturation (SvO_2). (4)

$$A = \varepsilon \times c \times l \tag{2.1}$$

Where A is the absorbance,

ε – molar absorption coefficient in $M^{-1}cm^{-1}$,

c – molar concentration in M,

l – pathlength.

2.2.2 NIRS parameters

NIRS technologies use three broad categories NIRS oximeters: continuous wave CW, time domain TD and frequency domain FD.

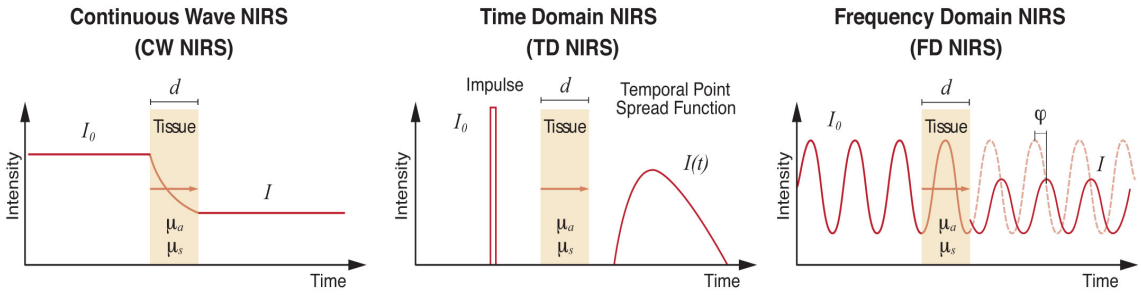


Figure 2.2: three main types of NIR instruments. (5)

Where d is the source-detector separation,

I_0 source light intensity

and I is the detected light.

CW light source is in a constant intensity and it measures the intensity attenuation as the transmitted light intensity is detected, it has also a fast acquisition rate. For the TD NIRS, an impulse light source is employed with the use of typically a laser, in a function of time by fast photon-counting detectors. FD NIRS technology works on using radio-frequency where its amplitude can be modulated, and the detected signal is compared to a reference one. (5)

NIRS technology offers additional insights into patient clinical status by representing rSO_2. Currently, rSO_2 provides the only non-invasive method to continuously monitor changes in local brain oxygen balance within the frontal cerebral cortex, as the Intracranial rSO_2 measurement is possible because the human skull is translucent to infrared light.

rSO_2 can also be used in multiple mathematical formulas, for different calculations, some common usage is mentioned below:

Fractional cerebral tissue oxygen extraction (FcTOE)

$$FcTOE = \frac{SpO_2 - r(c)SO_2}{SpO_2} \quad (2.2)$$

Fractional somatic tissue oxygen extraction (FsTOE)

$$FsTOE = \frac{SpO_2 - r(s)SO_2}{SpO_2} \quad (2.3)$$

cerebro-splanchnic oxygenation ratio (CSOR)

$$CSOR = \frac{r(s)SO_2}{r(c)SO_2} \quad (2.4)$$

2.2.3 Types and components of NIRS

There are several NIRS monitors, each one of it has its specific probes, number of channels, and also there is a difference in the wavelengths used in each one and number of detectors, as each one of the monitors can be used for a specific manner, some of the common ones are illustrated below.

X-100 Equanox

FORE SIGHT

INVOS 5100

ROOT + O3

NIRO 200n

Figure 2.3: common types of NIRS.

In study research, four different common types of NIRS were compared to each other to find out that they are highly significant differences in local cerebral tissue oxygenation levels, which results in not deciding one main uniform standard NIRS. (6)

NIRS main components are a source, a detector, or a sensor and a dispersive element to record different wavelengths intensities, those wavelengths are emitted directly to the capillaries in a certain measured depth, to be transmitted from the capillaries and recorded by the sensors as shown in figure 2.4, an optode was used in this case.

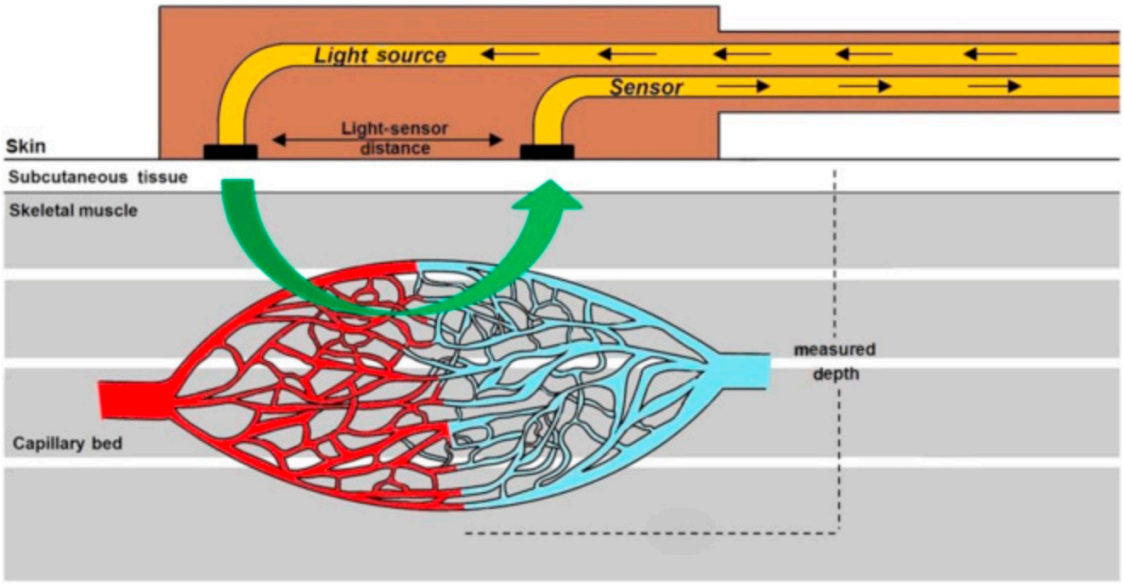


Figure 2.4: schematic representation of an NIRS optode overlying a skeletal muscle. (7)

The increase of accuracy of the NIRS can be improved by using more wavelengths, more detector separations, or both. The estimation of the oxyhemoglobin saturation is done by the differential absorption of the two wavelengths of light by oxygenated and deoxygenated hemoglobin in a volume of tissue beneath the probe. (4)

Wavelength-scanned lasers and frequency combs are used as a source for high precision, and the benefit of a laser is that no need for a dispersive element just a detector will be sufficient.

The range of the wavelength needed is the considered parameter for choosing the right detector for the device, silicon-based Charge-coupled devices (CCDs) are suitable for the shorter end of the near-infrared (NIR) range, Indium Gallium Arsenide (InGaAs) and Lead Sulfide devices are used for the fewer sensitivity purposes when there is a higher wavelength. The combination of silicon-based CCDs and InGaAs is possible for the same instrument, that give us a recording of both the ultra-violet UV, visible and NIR spectra together. (8)

The types of problems which could be detected by NIRS leading to altered cerebral oxygenation in an operating theatre include (but are not limited to) cardiopulmonary bypass (CPB) cannulation problems, effects of deep hypothermia and low flow CPB, effects of antegrade cerebral perfusion, and effects of ventilation or anesthetic strategies affecting cerebral blood flow. One of the most vital roles NIRS may play is the detection of an early low cardiac output by looking at the decrease in cerebral oximetry that is affected by the increased vertebral oxygen consumption, this allows early intervention that may save lives and improve the outcome of the patient. (4)

This is the crux in understanding the NIRS machine and the role that it plays both in the operating theatre and in intensive care. Our goal is to use the benefits of the device NIRS in our project, to get the signal of the patients and use it to compare the different locations we placed the probes at and analyze them

2.3 Previous study results

In a research, a comparison was done for neonates pre-Norwood procedure with a group who used NIRS before the operation to another one who did not, it was concluded that the group who used NIRS had fewer incidences of intubation and mechanical ventilation.(4)

A study was done on 30 healthy human volunteers where they measured there StO_2 levels in different bed elevations of 0 30 and 60 degrees angle to see the changes In the measurement values to found out that the higher the angle the lower the value becomes.(9) in another research study done in the University of Texas (10) showed that

the stage of sepsis is negatively correlated with the StO_2 value, as the higher the sepsis stage the lower the StO_2 percentage is. Also another study proved the correlation between the sepsis stages and the oxygen consumption as the more the sepsis severity is the lower the oxygen consumption is. (11)

3 Aims

The aim of this bachelor thesis is to design an experiment for comparison of cerebral regional oxygen perfusion with the somatic ones and to detect the presence of occult sepsis, before its overt clinical and laboratory manifestation, and by getting to that point, the following steps should be followed:

1. Record the signals taken from the NIRS and see how it changes in the time domain.
2. Analyze somatic and cerebral NIRS signals from different anatomical locations.
3. Use MATLAB software to represent the signals and their distribution.
4. Compare the cerebral and somatic NIRS signals during a septic shock.
5. Propose suitable somatic NIRS probe placement.

4 Methods

4.1 Study design and selection of participants

This was a prospective observational study of patients with suspected sepsis, it was conducted in the Masaryk Hospital Usti nad Labem In Prague Czech Republic, in the ICU. Full ethical approval for the study protocol was obtained from the hospital and written consent obtained from all participants. This is only a pilot study, the whole study was abandoned due to the Covid-19 pandemic. Eligible patients were adults who met any one component of the systemic inflammatory response syndrome (SIRS):

5) respiratory rate ≥ 20 breaths per minute.
6) Temperature > 38.3 C°, or < 36 C°.
7) heart rate >90 beats per minute.
8) white cell count <4 or >12 g/l.

Exclusion criteria were as follows: Patients were excluded if they were pregnant, incarcerated, prisoners, do-not-resuscitate status, a requirement for immediate surgery, has environmentally induced hypothermia or hyperthermia (<95 or >104_F), burns or tissue damages, or had any suspicion of coexisting traumatic, cardiogenic, or neurogenic shock, if the patient doesn't meet the exclusion criteria, then it is possible to take it as a cohort for the study unless there is a big amount of the data missing of the patient rSO_2 level because of some specific reason.

4.2 Study equipment and protocol

4.2.1 INVOS™ 5100C

The monitor used for the NIRS device is INVOS™ 5100C Cerebral/Somatic Oximeter, it is used to provide us a continuous, real-time, site-specific monitoring of changes in rSO_2 of blood in the brain or other body tissues beneath the sensor for effective oxygen monitoring in adults, children, infants and neonates. This unique system allows clinicians to measure site-specific oxygen levels rather than requiring them to infer the

data from systemic, whole-body measures such as blood pressure and pulse oximetry. Available in two or four data channels, clinicians can conveniently monitor multiple brain and body areas for a better patient outcome. For those specific reasons this system has been recognized as one of the best regional oximetry devices, and it is been used as a standard. (12) (13)

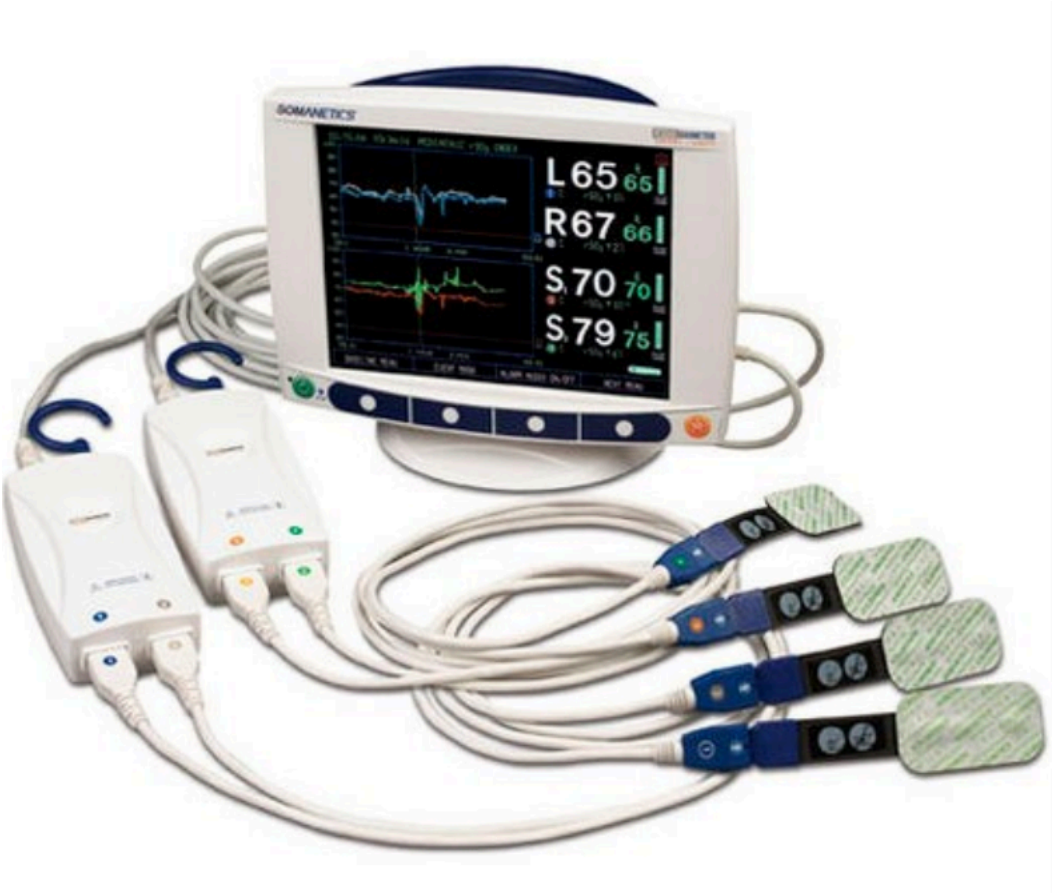


Figure 4.1: INVOS™ 5100C Cerebral/Somatic Oximeter.

Figure 4.1 is a picture for the monitor used and as mentioned above, it contains 4 channels that are attached to 4 probes, those probes will be connected directly to the patient body in different locations, to measure his regional oxygen saturation, from two sets of data collected from two different patients.

Multiple benefits of the use of the INVOS technology, like improving the patient stability, helping improve patient safety, increase positive outcomes and early indication of problems. It exists in may care areas from the ICU to the emergency department ED and electrophysiology labs, and its monitoring can provide an early indication of low cardiac output, renal dysfunction and other damages

System components are a monitor with LCD display, two-channel preamplifier, usable sensor cable and 3 different sensors for adults as SomaSensor SAFB-SM, pediatrics OxyAlert CNN and neonatal SomaSensor SPFB (figure 4.2). The SomaSensor and OxyAlert NIR Sensor are disposable transducers capable of producing and detecting optical data from the patient, converting that data to electrical signals, and sending them to the INVOS System. They are applied to the forehead or somatic region via a self-contained, medical-grade patient adhesive, where two specific wavelengths of NIR are used where they are detected from two separated detectors, a shallow detector and deep one. Electrical signals from the detectors are sent through the shielded cable to the INVOS System for processing. The sensors are designed for single use only and may not be reused. Reuse of the sensors may cause inaccurate readings, erratic readings, or no readings at all. Reuse will also cause an increased risk of cross-contamination. (12)

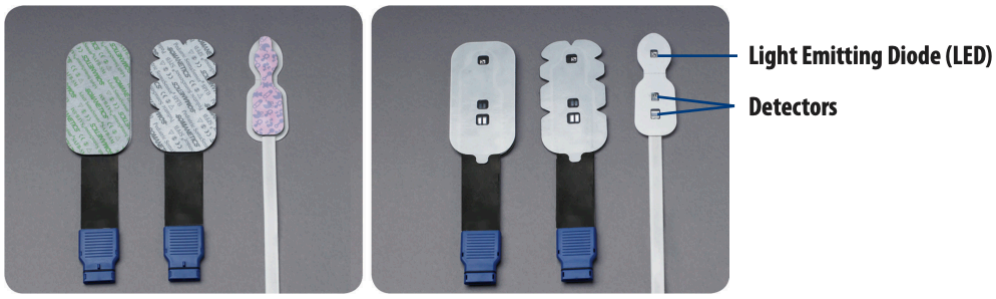


Figure 4.2: image of the used sensors and probes. (12)

4.2.2 Measurement locations of the StO_2

From here, the choice will be taken for the different locations that the measurement will be taken from, the cerebral area will be used as the main location and the somatic areas as a secondary location, so the comparison can be done between them, and finding the somatic location that will correspond the best to a cerebral location is one of the goals.

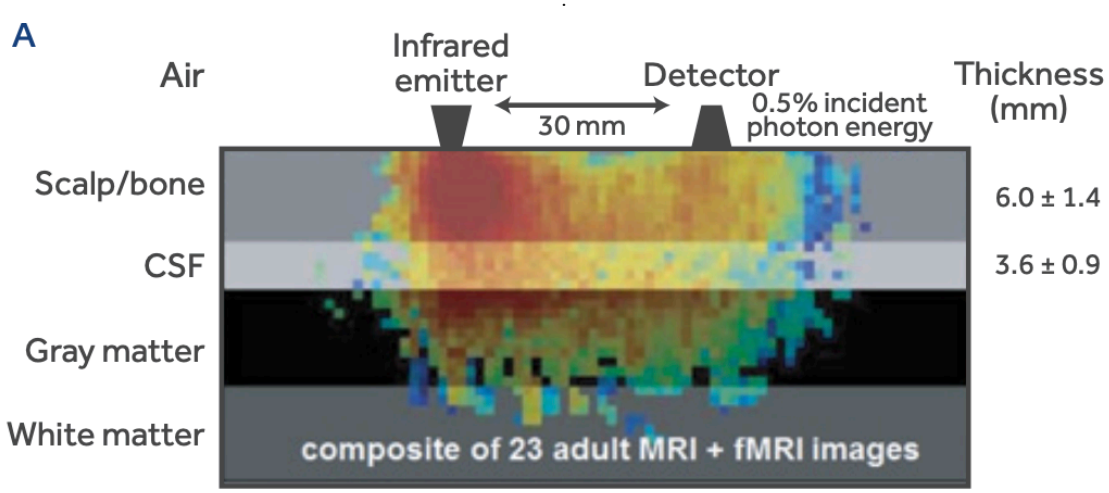


Figure 4.3: illustration of NIRS wavelength depth on the human brain, the photon source-detector location and distance. (13)

Figure 4.3 illustrates a visualization of the human brain and its reaction to the photon penetration and its depth as we can measure its distance from the MRI image, it is approximately half of the distance between the infrared emitter and the detector.

In this study, the probe used is SomaSensor SAFB-SM as all of the cohorts are adults, and this probe is known of containing two detectors one shallow detector and a deep one as mentioned before, what makes the distance between the source and the detector irrelevant.

For the different patients included in this project, different locations were taken for each, that is why the comparison between the patient results will be limited unless they share a specific location probe.

The location of the probes was decided with the help of the manufacturer suggestions, especially for the somatic areas as the cerebral one is the default location for analyzing the rSO_2 value, and the somatic locations are chosen where as follows:

Table 4.1: probe location for each patient.

Probe locations	Patient 1	Patient 2	Patient 3
Probe 1	Left forehead	Left forehead	Left forehead
Probe 2	Right forehead	Left forearm	Right forehead
Probe 3	Hand	Left hand	Right triceps
Probe 4	Loin	Left calf	Loin

4.3 Study steps and data analysis

To accomplish the goal of the project and have precise results, the following steps have to be completed:

1. define the main areas in the human body where the collecting NIRS signal will be beneficial and helpful to analyze it: Considering the experiment is done on septic patients, the location chosen has to be significant for us and give a good set of data with no artifacts, and also clear and easy to analyze. So, for that specific reason, we will choose multiple areas in the body: left forehead side - right forehead side – left forearm - loin – hands – left calf.

2. Attach the probes to each location separately and measure the signal simultaneously on the patient.
3. Measure the rSO_2 values for a sufficient time to see how they change, so we can make reasonable judgments and have accurate results.
4. Present the graphs of the signal using MATLAB software.
5. Calculate the mean and standard deviation for each probe of each patient.
6. Label and present the minimum and the maximum for each probe of each patient.
7. Analyze and compare the signal from the probes, by deciding which one has more gaps and the largest missing data, get the values both in seconds and percentage,
8. Analyze which signal are related to each other and their correspondence by calculating the correlation coefficient of each probe with the other of each patient.
9. Analyze the fluctuation happening in the signal and the percentage of the rSO_2 for each probe in specific segments of the signal, that will help in finding the suitable somatic NIRS probe placement for this group of patients.
10. Mark the main points where a big drop or rise of the signal happened as it can be a sign for a septic shock.
11. Select the somatic locations to remove if there is no benefit of it.
12. Select the suitable somatic location where is best to withdraw signals from, for the analyze, considering the correlation coefficient with the cerebral sites and the missing data percentage.

5 Results

5.1 Patients demographics and measurements

The patient demographics are presented below as a reference for each patient and their actual state during the measurement of the NIRS signal of each one of them, plus their diagnosis.

Table 5.1: patients demographics.

	Patient 1	Patient 2	Patient 3
Age	67	46	73
Gender	Male	Male	Male
Race	caucasian	caucasian	Caucasian
Weight	113	121	75
Height	183	191	178
Body mass index (BMI)	33.7	33.1	23.6
Smoking	Non-smoker	Smoker	Non-smoker
Diagnosis	sepsis due to knee joint infectin	sepsis due to pneumonia	sepsis due to pneumonia

The table 5.1 shows us different information about the patients that could be effective and has big a role on the outcome of the signal, as it also has the result of the diagnosis of each patient and as we can see that the diagnosis for the patients is heterogenous, what prove heterogeneity of the sepsis.

The third patient did not meet the criteria for the study, as the data collected from him was corrupted and missing for a big amount of time, and that is one of the exclusion criteria, for that reason he is not included in our study.

The results will be containing a variety of tables and graphs as examples for the final values, As illustrated in figure 5.1 and 5.3, the graphs consist of four different lines, and each is related to a specific location in the body, for the two patients, the selection of the probe's locations was different.

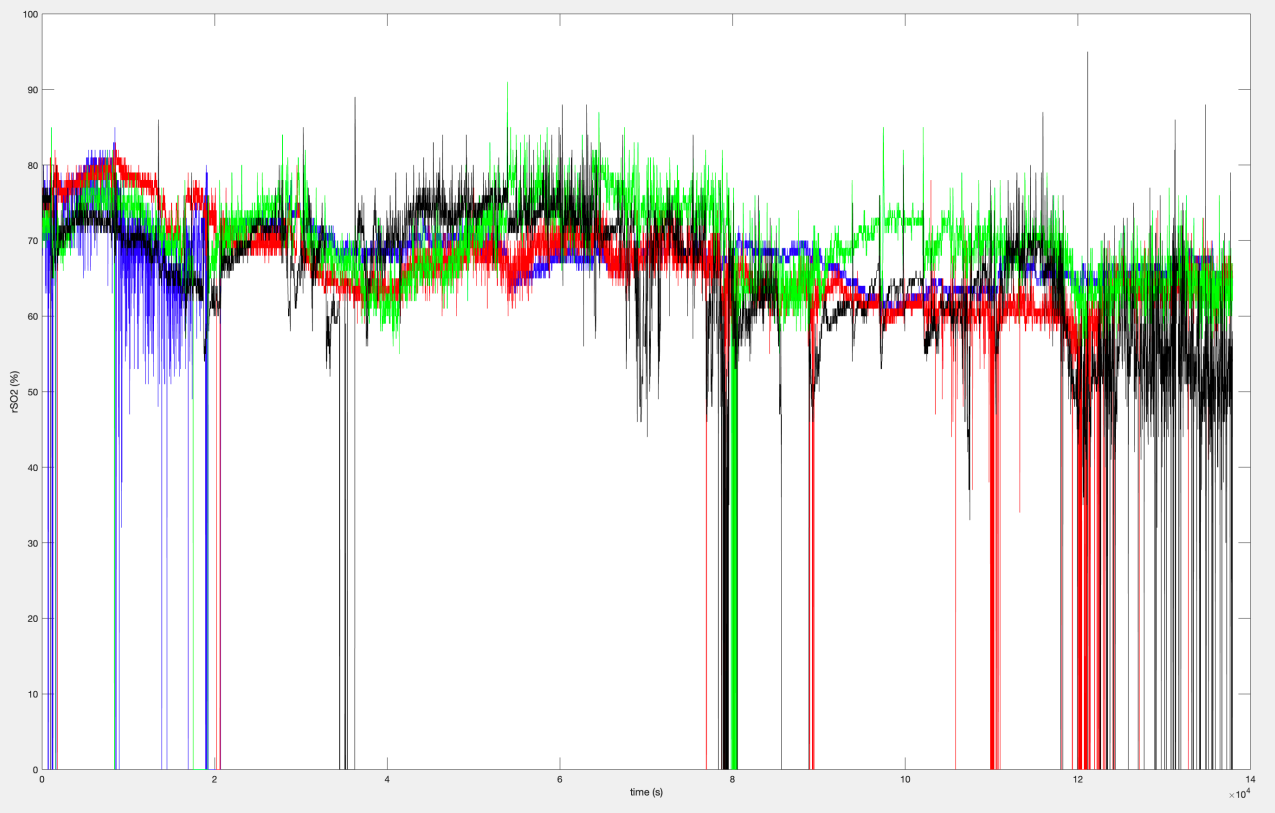


Figure 5.1: graph of rSO_2 values of the first patient during a period of 36 hours from multiple locations.

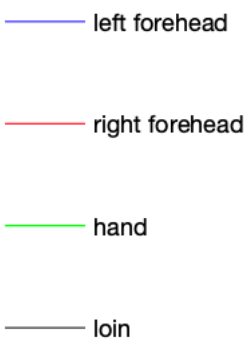


Figure 5.2: color coding for the signals of the locations from different probes for the first patient.

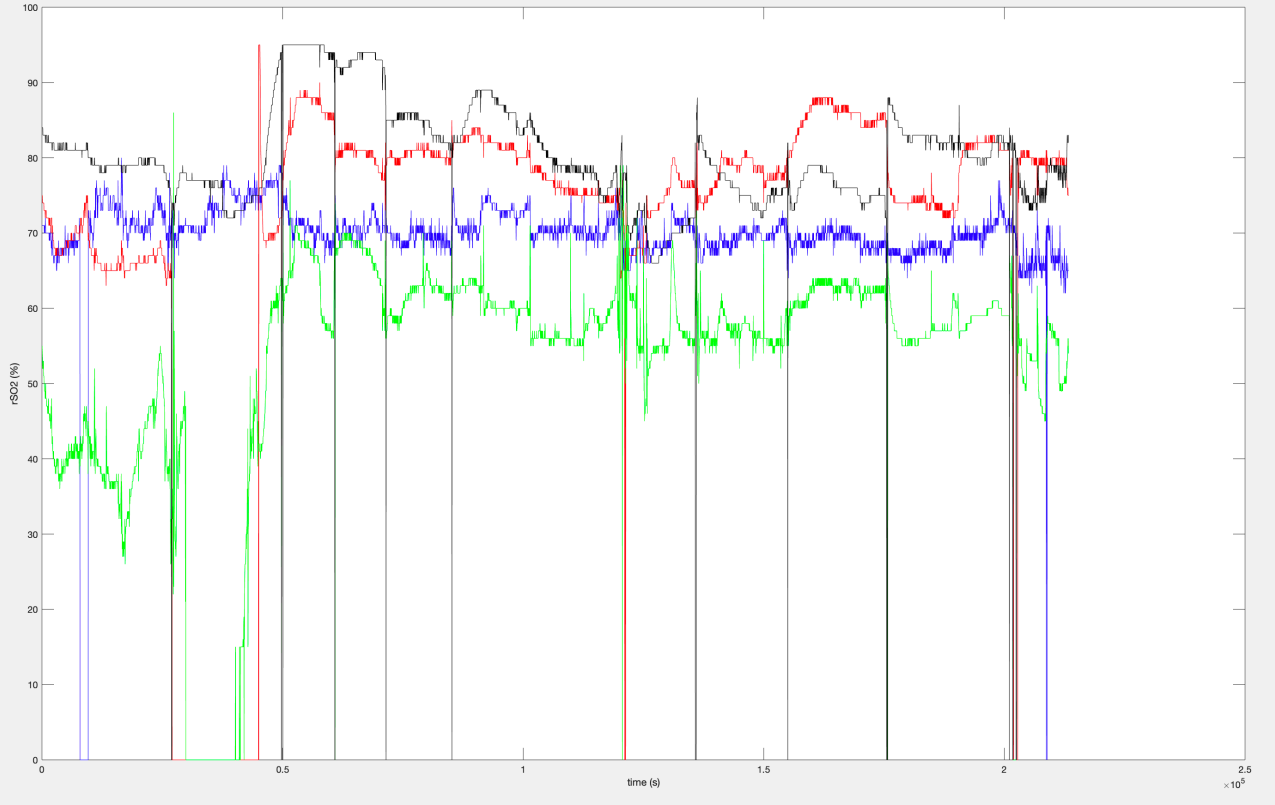


Figure 5.3: graph of rSO_2 values of the second patient during a period of 60 hours from multiple locations.

Figure 5.4: color coding for the signals of the locations from different probes for the second patient.

The aim of presenting the whole graph is to give a general view of the patient's signals to see the desaturation and the resaturation of the rSO_2values in the time domain

5.2 Statistical analyzes for the measurements

To analyze the signals in depth, the mean values for each probe of each patient had to be calculated so a general view of the signal can be set, also for the standard deviation to know the dispersion of our dataset, the following formulas were used to calculate them:

$$\bar{X} = \frac{\sum X}{N} \tag{5.1}$$

Where $\bar{X}$ is the mean value,
$\sum X$ is sum of all data values,
And N is the number of data items in the sample.

$$s = \sqrt{\frac{\sum(x-\bar{x})^2}{N-1}} \tag{5.2}$$

Where S is the standard deviation,
$\bar{X}$ is the mean value,
X is the set of numbers,
And N is the number of data items in the sample.

Table 5.2: the mean value for each probe location for the first patient.

rSO_2 location	MEAN ± SD
Left forehead	67,19 ± 8,33
Right forehead	65,76 ± 9,23
Hand	68,82 ± 9,69
Loin	62,92 ± 15,40

Table 5.3: the mean value for each probe location for the second patient.

rSO_2 location	MEAN ± SD
Left forehead	68,68 ± 10,63
Left forearm	69,60 ± 24,20
Left hand	52,20 ± 16,85
Left calf	78,98 ± 12,45

The minimum, maximum and the variance were also extracted from the signal to analyze the range of the values of rSO_2 for each probe, to see the change of it in the time domain and how the fluctuations happened. It is an example of the pattern taken from the signals that have been noticed in the experiment. On the left column is the locations of the probes, for which the experiment was completed and the other columns represent minimum, maximum and the variance

$$var.s = \frac{\Sigma(x-\bar{x})^2}{N-1} \tag{5.3}$$

Where var.s id the sample variance,

$\bar{X}$ is the mean value,

X is the set of numbers,

And N is the number of data items in the sample.

Table 5.4: Min, Max and variance values for the first patient for each probe.

locations	Minimum	Maximum	Variance
Left forehead	32	85	69,49
Right forehead	15	83	85,24
hand	51	89	94,08
loin	15	95	237,29

Table 5.5: Min, Max and variance values for the second patient for each probe.

locations	Minimum	Maximum	Variance
Left forehead	62	80	113,01
Left forearm	60	95	585,90
Left hand	15	86	284,03
Left calf	66	95	155,06

To evaluate the different probes and their reliability considering the location, a calculation for the missing data of each probe signal has to be done, this will give us a clear view about which location in the body is more reliable, stable and has the least missing data and noises. the focus will be mainly on the somatic locations as the cerebral ones are the standard site. The calculations are done in seconds and also in the percentage of the total time to get the bigger picture.

Table 5.6: the missing data for each probe for the first patient in seconds.

Locations	Time (seconds)	Percentage of total time (%)
Left forehead	1399	1.08
Right forehead	1180	0.91
hand	1717	1.33
loin	6129	4.77

Table 5.7: the missing data for each probe for the second patient in seconds.

Locations	Time (seconds)	Percentage of total time (%)
Left forehead	4777	2.20
Left forearm	21935	10.13
Left hand	15118	6.98
Left calf	3693	1.70

For the most important calculation, the correlation coefficient was extracted from each patient between each probe, to see how they correlate in the whole measurements including the missing data time and the artifacts, those values will be decisive for us to decide the most suitable somatic location that can be used and reliable beside the cerebral ones, the following formula was used to get the correlation coefficient:

$$Correl(X,Y) = \frac{\sum(x-\bar{x})(y-\bar{y})}{\sqrt{\sum(x-\bar{x})^2 \sum(y-\bar{y})^2}} \quad (5.4)$$

Where correl is the correlation coefficient,
X and Y are the selected arrays of the two chosen probes,
and $\bar{x}$ and $\bar{y}$ are the sample means for the average arrays of the signal values.

Table 5.8: correlation coefficient values for the probes of the first patient.

Correlation coefficient	Left forehead	Right forehead	Hand
Left forehead		0,314	0,032
Right forehead	0,314		0,084
Hand	0,032	0,084	
Loin	0,081	0,247	0,226

Table 5.9: correlation coefficient values for the probes of the second patient.

Correlation coefficient	Left forehead	Left forearm	Left hand
Left forehead		0,179	0,247
Left forearm	0,179		0,857
Left hand	0,247	0,857	
Left calf	0.576	0,405	0,467

To analyze the measurements in depth, small sections where the signal is not being corrupted and the data is not missed should be taken and analyzed separately to have a deep view on the changes of the signals. For the first patient, two segments from the signal were extracted as there is no missing data in that period.

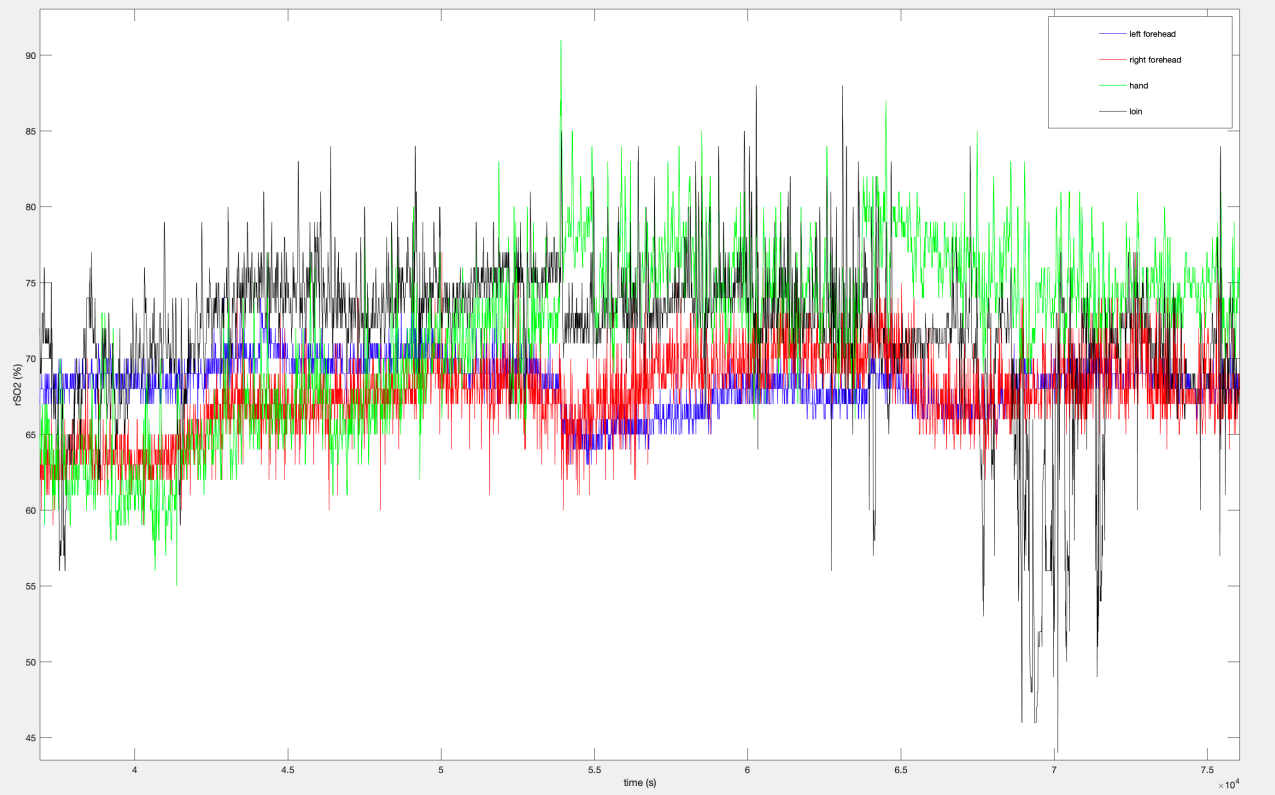


Figure 5.5: first segment of rSO_2 graph of the first patient during a period of 7 hours with no missing data.

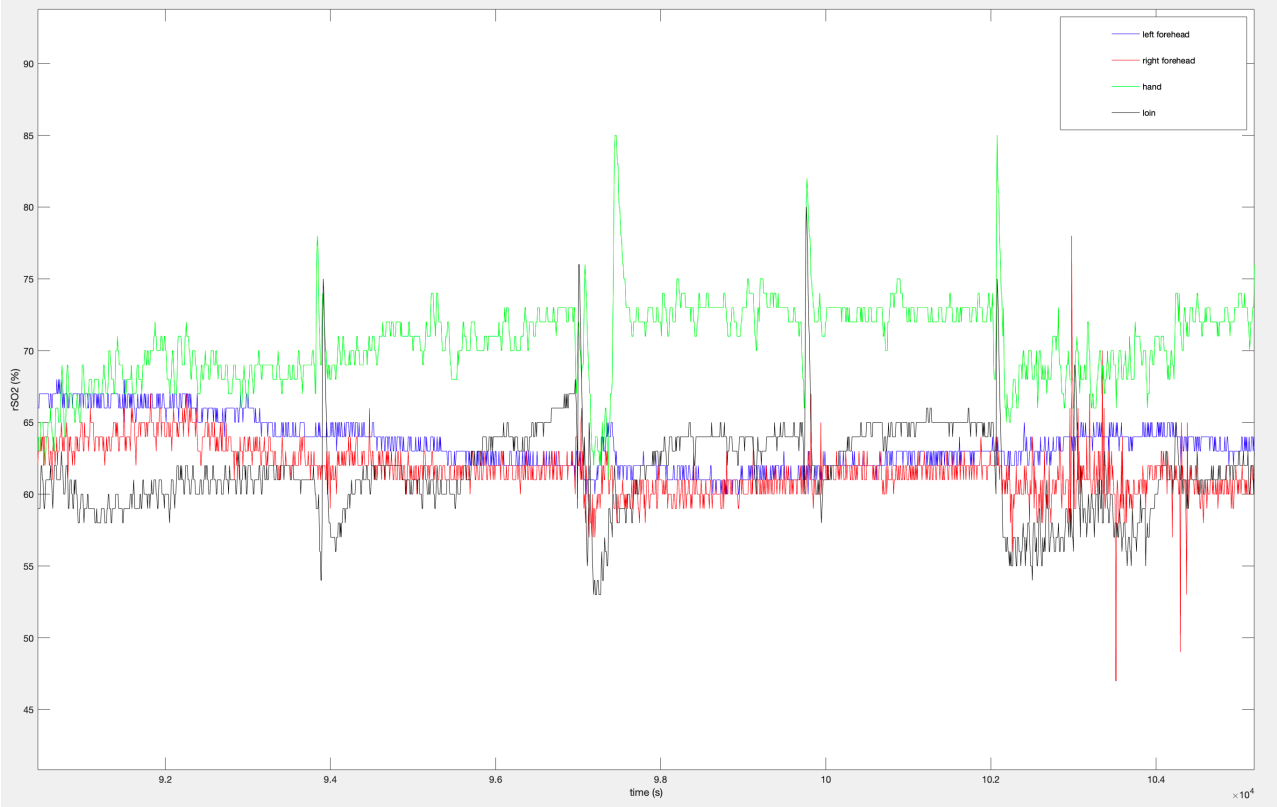


Figure 5.6: second segment of rSO_2 graph of the first patient during a period of 4 hours with no missing data.

The next step would be to calculate the correlation coefficient values for these segments, to understand the behavior of the signal how the probes are related in this period.

Table 5.10: correlation coefficient values for the probes of the first patient for the first segment.

Correlation coefficient	Left forehead	Right forehead	Hand
Left forehead		0,111	-0,446
Right forehead	0,111		0,451
Hand	-0,446	0,451	
Loin	0,006	0,110	0,091

Table 5.11 : correlation coefficient values for the probes of the first patient for the second segment.

Correlation coefficient	Left forehead	Right forehead	Hand
Left forehead		0,630	-0,592
Right forehead	0,630		-0,263
Hand	-0,592	-0,263	
Loin	-0,387	-0,010	0,597

The same concept will be applied for the second patient data, as two segments from the signal will be extracted to study their behavior and to calculate their correlation coefficient.

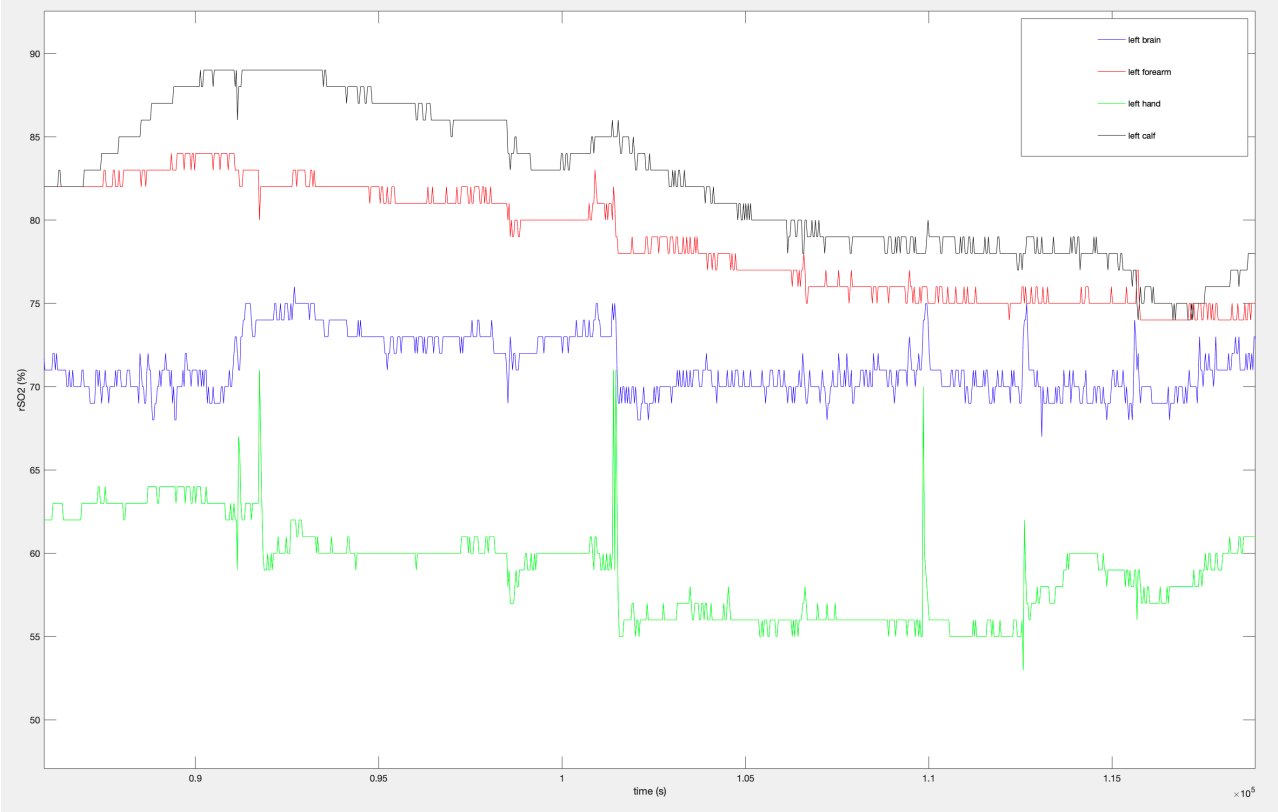


Figure 5.7: first segment of rSO_2 graph of the second patient during a period of 8 hours with no missing data

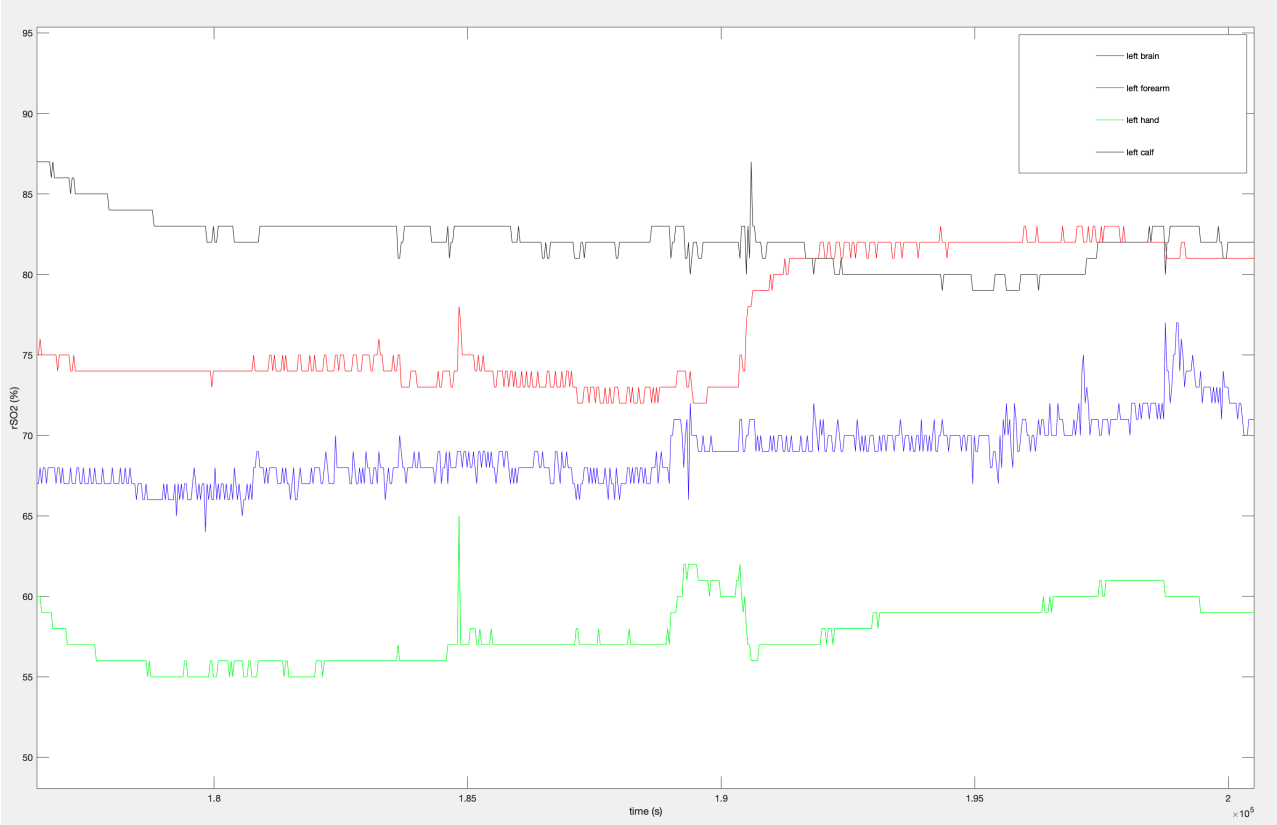


Figure 5.8: second segment of rSO_2 graph of the second patient during a period of 6 hours with no missing data

Table 5.12: correlation coefficient values for the probes of the second patient

Correlation coefficient	Left forehead	Left forearm	Left hand
Left forehead		0,461	0,331
Left forearm	0,461		0,804
Left hand	0,331	0,804	
Left calf	0.562	0,928	0,693

Table 5.13: correlation coefficient values for the probes of the second patient

Correlation coefficient	Left forehead	Left forearm	Left hand
Left forehead		0,705	0,682
Left forearm	0,705		0,511
Left hand	0,682	0,511	
Left calf	-0,547	-0.654	-0,419

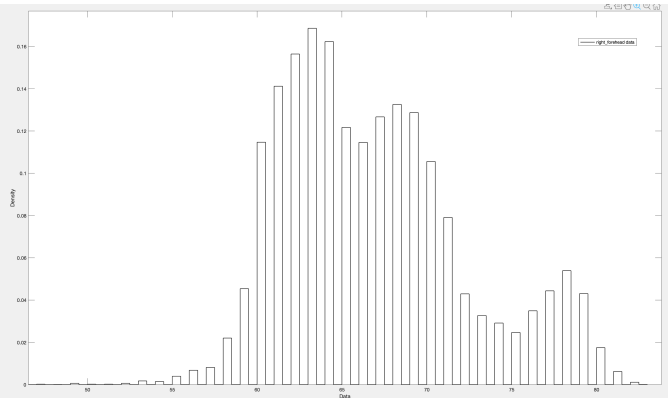
6 Discussion

The main finding of this pilot study is the possibility of using somatic locations that could somehow give us a sign of an upcoming septic shock, as it is feasible to analyze the data from sepsis patients using it, so its use as a parameter along the cerebral site is possible.

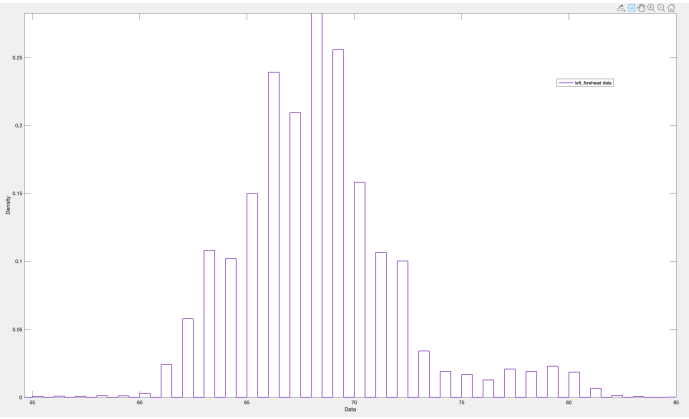
The use of SvO_2 ascertain the balance between oxygen delivery and consumption in patients with sepsis, but the fact that this process requires an invasive procedure, plus it requires time for those parameters to be collected (1), as the Placement of a central venous catheter, measuring its pressure and SvO_2 is considered as the largest and most time-consuming barriers to implementing sepsis protocols. From there we can see that the use of SvO_2 values is complicated, and it is where the suggestion of using the StO_2 values came from, NIRS offers the potential to efficiently and noninvasively assess StO_2 by a single monitoring lead. (14)

There are multiple differences between the patients, as in age, BMI and the diagnosis, not to forget about the main difference and is that the location where the measurements were taken from is very different, expect one location is the left forehead that they share.

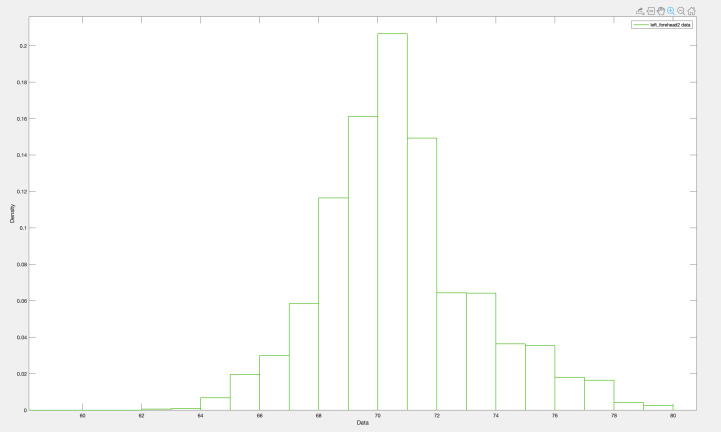
From the table of mean values for the different locations of the probe for both patients (table 5.2 5.3), it was clearly shown the relation between the mean value of the left forehead for both patients and the right forehead for the first patient, as they had very close values represented as 67% left forehead, 65% right forehead for the first patient and 68% left forehead for the second one (figure 6.1), it could be a potential sign of the value and range of the left forehead location for septic patients.



Density distribution for the right forehead.



Density distribution for the left forehead



Density distribution for the left forehead 2.

Figure 6.1: density distributions of cerebral locations for both patients.

For the INVOS™ systems as an example, it was found in a large sample of conscious adult cardiac surgery patients that the median normative rSO_2 was 66% (Figure 6.2), values <50 were thus statistically subnormal, left versus right hemisphere asymmetry of >10% occurred in only 5% of patients. In the high-risk patients, the rSO_2 values were very helpful in predicting the outcome of the patients as of postoperative morbidity and mortality (13), another study showed the same results with even a larger number of samples. (15)

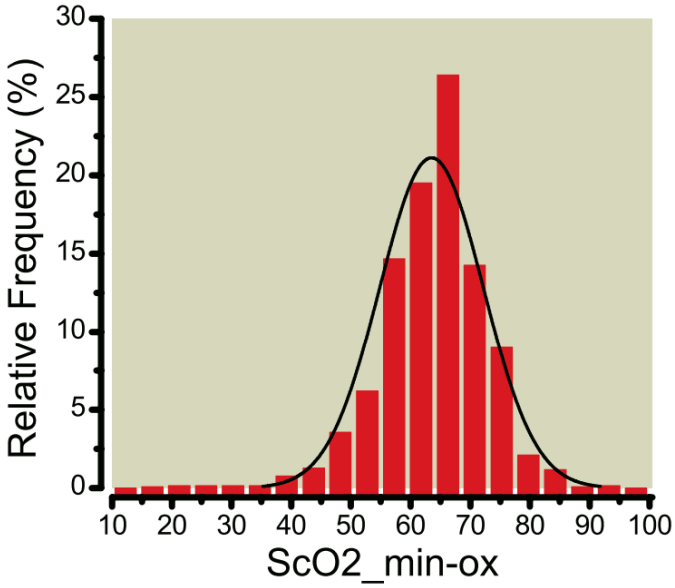


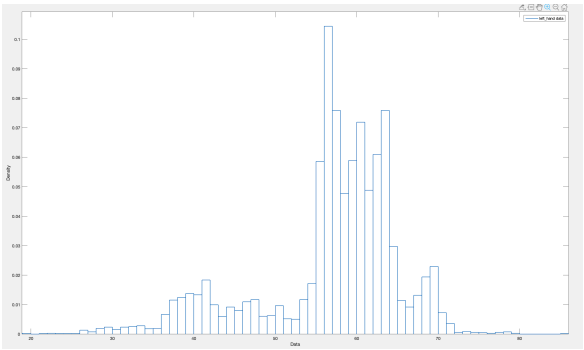
Figure 6.2: distribution of normative rSO_2 values obtained preoperatively from 1,178 adult cardiac surgery patients. (16)

The minimum and maximum values for the probe locations show us how the data is spread and how the range changed in the time period, falling typically between 15-95%, a study search represented normal StO_2 values at rest also claimed to have a wide range, falling between 46–95%. StO_2 measurements recorded from different anatomical sites have a broad overlap but have significantly different distributions and mean values. (17)

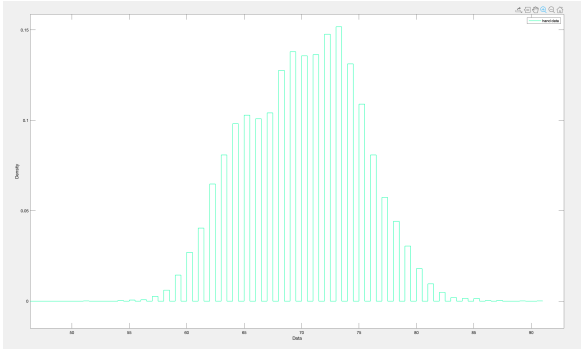
Table 6.1: Summary data for StO_2 values from each monitoring site at rest. (17)

Locations	StO_2 %	Range
Left deltoid	80	49-95
Right deltoid	79	46-95
Leg	68	47-85
Head	73	47-95

For the hand location, the mean values were significantly different, as the first patient had an average of 68% and the second one 52% (figure 6.3). Contradicting our results, a study showed that The thenar eminence tends to be a good anatomical site where clinical measure the regional oxygen saturation (rSO_2) level of the patients, and illustrated in figure 6.4, a graph of different values of thenar StO_2 and their frequency, what shows that the typical range for the thenar measurement is 70-95% rSO_2 level, the difference could be because of the small number of the sample we have.



Density distribution for the left hand of the second patient.



Density distribution for the left hand of the first patient

Figure 6.3: density distribution of hand location for both patients.

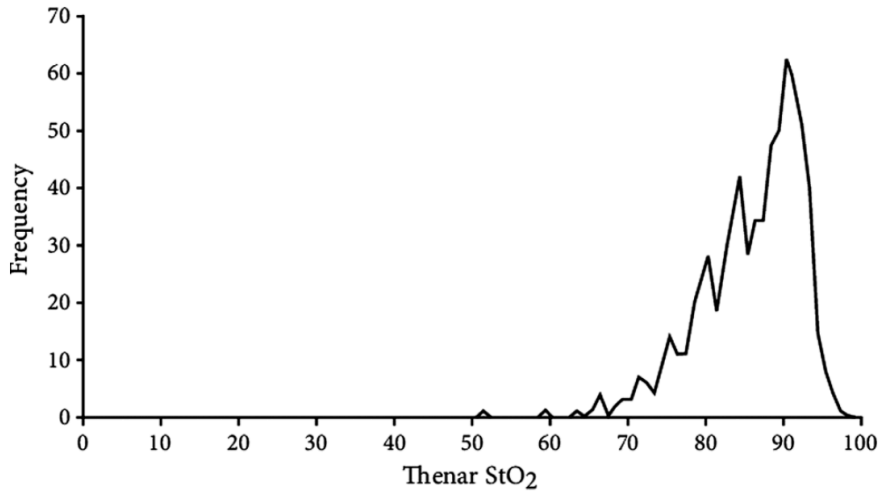


Figure 6.4: Thenar local tissue oxygenation (StO_2) values in normal human volunteers.(17)

The measurements of the rSO_2 values were accompanied by a lot of missing data and gaps, which made the analysis of the signal difficult. For the first patient, the percentages of the missing data were very small as the percentage didn't exceed 5%, as an explanation of the behavior, it was most probably an effect of the patient manipulation and movements, what causes the signal to drop to the values 0% but lasts for seconds to complete the recording again. In the case of the second patient, the time of missing data between the locations was different, so the analyze will be individually done, as of the left calf, the missing data is also described by signal drops for a very short period of time, what can be affected by the movements of the patient, but in the case of the other locations, the missing data reached to 10% of the total time especially for the left forearm, and for the left hand and left forearm as their somatic location is very close to each other, what explain that the removal of the probes for these sites was done by nurses or doctors for some specific reasons, at a close time range illustrated in figure 5.2 from the 8th hour to the 11th, the system also reacts to ambient lights that affect it by stopping the recording of the signals, some special techniques were used to prevent the missing data as with The hand, a special plastic film called "Tegaderm" was used to improve the adhesivity of the probe.

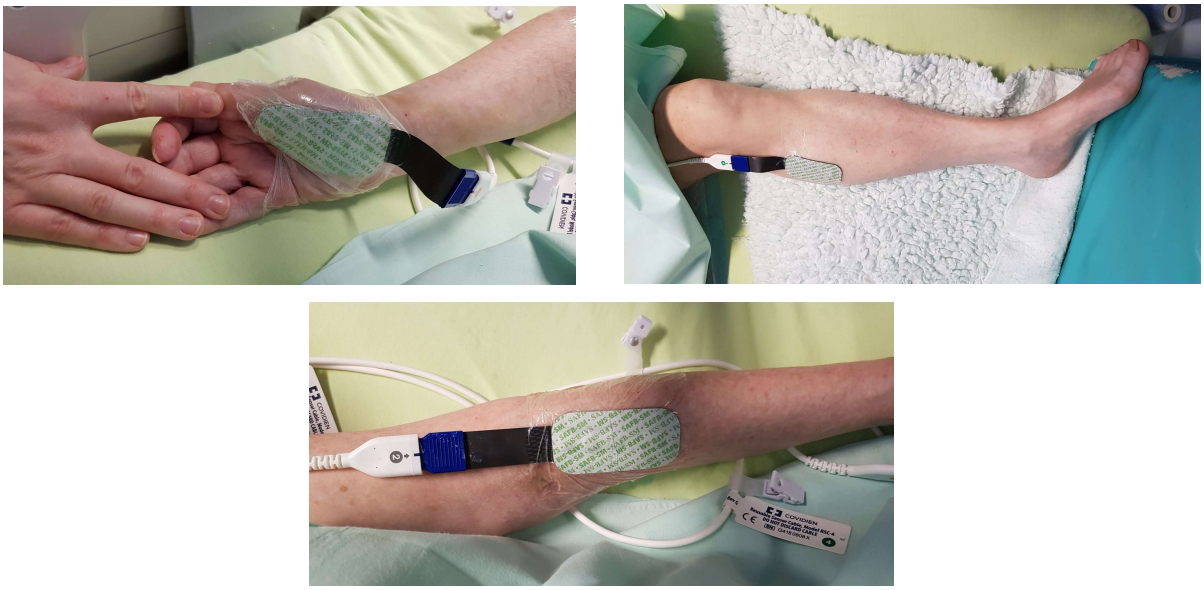


Figure 6.5: picture of the second patient for the locations of the probes.

The pictures were taken by the permission of the supervisor, and the limited usage of it is only for the bachelor thesis writing.

The analysis of the graphs by separating them into two small segments was crucial to understand the real behavior of the signals, which conclude that analyzing graphs with a lot of missing data can misguide and bring wrong pieces of information.

For the second patient, an observation was made about the behavior of the somatic locations of the rise of their rSO_2 signal simultaneously, as on the other hand the left forehead signal stays steady with no rise or fall. It is explained by the concept of the cerebral auto-regulation, where the brain continuously gets the same amount of blood leaving aside the blood pressure value, as it has a steady cerebral blood flow(CBF) (18), on the other hand, other organs and sites react differently to the blood pressure value as their perfusion rise or drops depending on it. it can also be a cause of some medications taken or the patient's state as if the patient is awake or asleep.

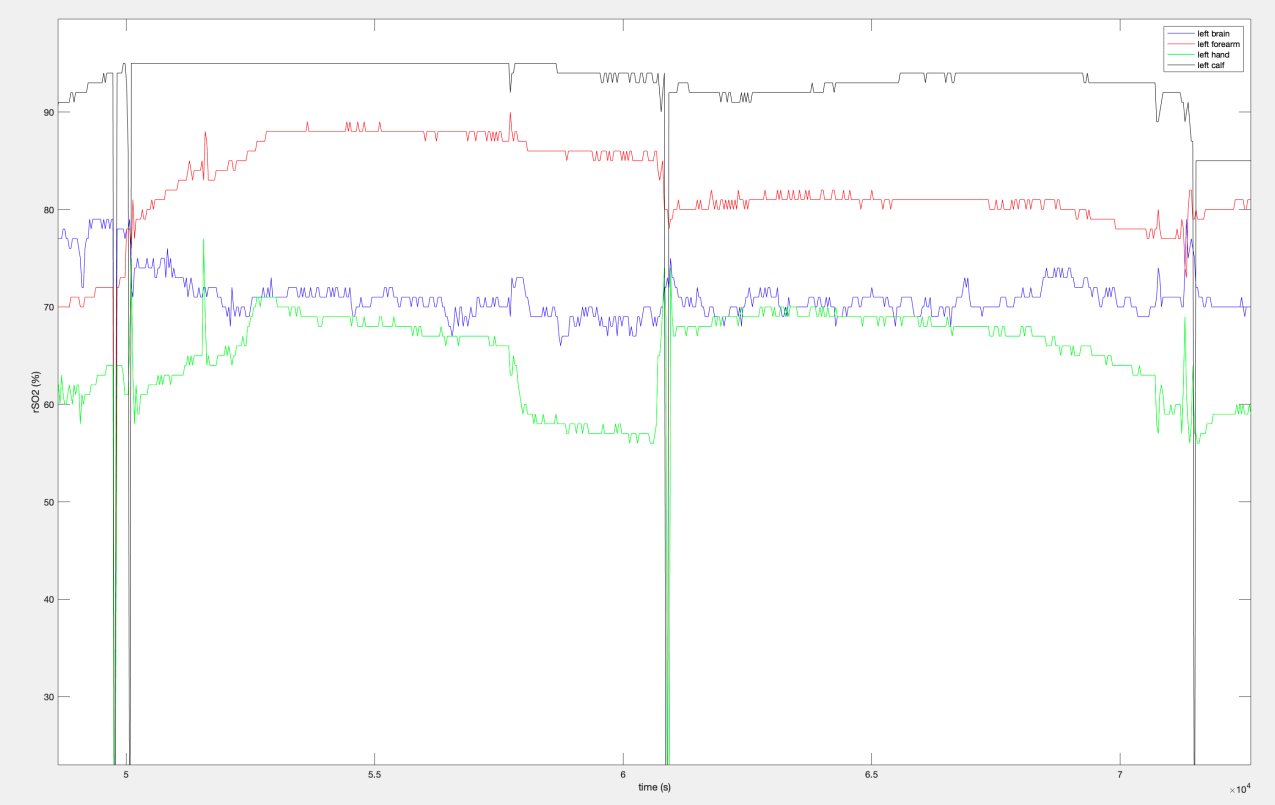


Figure 6.6: segment of the rSO_2 graph of the second patient

Analyzing the correlation coefficients values for different probes of the two patients, had some interesting results. To begin with, it is clear from the tables, we can observe that the loin location is a very weak location considering that it has no correlation with the cerebral sites neither the somatic ones, as its correlation coefficient values are always near the zero value, plus it is observed that this location has the most missing data for the first patient.

Another remark was done, is the correlation between the left forearm and the left forehead as it is a high one, also the slight lower correlation is between the left forehead and the left hand, those values were taken from the correlation tables of the segments of the graph where no data was missing, what approves that to properly analyze the data we cannot use the full graph with the missing values, as it corrupts the results.

From what mentioned before, we examined also the correlation between the left forearm and left hand for the second patient, to see that they have a high positive correlation between them, as there signals movements is slightly the same, with the left hand presenting a lower value of rSO_2, we can suggest using only one the probes as It

could be financial economic as the probes are not reusable, and we can profit from the other probe to test other locations.

For the left calf, the values were fluctuating from positive to a negative correlation from a segment of the graph to another, that what made it hard for us to conclude or mark something from this somatic location.

One of the main clinical signs of poor peripheral perfusion is the change of color of the skin, it is due to the difference in hemoglobin saturation. As an example, when patients are well saturated, their tongues and lips appear pink in color; when they are desaturated, they appear blue. Other signs of low peripheral perfusion could be a cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time. But to recognize those signs, it is very complicated and risky, that is why our purpose in this study to find it technically. When reading the values, usually the cerebral rSO_2 is lower than the somatic one because when the patient is at rest, the brain has greater demand and consumption for oxygen than other somatic areas, which is represented in the table for the mean values. But for the last and most important inspection, the left hand showed a mean value lower than the left forehead one, plus the correlation coefficient between the locations was highly negatively correlated that means when the cerebral site perfusion is higher the left hand rSO_2 level drops, for the segments taken where there is no missing data what could be a sign of a sepsis behavior.

When the sepsis occurs one of the first signs, is the diversion of the blood flow from the less important tissues (skin, subcutaneous, muscle, gastrointestinal tract) to vital organs (heart, brain, kidneys). And that is due to the importance of oxygen molecules in the blood for the main organs on the body, it is where we see the physical changes on the skin and tissues of the body as mentioned before. Thus, monitoring perfusion in these less vital tissues could be an early marker of vital tissue hypoperfusion. (19)

What was observed for the hand and left forearm for the first patient, was also due to this patient having a septic shock and his sepsis was more pronounced than the second one, as the second patient left hand and left forehead correlation was the opposite, as it was positively correlated as his sepsis was not pronounced yet.

In this observational study of septic patients, The suitable somatic locations proposed would be the upper limb locations as the left forearm and the left hand could be used for their values collected from them and their connection to the cerebral ones, but the consideration of improving their attachment of the probes to the body could be beneficial as their missing data was illustrated as a high percentage compared to other locations and by improving that, those somatic locations may have the potential in helping of the detection of patients with occult sepsis before their overt clinical manifestation.

6.1 Limitations

Our study has multiple limitations. First, in an attempt to analyze the rSO_2 of septic patients, the number of the sample was very low, that it cannot be an estimation for the population. The small sample size was due to the use of the NIRS device in the Masaryk Hospital Usti nad Labem for Covid19 patients. Plus, the data obtained was of a short time period, and to properly analyze a rSO_2 of a patient measurement, the time period recommended is 72 hours. We were also unable to establish an appropriate review for the tissue oxygenation values for some specific somatic locations like the chest, the triceps and the thighs. However, we were able to achieve completed readings in some other locations of the recruited patients. Despite this, we were able to generate new hypotheses based on these results and observed trends, for future researches with larger studies and better planning could confirm our hypotheses..

7 Conclusion

The aims of this thesis work were to analyze the cerebral and somatic NIRS signals and compare them together under patients with septic shocks, then from the results of the analysis, a proposal of a somatic location should be done.

A suggestion of the upper limb locations was given as it underwent statistical analyzes, that made it the most eligible location for the study purpose. The use of these specific somatic locations using NIRS to derive the rSO_2 values from it, could potentially detect occult sepsis and predict adverse clinical outcomes in sepsis patients. Larger studies are warranted in the future to investigate and determine the use of those locations as part of a non-invasive resuscitation protocol for septic patients to confirm their eligibility.

Hands and left forearm locations are still a new parameter that is being studied nowadays which is why the results from this pilot study were interesting regardless if they covered the aim of the thesis or not. to fully understand such a parameter's full capability, more researches should be done in this field of study. For now, it stands to be a promising parameter just not a predictor.

As conclusion, NIRS-derived measurement from Cerebral regional oxygen saturation with the addition of these somatic locations might be helpful as one of the perfusion parameters in patients with sepsis and it could have a prognostic value immortality prediction. However, further studies with a larger sample size are still needed to validate these results.

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Attachment A: code for the illustration of the graphs

```
% importing both data files
M = readtable('data1.xlsx');
M1= readtable('data2.xlsx');

% separating columns
time= M{:,1};
left_forehead= M{:,2};
right_forehead= M{:,3};
hand= M{:,4};
loin= M{:,5};

time2= M1{:,1};
left_forehead2= M1{:,2};
left_forearm= M1{:,3};
left_hand= M1{:,4};
left_calf= M1{:,5};

% ploting figures
figure(1)
 plot(time,left_forehead,'b')
 hold on
 plot(time,right_forehead,'r')

 hold on
 plot(time,hand,'g')

 hold on
 plot(time,loin,'black')
 legend('left forehead ','right forehead','hand','loin')
 xlabel('time (s)')
 ylabel('rSO2 (%)')
 hold off


 figure(2)
 plot(time2,left_forehead2,'b')
 hold on
 plot(time2,left_forearm,'r')

 hold on
 plot(time2,left_hand,'g')

 hold on
 plot(time2,left_calf,'black')
 legend('left brain','left forearm','left hand','left calf')
 xlabel('time (s)')
 ylabel('rSO2 (%)')
 hold off
```

Attachment B: graphs presented in EXCEL

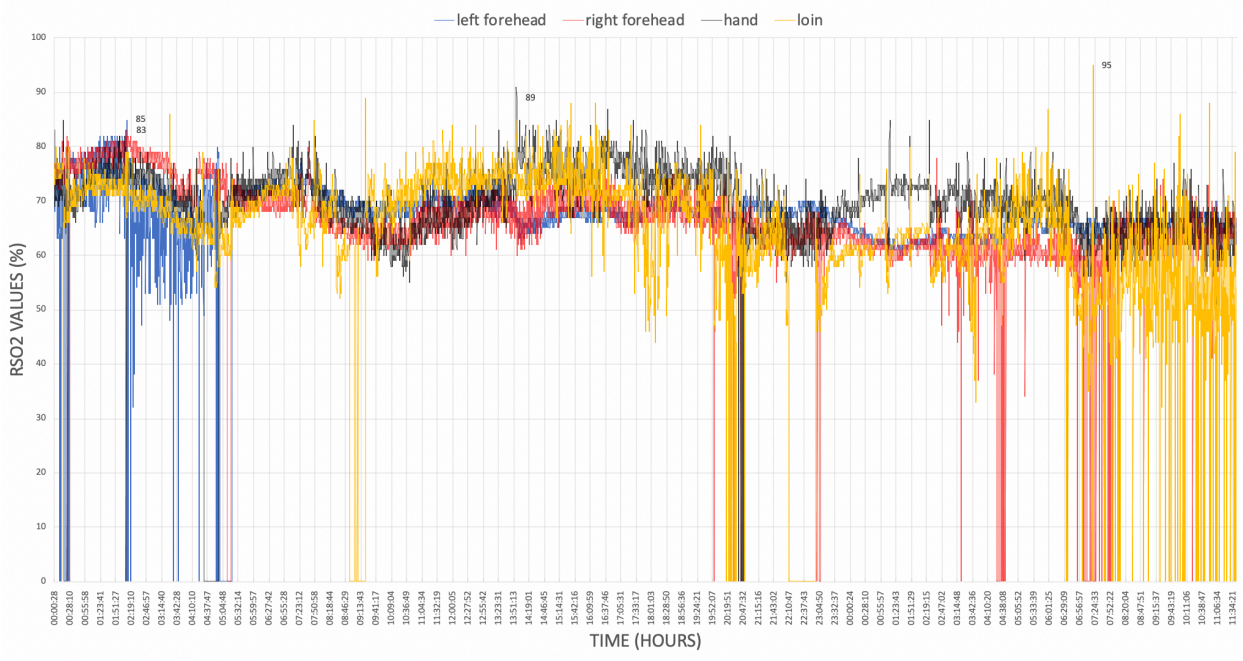

Figure C.1: graph of rSO_2 values of the first patient during a period of 36 hours from multiple locations.

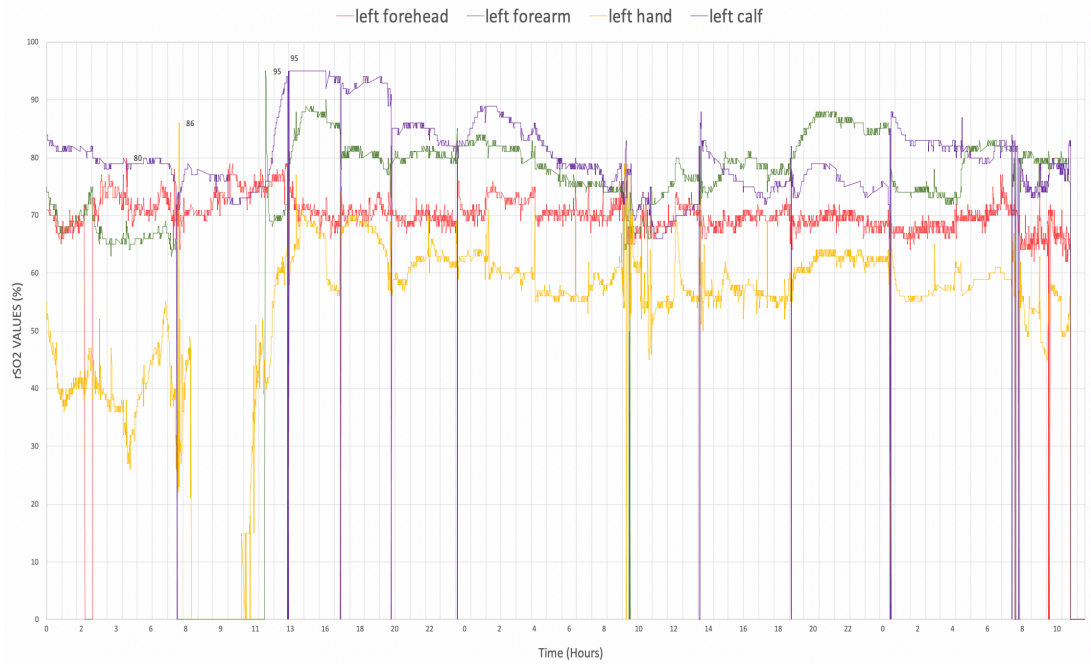

Figure C.2: graph of rSO_2 values of the second patient during a period of 60 hours from multiple locations.

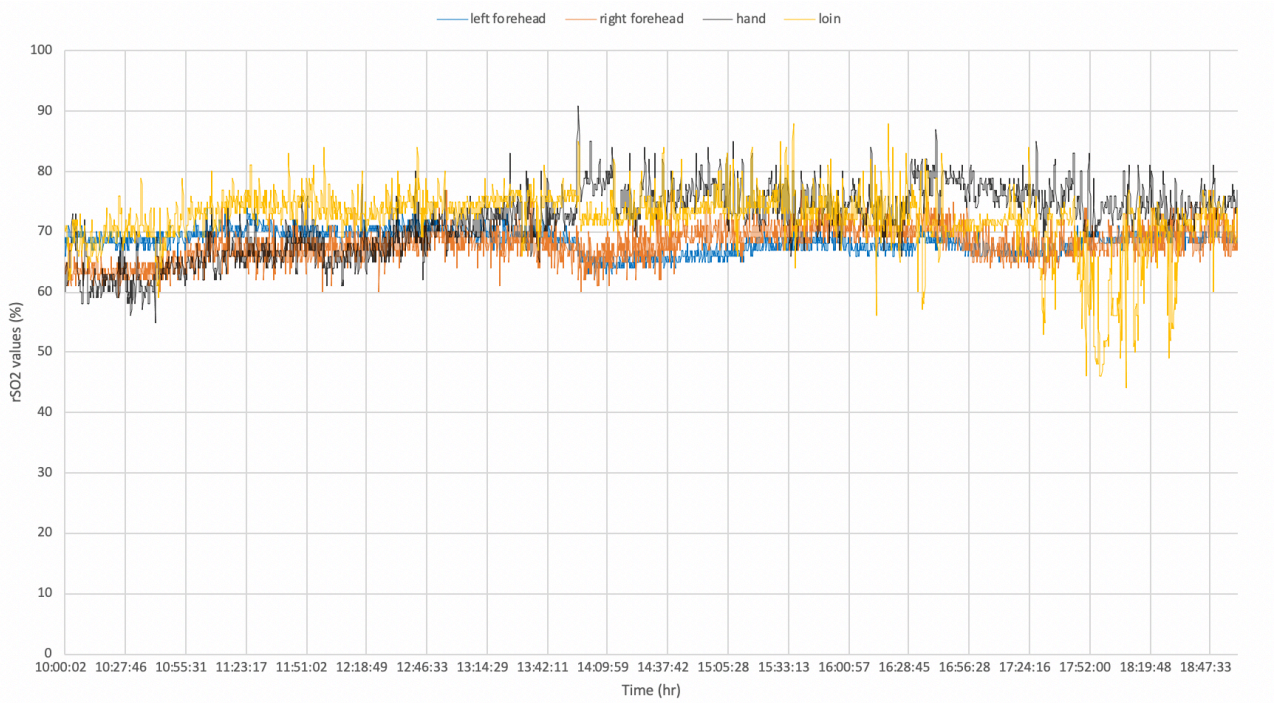

Figure C.3: first segment of rSO_2 graph of the first patient during a period of 7 hours with no missing data

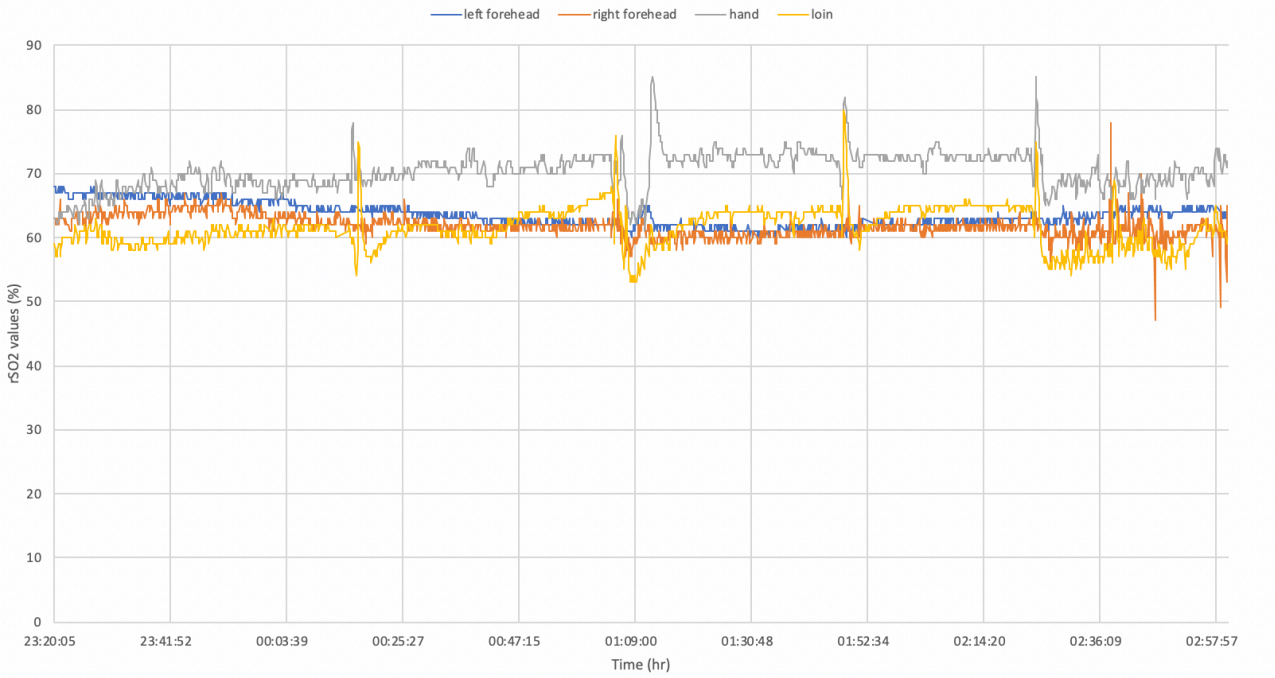

Figure C.4: second segment of rSO_2 graph of the first patient during a period of 4 hours with no missing data

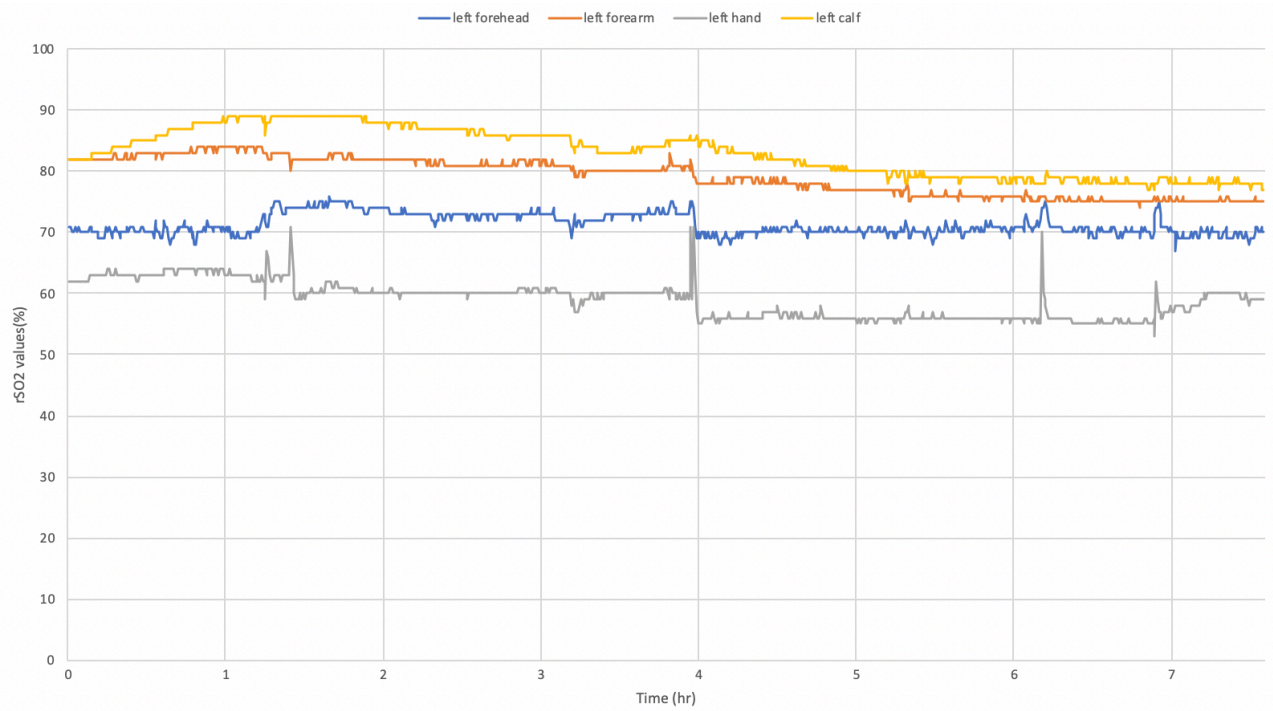

Figure C.5: first segment of rSO_2 graph of the second patient during a period of 8 hours with no missing data

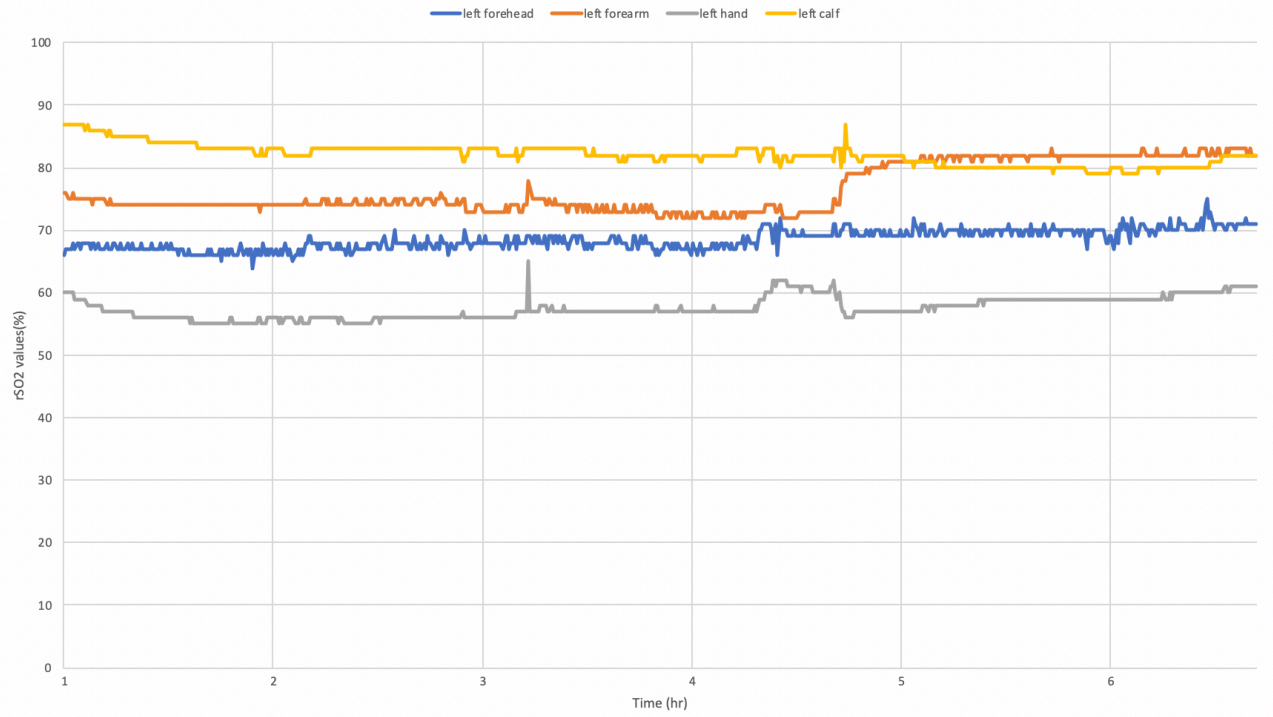

Figure C.6: second segment of rSO_2 graph of the second patient during a period of 6 hours with no missing data

Attachment C: Content of the enclosed CD

The thesis is accompanied by a CD which contains:

- Key words
- Abstract in Czech
- Abstract in English
- Scan of the assignment of the topic of the diploma thesis
- The complete diploma thesis