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DOCTORAL DISSERTATION

Evaluation of the feasibility and efficacy of measuring cerebral tissue oxygen saturation using near-infrared spectroscopy during shoulder surgery, therapeutic hypothermia and cardiopulmonary resuscitation

Doctoral dissertation submitted to obtain the degree of doctor of Biomedical Science, to be defended by

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Samenvatting

Het menselijk brein is het meest complexe en fragiele orgaan van ons lichaam: het heeft controle over de andere organen en wordt geassocieerd met de geest. Ondanks deze levensbelangrijke rol en fragiliteit, zijn de hersenen het minst gemonitorde orgaan van ons lichaam.

Standaard technieken kunnen hersenschade detecteren, maar enkel nadat de irreversibele schade al is opgetreden. Near infrared spectroscopy (NIRS) is een technologie die plaatselijk de zuurstof saturatie in de hersenen kan meten, continu en niet invasief. Op deze manier kunnen verstoringen in de zuurstof balans onmiddellijk gedetecteerd en, indien nodig, behandeld worden. De technologie is gebaseerd op de 'zuurstof vraag en aanbod' fysiologie, en zou zo een indirecte maatstaf voor cerebrale bloedflow kunnen zijn.

Wij hebben deze technologie gebruikt in observationele studies bij verschillende patiënten populaties. Op deze manier wilden we bepalen bij welke patiënten of in welke omstandigheden het gebruik van cerebrale NIRS-monitoring nuttig zou kunnen zijn.
De eerste patiënten populatie die beschreven wordt in deze thesis zijn gezonde patiënten die mogelijk in een risicovolle situatie terecht komen tijdens een schouderoperatie. Arthroscopische schouder operaties kunnen uitgevoerd worden met de patiënt in zijligging (laterale decubitus positie-LDP) rechtop zittend (*beach chair* positie–BCP). Hoewel de BCP geassocieerd wordt met minder risico op bloeding en een beter zicht voor de chirurg, wordt deze positie ook geassocieerd met hemodynamische veranderingen en cerebrale hypoperfusie. Levensbedreigende complicaties werden al gerapporteerd na operatie in de BCP. De combinatie van een lage bloeddruk en het rechtop zitten tijdens de operatie werd gezien als de oorzaak. Cerebrale NIRS monitoring zou kunnen zorgen voor een vroeg waarschuwingssignaal van cerebrale hypoperfusie tijdens schouderchirurgie in de BCP. In onze eerste studie bij patiënten die schouderchirurgie ondergaan, hebben we de incidentie van cerebrale desaturatie episodes onderzocht en geprobeerd om een waarde voor cerebrale oxygenatie te bepalen die veilig zou zijn voor de patiënt. Meer dan 75% van de patiënten die arthroscopische schouderchirurgie ondergingen in de BCP, maakten episodes van cerebrale desaturatie door in onze studie. De gemiddelde laagste waarde voor cerebrale oxygenatie was 55% (51-59) bij patiënten in de BCP, in vergelijking met 66% (62-69)($p<0.001$) in de LDP-groep. Bij gezonde vrijwilligers in de BCP was 60% de laagste waarde van cerebrale oxygenatie die kon gedetecteerd worden. Wij suggereren dan ook dat cerebrale oxygenatie boven de 60% als veilig kan beschouwd worden tijden schouderchirurgie in de BCP.

In een tweede studie bij deze patiënten, hebben we gebruik gemaakt van zeer gevoelige neurocognitieve testen, om te bepalen of cerebrale oxygenatie onder de 60% resulteert in detecteerbare neurologische schade. We hebben opnieuw patiënten geïncludeerd die een schouderoperatie in de LDP of BCP ondergingen en een groep van gezonde vrijwilligers. Iedere deelnemer werd onderworpen aan neurocognitieve testen, zowel voor de operatie als 90 minuten en 4-6 weken na de operatie. Gezonde vrijwilligers werden op dezelfde tijdstippen getest, maar ondergingen geen operatie. De vrijwilligers scoorden allemaal beter wanneer ze voor een tweede keer werden getest: het zogenaamde leereffect. Patiënten vertoonden geen leereffect na de operatie. In onze studie kon geen correlatie worden aangetoond tussen cerebrale desaturatie episodes tijdens de operatie en cognitieve problemen na de operatie.

De tweede patiënten populatie die aan bod komt in deze thesis, zijn patiënten die succesvol gereanimeerd werden na een hartstilstand. Door het gebrek aan zuurstof tijdens de hartstilstand, lopen de hersenen vaak schade op. In deze patiënten zijn de hersenen het belangrijkste orgaan wat betreft kans op overleving en levenskwaliteit van de patiënt. Hoewel de duur en exacte temperatuur nog ter discussie staan, is therapeutische hypothermie (TH) de enige vorm van behandeling die de kans op overleving en goede neurologische outcome kan verbeteren. Meerdere factoren kunnen de cerebrale zuurstof aanvoer verstoren en secundaire hersenschade veroorzaken in de uren tot dagen na een hartstilstand. Vroege opsporing en behandeling van cerebrale hypoxie/ischemie in deze kritieke periode kan bijdragen tot een betere neuroprotectie. Het doel van deze studie is om de cerebrale zuurstof saturatie te bepalen bij patiënten na een hartstilstand die behandeld worden met TH. De cerebrale zuurstof oxygenatie en arteriële CO_2 spanning ($PaCO_2$) daalden na de start van TH in onze studie. Drie uur na de start van TH was de cerebrale zuurstof saturatie significant lager bij patiënten die uiteindelijk stierven in het ziekenhuis, in vergelijking met patiënten die overleefden. Deze gegevens suggereren dat de inductie van TH veranderingen teweeg brengt in de balans tussen zuurstof aanvoer en verbruik in de hersenen van patiënten na een hartstilstand. Tijdens het verdere verloop van TH, steeg de cerebrale oxygenatie geleidelijk en werden de baseline waarden terug bereikt na 24 uur van hypothermie. $PaCO_2$ is een belangrijke regulator van de cerebrale bloed flow, maar tegenstrijdige data werden gepubliceerd over de relatie tussen $PaCO_2$, zuurstof en outcome bij post-hartstilstand patiënten. In onze studie was normocapnie geassocieerd met de hoogste kans op overleving en optimale cerebrale oxygenatie. Hypoxie werd dan weer geassocieerd met cerebrale desaturatie en een lagere kans op overleving. Onze data suggereren dat verstoringen van $PaCO_2$ mogelijk schadelijk kunnen zijn tijdens de eerste uren na een reanimatie. Een beter begrip van de cerebrale hemodynamische en metabole verstoringen in de post-reanimatie periode kunnen een impact hebben op het management van patiënten na een hartstilstand.

Tenslotte hebben we de cerebrale NIRS technologie gebruikt in omstandigheden waarvoor het niet initieel bedoeld was. Tijdens een reanimatie is het een bijzonder grote uitdaging om de adequaatheid van de circulatie en de zuurstofvoorziening aan de weefsels te meten. De monitoringsmogelijkheden tijdens een reanimatie zijn beperkt tot klinische observatie van het bewustzijn, de pols en de ademhaling. NIRS-sensoren zijn snel aan te brengen, het NIRS-signaal geeft een continue waarde en vereist geen pulsatiele flow. Hierdoor zou cerebrale NIRS monitoring mogelijk geschikt kunnen zijn voor toepassing tijdens een reanimatie. We hebben onderzocht of dit haalbaar is, zowel in als buiten het ziekenhuis. We concludeerden dat het mogelijk is om de cerebrale zuurstof saturatie te meten tijdens reanimaties en dit zowel in het ziekenhuis als daarbuiten. Meer nog, veranderingen in cerebrale zuurstof saturatie varieerden schijnbaar met de kwaliteit van de hartmassage waardoor het cerebrale NIRS signaal in de toekomst zou kunnen gebruikt worden bij de verbetering van CPR technieken.

Abstract

The brain is the most complex and fragile organ of our body: it exerts centralized control over the other organs of the body and forms the physical structure associated with the mind. Despite the brains' vital role and fragility, it is one of the least monitored organs of our body.

Standard monitoring or imaging technologies allows detecting brain injury after irreversible damage has occurred. Near infrared spectroscopy (NIRS) has the ability to detect regional cerebral tissue oxygen saturation in a continuous and non-invasive matter, allowing immediate detection of oxygenation disturbances and possible intervention when necessary. The technology is based on the 'oxygen supply and demand' physiology and could therefore be an indirect measurement of cerebral blood flow.

We used the NIRS technology in several observational studies in different patient populations. In this way, we did an effort to determine in which patients or circumstances cerebral NIRS monitoring might be useful.
The first patient population described in this thesis are healthy, but possible 'at risk' patients undergoing shoulder surgery. Arthroscopic shoulder surgery is a common procedure and can be performed with the patient in the lateral decubitus position (LDP) or beach chair position (BCP). Although the BCP is associated with better visualization and less bleeding, it has also been associated with hemodynamic changes and consequently cerebral hypoperfusion. Devastating events reported after surgery in the BCP were attributed to a combination of the upright position and hypotension. Cerebral NIRS monitoring might be able to provide an early warning sign of cerebral hypoperfusion during shoulder surgery in the BCP. In the first study, we investigated the incidence of cerebral oxygen desaturation events in these patients and did an effort to define a safe threshold for cerebral oxygen saturation in these patients. More than 75% of the patients undergoing arthroscopic shoulder surgery in the BCP experienced cerebral desaturation events in our study. We observed a mean lowest value for cerebral oxygenation of 55% (51-59) in the BCP-group, compared with 66% (62-69)($p < 0.001$) in patients in the LDP. We suggest maintaining cerebral oxygenation values above 60% during arthroscopic shoulder surgery in BCP. This strategy should provide a safety margin, as 60% was the lowest value for cerebral oxygenation in volunteers in BCP position.
In a second study, we used very sensitive neurocognitive tests, to determine whether absolute cerebral oxygenation values below 60% resulted in any detectable neurological dysfunction. Patients undergoing elective arthroscopic shoulder surgery in LDP or BCP were included, as well as a group of healthy

volunteers. All participants were subjected to pre-operative and postoperative (90 minutes and 4-6 weeks after surgery) neurocognitive tests. The group of volunteers followed the same time schedule for testing but without any surgery or anesthesia. Healthy volunteers showed a practice effect when neurocognitive tests were administered for a second time. Patients showed no practice effect after surgery. Furthermore, perioperative cerebral oxygen desaturations in patients in the BCP-group were not correlated with cognitive decline in our study.

The second patient population described in this thesis, are patients who are successfully resuscitated from cardiac arrest. Due to a lack of oxygen supply during cardiac arrest, the brain of these patients is mostly injured. In these patients, the brain is the most important organ concerning survival and quality of life. Although duration and exact temperature are under debate, therapeutic hypothermia (TH) is the only treatment that has shown the ability to improve survival and neurological outcome in patients after cardiac arrest. Several factors can potentially compromise cerebral oxygen delivery and induce secondary brain injury in the hours to days after cardiac arrest. Early detection and treatment of cerebral hypoxia/ischemia in this critical phase could contribute to a better neuroprotective approach. The aim of our study was to assess cerebral tissue oxygenation in these post-cardiac arrest patients, treated with TH. Cerebral oxygenation and arterial carbon dioxide tension ($PaCO_2$) decreased after the start of TH in our study. Cerebral oxygen saturation was significantly lower in non-survivors compared with survivors at 3 hours after the induction of TH. These data suggest that induction of TH changes the balance between cerebral oxygen delivery and supply during the early phase of hypothermia in post-cardiac arrest patients. During TH maintenance, cerebral oxygen saturation gradually returned to baseline values at 24 hours after TH induction. Carbon dioxide is an important regulator of cerebral blood flow, but conflicting data were published on the relationship between carbon dioxide, oxygen and outcome in post-CA patients. In our study, normocapnia was associated with maximal survival and optimal cerebral oxygenation in post-CA patients treated with TH. Hypoxia was associated with cerebral desaturation and poor survival. Our data suggest that derangements in $PaCO_2$ could be potentially harmful after resuscitation. A better understanding of cerebral hemodynamics and metabolic disturbances during the post-resuscitation phase may have an impact on the management of post-cardiac arrest patients.

Finally, we tested NIRS beyond its initial targets. During cardiopulmonary resuscitation (CPR), monitoring of the adequacy of circulation and oxygen supply remains a major challenge. Currently, this monitoring is limited to clinical observation of consciousness, pulse and breathing pattern. Due to the facts that NIRS-sensors are rapidly applied, the NIRS signal gives continuous information and does not require a pulsatile flow, we tested the feasibility of using the NIRS-technology during CPR in and outside the hospital. We concluded that it is

possible to monitor cerebral oxygenation during CPR after in-hospital or out-of-hospital cardiac arrest. Moreover, changes in cerebral oxygen saturation seemed to vary with the quality of chest compressions, reflecting changes in cerebral oxygenation.

General introduction

"And men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear, and know what are foul and what are fair, what are bad and what are good, what are sweet, and what unsavory... And by the same organ we become mad and delirious, and fears and terrors assail us... All these things we endure from the brain, when it is not healthy... In these ways I am of the opinion that the brain exercises the greatest power in the man. This is the interpreter to us of those things which emanate from the air, when the brain happens to be in a sound state."

Hippocrates

Hippocrates recognized the brain as the most complex and fragile organ in our body. It is the center of the central nervous system and controls the other organs of the body. Although it only accounts for approximately 2% of the total bodyweight of an average human, the brain consumes ~20% of all oxygen available in the body and needs ~15% of the cardiac output. Furthermore, the brain requires a continuous supply of glucose and account for ~60% of the utilization of glucose by the whole body in the resting state. Consequently, the brain is very sensitive for oxygen deprivation and irreversible neurological damage can occur within minutes.

Despite the brains' vital role and fragility, it is one of the least monitored organs of our body. Standard monitoring or imaging technologies allows detecting brain injury, but often only after irreversible damage has occurred. Near infrared spectroscopy (NIRS) has the ability to detect regional cerebral tissue oxygen saturation in a continuous and non-invasive matter, allowing immediate detection of oxygenation disturbances and possible intervention when necessary. The technology is based on the 'oxygen supply and demand' physiology and could therefore be an indirect measurement of cerebral blood flow. Since the report of Jobsis in 1977 (1) on the use of NIRS in humans, the technology has been used in a wide range of research and clinical scenarios. With its ability to measure cerebral oxygenation, continuously and non-invasive, and its user-friendly nature, one would expect to find cerebral oximeters as standard monitoring in every operating room and intensive care unit. Unfortunately, nothing is farther from the truth. Although substantial potential exist for this technology, there are still a number of uncertainties which currently prevent,

justified or not, NIRS devices from reaching their full potential. These uncertainties are related to the fact that there is no gold standard test to unequivocally validate that cerebral oximetry reflects frontal lobe tissue oxygenation. In Chapter 1 of this thesis, the NIRS technology, its physical principles, confounders and cerebral oximeters will be explained. Each of the addressed confounders could have an impact on the NIRS signal and its interpretation. Although the cerebral oximeters used in our studies, apply algorithms to lower the impact of these confounders, current technology cannot rule them out completely.

In the past decades, cerebral oximetry was used to monitor the healthy but 'at risk brain' as well as the injured brain. After cardiac surgery, poor neurological outcome (stroke, postoperative cognitive dysfunction) is a major concern. As cerebral hypoperfusion is a likely mechanism, several large studies have been conducted on cerebral oximetry during cardiac surgery. Retrospective as well as prospective trials associated early postoperative cognitive decline and complications with intraoperative decrease of cerebral oxygenation values (2-5). Another surgical procedure in which cerebral NIRS is often used is carotid endarterectomy, which involves a period of carotid occlusion with an associated risk of cerebral ischemia. This risk can be minimized by use of a shunt, but placement of the shunt is also associated with substantial risks. The threshold for cerebral oxygenation indicating the need for shunt placement was investigated (6). Although there were some promising results, it is very difficult to specify the threshold for cerebral hypoxia/ischemia during carotid endarterectomy. The same issue can be addressed during shoulder surgery. Although the majority of patients undergoing shoulder surgery have a healthy brain, they are considered 'at risk' by the position in which they are treated. Case-reports of devastating neurological events after shoulder surgery in the (highly used) upright position have been reported (7, 8). These events were attributed to cerebral hypoperfusion, resulting from a combination of the upright position and hypotension (9, 10). We investigated the incidence of cerebral oxygen desaturation events in these patients and did an effort to define a safe threshold for cerebral oxygen saturation in these patients (Chapter 2.2). We also investigated the incidence of neurocognitive dysfunction after shoulder surgery in the upright position by using multiple neurocognitive tests (Chapter 2.3).

Until recently, cerebral oxygen saturation monitoring occurred mainly in the operating room. Nowadays, several reports are published on the utility of this technology in the intensive care unit. The neonatal brain is readily accessible by NIRS. As neurodevelopmental impairment is common in infants born extremely preterm, monitoring of cerebral oxygenation showed potential benefit in this group (11). A completely different group in the intensive care unit that might benefit from cerebral oxygenation monitoring are comatose post-cardiac arrest patients. After cardiac arrest, the brain is the most important organ concerning survival and quality of life. Temperature controlled management has become

generally applied to protect the brain in these patients. Yet, the brain is rarely monitored during the first days of hospital admission. We continuously monitored cerebral oxygen saturation during the first 36 hours of therapeutic hypothermia (Chapter 3). This technology might find its place in the multimodality monitoring that is probably necessary to predict survival and adjust therapy to each patients' needs. In the past months, more studies were published concerning oximetry after cardiac arrest (12). Limited research was even performed on tissue oxygenation measured at the thenar eminence during and after resuscitation (13, 14).

Our study in post-cardiac arrest patients only included patients who survived the initial resuscitation. These patients were admitted to the intensive care unit, where physicians have access to several kinds of monitoring facilities (invasive blood pressure, cardiac output, …). However, most of these patients suffered from a cardiac arrest at home or at a public place. During resuscitation, monitoring is limited to clinical observation of consciousness, breathing pattern and the presence of a pulse. At the same time, the adequacy of cerebral oxygenation during resuscitation is critical for neurological outcome and thus survival. We investigated if cerebral oxygen monitoring is feasible in this out-of-hospital situation (Chapter 4).

To summarize, the future potential clinical benefit of cerebral NIRS is dependent on the (limitations of the) technology but also on the way it will be used and interpreted. We used the NIRS technology in several observational studies in different patient populations. In this way, we did an effort to determine in which patients or circumstances cerebral NIRS monitoring might be useful. Chapter 1 is focused on the NIRS technology, its physical principles, confounders and cerebral oximeters. In Chapter 2, we used cerebral oxygenation monitoring in patients undergoing arthroscopic shoulder surgery and investigated the link between cerebral desaturation and neurocognitive outcome. Chapter 3 involves cerebral oxygenation in patients resuscitated from cardiac arrest, treated with therapeutic hypothermia. Can we use cerebral oxygenation as a predictor for survival in these patients or is there potential for this technology to guide personalized treatment? And finally, is it possible and feasible to use cerebral NIRS beyond its initial targets? Therefore, in Chapter 4 we tested the technology outside the hospital, in patients during resuscitation.

CHAPTER 1

Near-infrared spectroscopy

1.1 Introduction

The human brain utilizes oxygen to continuously supply neurons with energy used for vital body functioning. In the absence of oxygen, cognitive and functional impairment resulting in death can occur.
Near-infrared spectroscopy (NIRS) is a non-invasive imaging technique used to quantify and measure the oxygenation status in human tissue. Based on the absorbance of near-infrared light by hemoglobin, NIRS can monitor *in vivo* changes of oxygen saturation of hemoglobin. This technology makes it possible to apply critical safety thresholds with regards to cerebral tissue oxygen saturation in order to avoid dangerously low levels. The primary goal is to reduce mortality rates and cognitive deficits due to cerebral hypoxemia.

Before 1977, quantification of hemoglobin concentrations in the human body was only possible using cuvette tubes containing sampled blood and large spectrophotometer units. These spectrometers measured the absorbance of a colored solution based on the magnitude of visible light attenuation per unit of colored solution. Because visible light is not able to penetrate superficial human tissue, it was impossible to quantify hemoglobin changes in the living tissue. In 1977, Jobsis was the first to report that near-infrared light could diffuse safely through the intact skull and scalp of an adult human (1). This enabled real-time non-invasive detection of cerebral tissue oxygen saturation and paved the way for today's research.

1.2 Physical principles of NIRS

NIRS relies on upon two principles (15):

1. Tissue is relatively transparent to near-infrared light
2. There are compounds in tissue in which absorption of light is dependent on the oxygenation status of the tissue

Transmission of light through tissue depends on the combination of absorption, scattering and reflection.

Absorption of light

Absorption occurs at specific wavelengths, determined by the molecular properties of the materials in the light path (1). Within the near-infrared range, the primary light absorbing molecules are metal complex chromophores: hemoglobin, bilirubin and cytochrome c oxidase. Primary chromophores of interest for cerebral oximetry are oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb): they are responsible for the transport, delivery and removal of oxygen and carbon dioxide and their concentration varies with time and oxygenation status

(15). Cytochrome c oxidase also changes with oxygen status, but does not have a significant effect on the measurement (16).
Each chromophore has a unique absorption spectrum, where the specific extinction coefficient (ε) is expressed as a function of the wavelength (17, 18). ε describes how strong a chromophore absorbs light at a particular wavelength (Figure 1.1).

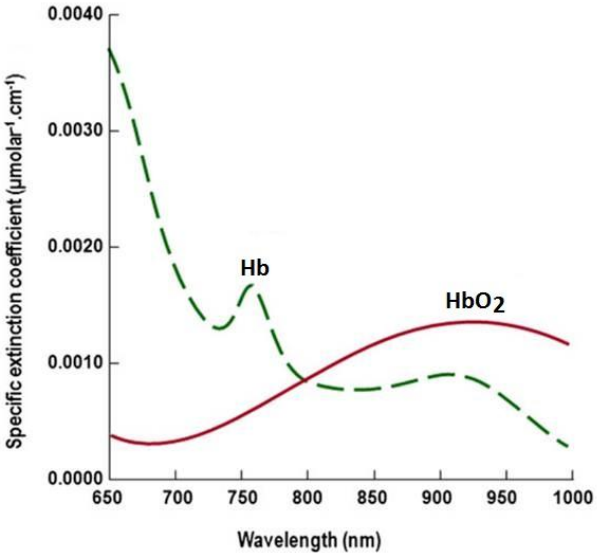

Figure 1.1: Absorption spectrum for oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) (Figure adapted from Pellicer *et al*. (18))

NIRS monitors utilize light in the 700-1000nm wavelength range. This range follows from an increased absorption of water above 1000nm and increased scattering and more intense absorption of Hb below 700nm. In the 700-1000nm range, Hb and HbO_2 have unique absorption spectra, which allows emitted light to propagate through tissue for several centimeters (19, 20). The attenuation of emitted light can be related to the change in chromophore concentration using the Beer-Lambert law.

Scattering of light

In addition to absorption, scattering also causes attenuation of light. When near-infrared light is scattered in tissue, photons change direction. The direction in which the scattered photons travel is dependent upon the wavelength, the refractive indices of the tissue layers and the size of the scattering particle (15). A complex structure such as the human head consists of multiple tissue layers, each with varying thicknesses and densities, resulting in varying degrees of scatter. Highly scattering tissue include bone, cerebral white matter and skin dermis (15).

Attenuation of light

When light travels through tissue, it is attenuated due to absorption and scatter. The attenuation by tissue can be related to the concentration of chromophores in tissue by the Beer-Lambert law (Figure 1.2).

$$A = \log\left(\frac{I_1}{I_0}\right) = \varepsilon \cdot C \cdot d$$

A = attenuation
I_0 = intensity of the incident light
I_1 = intensity of transmitted light
ε = extinction coefficient (as shown in figure 1.1)
C = the concentration of the chromophore
d = the path length of the photon from emitting to receiving optode (inter-optode distance)

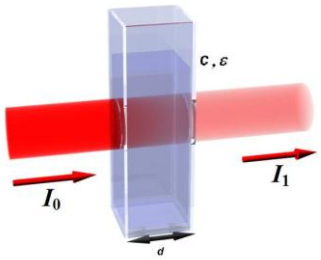

Figure 1.2: Beer-Lambert law. I_0: intensity incident light, I_1: intensity transmitted light, c: concentration of the chromophore, ε: extinction coefficient

Accurate estimation of chromophore concentration requires the same numbers of wavelengths as there are chromophores in the given tissue. To increase the sensitivity of the estimation, two wavelengths should be chosen in order to distinguish between Hb and HbO_2 extinction coefficients, such that HbO_2 has the highest extinction coefficient at one wavelength and the lowest at the other (21, 22). When three or more wavelengths are used, the accuracy of the measurements of Hb and HbO_2 can be improved (23, 24).
The path length *d* depends on the subject, the measured region and the wavelength of the light. Due to scattering, *d* will increase. Approximately 80% of the total attenuated near-infrared light is due to scattering, the remaining 20% due to absorption (25). Consequently, scattering is the biggest problem when attempting quantitative measurements with NIRS. In a highly scattered medium, photons travel a mean distance that is far greater than the inter-optode distance (*d*). A scaling factor to correct for the path length, the

differential path length factor(DPF), was incorporated in the Beer-Lambert law (26).

$$A = \log\left(\frac{I_1}{I_0}\right) = \varepsilon \cdot C \cdot d \cdot DPF + G$$

A = attenuation
I_0 = intensity of the incident light
I_1 = intensity of transmitted light
ε = extinction coefficient
C = the concentration of the chromophore
d = the path length of the photon from emitting to receiving optode
DPF = differential path length factor
G = the scattering coefficient of the tissue together with the geometry of the optodes

1.3 Absolute versus relative oxygen saturation

According to the law of Beer-Lambert, absolute chromophore concentration depends on G, DPF and d. However, G is unknown and therefore, an absolute calculation of chromophore concentration cannot be measured.
Assuming that G has the same value for each chromophore, G is cleared by using differential equation between two chromophores. Hence, unless path length can be determined, only relative changes in chromophore concentrations can be determined (24). However, modeling and computer simulation can be used to estimate the path length. This analysis can be calibrated to provide a measure of absolute change of chromophore concentration. Such an algorithm is used by some commercial devices.
Traditional NIRS devices were restricted to track changes over time. This trend is sufficient if a 'normal' baseline is assumed and the development of the patient status is monitored from that point on. This approach also minimizes confounds introduced by individual variations. However, in settings where the state of tissue oxygenation may be compromised at first measurement, e.g., in the emergency room, the collection of absolute readings is highly desired. Current technical developments are aiming to provide absolute measurements, but remain an issue of debate and scientific evidence is lacking. In literature, both relative as absolute measurements are reported and investigated.

1.4 Confounders

Other chromophores

Before the NIR light reaches the brain, it must pass through different tissue layers.
The epidermis contains melanin. Since its absorption is constant and not dependent on oxygenation, it does not produce time dependent attenuation changes (25). The dermis and skull contain bilirubin, cytochrome c oxidase and also hemoglobin, our chromophore of interest. Attenuation caused by this region will change with oxygenation. The magnitude of this effect is dependent on the thickness of dermis and skull and the chromophore concentration. Bilirubin, found in blood plasma, lowers brain oxygenation and attenuates the detection of changes in cerebral oxygenation (16). However, even at high bilirubin levels, changes in cerebral perfusion can be discerned (27). The small amount of muscle in the surface layers covering the skull, contain the chromophore myoglobin. The absorbency signals of hemoglobin and myoglobin overlap in the NIR range. Therefore, NIRS is unable to differentiate between the two chromophores. Fortunately, myoglobin is much less sensitive to tissue oxygenation than hemoglobin. Therefore, oxygen delivery must be greatly reduced before the myoglobin spectrum is affected (28, 29).

Extracerebral tissue

As stated above, the NIRS signal is contaminated with chromophores from the extracerebral tissue. Mean depth of photon penetration approximates 1/3 of the emitter/receiver separation (30). By using two different receiving optodes, housed in a single probe at different distances from the emitter, a degree of spatial resolution can be achieved. The closest receiver detects primarily superficial tissue (e.g. skin, scalp), while the other, farther, receiver detects deeper tissue (Figure 1.3). By means of a subtraction algorithm, calculation of the difference between both signals enables to measure the cortical tissue oxygen saturation. Therefore, differential spacing of receiving optodes can provide spatial resolution to distinguish signals from cerebral versus extracerebral tissue. It has been estimated that ~85% of cerebral regional oxygen saturation is derived from cortical tissue with the remaining 15% is derived from overlying extracerebral tissue.

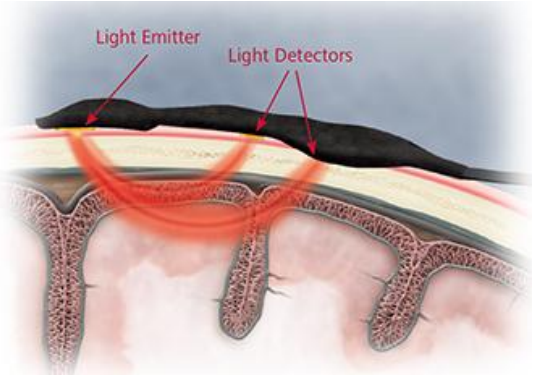

Figure 1.3: By using two different receiving optodes, housed in a single probe at different distances from the emitter, a degree of spatial resolution can be achieved. The closest receiver detects primarily superficial tissue, the other receiver detects deeper tissue. (Figure from www.nonin.com)

Arterial/venous blood partitioning

The signal, measured by cerebral NIRS devices, reflects hemoglobin saturation in venous, capillary and arterial blood. Based on correlations between positron emission tomography and NIRS, tissue hemoglobin in the cerebral cortex is distributed in a proportion of 70% venous and 30% arterial blood (31). However, clinical studies have demonstrated that there can be considerable variation in individual cerebral arterial/venous ratios in patients (32). The use of a fixed ratio can therefore produce deviations from the actual *in vivo* tissue oxygen saturation.

1.5 NIRS devices

A NIRS device consists of a light source (emitting optode), to deliver light to the tissues at a known intensity and wavelengths and one or more light detectors (receiving optodes), which measure the intensity of the exiting light. Currently, there are several commercially available NIRS devices, each with their own specifications. As only 2 different NIRS devices were used in this thesis, only they will be discussed here. There is no 'gold standard' to compare the values measured by a NIRS device. Furthermore, there is only limited information comparing e.g. cerebral blood flow (33) and brain tissue oxygen pressure (34) with NIRS. However, the two devices that we used were both validated against radial artery and jugular venous bulb oxygen saturation.

FORE-SIGHT®, Cas Medical Systems Inc, Brandford, CT

By means of continuous wave NIRS, FORE-SIGHT® uses four precise wavelengths (690, 780, 805, and 850 nm, bandwidth < 1 nm) of fiber optic laser light to measure absolute cerebral tissue oxygen saturation ($SctO_2$)(Figure 1.4).

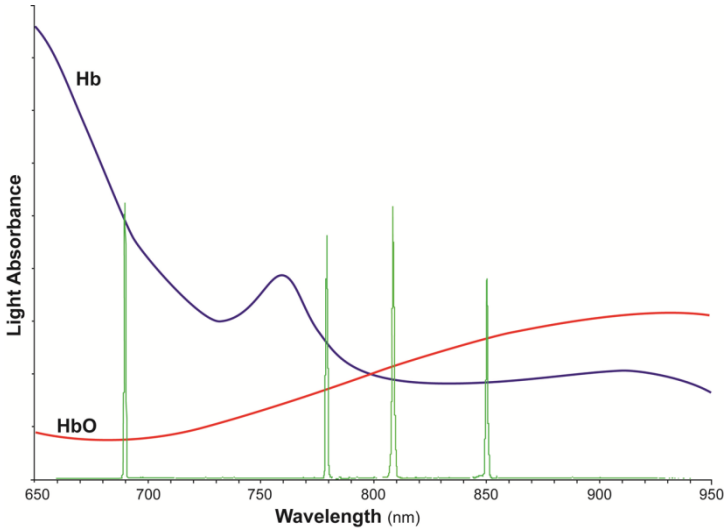

Figure 1.4: FORE-SIGHT® uses four wavelengths of laser light to measure cerebral tissue oxygen saturation
(Figure from www.casmed.com)

To decrease contamination of signals from extracerebral tissue layers, FORE-SIGHT® incorporates a degree of spatial resolution with two differentially spaced receiving optodes (Figure 1.7a). A study by Davie *et al.* investigated the contribution of extracranial tissue in 12 healthy volunteers (35). Using a circumferential pneumatic head cuff placed below the oximeter, they induced hypoxia-ischemia in the extracranial scalp tissue. Induction of hypoxia-ischemia resulted in a significant decrease of 12 ± 5% in cerebral oxygen saturation values measured with the FORE-SIGHT®-technology.
In a letter to the editor, Zaouter *et al.* investigated the influence of ambient light on the value displayed by several cerebral oximeters (36). FORE-SIGHT® passed the test with flying colors and showed no reading and a warning message whenever ambient light was detected.

The validation study of FORE-SIGHT® was presented in 2006 the form of an abstract (37) and just recently published in a paper (38). Eighteen healthy adult volunteers were subjected to an internal jugular bulb catheter, a radial arterial line and two cerebral NIRS sensors. Hypoxia was stepwise induced until SpO_2 <70%, blood sample were taken and compared to the reference values, which

was calculated based on the fixed arterial/venous ratio (30/70)(Figure 1.5). They concluded that $SctO_2$ showed a strong correlation with the reference value over the spectrum of SpO_2 values between 70 and 100%.

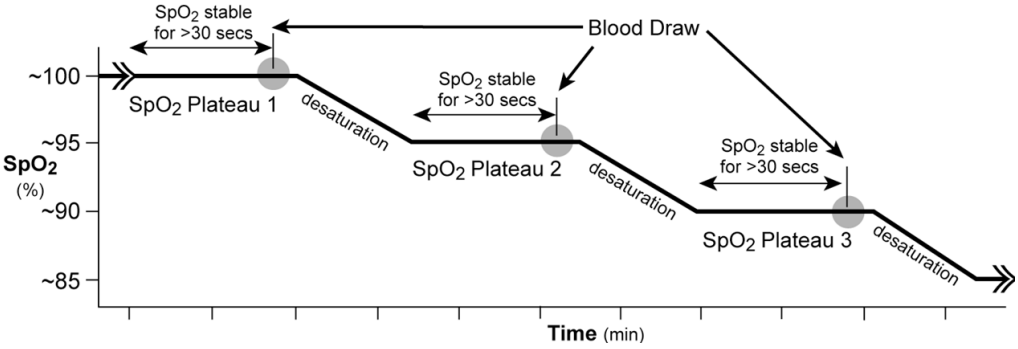

Figure 1.5: The protocol of the FORE-SIGHT validation study. Hypoxia was stepwise induced until SpO2 <70%. Venous jugular bulb and arterial blood samples were taken at several time points (37).

However, it was postulated that this 30/70% ratio is probably not fixed, but dynamically changes with hypoxia. Bickler *et al*. tested the hypothesis that cerebral oximeters accurately measure a fixed ratio of the oxygen saturation in cerebral mixed venous and arterial blood (39). They evaluated the performance of 5 commercially available cerebral oximeters during stable isocapnic hypoxia in volunteers (39). Over the entire range of oxygenation, FORE-SIGHT® showed a mean bias of 2 ± 4 and A_{rms} (root mean square error, the variability of the errors in the measurements) of 4% between $SctO_2$-values and the saturation measured in the venous/arterial blood. However, a positive bias was observed at low oxygenation levels, producing an overestimation of true cerebral oxygen saturation. This is probably due to a change in the ratio of venous to arterial blood volume during hypoxia. Ikeda *et al*. reported in the recently published validation study a A_{rms} of 2.92 between $SctO_2$-values and the saturation measured in the venous/arterial blood (38).

EQUANOX® Advance, Nonin Medical Inc., Plymouth, MN

EQUANOX™ also uses light emitting diodes (LEDs) with four wavelengths (730, 760, 810 and 880nm) to measures regional blood oxygen saturation (rSO_2) (Figure 1.6).

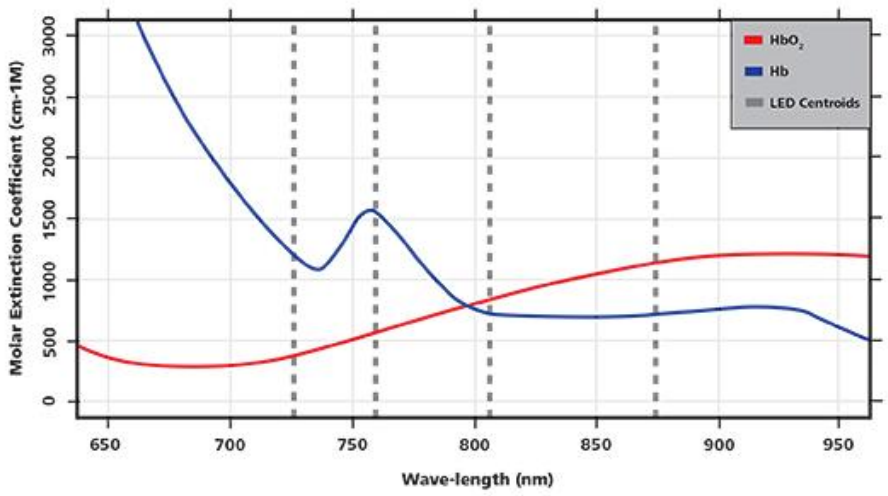

Figure 1.6: The four wavelengths used by EQUANOX Advance to measure cerebral oxygen saturation. (Figure from www.nonin.com)

EQUANOX® distinguishes itself from other cerebral oximeters by using dual receiving optodes as well as two emitting optodes to remove extracranial contamination (Figure 1.7b). Indeed, EQUANOX® has been shown to provide improved isolation of targeted cerebral tissue compared to a single emitting optode (35). Induction of hypoxia-ischemia in extracranial scalp tissue resulted in a significant decrease of 7 ± 6% in rSO_2 (35). Besides the extra emitting optode, EQUANOX® is user friendly due to its small size and low weight. However, the monitor appeared to be influenced by ambient light without any warning signal to indicate ambient light or artifact. High saturation values are achieved when the sensor is placed in direct light (36), which could be a problem in any clinical situation.

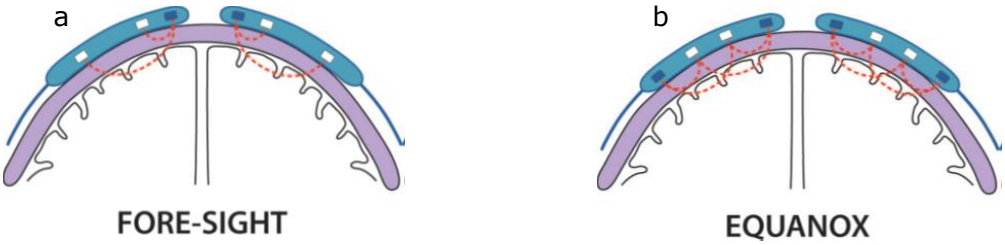

Figure 1.7:Emitting (dark) and receiver (white) optodes as used in sensors of FORE-SIGHT® (a) and EQUANOX® Advance (b). FORE-SIGHT® uses one emitting and two receiver optodes. EQUANOX® uses two emitting and two receiver optodes. (Figures adapted from Davie *et al*. (35))

Healthy adult volunteers were taken through a stepwise hypoxia protocol to a minimum saturation of peripheral oxygen in the validation study of MacLeod *et al*. (40)(Figure 1.8). As in the paper on the validation study of FORE-SIGHT®, 70% jugular bulb venous saturation and 30% arterial saturation was used as the reference value. They reported a high correlation (0.9) between rSO_2 and the arteriovenous saturation (A_{rms} 4.1), which remained stable over the entire oxygenation range.

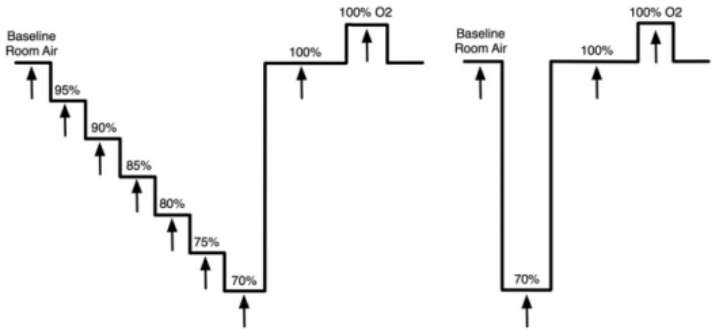

Figure 1.8: Protocol used for the validation of the EQUANOX Advance technology. Hypoxia was stepwise induced and venous jugular and arterial blood samples were taken at multiple time points (arrow) (38).

Bickler *et al.* reported a mean bias of 3 ± 6 and an A_{rms} of 7 over the entire range of oxygenation in his study on the accuracy of cerebral oximeters with a fixed arterial/venous ratio (39). EQUANOX showed no additional bias at the low oxygenation levels.

CHAPTER 2

Cerebral oxygen saturation and neurocognitive outcome

2.1 Near infrared spectroscopy and shoulder arthrosocopy

Cerebral tissue oxygen saturation during shoulder surgery in the beach chair and lateral decubitus position

Review

Ingrid Meex, *Cornelia Genbrugge, Cathy De Deyne, Frank Jans*

Submitted (Acta Anaesthesiologica Belgica)

2.1.1 Introduction

Arthroscopic shoulder surgery has become a common procedure to perform sub acromial decompression, rotator cuff repair and shoulder stabilizations. These procedures were first described with patients positioned in the lateral decubitus position (LDP). Since the report of Skyhar *et al.* on the use of the beach chair position (BCP) for arthroscopic shoulder procedures, both positions are used (41). Historically, a surgeon's preference for patient positioning has been based largely on training. Each position has its advantages and disadvantages. The LDP allows for easy access to all areas of the glenohumeral joint, sub acromial visualization is excellent and positioning of the patient requires less time than the BCP (42-44). However, suspension of the arm and traction is necessary when the patient is placed in the LDP. This has been shown to possibly cause injury to the local peripheral nerves, brachial plexus and surrounding soft tissue. Neurovascular injuries were also reported in the LDP (42, 43). Skyhar *et al*. described the ease of anatomical orientation, lack of brachial plexus strain, excellent intra-articular visualization and less bleeding as potential advantages of the BCP over the LDP (41). However, complications unique to the use of the upright position for surgical procedures were also published. Head and neck malpositioning in the sitting position have been associated with spinal cord infarction in neurosurgical procedures (45). Also after shoulder surgery in the BCP, devastating neurological events were reported (7, 8). Although the exact pathophysiological mechanisms of these events are not clear, hemodynamic changes with ensuing cerebral hypoperfusion have been argued as possible cause. For this reason, it has been recommended to continuously monitor cerebral oxygenation in patients undergoing shoulder surgery in the BCP (46, 47). The purpose of this article is to review the use of intra-operative cerebral oxygenation monitoring and the cause and consequences of cerebral oxygen desaturation in patients undergoing shoulder surgery.

2.1.2 Cerebral tissue oxygen saturation monitoring during shoulder surgery

Near infrared spectroscopy (NIRS) allows the measure of regional cerebral tissue oxygen saturation in a non-invasive and simple way. By measuring the levels of oxygenated and deoxygenated hemoglobin in the cerebral tissue (arterial, venous and capillary blood), it has been demonstrated that cerebral oxygen saturation monitoring reflects the balance between cerebral oxygen demand and supply. However, the accuracy of the NIRS technology in detecting cerebral ischemia in the BCP has been questioned. First, values for cerebral oxygenation are calculated based on the assumption of a fixed arterial (25-30%)/venous (75-70%) ratio (31). This ratio could potentially alter when position is changed to the BCP. Any difference in cerebral oxygenation could therefore be caused by a real changes in oxygen saturation levels or be the results of a change in the

cerebral arterial/venous ratio. However, in volunteers or patients under regional anesthesia, cerebral oxygen saturation was independent of body position and changed only minimally with a change to the sitting position (48-50). Second, although most NIRS monitors are provided with an algorithm to remove the signal of extracerebral tissues from the actual value, this still might contribute significantly to the signal. The impact of extracranial contamination on cerebral oxygenation values was determined in the supine position, and is dependent on the used technology (35). However, changes in jugular venous bulb oxygenation (51) and middle cerebral artery blood velocity (52) were reported in patients in the upright position, suggesting a large intracranial contribution to the signal. Third, there are some differences between the several commercially available NIRS-devices concerning the used technology (number of wavelengths, light source, absolute values vs relative values, …). However, each of these devices was previously used in studies related to cerebral oximetry during arthroscopic shoulder surgery and each of them was able to detect cerebral desaturations during surgery (Table 2.1). Closhen *et al*. compared the two most commonly used devices in volunteers and patients in the BCP and observed comparable measurements for both monitoring devices (50).

Currently, there is no universally accepted threshold of cerebral oxygen saturation values for ischemia. A decrease in cerebral oxygenation of 15-25% was associated with fainting and with symptoms of cerebral ischemia in carotid endarterectomy patients (16, 53). In cardiac or thoracic surgery patients, cognitive deterioration and prolonged hospital stay was observed when intraoperative cerebral oxygenation values decreased below an absolute value of 60% or 55% (2, 3). In literature on cerebral oxygen saturation during shoulder surgery, both a decrease from baseline (mostly ≥ 20%) (46-49, 54-56) and an absolute value below 55% (46, 49) are used as threshold.

Table 2.1 Studies included in the review on cerebral oxygenation during shoulder surgery

Paper	**Patients**	**monitor**	**position**	**Definition CDE**	**CDEs**
Fisher et al. 2009	N = 1	FORE-SIGHT	BCP	/	yes
Murphy et al. 2010	N = 124	FORE-SIGHT	BCP vs. LDP	≤55% or ≥20% decrease	Yes, in BCP
YaDeau et al. 2011	N = 99	INVOS 5100C	BCP	>20% decrease	yes
Lee et al. 2011	N = 28	INVOS 5100	BCP	Less than 80% of baseline	yes
Jeong et al. 2012	N = 56	INVOS 5100B	BCP	>20% decrease	yes
Moerman et al. 2012	N = 20	INVOS 5100	BCP	>20% decrease	yes
Ko et al. 2012	N = 50	INVOS 5100	BCP	Significant decrease	yes
Koh et al. 2013	N = 60	FORE-SIGHT	BCP	≤55% or >20% decrease	yes
Salazar et al. 2013	N = 51	INVOS5100	BCP	>20% decrease	yes
Salazar et al. 2013	N = 50	INVOS5100	BCP	>20% decrease	yes
Closhen et al. 2013	N = 35	INVOS FORE-SIGHT	BCP	Significant decrease	yes
Murphy et al. 2014	N = 70	FORE-SIGHT	BCP	≥20% decrease	yes

BCP: beach chair position; LDP¨: lateral decubitus position; CDE: cerebral desaturation event

2.1.3 Results and Discussion

Murphy *et al.* was the first to evaluate cerebral oxygen saturation (measured with FORE-SIGHT™) during arthroscopic shoulder surgery in a group of patients in LDP and BCP (46). They defined a cerebral desaturation event (CDE) as a decrease in cerebral oxygen saturation of ≥ 20% from baseline or an absolute value ≤ 55% for > 15 seconds. Cerebral oxygenation was lower in the BCP group compared with the LDP group throughout surgery ($p<0.001$). Both the percentage of patients (80%) developing CDEs as well as the median number of CDEs was higher in the BCP group. Also, the median number of interventions to treat CDEs was greater in the BCP group. Although with varying incidence, the observation that cerebral oxygenation decreases when the patient is placed in the BCP during arthroscopic shoulder surgery was confirmed by others (47, 48, 51, 55-58). Duration of CDEs (>20% from baseline) can range from one minute to more than one hour (51, 58). The magnitude of desaturation during BCP was investigated by Salazar *et al.*(using INVOS 5100™ (58). They reported a mean maximum desaturation of 32% (21-63%) from preoperative baseline levels. However, as in most papers on cerebral desaturation during shoulder surgery, anesthesiologists were not blinded and CDEs were treated according to a predefined protocol. It is therefore possible that desaturations could have been more severe if they would not have been identified and treated early. In a recent study by Moerman *et al*., anesthesiologists were blinded for the cerebral oxygenation measurements (measured with INVOS 5100™) during the study period (47). They reported 57% (42%-73%) and 59% (40%-76%) as mean lowest values for cerebral oxygenation for the left and right hemisphere respectively, a decrease of 22% from baseline. In conclusion, cerebral desaturation events occur frequently during shoulder surgery in the BCP. The degree and duration of desaturation events needs further research.

Potential causes of cerebral desaturation

Several factors may contribute to reductions in cerebral oxygenation during shoulder surgery in the BCP.

Blood pressure

Significant **hemodynamic changes** occur when patients' position is changed from supine to beach chair. It is assumed that these changes may impair cerebral perfusion. A decrease in stroke volume and systolic and mean arterial blood pressure (MAP) is observed in volunteers with change from supine to sitting position, inducing a decrease in cerebral blood flow of 12% (9, 10). In awake individuals, an immediate increase in sympathetic vascular resistance serves as a very effective compensatory response resulting in an increase in, among others, blood pressure (9). However, this response is attenuated or absent during anesthesia (59). In a recent study, Koh *et al.* compared cerebral oxygenation in patients undergoing elective shoulder surgery in the BCP either

under general or regional (interscalene block) anesthesia (49). Significantly more patients under general anesthesia (73%) required an intervention for a decrease in MAP (> 20%) compared to awake patients (10%, $p < 0.001$). Due to these interventions, MAP was adequate during surgery in awake as well as in anesthetized patients. Despite this, intraoperative cerebral oxygenation values were significantly lower throughout surgery and the incidence of CDEs (57% versus 0%) was higher in the group with general anesthesia compared with the awake group. With an incidence of 10%, YaDeau *et al.* supported the observation that cerebral desaturation in the BCP is less frequent with regional anesthesia (48).

The minimal **acceptable blood pressure** during surgery is a subject of discussion. A MAP between 50 mmHg and 150 mmHg is often suggested as the range of cerebral autoregulation and therefore a guarantee for adequate cerebral perfusion. However, there are a few issues that question the concept of lower limit autoregulation. A review of published results led to the conclusion that there is an enormous inter-individual variability in lower limit autoregulation thresholds (60). Due to this high variability, it is not only difficult to apply any lower limit value to a broad population, the average value is higher than 50 mmHg (probably 60-90 mmHg) in awake normotensive patients (60). In hypertensive patients, the lower limit of autoregulation might be shifted to the right (61). These reports suggest that the relative common practice of induced hypotension during shoulder surgery (to increase visibility and decrease bleeding) may compromise cerebral perfusion.

Another important issue concerning blood pressure is the **level of measurement**. Ko *et al*. measured invasive mean arterial pressure at the levels of both the heart and brain (external auditory meatus) (57). In the supine position, blood pressure measured at the arm (heart level) and the brain was the same (78 ± 14 mmHg at both levels). After changing to the sitting position, they reported a MAP at heart level of 84 mmHg (± 13) while MAP at brain level was 64 mmHg (± 11). This observation confirmed the results of McCulloch *et al.,* who observed a difference of 20 mmHg between the MAP measured at heart and brain level in patients in the BCP (52). Ko *et al.* also concluded that cerebral oxygenation decreased after changing to the sitting position and was significantly correlated with MAP measured at the level of the brain, but not with MAP at heart level (57). So, in practice, one should keep in mind that MAP measured non-invasively at the arm is about 20 mmHg lower than MAP measured at brain level.

General anesthesia

Besides the fact that anesthetics attenuate the compensatory response to increase systemic vascular resistance when changing from supine to the upright position, different anesthetic agents have a different influence on CBF. The influence of **intravenous** (propofol) anesthesia versus **inhalation** (sevoflurane) anesthesia on cerebral oxygenation in patients in BCP has been evaluated. Both anesthetics lower the cerebral metabolic rate for oxygen ($CMRO_2$), but their

effects on CBF differ. Due to the cerebral vasodilator properties of sevoflurane, CBF is in excess relative to the cerebral oxygen demand (62). In contrast, propofol reduces CBF more importantly than the $CMRO_2$ (63). It was therefore suggested that the cerebral oxygen balance could be better maintained in sevoflurane-based than in propofol-based anesthesia (64-66). In their study, Jeong *et al.* compared both jugular venous bulb and regional cerebral (INVOS 5100B) oxygenation during sevoflurane-nitrous oxide versus propofol-remifentanil anesthesia for patients in BCP (51). Although jugular venous bulb saturation was higher throughout surgery in the sevoflurane/nitrous oxide group compared to the propofol/remifentanil group, there was no difference between both anesthetics for regional cerebral oxygenation. With higher jugular bulb oxygen saturation and more stable hemodynamics, the authors concluded that sevoflurane/nitrous oxide anesthesia might be the better choice in patients undergoing surgery in the BCP.

Mechanical ventilation

Carbon dioxide (CO_2) is an important regulator of CBF (67, 68). It is therefore not surprising that, besides low blood pressure, a correlation between low $SctO_2$ and low end-tidal CO_2 (**$EtCO_2$**) has been described previously (47, 69). Recently, Murphy *et al*. published the results of a trial were patients were randomized into a control group ($EtCO_2$ 30-32 mmHg) or a study group ($EtCO_2$ 40-42 mmHg)(54). The effect of the ventilatory strategy on intraoperative cerebral oxygenation and incidence of CDEs was assessed. Cerebral oxygenation was significantly higher throughout surgery and the incidence of CDEs was lower in the study group compared with the control group (9% versus 56%, $p < 0.001$). The median number of CDEs that occurred in the presence of hypotension (≥ 20% decrease in MAP) was significantly higher in the 30-32 mmHg group. This led to the suggestion that ventilation to $EtCO_2$ of 30-32 mmHg may compromise cerebral oxygenation during low arterial blood pressure (54).

Also changes in inspired fraction of oxygen (FiO_2) were correlated with cerebral oxygenation. Picton *et al*. measured cerebral oxygenation in 10 anesthetized patients and monitored $EtCO_2$ and FiO_2 (70). While maintaining $EtCO_2$ in the 30-35 mmHg range, cerebral oxygenation was 8% higher when 100% oxygen was delivered compared to 30% oxygen.

Potential consequences of cerebral desaturation

In patients undergoing cardiac or thoracic surgery, the consequences of perioperative cerebral oxygen desaturations are extensively reported. Major organ morbidity, stroke, mortality, longer hospital stay and early postoperative cognitive decline were all correlated with lower values of cerebral oxygenation during surgery (3, 4, 71). In patients undergoing arthroscopic shoulder surgery, despite the numerous publications on the incidence of cerebral desaturations perioperatively, the consequences of these cerebral desaturations have not been well investigated so far. However, several case reports have highlighted the

potential risks of shoulder surgery in BCP, unfortunately, in none of the patients described in these case-reports, NIRS monitoring had been used. In 2003, Bhatti *et al*. described one case, a 64 year old healthy man, with unilateral **visual loss** and external ophthalmoplegia after shoulder surgery in the BCP under regional and general anesthesia (8). Pohl and Cullen reported four cases of healthy patients, between 47 and 53 years of age, who suffered cerebral ischemia during shoulder surgery in the sitting position (7). Although the perioperative course seemed uncomplicated, none of the patients awoke after surgery. Neurologic examination revealed **cortical and spinal cord infarctions** resulting in permanent neurological dysfunction, vegetative state and brain death. As mentioned previously, cerebral oxygenation was not measured in these patients, but cerebral hypoperfusion, due to the patients' position and hypotension, was assumed to be responsible for these complications. A total of 23 cases of devastating neurological outcomes have been reported in this way (72). However, complications after shoulder surgery are probably highly under-reported (72). In addition, without extensive neurocognitive monitoring, subtle changes may go unnoticed until major organ damage manifests. Currently, there is only one study who imposed their patients with neurocognitive tests before and after shoulder surgery in the BCP (56). Salazar *et al.* monitored cerebral tissue oxygenation (INVOS 5100^{TM}) intra-operatively in 50 patients undergoing arthroscopic in the BCP. Neuropsychological tests (Repeatable Battery for the Assessment of Neuropsychological Status) were conducted on the day of surgery (before and after surgery) and three days after surgery. Data from the tests given immediately after surgery were excluded due to lingering effects of anesthesia and postoperative narcotic pain medication. No cognitive decline was measured in pre-operative versus post-operative tests and therefore also no correlation with intraoperative cerebral desaturation events. However, in this study anesthesiologists were not blinded to the cerebral saturation values with consequently rapid intervention to reverse desaturation events (56). From animal studies, it has become clear that neurological impairment is related to the severity and duration of desaturation that cause cerebral ischemia, which remains undefined when anesthesiologist are not blinded for cerebral oxygenation data (73, 74). Besides neurocognitive outcome, Murphy and colleagues reported a higher incidence of postoperative **nausea** (50% versus 7%; $p = 0.001$) and **vomiting** (27% versus 3%; $p = 0.011$) in patients with intraoperative CDEs compared with subjects without CDEs (46, 54).

Future research should focus on subtle neurocognitive changes in patients undergoing shoulder surgery in the BCP, compared to the LDP. To prevent bias, the only way to correctly assess the effect of cerebral desaturation on cognitive dysfunction, is by blinding the anesthesiologist for the cerebral oxygenation values. In addition, as practice effects in neurocognitive tests are very common, a control group should be included to compensate for learning effects.

2.1.3 Conclusion

Case reports of devastating neurological events after shoulder surgery have been reported. These events were attributed to cerebral hypoperfusion, resulting from a combination of the upright position and hypotension. Besides position and blood pressure, ventilator management ($EtCO_2$) and anesthesia (product, general versus local) should be taken into account. Near infrared spectroscopy might be able to provide an early warning sign of cerebral hypoperfusion. It was recommended to continuously monitor cerebral oxygenation in patients undergoing shoulder surgery in the BCP, to potentially prevent devastating outcomes. However, extensive neurocognitive testing is needed to explore the potential consequences of cerebral desaturation events in patients undergoing elective shoulder surgery. Also, attention should be paid to patients who are probably more vulnerable (increasing age, low preoperative cognitive performance, …) to cerebral desaturation events. In this way, protocols aimed at detecting and reversing desaturation events should be developed.

2.2 Absolute values of cerebral tissue oxygen saturation

What are the normal absolute values of cerebral tissue oxygen saturation in beach chair position?

Comparison of healthy volunteers with patients undergoing arthroscopic shoulder surgery.

Original paper

***Ingrid Meex**, Francis Deburggraeve, Joris Vundelinkcx, Klaas Buyse, Stephanie Denaeyer, Veerle Desloovere, Ludwig Anné, Jan Truijen, Margot Vander Laenen, Rene Heylen, Cathy De Deyne, Frank Jans*

Submitted (Canadian Journal of Anesthesia)

2.2.1 Introduction

Surgery in the beach chair position (BCP) has repeatedly been associated to significant hemodynamic changes that have the potential to compromise cerebral circulation with ensuing risk for cerebral ischemia (9, 10). Moreover, for many surgical procedures (such as endoscopic shoulder surgery) optimal surgical visualization requires the use of controlled arterial hypotension. Combining BCP with induced arterial hypotension could increase the possible threat of inadequate cerebral perfusion. These assumptions were supported by several case-reports on neurological sequelae after shoulder surgery in BCP (7, 8).

Cerebral oximetry (near-infrared spectroscopy - NIRS) allows detecting changes in cerebral tissue oxygen saturation ($SctO_2$). This technology has been extensively used to provide a non-invasive, real-time indicator of cerebral hypoperfusion (75), mainly during cardiac surgery. Not surprisingly, several groups have reported their experience on the use of cerebral oximetry during shoulder surgery in BCP. They all revealed significant decreases in $SctO_2$ during the procedure (46, 47, 49, 50, 54, 56-58).

Although promising for improving patient outcome, a major drawback of the $SctO_2$ parameter is that the different commercially available cerebral oximetry devices use variations of the NIRS technology (number of wavelengths, trend-only versus absolute, algorithms, …) which makes comparison of the published results extremely difficult. A study on the performance of 5 commercially available cerebral oximeters, reported that the Fore-Sight® monitor has the highest precision (Arms 4%) (39). A high precision, implying a constant difference to jugular bulb saturation and a minimal extracerebral contamination, is a prerequisite for the $SctO_2$-value to be used as an *absolute*, rather than a relative, parameter. Therefore in this study we repeated the measurements of $SctO_2$ in healthy volunteers during several body positions using the Fore-Sight® monitor and compared the obtained results with measurements in patients.

The goal of this study was [1] to establish a range for normal *absolute* $SctO_2$ values for healthy (awake) volunteers in BCP and lateral decubitus position (LDP) and [2] to compare this $SctO_2$ range in volunteers to the range for *absolute* $SctO_2$ values measured in patients undergoing surgery under general anesthesia.

2.2.2 Methods

Cerebral tissue oxygen saturation monitoring

Between October 2008 and May 2010, Bilateral $SctO_2$ was measured using the FORE-SIGHT® technology (CAS medical systems Inc, Branford, CT, USA) in both volunteers and patients. The FORE-SIGHT® cerebral oximeter is a non-invasive device that uses 4 wavelengths of laser light to determine absolute cerebral oxygen saturation ($SctO_2$). $SctO_2$ represents the oxygen saturation level in the microvasculature of brain tissue, which contains a mixture of arterial and venous blood (30/70%). Sensors were applied to each frontotemporal area and covered to prevent external light interference. Data were collected every 2 seconds. Because we were interested in the optimal (safe) range of $SctO_2$-values in BCP, we used the lowest measured $SctO_2$-values for statistical analysis (and not the mean/median values during a defined time period). Therefore, for each body position, the lowest $SctO_2$ value measured, was recorded and used for statistical analysis. In case of shoulder surgery, the attending anesthesiologist was blinded to the $SctO_2$ data and therefore, any change in $SctO_2$ could not have resulted in any changes in therapy (f.i. blood pressure management).

Volunteers

The study protocol was approved by the local committee for medical ethics. Written informed consent was obtained from all participants (patients and volunteers).

Volunteers were healthy (ASA I) men and women between 18 and 30 years of age. Monitoring of baseline bilateral $SctO_2$ values was started in supine position. Hereafter, position was changed into beach chair, supine and lateral decubitus position for 15 minutes each. Monitoring included (besides bilateral $SctO_2$ monitoring) pulse rate, pulse oximetry and non-invasive blood pressure monitoring (/5min).

Patients

Patients scheduled to undergo elective arthroscopic shoulder surgery under general anesthesia in the BCP or LDP, were enrolled in the study. Exclusion criteria were preexisting cerebrovascular disease, peripheral vascular disease and age < 18 years. Monitoring of baseline bilateral $SctO_2$ values was started in supine position and continued with change in BCP or LDP. Allocation to the BCP or LDP groups was determined by surgical preference.

Anesthesia

Anesthetic management was performed in both patient groups by the same team of anesthesiologists. Thirty minutes prior to surgery, all patients received an interscalene plexus block with a single shot of 30 ml bupivacaine. All surgical procedures were performed under general anesthesia (propofol/rocuronium/remifentanil; F_iO_2 30%). Standard monitoring (non-invasive blood pressure measurement on the contralateral arm, electrocardiography, peripheral oxygen saturation and end-tidal capnography) was applied. Management of anesthesia and hemodynamics were left to the discretion of the attending anesthesiologist. As already mentioned, $SctO_2$ values were blinded for the anesthesiologist and abnormal values could by no way have guided any therapeutic intervention. In all patients, severe arterial hypotension was countered by reducing remifentanil/propofol infusion or by the administration of boluses of colloids, phenylephrine or ephedrine.

Statistical analysis

$SctO_2$ values were measured in patients and volunteers in different body positions. Statistical analysis was performed using SPSS V19.0 (SPSS Inc, Chicago, USA). Discrete data were compared using χ^2. Equal distribution was tested using the Kolmogorov-Smirnov test. Normally distributed continuous data were compared using the unpaired *t* test. Hemodynamic and cerebral oxygen saturation values were compared between groups using the Mann-Whitney U test. To compare values within the same group, the paired Wilcoxon test was used. To determine reference values for $SctO_2$ during BCP, the 95% interquartile range in healthy volunteers (97.5 and 2.5 percentile) was calculated. The results are represented as median (25-75 percentile range), mean (± SD) or percent (%) as indicated. A p-value below 0.05 was considered statistically significant.

2.2.3 Results

Characteristics of patient groups and healthy volunteers

A total of 91 healthy volunteers and 236 patients were recruited. Due to incorrect saving of cerebral oxygenation data, data of 6 volunteers and 41 patients were missing and they were excluded from further analyses. Characteristics of the 85 healthy volunteers are presented in table 2.2. Of the 195 patients, 101 patients underwent surgery in the BCP and 94 patients in the lateral decubitus position (LDP). The two patient groups were comparable regarding sex, ASA status, pre-existing hypertension and pre-operative hemoglobin levels (Table 2.3). Only the age of patients in BCP (56 ± 12 years) was significantly higher than the age of patients in LDP (51 ± 13 years)($p = 0.004$).

Table 2.2. Characteristics

	volunteers	**patients**	**p-value**
Number, n	85	195	-
Age, years (±SD)	23 ± 3	53 ± 13	< 0.001
ASA status, n (I/II/III)	85/0/0	124/67/4	< 0.001
Hypertension, n (%)	0 (0%)	26 (13%)	< 0.001

Data are presented as mean ± SD or %

$SctO_2$-values in healthy volunteers

In 85 healthy volunteers, lowest measured $SctO_2$-value in dorsal decubitus (DD) was 69% (66-71). A change in position to the BCP caused a small but significant decrease in lowest measured $SctO_2$ to 67% (65-70%) ($p = 0.028$). This decrease was associated with an increase in mean arterial pressure (MAP) from 83 mmHg (78-88 mmHg) in DD to 85 mmHg (81-93 mmHg) in BCP ($p < 0.001$). Heart rate (HR) and arterial oxygen saturation (SpO_2) remained stable (HR: 68 bpm (61-73 bpm) in DD to 68 bpm (63-76 bpm) in BCP ($p = 0.261$), SpO_2:98% (97-99%) in DD, 98% (97-99%) in BCP ($p = 0.224$). When position was changed again to DD, lowest $SctO_2$ remained stable at 68% (65-70%) ($p = 0.465$), MAP decreased to 80 mmHg (74-87 mmHg) ($p < 0.001$), HR and SpO_2 remained stable at respectively 67 bpm (61-75 bpm) ($p = 0.068$) and 98% (97-99%) ($p = 0.109$). When turned to right LDP, lowest $SctO_2$ value remained at 68% (65-71%). MAP decreased to 75 mmHg (69-83 mmHg) ($p < 0.001$), while heart rate (68 bpm (61-73 bpm)) and SpO_2 (98% (97-99%)) remained stable ($p = 0.922$ and $p = 0.775$ respectively) (Table 2.4).

When calculating the 95% interquartile range for the lowest cerebral oxygen saturation during BCP, a range between 60% and 77% was obtained.

Table 2.3. Characteristics of patients in BCP and LDP

	Beach chair position	Lateral decubitus position	p-value
n	101	94	-
Sex (male/female)	52 (51.5%)/49 (48.5%)	44 (46.8%)/50 (53.2%)	0.567
Age (years)	56 ± 12	51 ± 13	0.004
ASA status (I/II/III)	64/37/0	60/30/4	0.100
Hypertension	14 (14%)	12 (13%)	0.837
Pre-operative Hb (g/dl)	14 ± 1	14 ± 1	0.386

Hb: hemoglobin
Data are presented as mean ± SD or %

Table 2.4: Results healthy volunteers (grey) and patients

Position	$SctO_2$ (%)	HR (bpm)	MAP (mmHg)	SpO_2 (%)
Dorsal decubitus	69 (66-71) *	68 (61-76)	83 (78-88) *	98 (97-99)
Beach chair	67 (65-70)	68 (63-76)	85 (81-93) *	98 (97-99)
Dorsal decubitus	68 (65-70)	67 (61-75)	80 (74-87) *	98 (97-99)
Lateral decubitus	69 (65-71)	68 (61-73)	75 (69-83)	98 (97-99)
Dorsal decubitus	78 (74-82) *	79 (71-92) *	106 (98-121) *	99 (98-100)
Beach chair	55 (51-59)	59 (54-66)	59 (51-66)	97 (96-98)
Dorsal decubitus	80 (75-84) *	84 (66-91) *	110 (98-122) *	99 (98-99)
Lateral decubitus	66 (62-69)	54 (49-64)	63 (57-74)	98 (97-99)

*$p<0.05$, $SctO_2$ = cerebral tissue oxygen saturation, HR = heart rate, MAP = mean arterial pressure, SpO_2 = pulse oximetry
Data are presented as median (IQR)

$SctO_2$-values in patients undergoing surgery

In patients undergoing elective arthroscopic shoulder surgery, lowest $SctO_2$-value in supine position before induction of anesthesia (while breathing room-air) was 72% (70-75%) and 73% (71-76%) for the BCP group and LDP group respectively ($p = 0.18$). After induction, lowest $SctO_2$ was 78% (74-82%) for the BCP and 80% (75-84%) for the LDP ($p = 0.087$).

In patients undergoing surgery in BCP, the lowest $SctO_2$ value measured was 55% (51-59%), which was significantly lower than the lowest $SctO_2$ value in patients undergoing surgery in the LDP (66% (62-69%))($p < 0.001$). In accordance with the range for lowest cerebral oxygenation during BCP in volunteers, we used 60% as cut –off value. More patients in the BCP group (76%) showed $SctO_2$-values <60% compared to the LDP group (19%; $p < 0.001$). The time course of median $SctO_2$ values during surgery in BCP and LDP is shown in Figure 2.1.

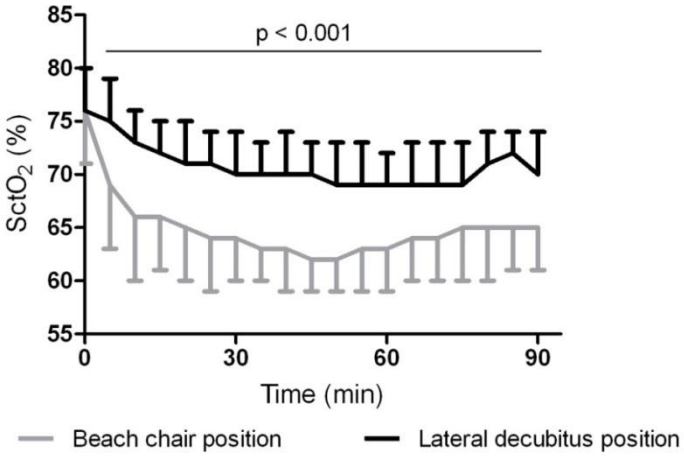

Figure 2.1: Cerebral oxygen saturation ($SctO_2$) during arthroscopic shoulder surgery in beach chair position (grey line) or lateral decubitus position (black line). Results are presented as median with interquartile range.

Comparison of volunteers and patients

Although data obtained from healthy volunteers cannot be directly compared to data from patients (difference in age, co-morbidity, F_iO_2, effect of general anesthesia …), an overview of the most relevant results is presented in figure 2.2. When changing from dorsal decubitus to BCP, lowest $SctO_2$ values in

anesthetized patients decreased from 78% (74-82%) to 55% (51-59%) ($p < 0.001$), while $SctO_2$ in healthy volunteers only decreased from 69% (66-71%) to 67% (65-70%). With the change in position, MAP at the moment of lowest $SctO_2$ in patients decreased from 106 mmHg (98-121 mmHg) to 59 mmHg (51-66 mmHg) ($p < 0.001$). Contrary, MAP in volunteers increased with 2 mmHg in BCP.

Lowest $SctO_2$-values in anesthetized patients undergoing surgery in LDP decreased from 80% (75-84%) in dorsal decubitus to 66% (62-69%) ($p <0.001$) in LDP. In volunteers, this position change had no influence on $SctO_2$-values and remained stable at 68% (65-71%). At the moment of lowest $SctO_2$ in patients, MAP decreased from 110 mmHg (98-122 mmHg) to 63 mmHg (57-74 mmHg) in patients in the LDP group. This decrease in MAP was not significant different compared to the decrease in MAP in the BCP-group ($p = 0.097$). In healthy volunteers, MAP decreased from 80 mmHg (74-87 mmHg) to 75 mmHg (69-83 mmHg) when position was changed to LDP.

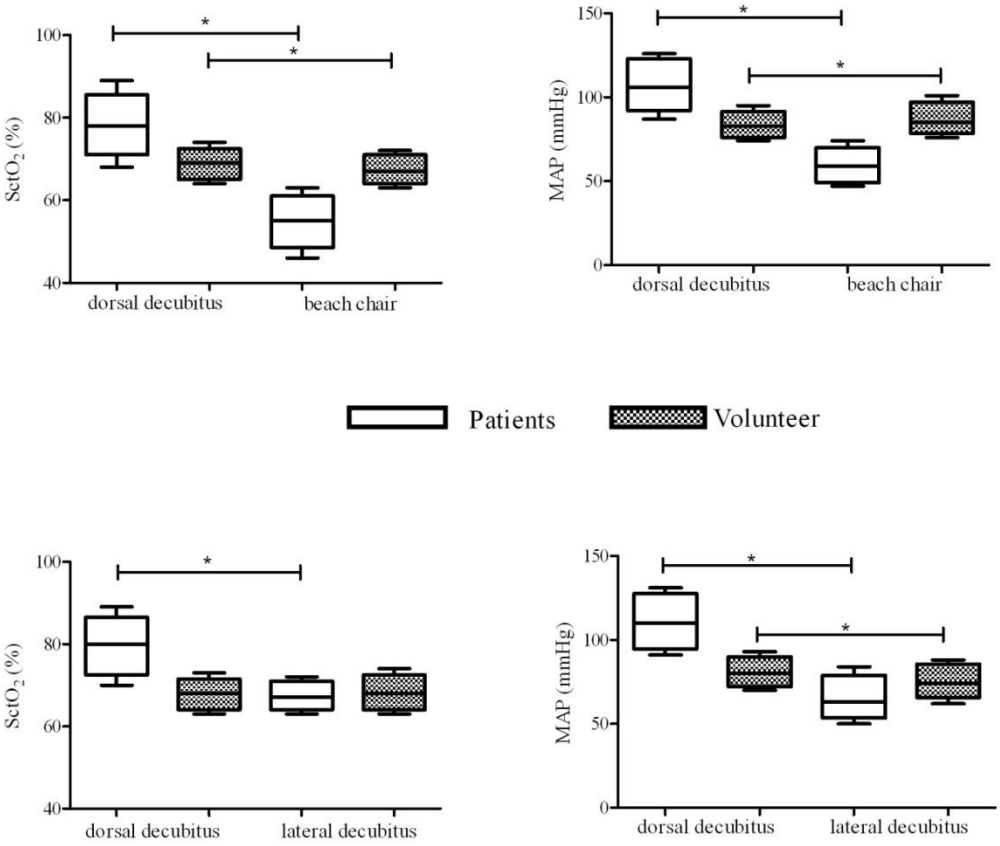

Figure 2.2: Cerebral tissue oxygen saturation ($SctO_2$) and mean arterial pressure (MAP) in patients under general anesthesia (white box) and volunteers (scattered box) in different positions. Results are presented as median with interquartile range.* $p < 0.05$

2.2.4 Discussion

In this study, $SctO_2$ was significantly lower in patients undergoing shoulder surgery in the BCP. With 76% of our patients revealing $SctO_2$ values below 60% in BCP, we confirm previous results on the frequent occurrence of cerebral tissue oxygen desaturation in patients undergoing arthroscopic shoulder surgery in BCP (46, 47, 49, 54, 56, 58).

Significant hemodynamic changes and a decrease in cerebral blood flow occur when patients' position is changed from supine to beach chair (9, 10). In awake subjects, upright positioning activates the sympathetic nervous system, resulting in, among others, an increase in blood pressure (9). In our group of healthy volunteers, MAP increased from 83 mmHg (78-88 mmHg) to 85 mmHg (81-93 mmHg) when changing position from supine to the upright position (Table 2.4). This increase in MAP was accompanied with a 2% (0-2%) decrease of $SctO_2$ in this group. There is few existing literature on the impact of body positioning on $SctO_2$ in healthy volunteers (76-79). Moreover, different cerebral oximeters were used (Niro™ (76), Oxymon™ (77), Invos™ (78, 79)), and the numbers of healthy volunteers that were studied were rather small (min n=5, max n=28). Generally a decrease (although not significant in all studies) in $SctO_2$ when changing from supine to the upright position was reported, which is confirmed by the results from our current study.

The normal regulatory mechanisms (activation of sympathetic nervous system) to maintain cerebral perfusion in the sitting position are often blunted or absent in patients under general anesthesia (59). The combination of general anesthesia and induced hypotension in BCP resulted in a median decrease of almost 50 mmHg in MAP and 23% (18-28%) in $SctO_2$ in this patient group. In contrast, general anesthesia and induced hypotension caused only a median decrease of 14% (9-18%) in $SctO_2$ values in patients in the LDP (with a decrease of almost 50 mmHg in MAP).

Mean arterial pressure was 59 mmHg (51-66 mmHg) at the moment of lowest $SctO_2$ measurements in the BCP. However, brachial noninvasive blood pressure monitoring likely overestimates the pressure in the elevated brain (57, 80). Following Sia *et al*. (80) we could calculate the difference between the actual pressure and the measured pressure. Assuming a 0.77 mmHg decrease for every centimeter gradient (1 mmHg for each 1.25 cm) and an approximate gradient of 10 to 30 cm between the carotid artery and the site of the blood pressure cuff in the seated position, this would suggest that carotid MAP is 7.7 to 23.1 mmHg lower than the non-invasively measured mean brachial artery pressure.

Although, NIRS might be able to provide an early warning sign of cerebral hypoperfusion, one of the major concerns with using this technique is the lack of

a uniform threshold identifying pathological cerebral saturation (75). One approach to determine the threshold would be to perform large scale prospective studies to determine which value of $SctO_2$ leads to neurological dysfunction. This is rather difficult because of ethical concerns and because the enormous amount of patients needed to be included (due the low incidence of neurological sequelae). Therefore, we chose for a different approach. By determining the 95% interquartile range of our measurements in 85 healthy volunteers in BCP, we calculated a range of 60-77% as 'normal' $SctO_2$-value during BCP. This lower limit of 60% is higher than the commonly used threshold for cerebral ischemia of 55%, which has been determined in pre-clinical studies. However, in support, it is interesting to note that Fischer *et al*. and Tang *et al.* showed that there was a significant correlation between the incidence of complications and early postoperative cognitive dysfunction and cerebral oxygen saturation under 60% (measured with the FORE-SIGHT® technology) during thoracic and cardiac surgery (2, 3). Also, the Fore-Sight monitor has been shown to have a positive bias in regions of very low $SctO_2$ (39), making 55% maybe a value too low to be clinically acceptable. During surgery, 76% of our patients in BCP revealed $SctO_2$-values below 60%. However, we did not observed any major neurological deficit. None of the patients in the LDP-group showed $SctO_2$-values < 60%. Of course, there are some concerns when an anesthetized brain is compared to an awake brain. Anesthetics produce a metabolic depression on the human central nervous system. Positron emission tomography showed a brain metabolic reduction of 57% in patients under propofol compared to the awake brain (81). Due to this decreased metabolism, patients might be less vulnerable to a decrease in cerebral oxygen saturation than awake volunteers. Therefore, the safer lower limit might be lower during surgery under general anesthesia. However, as mentioned before, $SctO_2$ < 60% has been associated with complications and cognitive impairment in patients after cardiac and thoracic surgery (2, 3).

There are several limitations to the present investigation. First, NIRS devices measure saturation in a mix of arterial, venous and capillary compartments. Change in body position may alter the ratio of these compartments in the cerebral circulation. Therefore, reductions in $SctO_2$ may also reflect changes in cerebral blood volumes/compartment and not only decreases in oxygen supply. However, in volunteers or patients under regional anesthesia, cerebral oxygen saturation was independent of body position and changed only minimally with a change to the sitting position (48-50). Second, we did not perform extensive neurocognitive tests. It is possible that cerebral desaturation events may result in more subtle dysfunction and cerebral injury which are not detected on routine clinical exams. Finally, patients were not randomized but allocated to BCP or LDP according to surgical treatment.

2.2.5 Conclusion

More than 75% of the patients undergoing arthroscopic shoulder surgery in the BCP experience cerebral desaturation events. NIRS might be able to provide an early warning sign of cerebral hypoperfusion and may potentially prevent devastating outcomes. We suggest maintaining absolute $SctO_2$-values, as measured with Fore-Sight®, above 60% during arthroscopic shoulder surgery in BCP. This strategy should provide us with same safety margin, as 60% was the lowest $SctO_2$ value in volunteers in BCP position. Further studies, using the most sensitive neurocognitive testing, are needed to determine whether absolute $SctO_2$ values below 60% result in any detectable neurological dysfunction.

2.3 Cerebral desaturation and neurocognitive outcome

Does low cerebral oxygen saturation during surgery in beach chair position result in a decrease in neurocognitive function in the immediate post-operative period?

A comparison to patients operated in the lateral decubitus position.

Original paper

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Submitted (Anesthesiology)

2.3.1 Introduction

Arthroscopic shoulder surgery can be performed with patients in beach chair position (BCP) or lateral decubitus position (LDP). With a claimed better visualization of the shoulder, improved airway access and reduced risk of brachial plexus injury (42, 82), the BCP is increasingly used for shoulder surgery (83). However, this position has been associated with hemodynamic changes and consequently reductions in cerebral blood flow (9, 10). Pohl and Cullen highlighted this issue with their publication of four relatively healthy patients who encountered major brain injury and death after shoulder surgery in the BCP (7). Also visual loss and opthalmoplegia were described after shoulder surgery (8). With only 23 reported cases, severe postoperative neurological dysfunction might be infrequent after shoulder surgery in the BCP (72). However, the incidence of adverse neurological outcomes after shoulder surgery in the sitting position is most likely substantially under-reported (72). Furthermore, without extensive neurocognitive monitoring, subtle changes may go unnoticed until major organ damage manifests. To avoid potential neurological complications, it was recommended to continuously monitor cerebral tissue oxygenation saturation ($SctO_2$) during surgery (84, 85).

Near-infrared spectroscopy (NIRS) is a non-invasive technology that allows detecting changes in $SctO_2$. In cardiac surgery patients, intra-operative desaturation was correlated with the incidence of stroke, postoperative cognitive decline and major organ dysfunction (3-5, 71, 86). During carotid endarterectomy, cerebral oxygen desaturation correlated with clinical (mental confusion, agitation) and EEG signs of cerebral ischemia (87). Therefore, cerebral oximetry monitoring is highly suitable to provide an early warning sign of cerebral hypoperfusion (75). Several publications have reported accurate detection of important desaturation periods by cerebral oximetry during shoulder surgery in the BCP (46, 47, 58, 84, 85). These publications have raised considerable concern about the safety of surgery and anesthesia in BCP.

The aim of this prospective study was to investigate if cerebral desaturation periods during shoulder surgery in BCP resulted in detectable neurological dysfunction in the immediate post-operative period. Multiple neurocognitive tests were used to detect even minimal neurological dysfunction. The neurocognitive results from patients operated in BCP were compared to the results from patients operated in LDP and to the results from a control group of healthy volunteers.

2.3.2 Patients and methods

Patients and volunteers

Following approval of the local medical ethics committee (11/066), written informed consent was obtained from all patients and volunteers. Every consecutive patient scheduled to undergo elective arthroscopic shoulder surgery (for sub-acromial decompression or rotator-cuff repair) in the BCP or LDP was contacted for participation in the study. Exclusion criteria included age less than 18, documented stenosis of carotid or vertebral arteries, history of cerebrovascular accident or transient ischemic attacks, inexplicable syncope's, uncontrolled arterial hypertension (systolic blood pressure >160 mmHg) or refusal of interscalene blockade.

Allocation of patients to the study groups

Two orthopedic surgeons were involved in this study: one surgeon (L.A.) performs arthroscopic shoulder surgeries with patients positioned in the BCP and the other surgeon (J.T.) always performs this type of procedures with patients positioned in the LDP. It was the general practitioner (not involved in this study protocol) who referred the patient to a specific orthopedic surgeon, based on his/her usual referral pattern. Solely this fact determined whether a patient was allocated to the BCP group or the LDP group.

Cognitive testing

Patients were contacted by telephone before surgery. After explanation of the study protocol, patients were asked to participate in the study. If the answer was positive, the patient was subjected to several questionnaires and cognitive tests on the morning of the surgery (T1). The test battery took approximately one hour. The cognitive tests were repeated 90 minutes after the end of the surgery (T2) and 4-6 weeks post-surgery (T3), when the patient presented to the surgeon for routine follow-up. The questionnaires were repeated after 4-6 weeks (T3). Practice effects have been noted for most neuropsychological tests (88). The impact of this effect is dependent on the particular test and on the performance level of the patients (88, 89). We therefore constructed a group of volunteers with the same age and level of education as our patient population. The group of volunteers followed the same time schedule for testing but without any surgery or anesthesia.

We selected the following tests for patients and volunteers:

- Buschke Selective Reminding Test (90) (SRT): a test designed to measure verbal learning and memory. The test involves reading the subject a list of 12 unrelated words. The subject is asked to recall as many of these 12 words as possible. Every trial after the first involves

selective presenting only those words the subject did not recall in the previous trial. The trials proceed until the subject is able to recall all 12 words or until 12 trials have been completed. A parallel version, with different words, was used for testing 1.5 hour after surgery.

- Computerized Visual Searching Task (91) (CVST): The task consists of finding a grid pattern out of 24 which matches the one in the center of the screen. The subject is asked to react as fast as possible. Results show accuracy and speed of responses and are evaluated within the context of visual information processing and perceptual-mental strategies.
- Controlled Oral Word Association Test (92) (COWAT: animals, letter 'n'): subjects have to say as many words as possible from a category in one minute. This category can be semantic (animals) or phonemic (words that begin with letter 'n'). Results give information on verbal fluency and semantic memory.
- Symbol digit substitution test (93): This test consists of nine digit-symbol pairs followed by a list of digits. The subject needs to match symbols with their corresponding digit, as fast as possible. The number of correct symbols within the allowed time (90 sec) is measured. This test measures memory, attention, visual scanning and speed of processing.
- Stroop color-word test (94): In this test, the name of a color is printed in the ink of another color (e.g. the word 'red' is printed in blue ink). The subject is asked to name the color of the ink, unless the word is surrounded by a box (stroop IV). The test measures selective attention, cognitive flexibility and is an evaluation of executive function.

Questionnaires were added to explore patients' anxiety, depression and pain level:

- Hospital Anxiety and Depression Scale (95) (HADS): This questionnaire consists of two subscales of 7 items each, that determine the level of anxiety and depression that a patient is experiencing. It was created for the detection of states of anxiety and depression in the hospital setting.
- Fatigue Assessment Scale (96) (FAS): This 10 item scale evaluates symptoms of general, chronic fatigue.
- Visual Analogue Scale (97) (VAS): This is a scale from 1 to 10, were 1 is no pain and 10 is the worst pain the subject has ever experienced. The subject is asked to indicate their level of current pain.
- State-Trait Anxiety Inventory (98) (STAI): This questionnaire consists of 40 questions and measures two types of anxiety. State anxiety can be defined as fear or the arousal of the autonomic nervous system induced by a specific situation considered dangerous (e.g. surgery). Trait anxiety

can be defined as feelings of worry or discomfort that one experiences on a daily basis, across typical situations.

Intra-operative monitoring

On arrival in the preoperative holding area, an intravenous line was inserted and an ultrasound guided interscalene block (single shot of 30-40 ml ropivacaine 0.5%) was performed.
Patients were transferred to the operating room were 2 non-invasive near-infrared spectroscopy sensors were bilaterally applied to the patients frontotemporal head before anesthesia was started. With the use of these sensors, cerebral tissue oxygen saturation ($SctO_2$) was measured continuously throughout the surgery using the FORE-SIGHT® system (Cas Medical Systems, Inc. Branford, CT). The FORE-SIGHT® system is developed to measure regional oxygen saturation in the arterial, venous and capillary compartment, by using 4 wavelengths of laser light. Both the surgeon and anesthesiologist were blinded to the measured cerebral oxygen saturation.
Bispectral index (BIS) monitoring was started at the same time. The system processes raw electroencephalographic information and calculates a number between 0 and 100. This number is routinely used to assess the patient's level of consciousness during anesthesia. BIS (Aspect Medical Systems Inc., Norwood, MA) sensors were applied according to the instructions from the producer; BIS and cerebral oximetry sensors were secured and covered to prevent ambient light interference. BIS values were used to guide anesthesia and therefore not blinded for anesthesiologist.
Besides BIS and NIRS monitoring, intraoperative monitoring consisted of electrocardiography, automatic blood pressure assessment using a non-invasive cuff attached to the arm on the non-operative side (supported on a horizontal arm-rest), pulse oximetry and capnography. All data were continuously collected until extubation and downloaded directly to a computer using custom designed software.
A standardized anesthesia protocol was used in all patients. Anesthesia was induced with propofol TCI 8 µg/ml, remifentanil 0.5 µg/kg/min and rocuronium 0.6 mg/kg. Maintenance of anesthesia consisted of propofol TCI 3-4 µg/ml, remifentanil 0.5 µg/kg/min, O_2/air 30/70%. For optimal surgical visualization, controlled arterial hypotension was allowed. A systolic blood pressure of 90 mmHg and a mean blood pressure of 65 mmHg were considered as minimal acceptable blood pressures. Severe hypotension was countered by adjusting the rate of remifentanil infusion or by the administration of phenylephrine or ephedrine. A lower body forced air warming device (Bair Hugger) was used to maintain a normal core temperature. After the airway was secured, head and neck positioning was secured in the lateral decubitus or beach chair (30°-40°) position.

Statistics

All analyzes were conducted by SPSS, version 20.0. Kolgomorov-Smirnov was used to test the equality of the probability distributions. Group differences for demographic variables between volunteers, patients in BCP and patients in LDP were compared using one way analysis of variance (ANOVA), with *post hoc* Bonferonni test. Results of questionnaires were statistically compared using the non-parametric Mann-Whitney U test.
Differences in $SctO_2$, $EtCO_2$, MAP, SAP or BIS-values between the BCP and LDP group were compared using the students' t-test. Two-way ANOVA, with Bonferonni *post hoc* analysis, was used for testing within and between groups of neurocognitive results. A p-value ≤ 0.05 was considered statistically significant.
With a sample size of 40 patients per group, a power of 0.9 and an alpha of 0.05, we calculated that we would have been able to detect a difference of 2 seconds between the LDP and the BCP for the CVST-test. A difference of 2 seconds or more on this test would be considered to be clinically relevant. The CVST is a commonly used and accurate test, and marked as highly relevant for our population by the psychologists, who were involved in this study. We therefore used the results of the CVST-test to perform these post-hoc analyses.

2.3.3 Results

Between July 2012 and April 2014, 97 patients (47 BCP, 50 LDP) were included in the study. Two patients (LDP) were excluded because of refusal of the interscalene block. Fifteen patients (7 BCP, 8 LDP) refused further participation after surgery. These patients showed no significant difference in age (55 ± 11 years; p=0.812), length of anesthesia (97 min ±34; p=0.911), average $SctO_2$ during surgery (68% ±4; p=0.694), lowest $SctO_2$ during surgery (62 ±6%; p=0.512) or pre-operative neurocognitive test results (p >0.05) compared to patients who did not refused postoperative co-operation. Data of 80 patients will be shown; 40 patients who underwent surgery in the BCP and 40 patients in LDP. Twenty-six patients did not show up for the last neurocognitive tests (T3;4-6 weeks after surgery) (13 in BCP, 13 in LDP), which resulted in 54 patients for the last test moment. Forty-one volunteers were enrolled in the study.

There was no significant difference in age (p=0.562), gender (p=0.797) or level of education (p=0.581) between patients and volunteers or between the two patient groups. Neither duration of anesthesia (p=0.096) nor level of consciousness (mean BIS) (p=0.896) was significant different between patients in LDP and BCP (Table 2.5).

Table 2.5: Demographics

	Volunteers	Patients	BCP	LDP	p-value
Number , n	41	80	40	40	-
Age, years (± SD)	55 (± 5)	53 (± 10)	54 (± 9)	53 (± 10)	0.562
Gender, M/F	17/24	33/47	18/22	15/25	0.797
Level of education, years (± SD)	12 (± 4)	11 (± 3)	11 (± 3)	12 (± 3)	0.581
Length of anesthesia, min (± SD)	-	90 (± 30)	96 (± 34)	84 (± 25)	0.096
Length of BCP, min (± SD)	-	-	88 (± 36)	0 (± 0)	< 0.001
Procedure RCR/SAD, n	-	47/33	23/17	24/16	0.820
Pulmonary disease, n (%)	-	2 (3)	0 (0)	2 (5)	0.152
Hypertension, n (%)	-	7 (9)	3 (8)	4 (10)	0.692
Diabetes, n (%)	-	1 (1)	1 (3)	0 (0)	0.314
Rheumatoid arthritis, n (%)	-	1 (1)	1 (3)	1 (3)	1.000

BCP: beach chair position, LDP: lateral decubitus position, M: male, F: female
Values are presented as mean (± standard deviation)
RCR: rotator cuff repair, SAD: sub-acromial decompression

Cerebral tissue oxygen saturation

Patients undergoing surgery in the BCP showed significantly lower averaged $SctO_2$-values throughout surgery (65 ±4%) compared with patients in LDP (72 ±5%) ($p<0.001$). The mean lowest value for cerebral oxygenation was 59% (±5%) in patients in the BCP group compared to a mean lowest value of 68% (±5%) in the LDP group ($p <0.001$). Systolic blood pressure at the moment of lowest $SctO_2$ values was significantly lower in patients in the BCP (81 ±19 mmHg) compared to the LDP (92 ±16 mmHg) group ($p=0.009$). The average systolic blood pressure throughout the surgery was not statistically different in both groups (BCP: 97 ± 11 mmHg; LDP: 94 ±6 mmHg; $p=0.112$). End-tidal carbon dioxide ($EtCO_2$) or peripheral oxygen saturation (SpO_2) at the moment of lowest $SctO_2$ was not significantly different between both groups ($EtCO_2$: BCP:31 ±3 mmHg; LDP: 31 ±3 mmHg; $p=0.430$) (SpO_2: BCP: 98 ±2%; LDP: 98 ±1%; $p=0.175$).
Twenty-five percent of the patients in the BCP showed a desaturation ≤ 55% for a mean of 17 minutes (±21.5 minutes). No desaturation values ≤55% were observed in patients in the LDP, and only two patients showed values ≤60%. Table 2.6 further illustrates perioperative values.

Table 2.6: Perioperative values of cerebral oxygenation, blood pressure, $ETCO_2$, SpO_2, BIS and vasopressor use

	BCP	LDP	p-value
$SctO_2$ awake, % (± SD)	71 (± 5)	70 (± 4)	0.273
$SctO_2$ before position change, % (± SD)	76 (± 4)	76 (± 5)	0.575
Mean $SctO_2$ during surgery, % (± SD)	65 (± 4)	72 (± 5)	**< 0.001**
Mean MAP during surgery, mmHg (± SD)	71 (± 9)	71 (± 5)	0.939
Mean SAP during surgery, mmHg(± SD)	97 (± 11)	94 (± 6)	0.112
Lowest $SctO_2$ during surgery, % (± SD)	59 (± 5)	68 (± 5)	**< 0.001**
MAP at lowest $SctO_2$, mmHg (± SD)	62 (± 17)	65 (± 11)	0.293
SAP at lowest $SctO_2$, mmHg(± SD)	81 (± 19)	92 (± 16)	**0.009**
SpO_2 at lowest SctO2, % (± SD)	98 (± 2)	98 (± 1)	0.175
$EtCO_2$ at lowest SctO2, mmHg (± SD)	31 (± 3)	31 (±3)	0.430
$SctO_2$ ≤ 60%, n (%)	27 (68)	2 (5)	**< 0.001**
$SctO_2$ ≤ 55%, n (%)	10 (25)	0 (0)	**0.001**
Time $SctO_2$ ≤ 60%, min (± SD)	20 (± 30)	9 (± 13)	0.377
Time $SctO_2$ ≤ 55%, min (± SD)	17 (± 21.5)	0 (± 0)	**0.038**
Mean BIS during surgery, (± SD)	33 (± 9)	33 (± 8)	0.896
Total vasopressor dose, Ephedrine, mg (± SD) Phenylephedrine, µg (± SD)	 14 (± 14) 313 (± 309)	 12 (± 4) 150	 0.640 0.670

$SctO_2$: cerebral tissue oxygen saturation, MAP: mean arterial pressure, SAP: systolic arterial pressure, SpO_2: peripheral oxygen saturation, $EtCO_2$: end-tital carbon dioxide, BIS: Bispectral index, BCP: beach chair position, LDP: lateral decubitus position. Values are presented as mean (± standard deviation).

Neurocognitive tests

There was no significant difference in pre-operative questionnaires on pain, anxiety or depression between patients allocated in the BCP or LDP group (Table 2.7). Volunteers scored significantly better on pain (VAS; $p<0.001$) and state anxiety test (STAI state; $p=0.030$) tests compared to patients.

The SRT and stroop color-word tests consist of several subtests. Since results of all subtests are highly correlated (99, 100), SRT and stroop will be presented in its entirety.

Statistical analysis showed no significant differences ($p>0.05$) between the BCP and LDP groups on the neurocognitive tests performed before (T1) or immediately after surgery (T2). Both patient groups (BCP and LDP) scored significantly less on the SRT ($p<0.05$) and symbol digit substitution ($p=0.011$) test compared to volunteers at the first (pre-operatively) test moment (T1). For the other neurocognitive tests (CVST, COWAT, stroop), there was no significant difference between patients and volunteers at T1 ($p>0.05$).
In the group of volunteers, a practice effect was observed when the tests were repeated for a second and a third time (T2 and T3) ($p<0.01$) (Figures 2.3, 2.4, 2.5 and 2.7, purple line). This practice effect was not observed for the memory task ($p=0.324$)(Figure 2.6), where a parallel version was used for the second test (T2). Patients in BCP and LDP showed no improvement (no practice effect) or performed even less when tests were repeated for the second time, 90 minutes after the end of surgery (T2). When compared to volunteers on the first postoperative test moment (T2), both BCP and LDP patient groups performed significantly less on SRT ($p<0.05$), symbol digit substitution ($p=0.001$) and COWAT ($p<0.05$) tests. CVST and stroop showed no significant difference on T2 between patients in BCP or LDP compared to volunteers. On their postoperative stroop tests (T2), patients in the BCP group showed significantly more errors ($p=0.045$) compared to volunteers, while patients in the LDP did not ($p=1.000$). Both patient groups showed improvement on their second postoperative test, 4-6 weeks after surgery (for symbol digit substitution, stroop and SRT).
There were no significant differences in test results on T1 and T2 between patients with $SctO_2$ values ≤60% or ≤55% and patients with $SctO_2$ values >60% or>55% ($p>0.05$).

Table 2.7: Results of pre-operative questionnaires in patients and volunteers

Questionnaire	Volunteers	p-value	Patients		
			BCP	p-value	LDP
VAS	1 (0-1)	**< 0.001**	5 (3-7)		
			5 (3-7)	0.976	5 (3-8)
FAS	18 (16-21)	0.633	19 (15-22)		
			19 (14-22)	0.558	19 (15-23)
STAI state	32 (25-39)	**0.030**	36 (30-46)		
			35 (28-47)	0.552	37 (32-46)
STAI trait	37 (30-42)	0.494	38 (30-44)		
			36 (29-43)	0.088	39 (33-46)
HADS anxiety	5 (3-7)	0.338	6 (4-8)		
			5 (3-8)	0.509	6 (4-8)
HADS depression	2 (1-4)	0.223	3 (1-5)		
			3 (1-5)	0.615	3 (1-6)

VAS: Visual Analogue Scale, FAS: Fatigue Assessment Scale, STAI: State-Trait Anxiety Inventory, HADS: Hospital Anxiety and Depression Scale, BCP: beach chair position, LDP: lateral decubitus position
Results are presented ad median (IQR)

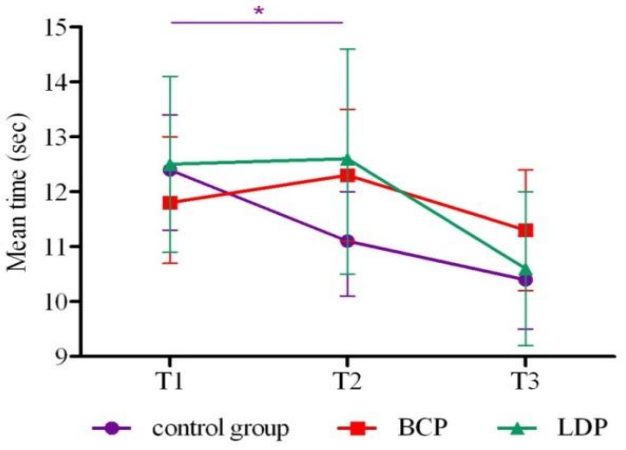

Figure 2.3: Computerized Visual Searching Task (CVST). Results show speed of responses, which should be as short as possible. Control group (purple line) performed better when the test was repeated (T2, *). Patients (red line: BCP, green line: LDP) showed no improvement when tested at T2. There was no significant difference between LDP and BCP at any test moment (p = 1.000). There was no significant difference between patients and volunteers at any test moment. Results are presented as mean with 95% CI. * p<0.05
T1: preoperative test, T2: 1.5h postoperative test, T3: 4-6 weeks postoperative test
BCP: beach chair position, LDP: lateral decubitus position

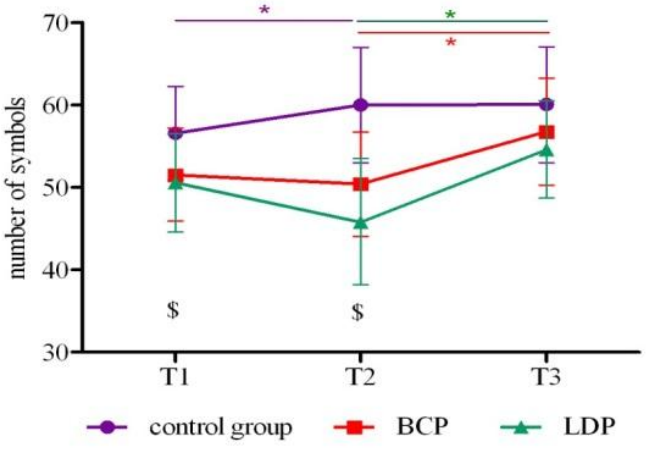

Figure 2.4: Symbol digit substitution test. This test measures memory and speed of processing. Control group (purple line) performed better when the test was repeated (T2,*). Patients (red line: BCP, green line: LDP) showed no improvement when tested at T2. There was a significant difference between patients and the control group at T1 (p = 0.011, $). There was no significant difference between LDP and BCP at any test moment (p = 1.000). Patients performed significantly less at T2 compared with the control group (p = 0.001, $). Results are presented as mean with 95% CI.*, $ p<0.05
T1: preoperative test, T2: 1.5h postoperative test, T3: 4-6 weeks postoperative test
BCP: beach chair position, LDP: lateral decubitus position

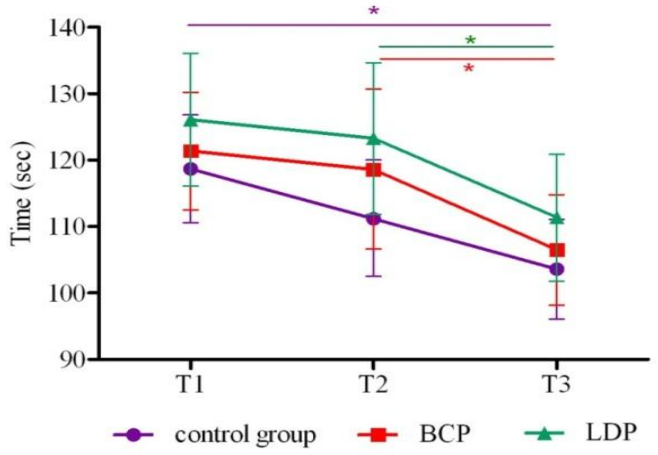

Figure 2.5: Stroop color-word test IV, a very sensitive test to even subtle cognitive impairment. The test measures selective attention, cognitive flexibility and is an evaluation of executive function. Control group (purple line) performed better when the test was repeated (T2, T3, *). Patients (red line: BCP, green line: LDP) showed no improvement when tested at T2. There was no significant difference between LDP and BCP at any test moment (p > 0.05). There was no significant difference between patients and volunteers at any test moment. Results are presented as mean with 95% CI. * p<0.05
T1: preoperative test, T2: 1.5h postoperative test, T3: 4-6 weeks postoperative test
BCP: beach chair position, LDP: lateral decubitus position

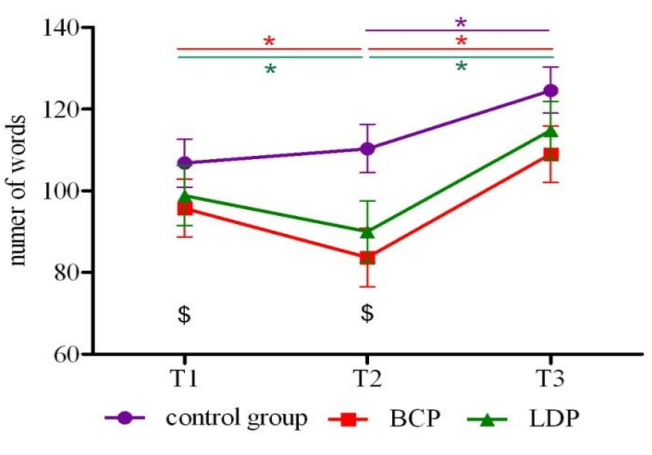

Figure 2.6: Buschke Selective Reminding Test (SRT) Total recall. A test designed to measure verbal learning and memory. There was a significant difference between patients and the control group at T1 ($,p < 0.05). Control group (purple line) did not performed significantly better when the test was repeated (T2). Patients (red line: BCP, green line: LDP) scored significant less when tested at T2 (p < 0.001, *, *). There was no significant difference between LDP and BCP at any test moment (p > 0.05). Patients performed significantly less at T2 compared with the control group (p < 0.001, $). Results are presented as mean with 95% CI. *, $ p < 0.05
T1: preoperative test, T2: 1.5h postoperative test, T3: 4-6 weeks postoperative test
BCP: beach chair position, LDP: lateral decubitus position

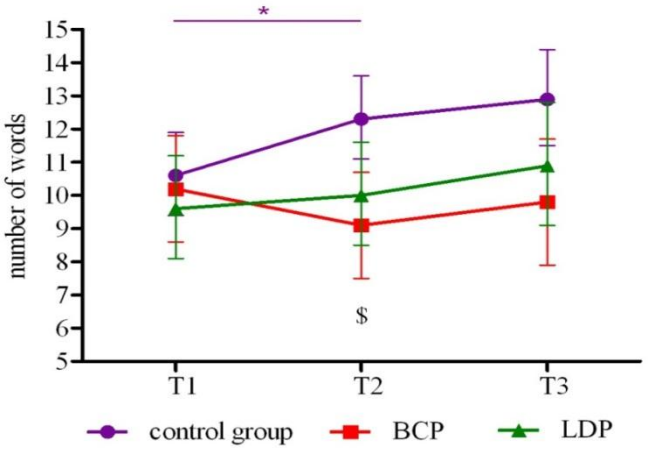

Figure 2.7: Controlled Oral Word Association Test (COWAT letter 'n'). Results give information on verbal fluency and semantic memory. The test measures selective attention, cognitive flexibility and is an evaluation of executive function. Control group (purple line) performed better when the test was repeated (T2, *). Patients (red line: BCP, green line: LDP) showed no improvement when tested at T2. There was no significant difference between LDP and BCP at any test moment ($p > 0.05$). Patients performed significantly less at T2 compared with the control group ($p < 0.05$,$).Results are presented as mean with 95% CI.*,$ $p < 0.05$
T1: preoperative test, T2: 1.5h postoperative test, T3: 4-6 weeks postoperative test
BCP: beach chair position, LDP: lateral decubitus position

2.3.4 Discussion

In the present study, cerebral oxygenation was significantly lower in patients who underwent arthroscopic shoulder surgery in the BCP compared to the LDP. Twenty-five percent of the patients in the BCP showed a desaturation ≤55%. In the past years, several authors reported the use of NIRS to assess the adequacy of cerebral perfusion during shoulder surgery. Murphy *et al*. was the first to compare cerebral oxygenation in the BCP and LDP in a group of 124 patients (46). Cerebral oxygen saturation was significantly lower during surgery and cerebral desaturation events occurred significantly more (80% versus 0%) in patients in the BCP compared to the LDP. This correlation between cerebral desaturation and the sitting position was thereafter confirmed by other investigators (47, 56-58). Most studies however incorporated a predefined protocol to treat cerebral desaturation events as they occurred, making it impossible to investigate the magnitude of these cerebral desaturation events and their possible post-operative consequences (46, 56, 58). In accordance to the study by Moerman *et al.*(47), in our study only standard monitoring was used to guide anesthesia management, but the anesthesiologist was blinded to $SctO_2$ values.

Compared to the supine position, the BCP has been shown to induce hemodynamic changes (e.g. decrease in blood pressure) and a decrease in cerebral blood flow (10). We observed a decrease in systolic arterial pressure (SAP) when patients were changed to the sitting position. At the moment of lowest $SctO_2$, SAP was significantly lower ($p=0.009$) in patients in the BCP compared to the LDP. An increase in systemic vascular resistance, a very effective compensatory mechanism to maintain adequate cerebral perfusion in conscious subjects, is attenuated or absent during anesthesia (9, 59). During surgery, low blood pressure is usually treated with fluid administration or medication (phenylephrine, ephedrine)(46, 101). In our study, a MAP >65 mmHg and SAP >90 mmHg was targeted and successfully achieved during surgery in each patient (Table 2.6). However, we measured blood pressure at the level of the heart (upper arm), which can be an overestimation of blood pressure in the brain (57). In our patients, a distance of about 22 cm between the blood pressure cuff and the brain (external auditory meatus) was measured. When we apply the proposed correction of 0.77 mmHg for each cm difference in height (102, 103), the arterial pressure at the level of the brain would be ±17 mmHg lower than at the level of the heart.
Besides the sitting position and hypotension, ventilator strategies such as hyperventilation, can influence cerebral blood flow and thus cerebral oxygenation. Recently, Murphy *et al*. observed a lower incidence of desaturation events and higher cerebral oxygenation values in a patient group with $EtCO_2$

between 40 and 42 mmHg compared to the group with $EtCO_2$ between 30 and 32 mmHg (54). We report $EtCO_2$-values of 31 mmHg (±3 mmHg) and 31 mmHg (±3 mmHg) which fits into the standard practice-group of Murphy *et al*., with lower $SctO_2$-values. However, $EtCO_2$ was not significantly different between both patient groups (p=0.430) in our study (Table 2.6).

Regardless of the physiological cause of desaturation, the main goal of our study was to evaluate the consequences of cerebral desaturation on neurocognitive outcome.
Mood changes, pain and depression have a negative impact on motivation and ability to complete neuropsychological testing (104). We therefore assessed pain, depression and anxiety by giving questionnaires to patients before surgery and to volunteers at the first test moment. There was no significant difference between both patient groups in any of the given questionnaires. As could be expected, patients scored significantly higher on the pain and STAI state (anxiety for surgery) test than volunteers (Table 2.7). This could be a reason of lower performance of patients on the SRT (memory) and symbol digit substitution test before surgery compared to volunteers (Figure 2.4 and 2.6).

Volunteers showed a significant improvement when conducting the test for the second time (T2). This practice effect is a well-known phenomenon and involves implicit learning of the person who is tested (88). The only exception in our study was the SRT-test for memory, were we used a parallel version for the second test (T2)(Figure 2.6). Our patient population showed no practice effect at T2. Instead, patients in both groups performed less on some of the tests (SRT) than they did before surgery (Figure 2.6). This created a significant difference at T2 between volunteers and patients on tests for memory (SRT, COWAT, symbol digit substitution), verbal fluency (COWAT) and speed of processing (symbol digit substitution). At T3, 4-6 weeks after surgery, no significant differences between patients in BCP or LDP and volunteers were observed.
The only published study that has similarities with our study design was performed by Salazar *et al.*(56). They monitored cerebral tissue oxygenation (INVOS 5100) intra-operatively in 50 patients undergoing arthroscopic in the BCP but included no type of control group. As in our study, neuropsychological tests were conducted on the day of surgery, immediately after the surgery and during routine follow-up (3 day post-surgery in Salazars *et al*. paper). They used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which also includes tests for, among others, memory and attention. In this study, there was no difference in pre-operative versus post-operative (3 day post-surgery) RBANS and therefore no correlation with intraoperative cerebral desaturation events. Unfortunately, data from the RBANS obtained immediately after surgery were excluded due to lingering effects of anesthesia and postoperative narcotic pain medication. The target organ for anesthetics is the brain. It has been assumed that the effect of anesthetics do not outlast their pharmacological action. However, patients who are still under the influence of

anesthetics and analgesics may have impaired cognitive performance, which was probably the case in Salazar's study. In order to obtain reliable test results in the immediate post-operative period, an interscalene block was performed before surgery in our study. Therefore, there was no need for postoperative narcotic pain medication. Furthermore, according to the protocol, only anesthetic agents (propofol and remifentanil) with a short half-time were used. We therefore believe that our neurocognitive results immediately after surgery are reliable. Clinical trials have neither proven nor excluded a direct causal link between anesthetics and cognitive impairment (105, 106). Although our patients seemed to be very well awake and co-operative after surgery, lingering effects of anesthetics (despite the use of short-acting products) which could have caused less motivation and tiredness at T2 cannot be excluded. This could explain the lack of implicit learning at T2. At T3, no residual effects of anesthesia should be present, and patients in both groups performed not significantly different than volunteers at 4-6 weeks after surgery.

Cerebral saturation values in Salazars' study were not blinded for anesthesiologist with consequently rapid intervention to reverse desaturation events (56). As this could bias the purpose of the study, the only way to correctly assess the effect of cerebral desaturation on cognitive dysfunction, is by blinding the anesthesiologist for the $SctO_2$ values.

Although our patients showed no practice effect after surgery, we could not correlate cerebral desaturation with cognitive decline, since both the BCP group (with significant perioperative desaturation) and the LDP group (with no such desaturations) had almost similar results on their post-op neurocognitive tests. Besides the lingering effect of anesthesia, the used technology could also contribute to this lack in correlation. NIRS measurements are limited to the prefrontal cortex. We were therefore not able measure oxygenation in other parts of the brain. However, the prefrontal cortex is important for, among others, executive functioning, one of the targets in our neurocognitive tests. Although NIRS correlated with clinical and EEG signs of cerebral ischemia (87), there is no clear validation study on cerebral oximetry and cerebral blood flow. However, in cardiac, thoracic and abdominal surgery patients, early postoperative cognitive decline and complications were related to intraoperative decrease of cerebral oxygenation values (2-5, 71, 86, 107). Tang *et al.* showed an increasing risk for deterioration in mini-mental state results as exposure time below cerebral thresholds (65%, 60%, 55%) increased (3). Fischer *et al*. noticed an extended hospital stay when aortic arch surgical patients spent more than 30 minutes under 60% (2). A piglet model on cerebral hypoxia-ischemia showed that only low $SctO_2$ for more than two hours resulted neurological injury (74). These results suggest that there is a time-threshold before ischemia results in brain injury. In our study, time below 60% and 55% was not related with outcome. However, time spent below 60% was shorter in our study than in the patients who underwent cardiac or thoracic surgery: mean 20 min ≤60% in our study versus median 45 min in the study of Tang *et al.*(3) and more than 30 min in the study of Fischer *et al.*(2). Furthermore, the patients in their studies were

older, had more co-morbidities and underwent longer and major surgery compared to our study. Moreover, cognitive decline might be mediated by the body's inflammatory response to surgery (108, 109). The inflammatory response and subsequent cognitive decline, after major (cardiac) surgery is probable more extensive than with short-lasting shoulder surgery. Our patients, both in BCP as well as in LDP, underwent sub-acromial decompression or rotator cuff repair procedures.
Besides cerebral oxygenation, an association between low intraoperative BIS-values and postoperative mortality was reported in several studies (110, 111). Recently, Radtke *et al.* showed a correlation between BIS <20 and postoperative delirium, but not cognitive dysfunction(112). However, in most BIS studies, low blood pressure and co-morbidities account as possible confounders (110, 113). In our study, BIS was used to guide anesthesia and therefore, no significant differences in mean BIS values during surgery were observed in patients in BCP compared to LDP (Table 2.6).
Patients with impaired cognitive performance before surgery or increasing age may be at particular risk for intraoperative cerebral insults (114, 115). Furthermore, none of our patients had vascular –or other comorbidities that made them at risk for surgery. These patients might benefit the most from neuromonitoring protocols during surgery. More research is needed concerning depth and duration of low cerebral oxygenation and the BCP in these 'at-risk' patients.

Remarks and limitations

We chose for a rather large group of neurocognitive tests. All of the tests used are able to identify cognitive decline and have been proven to be sensitive enough to detect mild cognitive impairment (88). Tests were able to distinguish between volunteers and patients. For $SctO_2$, we used an absolute value as threshold value. There is some inconsistency on the use of absolute or relative changes during surgery, owing to different monitoring technologies and lack of consensus in moment of capturing the baseline value. In accordance with some other studies (2, 3, 46), we chose 55% and 60% as threshold values.
Several limitations should be considered. First, the study was conducted in a single center with a moderate sample size. Second, although most NIRS monitors are provided with an algorithm to remove the signal of extracerebral tissues from the actual value, this still might contribute significantly to the signal(35). Third, values for rSO_2 are calculated based on the assumption of a fixed arterial (25-30%)/venous (75-70%) ratio (31). This ratio could potentially alter when position is changed to the BCP. Any difference in regional tissue oxygenation could therefore be the consequences of a real change in oxygen saturation levels or be the results of a change in the cerebral arterial/venous ratio.

2.3.5 Conclusion

Significant reductions in cerebral oxygen saturation values are observed when patients undergo arthroscopic surgery in the beach chair position under general anesthesia. The practice effect in neurocognitive test results, demonstrated by volunteers, was not observed in patients after surgery (T2). Perioperative cerebral oxygen desaturation in BCP was not correlated with cognitive decline (at T2 or T3) in our study, as compared to patients undergoing surgery in LDP. Although we did not observed an association between cerebral desaturation and neurocognitive outcome in our patient population, more research should be performed in high-risk patients.

CHAPTER 3

Cerebral oxygen saturation during hypothermia

3.1 Cardiac arrest and therapeutic hypothermia

Based on

Therapeutic hypothermia after cardiac arrest; yes, but who, when and how?

review

***Ingrid Meex**, Jo Dens, Cornelia Genbrugge, Frank Jans, Cathy De Deyne*
International Journal of Intensive Care 2013;20(3):93-98

3.1.1 Cardiac arrest

Cardiac arrest (CA) or sudden cardiac death is the abrupt cessation of normal circulation of the blood due to failure of the heart to contract effectively. Due to inadequate cerebral perfusion, the patient will lose consciousness and stop breathing. The causes of CA are numerous (trauma, drowning, asphyxia, …) but the most common in adults is acute coronary syndrome. The arrest is usually associated with lethal arrhythmia (ventricular fibrillation) triggered by an infarcted myocardium or by an primary electrical disturbance (116).

Approximately 375 000 people suffer from a CA in Europe each year (117). Despite considerable efforts to improve the management of cardiopulmonary resuscitation (CPR), survival rate of out-of-hospital CA (OHCA) patients remains low. According to the European Registry of Cardiac arrests (EuReCa), mortality rates differ between and within regions and countries (118). In Belgium, approximately 33% of CA-patients survives the initial arrest and is admitted to the hospital (118). However, more than 55% of the admitted post-CA patients do not survive to hospital discharge (119, 120). This high in-hospital mortality rate is attributed to the post-CA syndrome; including brain injury, myocardial dysfunction, systemic ischemia/reperfusion response and the persistent precipitating pathology (121). With nearly 68% of deaths in admitted post-CA patients, excessive neurological damage is the major cause of death in post-CA patients (119). Fortunately, due to intensified post-resuscitation treatment, survival rates increased over the past years (120, 122). It is assumed that the addition of therapeutic hypothermia (TH) to the post-CA treatment protocol, attributes to the increase in survival rates and good neurological outcome (120).

3.1.2 Therapeutic hypothermia

Abstract

Therapeutic hypothermia (TH) has been shown to improve survival and neurological outcome after CA due to ventricular fibrillation. Although TH is also used following CA after other forms of initial rhythm, contradictory results are published on its benefit in these patients. Research has elucidated two windows of opportunity for the use of TH. Early intra-ischemic (pre-hospital) induction of TH has shown to be feasible, without major adverse events and may provide a rapid decrease in core temperature. However, there is no conclusive evidence on the role of pre-hospital cooling in improving outcome. Currently, TH is mostly induced in the post-reperfusion window, when patients are admitted to the hospital. Various methods are available to induce and maintain hypothermia. Despite the widespread use of TH in post-CA patients, several issues on optimal time to start cooling, target temperature, length of cooling and rate of rewarming is in need of more research and larger randomized controlled studies.

Introduction

The use of hypothermia after cardiac arrest was already reported in 1958 (123, 124). Although a beneficial neurological effect was observed in a series of patients, there were no further investigations of hypothermia in the post-cardiac arrest phase until 1997 (125). In 2002, two randomized clinical trials on the use of TH were published. Both The Hypothermia After Cardiac Arrest (HACA) study group as well as Bernard *et al.* showed a significant increase in favourable neurological outcome in post-CA patients treated with TH (126, 127). Although the International Liaison Committee on Resuscitation (ILCOR) recommends the use of TH in post-cardiac arrest patients since publication of these studies (128), several issues remain debatable.

Who should be treated with hypothermia?

Bernard *et al.* and the HACA trial showed a neurological benefit for TH-treated post-CA patients, but only included ventricular fibrillation/ventricular tachycardia (VF/VT) as initial rhythm (126, 127). They showed that significantly more patients in the TH-group survived to hospital discharge with a good neurological outcome (CPC 1-2) and lower mortality rates up to 6 months after CA. Several studies confirmed these results in patients with a shockable cardiac rhythm after CA (129-132). To date, the benefit of hypothermia for patients with non-shockable rhythms is still under debate. Only two randomized trials described the use of TH in patients resuscitated from non-VF/VT CA (133, 134). But neither study was designed to assess the benefit of TH. In 2007, Arrich *et al.* observed a significant mortality benefit in patients with pulseless electrical activity (PEA) or asystole as initial cardiac rhythm treated with TH. However, there was no effect on neurological outcome (129). Testori *et al.* confirmed the beneficial effect of TH on mortality in non-shockable patients, but also observed an improvement in neurological outcome in these patients (135). In contrast, several studies reported no significant improvement after TH, nor in neurological outcome neither in survival in patients with non-shockable cardiac rhythms compared to shockable rhythms (130, 131, 136). Important to note, time to return of spontaneous circulation (ROSC) was significantly longer in patients with asystole/PEA than in patients with VF/VT (130, 136), and could therefore explain lower survival rates. In a large cohort of OHCA patients with non-shockable rhythms, Dumas *et al.* showed a trend towards a worse prognosis in TH-treated patients (132). Recently, Lundbye *et al.* retrospectively studied the effect of hypothermia in 100 patients with CA due to asystole or PEA. Twenty-nine per cent (15 of 52) of patients of the TH group had a favourable neurological outcome at hospital discharge compared to 10% (6 of 48) of the patients in the normothermia group (137). After adjusting for age, location of arrest, witnessed arrest and time to ROSC, both mortality as well as neurological

outcome at hospital discharge was improved after TH. They concluded that for every 6 patients with CA due to a non-shockable rhythm that undergo TH, one favourable outcome is gained. This result is comparable with patients with CA due to VF/VT (127).

In children, the mechanism of cardiac arrest differs from adults, with respiratory causes outnumbering cardiac causes. Furthermore, asphyxia is associated with worse outcome compared to arrhythmia-induced cardiac arrest. In 2005, two randomized controlled trials of therapeutic cooling after perinatal asphyxia were published. Both studies cooled neonates with hypoxic-ischemic encephalopathy for 72 hours within 6 hours after birth (138, 139). Gluckman *et al.* observed no beneficial effect of TH in infants with the most severe aEEG abnormalities. In infants with less severe aEEG changes, death or severe disability was reduced from 66% in controls to 48% in TH-treated patients.(138) TH has also been shown to reduce the risk of death and increase the rate of survival free of disability at 18 to 24 months of age in patients subjected to whole-body cooling for neonatal encephalopathy (139). At follow-up, infants of 6 to 7 years of age treated with TH as newborns, confirmed the beneficial effect of TH with reduced mortality and no increase in rates of low IQ scores, indicating that there was no increase in survival with disability (140). Most recently, Lin *et al.* reported on the use of TH for 72h after CA in children from 2 months to 18 years of age. They reported a survival rate that was significantly higher in the TH group compared to the normothermia group. Neurological outcome was better in the TH group, but did not reach statistical significance (141). Currently, the American Heart Association and the ILCOR recommend that hypothermia should be considered after neonatal or paediatric resuscitation (142). Due to the fact that there is limited data on the use of TH in children (between 2 months and 18 years of age), this recommendation was extrapolated from adult data.

When to start hypothermia?

Most of the deleterious reactions suppressed by TH are either initiated at or exacerbated rapidly after ROSC following successful resuscitation. In experimental studies, reduced brain damage and improved cerebral function was observed when TH was started during or immediately after CA, whereas delaying reduced the beneficial effects (143).
Bernard *et al.* started cooling in the field by removing patient's clothing and applying cold packs and achieved a target temperature of 33.5°C within 120 min after ROSC (126). In the HACA trial, cooling was started at hospital admission (105 min after ROSC) and the target temperature was reached within 8 hours after ROSC (127). Despite the difference in time to start cooling, both studies showed a significant improvement in neurological outcome.

Although clinical studies showing that a delay in cooling results in less benefit (144, 145) are scarce, TH is recommended to be induced as soon as possible (ILCOR guidelines)(128).
Several studies evaluated the safety, feasibility and efficacy of pre-hospital induction of hypothermia immediately after ROSC (146). They showed a significant lower body temperature at hospital admission compared to patients in which TH was started at hospital admission, without increased complications. In a recent randomized control trial with the use of cold fluids to induce TH in patients with VF as initial cardiac rhythm, survival was not improved at hospital discharge when compared with patients in whom TH was initiated in the hospital (147). The first randomized controlled trial on intra-arrest cooling used transnasal evaporative cooling in OHCA patients (148). Both groups (intra-arrest cooling vs. standard care) were (further) cooled after hospital arrival. Mean tympanic temperature at hospital arrival was significantly lower in the intra-arrest cooling group (34.2°C vs 35.5°C in standard care patients). There were no significant differences between both groups concerning the proportion of patients who achieved ROSC, the overall survival or neurological outcome (44% in intra-arrest cooled patients vs. 31% in the control group). However, in a subgroup of patients in whom CPR was started within 10 minutes, neurological intact survival to discharge was significantly higher in the intra-arrest cooled population.
Despite its potential benefit, there are no specific guidelines for the use of hypothermia in the pre-hospital setting. Moreover, there is no conclusive evidence on the role of pre-hospital cooling in improving outcome. Therefore, most post-CA patients are currently cooled after arrival at the hospital.

How to cool?

Which method should be used?

Several cooling methods, from simple, non-invasive and non-expensive to sophisticated invasive and expensive methods, are currently available for clinical use.
Most studies have used conventional surface-based cooling techniques such as ice packs or cool air or water blankets. Ice packs can be easily applied, are inexpensive and can be used in the pre-hospital setting. However, like cooling blankets, they provide a rather slow cooling rate and have been demonstrated to unintentionally overcool patients below the target temperature (149). Infusion of cold intravenous fluids has been shown to be feasible in patients after CA, can be used in the pre-hospital setting and was not associated with increased adverse events such as pulmonary oedema, haemodynamic instability or rate of rearrest (150, 151). With this technique, a mean reduction of core temperature of 1.5°C can be achieved at hospital admission. Although it is difficult to

maintain a target temperature with intravenous cooling, Kliegel *et al.* showed that it could be the first step in the induced hypothermia protocol (151).
For in-hospital cooling, most studies have compared modern cooling devices to no or basic cooling (cold air blankets or ice packs) and observed a faster cooling and less unintentional overcooling with modern cooling devices (152-154). TØmte *et al.* compared two frequently used modern whole-body cooling devices: the endovascular core cooling device Coolgard™ and the surface cooling device ArcticSun® [155]. Both cooling technologies operate with a continuous temperature feedback mechanism and have shown to be feasible in post-CA patients (156). Except for a higher rate of hyperglycemia in surface cooled patients and a higher incidence of low serum magnesium in core cooled patients, TØmte *et al.* observed no significant differences in cooling rate or side effects between both groups. Furthermore, there was no significant difference in survival with good neurological outcome between endovascular cooled and surface cooled patients (155).
An alternative to whole-body TH, is to induce targeted brain hypothermia. Rapid onset of intra-arrest cooling can be achieved with the intranasal cooling device RhinoChill®. A liquid coolant-oxygen mixture is sprayed in to the nasal cavity and rapidly evaporated, which results in a decrease in tympanic temperature of 1.3°C from ROSC to hospital arrival, 26 minutes later. The system is safe, portable, can be rapidly initiated and therefore suitable to use in the pre-hospital setting (148). However, long term use has not been studied.
Another way to induce local cooling are cranial cooling cap devices, which can be placed around the neck and head. This technology is feasible, effective and inexpensive to induce TH in adults, but may give the best results for maintenance of TH in children (133, 138). Figure 3.1 illustrates the Course of therapeutic hypothermia after out-of-hospital cardiac arrest with the use of different cooling systems.

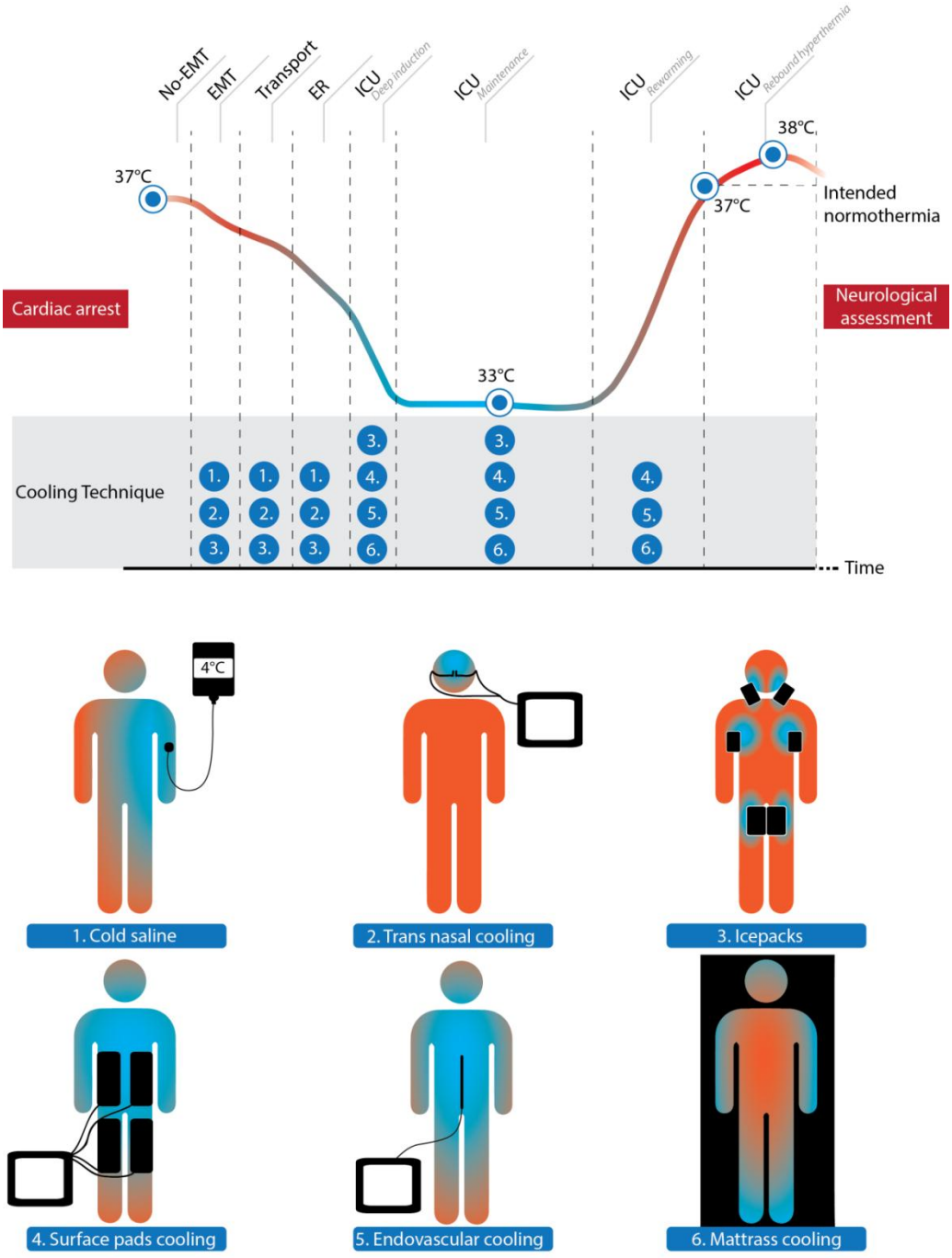

Figure 3.1: Course of therapeutic hypothermia after out-of-hospital cardiac arrest with the use of different cooling systems.
EMT: emergency medical team ER: emergency room ICU: intensive care unit

What about target temperature and length of cooling?

The recommended target temperature is 32°C to 34°C.(128) However, it is unknown which target temperature is the most efficient. Experimental models suggest that for every 1°C reduction in body core temperature, the cerebral metabolic rate decreases by 6%. Therefore, lower temperature rates could provide more protection. Kim *et al.* prospectively evaluated outcome and adverse events of three target temperatures (32°C, 33°C and 34°C) in post-CA patients (157). They observed no significant difference in mortality or neurological outcome between these target temperatures. However, the risk of hypotension was increased more than 6 times at a target temperature of 32°C compared with 33°C and 34°C. Lopez-de-Sa *et al.* assigned 36 patients to a target temperature of 32°C or 34°C (158). 11% of patients in the 34°C group were alive free from severe dependence at six months compared with 44% in the 32°C group. In patients of whom the initial rhythm was ventricular fibrillation, the survival rate at 6 months was 62% (32°C group) compared with 15% (34°C group). There was a trend of higher incidence of bradycardia in patients assigned to 32°C, but a lower incidence of clinical seizures than those assigned to 34°C. There is an ongoing trial comparing a target temperature of 33°C versus 36°C. However, this trial is designed to unravel the most important mechanism of protection: avoidance of hyperthermia or hypothermia per se (159). Until more data are available, consensus supports a target temperature of 33°C.

Not only the ideal target temperature is an issue of discussion, also the length of hypothermia is still under debate. Guidelines recommend inducing hypothermia for 12 to 24 hours (128). Shinozaki *et al.* showed that a core temperature of 33°C for at least 18 hours independently correlates with favorable neurological outcome. They concluded that differences in duration of well controlled body temperature could influence neurological outcome in post–CA patients (160). Current consensus supports duration of 24 hours of TH.

Rewarming

Failure to rewarm spontaneously after TH is often interpreted as a sign of extensive brain damage, but studies on this issue are inconclusive. Bouwes *et al.* investigated if active rewarming or the rate of rewarming after TH in post-CA patients had an influence on outcome (161). Active rewarming was started when patients did not reach a normal body temperature after 12h of passive rewarming which was needed in 38% of the patients. After adjustment for age and initial rhythm, there was no correlation between the need for active rewarming and outcome. Rewarming rate was calculated and divided in a high (≥ 0.5°C/h) and normal rate (< 0.5°C/h) group. A poor outcome was observed in 71% of patients with a high warming rate compared to 52% with a normal warming rate, but was not statistically significant. In contrast, in the study of

Benz-Woerner *et al.* on temperature regulation in post-CA patients treated with TH, a longer time of passive rewarming was associated with in-hospital mortality (162). They concluded that patients with more severe global ischemia-reperfusion injury have impaired thermoregulation, which could be an important physiologic determinant in CA prognosis.
Clinical randomized studies about the optimal rewarming rate after TH in post CA patients are lacking, but studies about the effects of rewarming after cardiac surgery suggest a negative impact of fast rewarming on neurological recovery (163). The current recommendation is to rewarm the patients after TH at a rate of 0.25-0.5°C/h.

What about postcooling fever?

Before the TH era, hyperthermia after cardiac arrest was associated with an unfavourable neurological outcome (164, 165). With the use of TH, one study reported 74% of patients who experienced rebound hyperthermia (temperature ≥ 38.5°C) after rewarming (166). A retrospective study by Winters *et al*. observed an association between rebound hyperthermia (temperature ≥ 38.5°C) and increased neurological morbidity in post-CA patients treated with TH (167). In a retrospective multicentre study, post-rewarming hyperthermia (temperature > 38°C) was observed in 41% of patients who survived at least 24 hours after TH discontinuation. There were no significant differences between patients with any pyrexia and no pyrexia with regard to survival to hospital discharge or good neurologic outcome. However, among patients who experienced pyrexia, a higher maximum temperature was associated with a lower proportion of CPC 1-2 survivors (168). In a recent report of Gebhardt *et al*., fever after rewarming was not associated with survival (165). Nevertheless, in some TH protocols, a 12 to 24 hour period of active normothermia is included. However, the contradictory results show that there is no firm evidence for the benefit of such controlled normothermia after rewarming post-CA patients.

Conclusion

Therapeutic hypothermia after CA is an effective tool to protect the brain from further damage initiated by the initial arrest and reperfusion. Although the benefit of early cooling has been demonstrated in experimental models, translation to critical care is not straightforward and needs to be further defined. The use of TH in the emergency and intensive care department has become increasingly implemented in the standard post-CA protocol. However, at this moment there are still more questions than answers concerning the optimal time to start cooling, the optimal target temperature and length of cooling. And what about rebound hyperthermia: is it necessary to implement a post rewarming normothermic phase to increase full neurological recovery? Considerable effort is needed to optimize and standardize the hypothermia protocol.

3.2 Cerebral tissue oxygen saturation during therapeutic hypothermia

Cerebral tissue oxygen saturation during therapeutic hypothermia in post-cardiac arrest patients

Original paper

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3.2.1 Abstract

This observational study was performed to assess the cerebral tissue oxygen saturation during and after therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest.
We performed a prospective observational study on the cerebral tissue oxygen saturation ($SctO_2$) in post-cardiac arrest patients treated with therapeutic hypothermia (TH) between March 2011 and April 2012. $SctO_2$ (measured by near-infrared spectroscopy) was non-invasively and continuously measured in 28 post-cardiac arrest patients during hypothermia and active rewarming.
At the start of mechanically induced TH, $SctO_2$ was 68% (65-72%) and PaCO2 was 47 mmHg (37 – 51 mmHg). $SctO_2$ and $PaCO_2$ significantly decreased to 59% (57-64%; p = 0.006) and 37 mmHg (34 – 45 mmHg; p = 0.002) respectively within the first three hours of mechanically induced TH. Cerebral tissue oxygen saturation was significantly lower in non-survivors (n = 10) compared with survivors (n = 18) at three hours after induction of hypothermia (p = 0.02) while the decrease in $PaCO_2$ was similar in both groups. During TH maintenance, $SctO_2$ gradually returned to baseline values (69% (63-72%)) at 24 hours, with no differences between survivors and non-survivors (p = 0.65). Carbon dioxide remained within the range of mild hypocapnia (32-38 mmHg) throughout the hypothermic period. During rewarming, $SctO_2$ further increased to 71% (67-78%).

Induction of TH in comatose post-CA patients changes the balance between oxygen delivery and supply. The decrease in SctO2 was less pronounced in patients surviving to hospital discharge.

3.2.2 Introduction

Approximately 375 000 people suffer from a sudden cardiac arrest (CA) in Europe each year (117). Despite improved management of cardiopulmonary resuscitation, survival rate of out-of-hospital cardiac arrest (OHCA) patients remains low. If spontaneous circulation is restored, the major cause of death in survivors of CA is brain damage (119). Additionally, a minority of patients who survive to hospital discharge, recover without any residual neurological damage (169, 170). Due to the brain's limited tolerance of ischaemia, one can assume that the severity of brain damage is influenced by the length of ischemia. Moreover, return of spontaneous circulation (ROSC) and reperfusion is followed by a post-resuscitation syndrome, which could lead to secondary neurological damage (121). Currently, mild hypothermia is the only treatment that has shown the ability to improve both survival and neurological outcome in patients after CA (126, 171).

Several factors can potentially compromise cerebral oxygen delivery and induce secondary cerebral injury in the hours to days after CA (e.g. hypotension, hypoxemia and impaired autoregulation). Early detection and treatment of cerebral hypoxia/ischemia in this critical phase could contribute to a better neuroprotective approach. However, currently used brain monitoring techniques are mainly focused on the prediction of prognosis of neurological outcome in de post-CA patient rather than on therapeutic management.

Near-infrared spectroscopy (NIRS) offers the potential for non-invasive cerebral oxygen saturation monitoring and has been shown to correlate with jugular bulb oxygenation (172, 173) as a measure of adequacy of cerebral perfusion (174-176). By measuring the levels of oxygenated and deoxygenated hemoglobin in arterial, venous and capillary blood, regional cerebral oxygenation ($SctO_2$) reflects the balance between cerebral metabolic supply and oxygen demand (32). Low intra-operative $SctO_2$ values have shown to be correlated with postoperative neurological complications and increased length of hospital stay after cardiac surgery (4, 71, 86). Treatment of intra-operative cerebral oxygen desaturation significantly reduced the incidence of major organ morbidity and mortality in coronary artery bypass patients (4). Furthermore, cerebral oxygen saturation was correlated with cerebral perfusion pressure and outcome in patients with traumatic brain injury (34). Previously, conflicting results were published on the use of NIRS as a prognostic tool during CA and in the early post resuscitation phase (177-181). However, the potential role of NIRS in the therapeutic management of the post-cardiac arrest patients has yet to be defined.

The aim of this study was to assess non-invasive cerebral tissue oxygen saturation in patients after CA. NIRS was used for continuous monitoring of regional cerebral tissue oxygenation ($SctO_2$) during and after induced mild (33°C) hypothermia.

3.2.3 Patients and methods

Patients

According to the protocol of our hospital (Ziekenhuis Oost-Limburg, Genk, Belgium), comatose patients successfully resuscitated from cardiac arrest are treated with therapeutic hypothermia. Between March 2011 and April 2012, all adult (age > 18 years) comatose OHCA patients were enrolled in this observational study. The study protocol and consent procedure was approved by the local Committee for Medical Ethics (11/066). Written informed consent was obtained from patient's next of kin.

All patients were initially admitted to the emergency department and immediately transferred to the Catheterization Lab or Coronary Care Unit. Urgent coronary angiograms were performed and followed by percutaneous coronary intervention when indicated.

Patient management

Sedation was maintained by intravenous administration of propofol (1 mg/kg/h) and remifentanil (7.5 µg/kg/h). All patients were intubated and mechanically ventilated. Cisatracurium was administered in case of muscle shivering during TH. The radial artery was cannulated for invasive monitoring of blood pressure and sampling of arterial blood. A Swan-Ganz catheter provided information about cardiac output, cardiac index and mixed venous blood oxygen saturation. Glycaemic control (120-180 mg/dl) was maintained by intravenous titration of insulin. Noradrenaline (norepinephrine) was titrated to maintain a mean arterial pressure (MAP) above 65 mmHg. A cardiac index below 2.0 l/min/m^2 was treated with dobutamine and/or an intra-aortic balloon pump. Ventilation was adjusted to maintain mild hypocapnia ($PaCO_2$ between 32 and 38 mmHg – pH-stat approach), guided by hourly arterial blood gas analyses. Full EEG-analyses was performed at day 1 of admission. After rewarming, sedation was titrated towards patient comfort, with efforts directed towards minimizing sedation. Patients were extubated when their neurological, hemodynamic and respiratory status was sufficiently recovered.

Hypothermia

Cold saline (4°C - 30 ml/kg) was administered immediately at hospital admission. Therapeutic hypothermia was further mechanically induced and maintained by endovascular (Icy-catheter, CoolGard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGel™ pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling. All systems were provided with a feedback loop controlling target temperature using an oesophageal temperature probe. Patients were cooled to a target temperature of 33°C for 24 hours followed by

active rewarming (0.3°C/h). Oesophageal temperature was recorded every minute during hypothermia and rewarming.

Cerebral tissue oxygen saturation

Cerebral tissue oxygen saturation was continuously measured with near infrared spectroscopy (NIRS), using the FORE-SIGHT® technology (CAS Medical systems, Branford, CT, USA). Sensors were bilaterally applied to each frontotemporal area before the start of mechanically induced hypothermia. Sensors were covered to prevent ambient light interference. Data was collected every 2s during hypothermia and rewarming. Since this is an observational study, treatment was guided according to the guidelines of the European Resuscitation Council and not by the collected NIRS data.

Outcome Measurement

The Cerebral Performance Category (CPC) scale was used to define patients' outcome. According to the scale classification, CPC 1 indicates good cerebral performance, CPC 2 moderate disability (sufficient for independent activities in daily live), CPC 3 indicates severe disability (dependent on others), CPC 4 implies coma or vegetative state and CPC 5 stands for death. Neurological performance was assessed at hospital discharge by a psychologist.

Statistical methods

Statistical analysis was performed using SPSS V19.0 (SPSS Inc, Chicago, USA). Discrete data were compared using $\chi 2$. Equal distribution was tested using the Kolmogorov-Smirnov test. Normally distributed continuous data were compared using the unpaired t test.

Changes in $SctO_2$ and hemodynamic measurements over time were compared using one-sample Wilcoxon Signed Rank test. Values for cerebral oxygenation were compared between survivors and non-survivors using Mann-Whitney U test. The results are represented as median (interquartile range), mean (± SD) or percent (%) as indicated. A p-value below 0.05 was considered statistically significant.

3.2.4 Results

During the study period, 39 patients successfully resuscitated after cardiac arrest were admitted to the emergency department. Eleven patients were excluded: 3 patients were admitted with a temperature below 33°C, 3 patients died within the first 24h, 2 patients suffered from an in-hospital CA and 3 patients had incomplete data. Consequently, data of 28 patients were analyzed, of whom 18 (64%) survived to hospital discharge. Fifteen (83%) of the discharged patients corresponded to Cerebral Performance Category (CPC) of 1 – 2 at the time of hospital discharge. Three (11%) patients corresponded to CPC class 3. In non-survivors (CPC 5), the cause of death was severe brain damage (Table 3.1).

Table 3.1: Patient outcome according to the CPC scale

Outcome	n (%)
Survival at hospital discharge (CPC 1-3)	18 (64)
CPC 1	9 (32)
CPC 2	6 (21)
CPC 3	3 (11)
CPC 4	0 (0)
CPC 5	10 (36)

CPC: cerebral performance category

Of the 28 patients, 21 (75%) were men and seven were (25%) women, with a mean age of 61 years (± 14 years). There was no difference between the age of survivors (61 years (± 15 years)) and non-survivors (61 years (± 13 years) p = 0.95). The initial monitored cardiac rhythm was ventricular fibrillation in 21 (75%) patients. The mean delay from onset of arrest to return of spontaneous circulation (ROSC) was 22 min (± 15 min), with a non-significant difference between hospital survivors (19 ± 13 min) and non-survivors (29 ± 16 min, p = 0.15).

Oesophageal temperature at the start of mechanically induced TH was 34.8 °C (± 0.8 °C). Therapeutic hypothermia was successfully maintained in all patients for 24h without interruption. The target temperature of 33°C was reached within 275 min (± 321min) after the start of mechanically induced hypothermia, with no significant difference between survivors and non-survivors (p = 0.45). Table 3.2 further illustrates patient's characteristics and demographics.

Table 3.2: Patient characteristics

	All patients	Survivors	Non-survivors	p-value
Patients, n (%)	28	18 (64)	10 (36)	-
Age, mean (±SD)	61 (14)	61 (13)	61 (15)	0.945
Sex, male/female, n (%)	21 (75)/7 (25)	13 (72)/5 (28)	8 (80)/2 (20)	1.000
First cardiac rhythm **Ventricular arrhythmia, n (%)** **Asystole/pulseless activity, n (%)**	 21 (75) 7 (25)	 13 (72) 5 (28)	 8 (80) 2 (20)	 1.000 1.000
Time to ROSC, min (±SD)	22 (15)	19 (13)	29 (16)	0.146
Temperature at CCU-admission, °C (±SD)	34.8 (0.8)	34.7 (0.7)	34.8 (1)	0.936
Time to target temperature, min (±SD)	275 (321)	235 (271)	347 (401)	0.445
Cooling, endovascular/surface (%)	22 (79)/6 (21)	15 (83)/3 (17)	7 (70)/3 (30)	0.634
Intra-aortic balloon pump, n (%)	8 (29)	6 (33)	3 (30)	1.000
PCI, n (%)	16 (57)	10 (56)	6 (60)	1.000

ROSC: return of spontaneous circulation, CCU: coronary care unit, PCI: percutaneous coronary intervention
Values are expressed as mean values.

At the start of mechanically induced TH, cerebral tissue oxygen saturation ($SctO_2$) was 68% (65-72%). There was no difference between survivors (68% (65-72%)) and non-survivors (68% (66-72%) p = 0.96). Within three hours after the start of mechanically induced TH, $SctO_2$ significantly decreased to 59% (57-64%)(p = 0.006) (Fig. 3.2). At this point of lowest $SctO_2$, there was a significant difference between survivors (62% (59-66%)) and non-survivors (58% (55-59%) p = 0.02) (Fig. 3.3). Three patients (non-survivors) showed epileptic activity on EEG during TH. Data-analysis without these patients showed $SctO_2$ values of 58% (54-60%) for the non-survivor group at three hours after the start of mechanically induced TH.
Subsequently, $SctO_2$ gradually increased to reach baseline values (69% (63-72%)) within 24 hours, with no differences between survivors (69% (63-74%)) and non-survivors (67% (64-72%)) (p = 0.65) (Fig. 3.4).

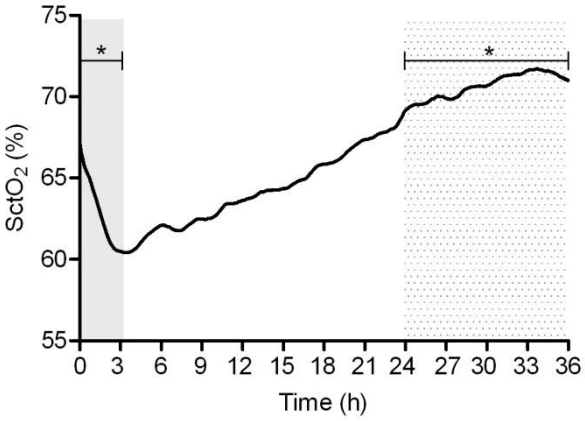


Figure 3.2: Cerebral oxygenation (%) during therapeutic hypothermia and rewarming in comatose patients after CA. Cerebral oxygenation significantly decreased during induction of therapeutic hypothermia (grey area) and increased to reach baseline values at the end of therapeutic hypothermia. During rewarming (dotted area), there is a significant increase in oxygenation. Data are presented as median values, * = p < 0.05

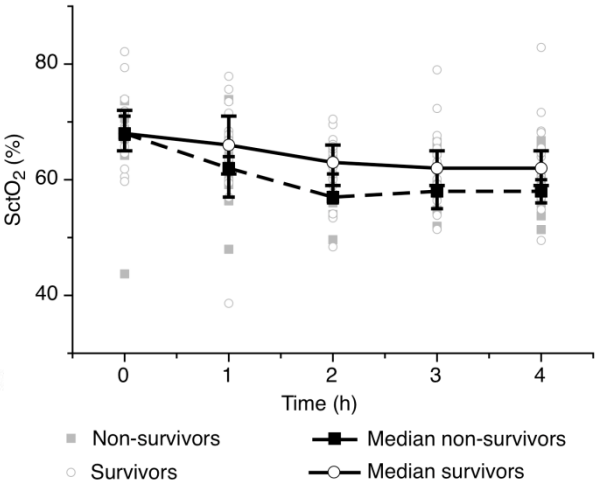


Figure 3.3: Cerebral oxygenation (%) during induction of therapeutic hypothermia. There is a significant difference between survivors (dots) and non-survivors (cubics) of CA. Data are represented as median values with interquartile range.

At the start of mechanically induced hypothermia, $PaCO_2$ was 47 mmHg (37-51 mmHg), with no difference between survivors and non-survivors (47 mmHg (39-52 mmHg) versus 45 mmHg (36-52 mmHg), p = 0.74). Over the following three hours, ventilation was adjusted to reach mild hypocapnia (32 – 38 mmHg) and $PaCO_2$ decreased significantly (p = 0.002) to 37 mmHg (34-45 mmHg). Mild hypocapnia was maintained throughout the hypothermic period. Mean arterial pressure (MAP) started at 84 mmHg (77-98 mmHg) and remained above 70 mmHg during maintenance of TH. Cardiac index (CI) was significantly lower at the start of mechanically induced TH for non-survivors (1.6 l/min/m^2) compared with survivors (2 l/min/m^2 (1.9-2.2 l/min/m^2) p = 0.02). Over the next 24 hours, CI increased to 2.4 l/min/m^2 (1.7-3 l/min/m^2) and 2.1 l/min/m^2 (1.8-3.5 l/min/m^2) for the survivors and non-survivors respectively (Table 3.3).

Table 3.3: Mean arterial pressure, pCO_2, cardiac index and hemoglobin changes over time

	All patients	**Survivors**	**Non-survivors**	**p - value**
Start TH				
MAP (mmHg)	84 (77-98)	86 (80-99)	78 (75-96)	0.291
$PaCO_2$ (mmHg)	47 (367-51)	47 (39-52)	45 (36-52)	0.744
CI (l/min/m^2)	1.9 (1.7-2.2)	2 (1.9-2.2)	1.6 (1.6)	0.024*
Hb (g/dl)	14 (12-16)	14 (13-16)	13 (12-16)	0.976
Three hours				
MAP (mmHg)	82 (76-90)	82 (75-90)	82 (76-90)	0.918
$PaCO_2$ (mmHg)	37 (34-45)	38 (34-46)	37 (33-44)	0.571
CI (l/min/m^2)	1.9 (1.4 – 2.4)	2.2 (1.4-2.6)	1.5 (1.4-2.3)	0.474
Hb (g/dl)	14 (13-16)	14 (14-17)	14 (13-16)	0.743
24 hours				
MAP (mmHg)	78 (65-85)	79 (68-83)	75 (68-96)	0.451
$PaCO_2$ (mmHg)	36 (34-39)	37 (34-40)	36 (34-38)	0.291
CI (l/min/m^2)	2.3 (1.8-3.2)	2.4 (1.7-3)	2.1 (1.8-3.5)	0.910
Hb (g/dl)	13 (11-15)	13 (11-15)	13 (11-17)	0.458
36 hours				
MAP (mmHg)	72 (70-72)	72 (71-74)	71 (69-77)	0.561
$PaCO_2$ (mmHg)	36 (33-40)	35 (32-39)	37 (34-44)	0.332
CI (l/min/m^2)	3.1 (2.9-3.4)	3.1 (2.7-3.4)	3.1 (2.9-3.4)	0.874
Hb (g/dl)	13 (11-15)	13 (11-15)	13 (10-15)	0.910

Values are expressed as median (interquartile range)
MAP: mean arterial pressure, CI: cardiac index, Hb: haemoglobin
Significant differences between survivors and non-survivors are indicated with *

The mean dose of norepinephrine, used to maintain a mean blood pressure above 65 mmHg, was at 8.3 γ/min (± 6.1 γ/min) at start in survivors and increased to 15.3 γ/min (± 15.6 γ/min) within the first three hours after the start of mechanically induced TH (Figure 3.4). In non-survivors, norepinephrine

was started at a mean of 7.8 γ/min (± 3 γ/min) and increased to 19.8 γ/min (± 5.2 γ/min) during maintenance of TH (Figure 3.4). There was no significant difference in start dose between survivors and non-survivors (p = 0.56). Also, there was no significant correlation between use/dose of norepinephrine and $SctO_2$ in survivors (p = 0.79) or non-survivors (p = 0.81).

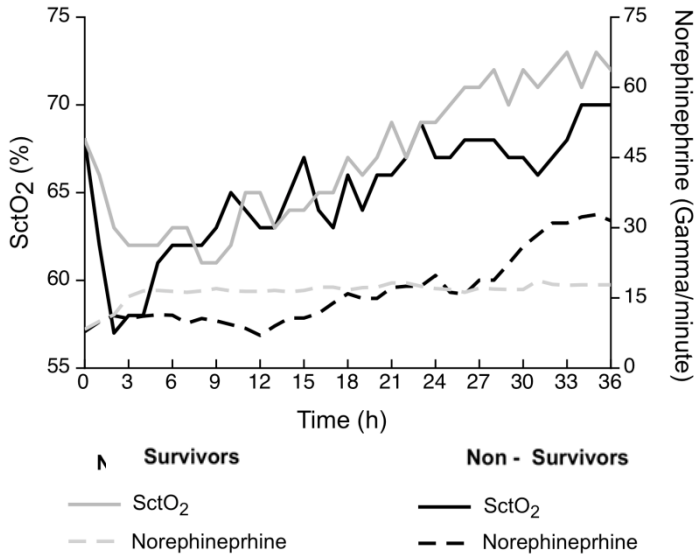


Figure 3.4: Cerebral oxygenation (%) during therapeutic hypothermia and rewarming in comatose survivors (grey line) and non-survivors (black line) of CA compared to use of norepinephrine (dotted line). Cerebral oxygenation significantly decreased during induction of therapeutic hypothermia and increased to reach baseline values at the end of therapeutic hypothermia. Norepinephrine (γ/min) increased during the first hours in survivors but remained stable throughout maintenance of hypothermia. In non-survivors, norepinephrine increased during hypothermia and rewarming. Data are represented as median values.

Throughout the hypothermia, there was no difference in haemoglobin-levels between survivors and non-survivors (Table 3.3).

After 24 hours of hypothermia, patients were rewarmed at 0.3°C/hour. $SctO_2$ significantly (p = 0.009) increased during this 12 hour rewarming period to 71% (67-78%) (figure 3.2). There was no difference between survivors (72% (66-78%)) and non-survivors (71% (67-77%) p = 0.83) (figure 3). During rewarming, $PaCO_2$ and MAP remained stable at 36 mmHg (33-40 mmHg) and 72 mmHg (70-72 mmHg) respectively, with no differences between survivors and non-survivors. Norepinephrine dose remained stable in survivors, but increased

to 32.8 γ/min (±9.1 γ/min) in non-survivors (Figure 3.4). Cardiac index increased to 3.1 l/min/m^2 in both survivors and non-survivors (Table 3.3).

3.2.5 Discussion

The human brain is a highly aerobic organ with limited energy stores, making neuronal activity and energy metabolism dependent on constant oxygen and glucose delivery. In patients resuscitated from CA, neurological outcome depends on the duration of ischemia and the restoration of systemic circulation and oxygenation. Moreover, reperfusion followed by the post-resuscitation syndrome could lead to secondary cerebral injury and compromise neurological outcome. In order to avoid additional detrimental effects of cerebral hypoperfusion and maximize the potential beneficial effect of induced hypothermia in the post-CA patient, it is necessary to avoid and thus detect episodes of cerebral hypoxia or inadequacy of cerebral perfusion.

The results of this study show a significant decrease in cerebral oxygenation, measured by $SctO_2$, within the first hours after mechanically induced TH in post-CA patients (Fig. 3.2). This observation is in contrast to the expected increase in $SctO_2$ in response to global reduction in brain metabolism during hypothermia. Furthermore, TH causes a leftward shift of the oxygen dissociation curve with an enhanced affinity of oxygen to hemoglobin. In previous studies, an increase in cerebral oxygenation, measured by NIRS (INVOS® 4100) and jugular bulb oximetry, was reported during hypothermia in patients during deep hypothermic circulatory arrest (182, 183). It should be noted that, during deep hypothermic circulatory arrest, a temperature of 18°C is targeted, while our patients' temperature did not decrease below 33°C. Joshi *et al*. reported on cerebral oxygenation during cardiopulmonary bypass surgery in patients that were cooled from 35.2°C to 30.9°C, and showed a decrease in $SctO_2$ values (184). Both the temperature gradient as well as the decrease in $SctO_2$ is comparable with our results.

Previously, it was shown that α-agonist treatment has a negative impact on cerebral oxygenation and cardiac output in anaesthetized patients (185). This effect was even more intensified during hypocapnia (186). In our study, norepinephrine, an α-agonist, was used to maintain an adequate mean arterial blood pressure. However, there was no correlation between the increasing dose of norepinephrine and the decrease in cerebral oxygenation at the start of mechanically induced TH. Furthermore, $SctO_2$ and cardiac index increased during rewarming while the dose of norepinephrine was stable (survivors) or uptitrated (non-survivors) (Figure 3.4).

Perhaps cerebrovascular reactivity induced by changes in $PaCO_2$ is a more important mechanism to explain the decrease in cerebral oxygenation. This mechanism is preserved in comatose post-CA patients (67, 187, 188). Consequently, hyperventilation will cause vasoconstriction and a decrease jugular bulb oxygen saturation below the ischemic threshold (187, 189). In line with the decrease in $PaCO_2$ during induction of (mechanically induced) TH in our

study, $SctO_2$ decreased from 68% (65-72%) to 59% (57-64%) within the first three hours. A correlation between $PaCO_2$ and jugular bulb oxygenation during TH in post-CA patients was observed previously. Bisschops *et al*. increased the minute ventilation with 20%, which resulted in a decrease in $PaCO_2$ accompanied by a decrease in mean flow velocity (measured with transcranial doppler) and jugular bulb oxygen saturation (67). Together with low mean flow velocities, a high pulsatility index was noted, which suggests an increase in cerebrovascular resistance during TH (67). Thus, the increase in cerebrovascular resistance, due to TH and reduction in $PaCO_2$, could play a role in the observed decrease in cerebral oxygen saturation in our study.

Normally, metabolic autoregulation of cerebral blood flow provides a powerful mechanism to counteract regional imbalances in oxygen supply. In the first hours after CA, global cerebral blood flow (CBF) is decreased, together with a low cerebral oxygen extraction (CEO_2), cerebral metabolic rate of oxygen ($CMRO_2$) and a normal jugular bulb oxygen saturation (67, 190-192). This suggests that CBF is sufficient for the metabolic metabolism in brain tissue in post-CA patients. However, the energy metabolism of the brain is often heterogeneous after successful resuscitation (191). Therefore, focal ischemic events could be missed with global measurements of CBF, CEO_2 and $CMRO_2$. As 50% of the CA survivors suffer from frontal lobe dysfunction (170, 193), regional imbalances between oxygen demand and oxygen supply, as measured in our study, are important for a better understanding of cerebral hemodynamic changes in the post-CA patient.

Epileptic activity can increase cerebral oxygen use (194). In the non-survivors group, three patients suffered from epileptic activity on EEG during induction and maintenance of therapeutic hypothermia. However, these epileptic activities did not influence the $SctO_2$ values measured in our study.

We observed that cerebral oxygenation was similar between post-CA survivors and non-survivors at the start, but significantly diverged during the first four hours of mechanically induced TH (Fig. 3.3). In patients after cardiac surgery, intra-operative cerebral oxygen desaturation has been associated with an increased risk of cognitive impairment and prolonged hospital stay (4, 71, 86). According to Lemiale *et al*., CBF and CEO_2 between survivors and non-survivors were neither different at admission nor at 12 and 24 hours of hypothermia (190). However, they show only results at discrete times, while our results show real time differences within the first three hours of TH.

In all patients, after the initial decrease in cerebral oxygenation, $SctO_2$ increased within the 24 hour period of TH and reached baseline values towards the end of TH. During rewarming, $SctO_2$ further increased to 71% (Fig. 3.2), without a change in $PaCO_2$ (Table 3.3). Although $SctO_2$ is lower during rewarming in non-survivors, there were no significant differences compared with survivors.

Previous authors have suggested that a primary increase in CBF, together with a decrease in pulsatility index, could be responsible for the increase in cerebral oxygenation during rewarming (67).

The first limitation of our study is that we did not assess cerebral hemodynamic parameters (measured by transcranial doppler) in conjunction with changes in cerebral tissue oxygen saturation. Although previous studies have shown a decrease in CBF and increase in pulsatility index in the post-CA phase, it was only measured at discrete time points. A continuous measurement of cerebral hemodynamic parameters with transcranial doppler, together with the continuous measurement of $SctO_2$, could lead to a better understanding of cerebral hemodynamic disturbances. The second limitation is that we have not measured jugular bulb oxygen saturation or brain tissue oxygen tension. However, jugular bulb oxygenation and brain tissue oxygen are both invasive techniques and difficult to perform or justify in a post-CA patient. Furthermore, jugular bulb oximetry measures global cerebral oxygenation and could therefore be insensitive to regional ischemic events (195). The third limitation is that we were not able to compare our data with normothermic post-CA patients. As TH has shown to improve both survival and neurological outcome (126, 171), there are ethical concerns against a normothermic control group.

3.2.6 Conclusion

In conclusion, our data suggest that induction of TH changes the balance between oxygen delivery and supply, with a decrease in regional cerebral oxygen saturation during the early phase of hypothermia in post CA-patients. This decrease is significantly more marked in non-survivors compared with survivors. Because resuscitation of a CA victim does not end with ROSC, a better understanding of cerebral hemodynamic and metabolic disturbances during the post-resuscitation phase may have an impact on the management of post CA patients. Further research is needed.

3.3 Cerebral tissue oxygen saturation and carbon dioxide

The association between carbon dioxide, oxygen tension, cerebral saturation and outcome in post-cardiac arrest patients

Preliminary results

3.3.1 Introduction

Cardiac arrest (CA) is associated with high mortality and morbidity worldwide. The additional high in-hospital mortality is attributable to the post-CA syndrome, in which anoxic brain injury plays a major role (196). Post-CA care is therefore tremendously important. The use of therapeutic hypothermia (TH) has been shown to improve survival and neurological outcome (126, 171), but target temperature and length of TH is still under investigation (197). As carbon dioxide (CO_2) is an important regulator of cerebral blood flow (67, 68), treatment goals for mechanical ventilation could also have an impact on outcome. Hypocapnia and hypercapnia exposure are common after CA (198-200). Current guidelines recommend targeting arterial carbon dioxide ($PaCO_2$) between 40-45mmHg and oxygen saturations above 94% in post-CA patients (201). However, in recent history conflicting data were published on the relationship between carbon dioxide, oxygen and outcome in post-CA patients. All previous studies were retrospective and further biased by heterogeneity in the use of TH, ventilation strategy and timing of blood gas sampling among patients in the same study. Moreover, the association between $PaCO_2$, PaO_2 and cerebral oxygen saturation ($SctO_2$) is not addressed in previous studies. Therefore the aims of the present study were [1] to determine the optimal $PaCO_2$ and PaO_2 associated with maximal patient survival and [2] to determine the relationship between $PaCO_2$, PaO_2 and $SctO_2$ in post-CA patients treated with TH.

3.3.2 Methods

Study population

All comatose survivors after cardiac arrest, referred to our tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium), were treated according to the institutional post-cardiac arrest protocol. As part of this protocol, patients are routinely monitored by cerebral saturation monitoring on hospital arrival. This observational study includes all consecutive comatose survivors after non-traumatic cardiac arrest prospectively enrolled in our database between 3/2011 and 2/2014. Patients who died during the first 24 hours were excluded from analysis. Written informed consent was obtained from a next of kin. The study protocol was approved by the local medical ethics committee.

General management

Our institutional post-cardiac arrest protocol has been described previously (202). Shortly, all patients were intubated and intermittent positive pressure ventilated (IPPV). Ventilation was adjusted at the discretion of treating physicians guided by hourly arterial blood gas analyses (pH-stat). Patients were sedated with propofol and remifentanil if hemodynamically tolerated. Cisatracurium was administrated in case of shivering. Unless an obvious non-cardiac cause could be identified, all patients were referred for urgent coronary angiography followed by percutaneous coronary intervention when indicated. Therapeutic hypothermia was induced shortly after admission by cold saline (4°C – 30 ml/kg) and further maintained in the coronary care unit by endovascular (Icy-catheter, CoolGard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGelTM pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems at 33°C for 24-hours. All patients received hemodynamic optimization according to current guidelines with a main focus on achieving a mean arterial pressure above 65mmHg. Fluid resuscitation and the use of inotropics and vasopressive agents were guided by invasive arterial blood pressure and pulmonary artery catheter (unless placement of pulmonary artery catheter was considered inappropriate or contra-indicated by treating physicians). After rewarming (0.3°C/hr) sedation was titrated towards patient's comfort with efforts towards minimizing sedation. Patients were extubated when their neurological, respiratory and hemodynamic status was sufficiently recovered.

Cerebral saturation monitoring

Cerebral tissue oxygen saturation was continuously measured with near infrared spectroscopy (NIRS), using the FORE-SIGHT^{TM} technology (CAS Medical systems, Branford, CT, USA). Sensors were bilaterally applied to each frontotemporal area before the start of hypothermia. Sensors were covered to

prevent ambient light interference. In all patients, cerebral saturation data were transmitted electronically to a personal computer with a 2 seconds time interval during hypothermia and rewarming.

Statistics

Results are expressed as mean (±SD, standard deviation) unless otherwise stated. First, for each patient, the mean pCO_2 and pO_2 were calculated by averaging all obtained values during the first 24 hours. To determine the pCO_2 and pO_2 associated with maximal patient survival, odds ratios for survival (and 95% confidence intervals) were calculated per 4 mmHg pCO_2 and per 20 mmHg pO_2 intervals. To test for significance, a chi-square test was performed (all expected frequencies were more than 5). Similarly, other candidate binary variables were evaluated by a chi-square test. Second, a physiological model was constructed to describe the relationships between pCO_2, pO_2, hemoglobin and cerebral saturation. The average cerebral saturation was calculated per mmHg pCO_2 and pO_2 and per g/dl hemoglobin. Univariate linear regression with calculation of Pearson's correlation coefficient was used for the pCO_2 and hemoglobin model and logistic regression for the pO_2 model (since this fitted better then linear regression). Third, the optimal pCO_2 and pO_2 ranges were defined based on the survival analysis and the hemodynamic model. According to their average values during the first 24 hours after admission, patients were stratified to be in the low/optimal/high pCO_2 subgroups. These subgroups were compared using one way ANOVA. Statistical analysis was performed using Matlab software (version R2010b, Mathworks, USA). A p-value <0.05 was considered significant.

3.3.3 Results

A total of 82 patients were included in the analysis, of whom 43 (52%) survived to hospital discharge. Characteristics of the included patients are shown in Table 3.4.

Table 3.4: Patient characteristics

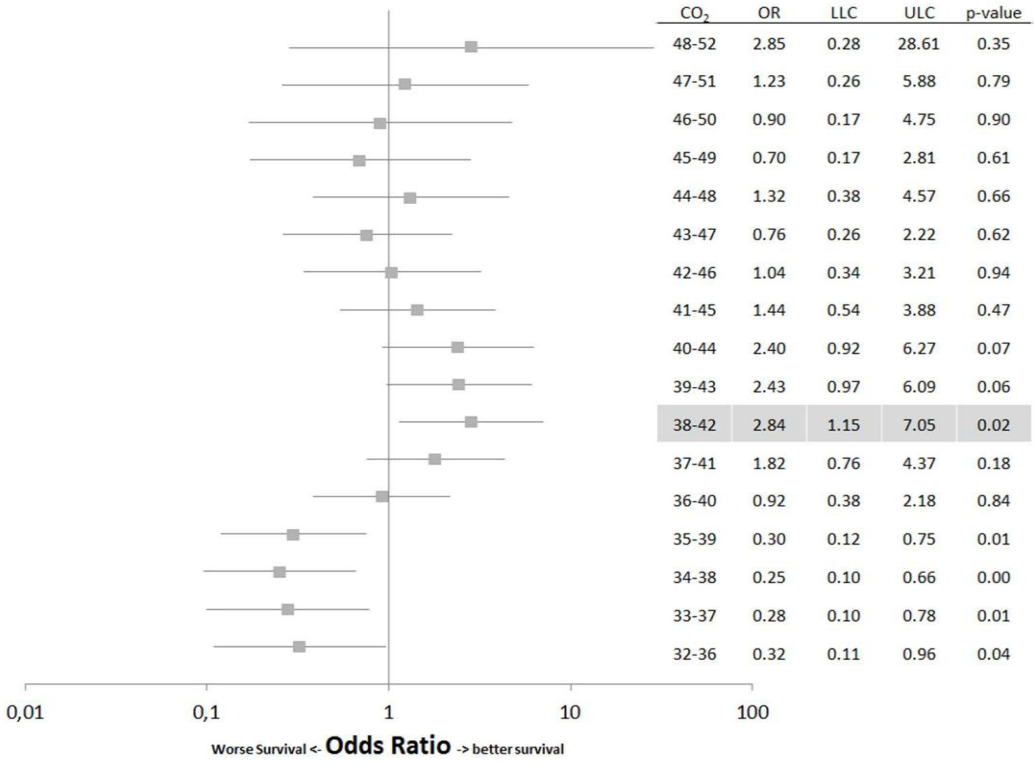
	All	Per pCO_2			
		Low ≤ 37 mmHg	Optimal [38,42]mmHg	High ≥ 43 mmHg	p-value
Number patients	82	24/82 (29%)	35/82 (43%)	23/82 (28%)	
Demographics					
Age (years)	63±13	63±12	60±14	66±13	0.24
Male (%)	70	46	77	83	0.01
Resuscitation Parameters					
Out of Hospital (%)	85	84	82	91	0.64
Bystander CPR<10 min (%)	82	81	82	82	0.99
Initial Rhythm Shockable (%)	66	45	77	70	0.04
Cardiac Cause	90	84	94	91	0.44
Hemodynamic Parameters					
Heartrate (BPM)	68±16	64±16	67±17	72±14	0.22
Echocardiographic LVEF (%)	42±17	40±17	44±17	39±19	0.51
MAP (mmHg)	76±8	76±8	78±8	75±8	0.35
CVP (mmHg)	17±13	17±16	16±7	19±16	0.69
SVO2 (%)	67±9	69±9	69±9	65±10	0.22
TDCCO (l/min)	3.88±1.26	3.47±1.36	4.12±1.08	3.90±1.40	0.14
Blood Gas					
First Lactate (mmol/l)	6.20±4.40	6±3	5±4	8±6	0.04
Mean Lactate (mmol/l)	3.06±1.92	3±2	3±2	3±2	1.00
pH	7.33±0.06	7.37±0.04	7.34±0.05	7.29±0.07	<0.0001
pCO2 (mmHg)	40±5	36±2	40±1	46±3	<0.0001
pO2 (mmHg)	104±20	118±24	100±15	97±15	<0.0001
Survival (%)	52	29	69	52	0.009

CPR: cardiopulmonary resuscitation; BPM: beats per minute; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; CVP: central venous pressure; SvO_2: Mixed venous oxygen saturation; TDCCO: thermodilution continuous cardiac output

Data are presented as mean ± SD

The mean $PaCO_2$ range during the first 24 hours after admission associated with maximal survival was 38-42 mmHg (OR 2.84, 95% CI [1.15; 7.05], p=0.02, Figure 3.5). Based on this range, patients were categorized into three groups: low $PaCO_2$ (≤ 37 mmHg, n = 24), optimal $PaCO_2$ (38-42 mmHg, n = 35) and high $PaCO_2$ (≥ 43 mmHg, n = 23). Patients in the three groups significantly differed in gender (p = 0.01) and the presence of an initial shockable rhythm (p

= 0.04). Also, survival, pH and PaO_2 were significantly different between the three groups (Table 3.4).



CO_2	OR	LLC	ULC	p-value
48-52	2.85	0.28	28.61	0.35
47-51	1.23	0.26	5.88	0.79
46-50	0.90	0.17	4.75	0.90
45-49	0.70	0.17	2.81	0.61
44-48	1.32	0.38	4.57	0.66
43-47	0.76	0.26	2.22	0.62
42-46	1.04	0.34	3.21	0.94
41-45	1.44	0.54	3.88	0.47
40-44	2.40	0.92	6.27	0.07
39-43	2.43	0.97	6.09	0.06
38-42	2.84	1.15	7.05	0.02
37-41	1.82	0.76	4.37	0.18
36-40	0.92	0.38	2.18	0.84
35-39	0.30	0.12	0.75	0.01
34-38	0.25	0.10	0.66	0.00
33-37	0.28	0.10	0.78	0.01
32-36	0.32	0.11	0.96	0.04

Figure 3.5: Odds ratio for survival, based on carbon dioxide tension ($PaCO_2$). The mean $PaCO_2$ range during the first 24 hours after admission associated with maximal survival was 38-42 mmHg (OR 2.84, 95% CI [1.15; 7.05], p=0.02.
OR: odds ratio; LLC: lower limit of confidence; ULC: upper limit of confidence

The $PaCO_2$/$SctO_2$ correlation curve is depicted in Figure 3.6. The scatterplot can be divided into 3 groups: (1) $PaCO_2$ between 29 and 39 mmHg, which are linear correlated ($SctO_2$=0.50 x $PaCO_2$ + 47, R^2 0.76) with average $SctO_2$-values, (2) in the normocapnic range, there is a plateau phase which corresponds to $SctO_2$-values between 66.5% and 67.5% and (3) there is a linear relationship between $SctO_2$ and $PaCO_2$ values between 46 and 62 mmHg ($SctO_2$=0.40 x $PaCO_2$ + 47, R^2 0.39). The $PaCO_2$-range (38-42mmHg) associated with maximal survival correspond with a $SctO_2$-value of 67%.

The mean PaO_2 range during the first 24 hours of admission associated with maximal survival was 80-100 mmHg (OR 2.78, 95% CI [0.94;8.18]). However, this survival benefit was borderline insignificant when compared with patients with lower or higher mean PaO_2's (p = 0.06) (Figure 3.7).

The $PaO_2/SctO_2$ correlation curve is shown in Figure 3.8. Also this scatterplot can be divided in (1) a linear $PaO_2/SctO_2$ correlation ($SctO_2$ = 0.33 x PaO_2+42, R^2 0.61) for PaO_2's between 40 and 80 mmHg and (2) a plateau phase in the PaO_2 80-100 mmHg range and $SctO_2$ values between 65% and 68%.

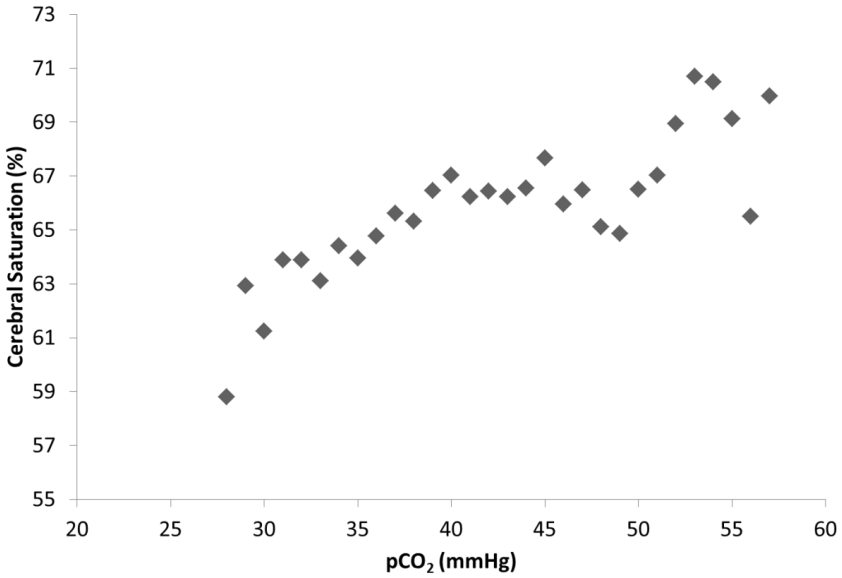


Figure 3.6: Cerebral oxygen saturation/carbon dioxide scatterplot. The scatterplot can be divided into 3 groups: (1) $PaCO_2$ between 29 and 39 mmHg, with linear correlation with average $SctO_2$-values ($SctO_2$=0.50 x $PaCO_2$ + 47, R^2 0.76), (2) normocapnic range, a plateau phase which corresponds to $SctO_2$-values between 66.5% and 67.5%, (3) linear relationship between $SctO_2$ and $PaCO_2$ values between 46 and 62 mmHg ($SctO_2$=0.40 x $PaCO_2$ + 47, R^2 0.39).

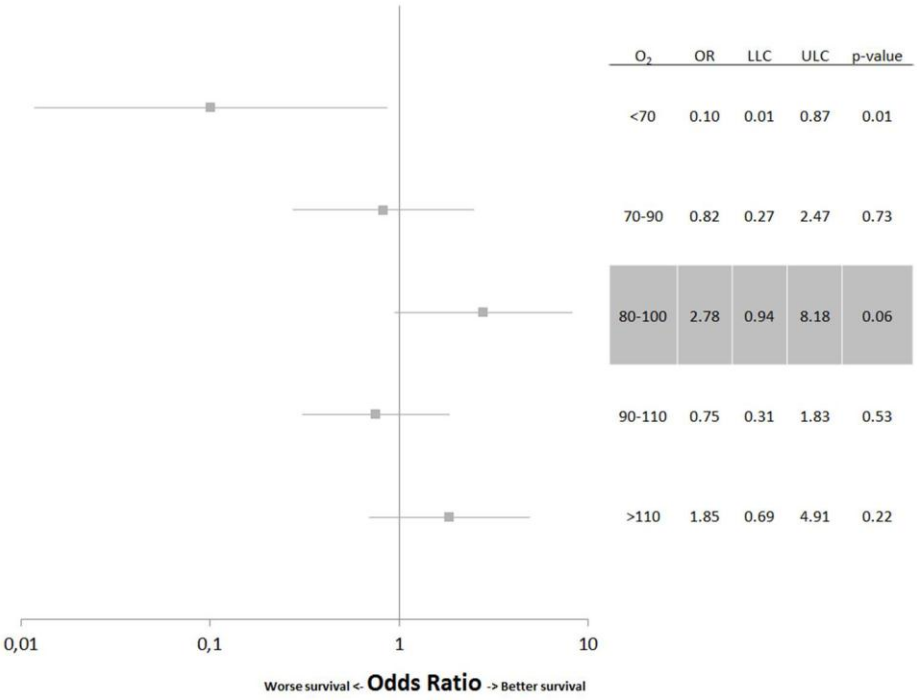


Figure 3.7: Odds ratio for survival, based on arterial oxygen tension (PaO_2). The mean PaO_2 range during the first 24 hours of admission associated with maximal survival was 80-100 mmHg (OR 2.78, 95% CI [0.94;8.18]). The survival benefit was borderline insignificant when compared with patients with lower or higher mean PaO_2's (p = 0.06).
OR: odds ratio; LLC: lower limit of confidence; ULC: upper limit of confidence

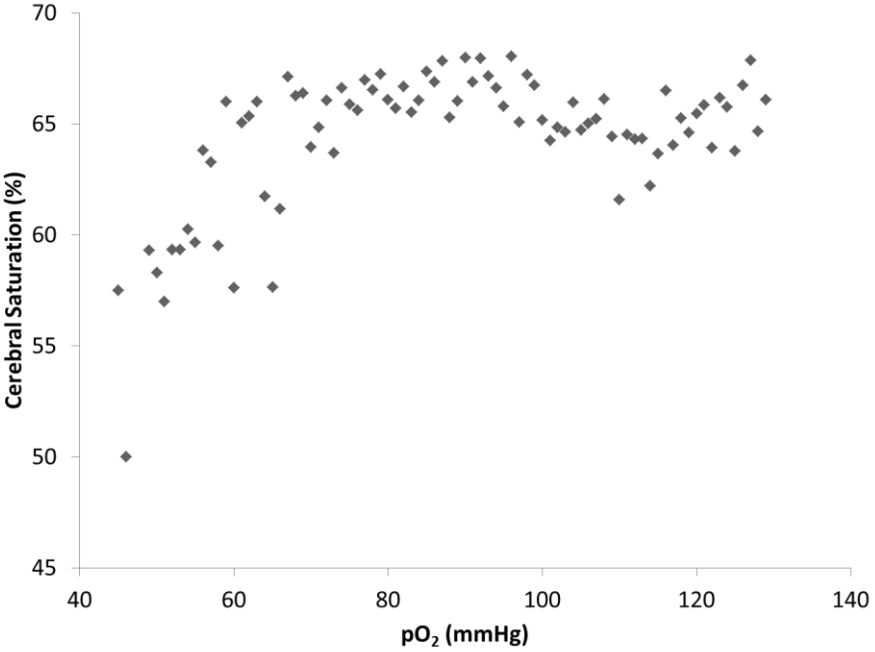


Figure 3.8: Cerebral oxygen saturation/oxygen tension scatterplot. The scatterplot can be in (1) a linear $PaO_2/SctO_2$ correlation ($SctO_2 = 0.33 \times PaO_2+42$, R^2 0.61) for PaO_2's between 40 and 80 mmHg and (2) a plateau phase in the PaO_2 80-100 mmHg range and $SctO_2$ values between 65% and 68%.

3.3.4 Discussion

In this study, we found that normocapnia was associated with optimal cerebral saturation and maximal survival in post-CA patients. Our results are in line with current guidelines of the American Heart Association recommending a target $PaCO_2$ between 40-45 mmHg in post-CA patients (201). In a landmark trial on this topic, Roberts *et al*. previously described that both hypocapnia and hypercapnia were independently associated with poor neurological outcome in post-CA patients (198). Nevertheless, near half of post-CA patients are exposed to either hypocapnia or hypercapnia (198-200, 203). Our results provide a pathophysiological insight in to the deleterious effects of hypo- and hypercapnia.

Based on a previous study by our group, the optimal cerebral saturation associated with maximal survival was determined to be 67% in post-CA patients (unpublished results). Also, in cardiac and thoracic surgery, $SctO_2$ values below 65% were correlated with neurocognitive dysfunction, prolonged hospital stay and major organ morbidity (2-4, 86). We identified 40 mmHg (38-42 mmHg) as the optimal $PaCO_2$ since this corresponded with the highest chance of survival and was associated with a plateau phase of cerebral oxygenation around 67%. In this way, hypocapnia resulted in cerebral desaturation (<65%) and poor survival (only 29%) in our post-CA patients. In line with our results, hypocapnia was previously shown to be associated with an increased risk of in-hospital mortality and poor neurological outcome in post-CA patients (198, 200, 203). In patients with traumatic brain injury, cerebral blood flow decreases about 3% for 1 mmHg decrease in $PaCO_2$ (204). Analogously, we found that cerebral saturation drops with 0.5% for every mmHg decrease in $PaCO_2$. Therefore, hypocapnia-induced cerebral vasoconstriction impairs cerebral perfusion (189, 202, 205). Since all study patients received fully controlled mechanical ventilation (IPPV), it is very likely that there is causal relationship between iatrogenic hyperventilation, hypocapnia, cerebral desaturation and increased mortality. Unnecessary hypocapnia should therefore be avoided in post-CA patients. It should be noted that $PaCO_2$ levels drop during the induction of TH due to reduced metabolism and decreased CO_2 solubility in the blood. Consequently, clinicians should frequently monitor $PaCO_2$ to adjust minute ventilation and avoid iatrogenic hyperventilation.

In contrast, the association between hypercapnia and outcome is still under debate. We report a lower chance of survival with higher $PaCO_2$-values compared to $PaCO_2$-values within the suggested 38-42 mmHg range. Hypercapnia has been associated with cerebrovascular vasodilatation and increased cerebral blood flow. Moreover, hypercapnia may result in improvement of the oxidative metabolism and inhibition of glutamate secretion (206, 207). However, severe hypercapnia was also associated with increased intracranial pressures and decreased cerebral perfusion (208, 209). Roberts *et*

al. reported an incidence of 42% post-CA patients with hypercapnia (≥50mmHg) exposure, which was an independent predictor of poor neurologic outcome at hospital discharge (198). In contrast, Vaahersalo *et al*. associated hypercapnia ($PaCO_2$ >45 mmHg) with good 12-month outcome after CA (210). This was confirmed by Schneider *et al*. who correlated hypercapnia ($PaCO_2$ >45 mmHg) with a greater likelihood of discharge home among survivors (203). At least two potential explanations apply for these conflicting results. First, hypercapnia is defined differently in several studies (Roberts *et al.*(198) ≥50mmHg, Schneider *et al.* (203) and Vaahersalo *et al*. (210) >45 mmHg). In a rat model of cerebral ischemia-reperfusion injury, moderate hypercapnia was neuroprotectieve while severe hypercapnia increased brain injury (211). Analogously, in our pathophysiological model, severe hypercapnia results in cerebral hypersaturation. We previously described an association between hyperdynamic circulation, cerebral hypersaturation and poor outcome (unpublished results). Alternatively, the relationship between hypercapnia and adverse outcome can also be explained by more severe lung injury and systemic inflammatory response syndrome. Importantly, extensive subgroup analysis did not show important differences related to resuscitation characteristics, global hemodynamics and oxygenation between the normocapnic and hypercapnic subgroup. Second, there are two possibilities to analyze blood gasses which could potentially influence $PaCO_2$ management and outcome: pH-stat (adjusted to the patients' temperature) and alpha-stat (37°C, unadjusted tot patients' temperature). In previously mentioned papers, no information was given concerning the strategy (198, 203), or both strategies were used interchangeably (210). We used the pH-stat approach to analyze $PaCO_2$. Recently, Voicu *et al*. showed that the pH-stat approach might be considered as the more secure management strategy (212). This was also reported by Pynnönen *et al*. (189) and Hoover *et al*.(213).

Finally, we showed a trend to better survival in patients with a mean PaO_2 during the first 24 hours after admission between 80-100mmHg. We also found that this same PaO_2 range results in optimal cerebral saturation (67%). It is clear from our data that hypoxia (PaO_2 below 70 mmHg) results in cerebral desaturation and significantly increased mortality. In contrast, there is much debate on the association between exposure to hyperoxia (PaO_2 > 300 mmHg) and outcome in post-CA patients. In the present study, we did not find any association between higher average PaO_2 and worse outcome. Previously, Kilgannon *et al*. observed an independent association between exposure to hyperoxia (PaO_2 > 300 mmHg) and increased in-hospital mortality (214), which was confirmed by Janz et al. (215). In contrast, Bellomo *et al*. reported that hyperoxia was relatively uncommon in their large multicenter study and was not independently associated with mortality after CA (216). These inconsistent results may be related to the used time-point or method to measure PaO_2. Bellomo *et al*. (216) used the worst PaO_2 in the first 24 hours after admission, Kilgannon *et al*. (214) used the first arterial blood gas value in the ICU, while

Janz *et al*. (215) used the highest measured PaO_2. Finally, we used the mean PaO_2 value over the first 24 hours of admission.

All previous studies were retrospective and further biased by heterogeneity in the use of therapeutic hypothermia (TH), ventilation strategy and timing of blood gas sampling among patients in the same study. The major strength of this study is that all patients were prospectively included and treated according to the same institutional post-CA protocol thereby excluding these sources of error. Moreover, this study is the first to associate $PaCO_2$ and PaO_2 with outcome and cerebral saturation. Finally, the high frequency of arterial blood gas sampling (hourly) excluded the possibility of sampling error. The major limitation is the smaller sample size compared with previous studies.

3.3.5 Conclusion

In summary, we found that normocapnia is associated with maximal survival and optimal cerebral oxygenation in post-CA patients treated with TH. Hypoxia was associated with cerebral desaturation and poor survival. Our data suggest that derangements in $PaCO_2$ and PaO_2 could be potentially harmful after resuscitation. Further research concerning $PaCO_2$ and PaO_2 management and its possible impact on outcome is warranted.

CHAPTER 4

Cerebral oxygen saturation during cardiac arrest

4.1 Near infrared spectroscopy during cardiopulmonary resuscitation

Feasibility of absolute cerebral tissue oxygen saturation during cardiopulmonary resuscitation

Original paper

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Critical Care 2013; 17(2):R36

4.1.1 Abstract

Current monitoring during cardiopulmonary resuscitation (CPR) is limited to clinical observation of consciousness, breathing pattern and presence of a pulse. At the same time, the adequacy of cerebral oxygenation during CPR is critical for neurological outcome and thus survival. Cerebral oximetry, based on near-infrared spectroscopy (NIRS), provides a measure of brain oxygen saturation. Therefore, we examined the feasibility of using NIRS during CPR.
Recent technologies (FORE-SIGHT® and EQUANOX®) enable the monitoring of absolute cerebral tissue oxygen saturation ($SctO_2$) values without the need for pre-calibration. We tested both FORE-SIGHT® (5 patients) and EQUANOX Advance® (11 patients) technologies in the in-hospital as well as the out-of-hospital CPR setting. In this observational study, values were not utilized in any treatment protocol or therapeutic decision. An independent t-test was used for statistical analysis.
Our data demonstrate the feasibility of both technologies to measure cerebral oxygen saturation during CPR. With the continuous, pulseless near-infrared wave analysis of both FORE-SIGHT® and EQUANOX® technology, we obtained $SctO_2$ values in the absence of spontaneous circulation. Furthermore, both technologies were able to assess the efficacy of CPR efforts: improved resuscitation efforts (improved quality of chest compressions with switch of caregivers) resulted in higher $SctO_2$ values. Until now, the ability of CPR to provide adequate tissue oxygenation was difficult to quantify or to assess clinically due to a lack of specific technology. With both technologies, any change in hemodynamics (e.g. ventricular fibrillation) results in a reciprocal change in $SctO_2$. In some patients, a sudden drop in $SctO_2$ was the first warning sign of reoccurring ventricular fibrillation.

Both the FORE-SIGHT® and EQUANOX® technology allow non-invasive monitoring of the cerebral oxygen saturation during CPR. Moreover, changes in $SctO_2$ values might be used to monitor the efficacy of CPR efforts.

4.1.2 Introduction

Monitoring the adequacy of oxygenation and circulation in patients during cardiopulmonary resuscitation (CPR) and advanced life support (ALS) remains a major challenge. Monitoring is limited to clinical observation of consciousness, pulse and breathing pattern (217). During CPR and ALS, pulse oximetry and non-invasive blood pressure measurement are unreliable. Additionally, an intermittent (every 2 minutes) rhythm check with ECG-electrodes or defibrillator paddles necessitates interruption of chest compressions. Currently, end-tidal CO_2 measurement is the best technique to monitor adequate circulation; it will increase sharply on return of spontaneous circulation (ROSC). However, end-tidal CO_2 can only be used in the intubated patient, is dependent on the ventilatory strategy and does not give information on the adequacy of cerebral oxygenation.

An "ideal" parameter to monitor the adequacy of oxygenation and circulation during CPR and ALS would have the following characteristics: easily (non-invasively) measured, continuous rather than intermittent information, neither requirement of pulsatile flow nor interruption of chest compressions. And last but not least, it should provide information on the oxygenation of vital organs (heart, kidney, brain).

Cerebral oximetry, based on near-infrared spectroscopy (NIRS) technology, provides information on brain oxygenation and the adequacy of cerebral perfusion (29). It measures regional cerebral oxygen saturation at the microvascular level (arterioles, venules and capillaries) (1, 16, 32, 218-220). There have been previous efforts to use cerebral oximetry during CPR with conflicting results (180, 221, 222). Recent developments allow to monitor absolute cerebral tissue oxygen saturations ($SctO_2$), without the need for calibration (FORE-SIGHT® technology)(173). The EQUANOX Advance® uses similar technology (40), but has the advantage of being portable and is as such more user friendly in the pre-hospital setting. Moreover, the EQUANOX® technology reveals minimal extracranial contamination compared to other commercially available NIRS technologies (35). Because of these promising properties (absolute saturation monitoring and transportable monitoring device), we tested the feasibility of both technologies in the CPR setting.

4.1.3 Patients and methods

In this observational study, data on cerebral tissue oxygen saturation was collected during in- and out-of-hospital cardiac arrest. The $SctO_2$ values were not blinded to the attending emergency physicians but were not used in any treatment protocol or therapeutic decision. The study was approved by the Committee for Medical Ethics, Ziekenhuis Oost-Limburg, Genk, Belgium. Requirement for informed patient consent was waived because of emergency setting.

Cerebral tissue oxygen saturation

Two emergency physicians, members of the medical emergency intervention team, used non-invasive cerebral monitoring during ALS for patients suffering from cardiac arrest (CA). Initially, a FORE-SIGHT® monitor (CAS Medical systems, Branford, CT, USA) was transported to the scene of CA. Due to its weight (9.8kg), a third person, not taking part in the medical rescue intervention, carried the monitor. On arrival, bilateral NIRS sensors were applied on the patient's forehead. From December 2011 on, the EQUANOX Advance® monitor (Nonin Medical Inc., Plymouth MN, US) was used. Since this monitor is light (0.9kg) and easily transportable, aid from a third person was not necessary. To minimize time delay, only one sensor was applied on the patient's right forehead. With both monitoring devices, cerebral tissue oxygen saturation ($SctO_2$) values were electronically collected from arrival until termination of CPR (or until transfer to the emergency unit of the hospital). With both technologies, protective adhesive tape was applied over the sensor(s) in order to minimize possible external light interference.

Cardiopulmonary resuscitation

Resuscitation procedures were performed in accordance with the Guidelines of the European Resuscitation Council. During ALS, patients were monitored with 3-lead ECG and $EtCO_2$. Once ROSC had been established, pulse oximetry and non-invasive blood pressure were monitored. In one patient, suffering from in-hospital cardiac arrest, invasive blood pressure monitoring was available during ALS.

Statistical analysis

Statistical analysis was performed using SPSS V19.0 (SPSS Inc, Chicago, USA). Equal distribution was tested using the Kolmogorov-Smirnov test. Values for cerebral oxygen saturation at each time point were compared using the

independent t-test. The results are represented as mean (± Standard Deviation). A p-value below 0.05 was considered statistically significant.

4.1.4 Results

In 16 cardiac arrest patients, NIRS monitoring was applied during CPR (five with FORE-SIGHT® and eleven with EQUANOX Advance® technology).
In two patients (EQUANOX®), it was impossible to obtain a value within the first three minutes of monitoring, and no further attempts were made to monitor $SctO_2$. Therefore, the results of only 14 patients will be reported.
Three of the five patients monitored with the FORE-SIGHT® monitor suffered from in-hospital cardiac arrest (IHCA), while the majority of patients (7 out of 9) monitored with the EQUANOX® monitor suffered from out-of-hospital cardiac arrest (OHCA). Two patients (both OHCA victims) monitored with the FORE-SIGHT® monitor survived (ROSC > 20 min). ROSC was observed in four patients (3 OHCA and 1 IHCA) monitored with the EQUANOX® monitor (Table 4. 1).
With both technologies, stable NIRS signals and reliable $SctO_2$ values were obtained within the first minute of sensor application, except for both patients previously described and excluded from further analysis.
Starting $SctO_2$ values (during basic life support) were between 0% and 51%, with a mean value of 27% (± 19%) (Table 4.1). Mean starting $SctO_2$ for IHCA was 34% (± 22%) whereas mean starting $SctO_2$ in OHCA was 23% (± 17%), which was not statistically significant ($p = 0.296$). Mean starting $SctO_2$ in survivors was 29% (± 15%) which was not significantly different from mean $SctO_2$ in non-survivors (25 ± 22%) ($p = 0.748$). Mean time of CPR before the first $SctO_2$ value was monitored is 29 ± 9 minutes in OHCA patients and 16 ± 6 minutes in IHCA patients (Table 4.2).
The highest $SctO_2$ values observed during CPR efforts were between 10 and 61%, with a mean value of 44% (± 15%). Highest $SctO_2$ values during CPR were neither significantly different between OHCA patients (41 ± 15%) and IHCA patients (48 ± 15%; p=0,442) nor between survivors (43 ± 18%) and non-survivors (45 ± 13%; p=0.778) of CA.

Table 4.1: Cerebral oxygen saturation during cardiopulmonary resuscitation

Patient	OH/IH	FS/EQ	ROSC?	Startvalue $SctO_2$ (%)	Highest $SctO_2$ (%) during CPR	Highest $SctO_2$ (%) during ROSC	$SctO_2$ (%) before transport
1	OH	FS	Yes	33	38	73	67
4	OH	FS	Yes	44	53	61	60
6	IH	EQ	Yes	15	58	81	82
11	OH	EQ	Yes	40	41	51	47
13	OH	EQ	Yes	5	10	58	65
14	OH	EQ	yes	37	55	67	46
Mean (± SD)				29 15	43 18	65 11	61 13
Patient	**OH/IH**	**FS/EQ**	**ROSC?**	**Startvalue $SctO_2$ (%)**	**Highest $SctO_2$ (%) during CPR**	**Highest $SctO_2$ (%) during ROSC**	**$SctO_2$ (%) at end CPR**
2	IH	FS	No	47	45		36
3	IH	FS	No	52	61		35
5	IH	FS	No	51	52		41
7	OH	EQ	No	3	38		0
8	OH	EQ	No	14	61		11
9	IH	EQ	No	7	24		8
10	OH	EQ	No	0	35		25
12	OH	EQ	No	30	42		36
Mean (± SD)				25 22	45 13		24 16

OH: out-of-hospital cardiac arrest; IH: in-hospital cardiac arrest; FS: Fore-Sight technology; EQ: Equanox Advance technology; ROSC: return of spontaneous circulation; $SctO_2$: regional cerebral tissue oxygen saturation

Table 4.2: Characteristics

	All patients	**OHCA**	**IHCA**
Number, n	14	9	5
Age, years (± SD)	66 (20)	65 (24)	67 (13)
Male, n	10	6	4
ROSC > 20 min	6	5	1
*Time between CA and first $SctO_2$ value, min.	25 (10)	29 (9)	16 (6)

Results are presented as mean (± SD).
OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest
* the exact time frame is missing in a number of patients

ROSC > 20 min (survivors) was observed in six patients (5 OHCA, 1 IHCA). In the five OHCA patients, highest $SctO_2$ values after ROSC were between 51 and 73% with a mean value of 62% (± 8%). The only IHCA-survivor showed $SctO_2$ values of 81% after ROSC. In these CA-survivors, $SctO_2$ values before transfer to the emergency unit were between 46 and 67% with a mean $SctO_2$ value of 57% (± 10%).
In OHCA patients where any further CPR effort was terminated, $SctO_2$ values at stop of CPR were between 0 and 36%, with a mean $SctO_2$ value of 18% (± 16%). In IHCA patients, $SctO_2$ values were between 8 and 41% (mean 30 ±15%) when CPR was stopped, which was not different from OHCA patients (p=0.311) (Table 4.2). $SctO_2$ values at the end of CPR were significantly lower (p=0.001) in patients not surviving CA compared with those who were transferred to the emergency unit.
As $SctO_2$ monitoring during CPR provides continuous information during extremely difficult and rapidly changing conditions, relevant information from $SctO_2$ during the CPR efforts is further elucidated by presenting the data of 4 individual patients (Figures 4.1-4.4).

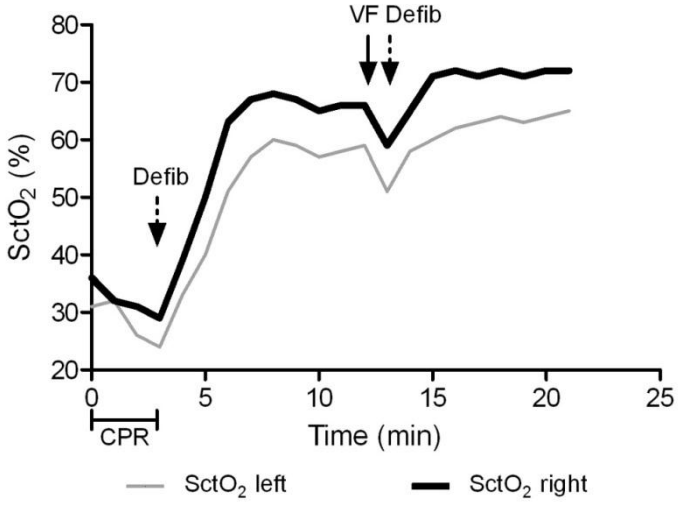

Figure 4.1: Cerebral tissue oxygen saturation ($SctO_2$ (%))(monitored with FORE-SIGHT® technology) during out-of-hospital cardiac arrest (patient 1). After 15 min of BLS, first measured $SctO_2$ values were 31% and 38% over the left (grey line) and right (black line) fontal region. Defibrillation (dotted arrow) resulted in ROSC and an immediate increase in $SctO_2$ to 60% (left) and 69% (right). During preparation for transport, ventricular fibrillation (arrow) reoccurred and was accompanied with an immediate decrease in $SctO_2$. Again, defibrillation (dotted arrow) resulted in sinus rhythm and $SctO_2$ values above 65%.
CPR: Cardiopulmonary resuscitation Defib: defibrillation VF: ventricular fibrillation

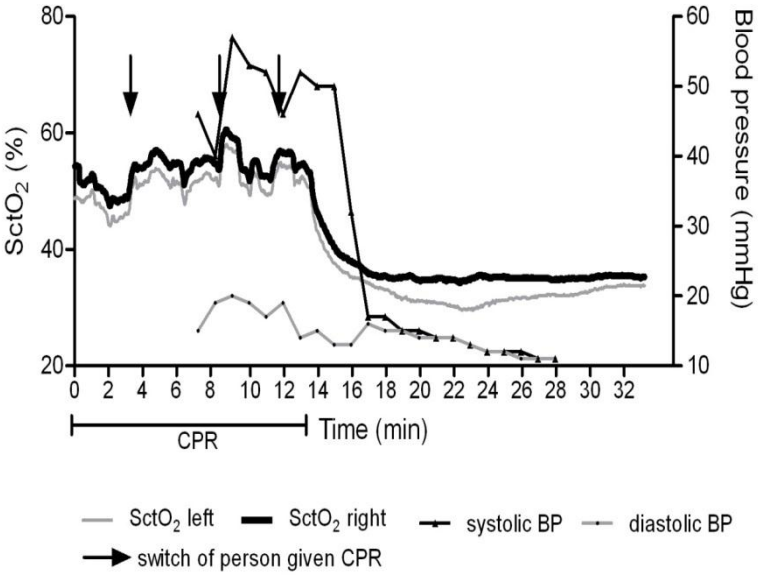

Figure 4.2:Cerebral tissue oxygen saturation ($SctO_2$ (%)) (monitored with FORE-SIGHT® technology) and arterial blood pressure (mmHg) in an in-hospital cardiac arrest patient (patient 3). After 14 min of BLS by a trained caregiver, first measured $SctO_2$ values were 48% and 52% over the left (grey line) and right (black line) fontal region. Switch of person given CPR (arrows) resulted in increased cerebral oxygen saturations. Parallel

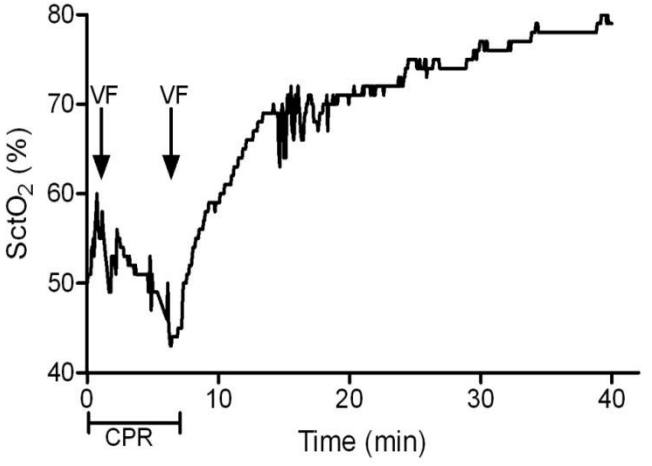

Figure 4.3: Cerebral tissue oxygen saturation ($SctO_2$ (%)) (monitored with EQUANOX Advance® technology) in a patient (patient 6) who collapsed at the ER entrance. The sensor was applied after six minutes of CPR and two defibrillation attempts. $SctO_2$ started at 50% and increased to 60%, right before ventricular fibrillation reoccurred (arrows). When ROSC was achieved, $SctO_2$ increased immediately above 70%.
CPR: Cardiopulmonary resuscitation VF: ventricular fibrillation

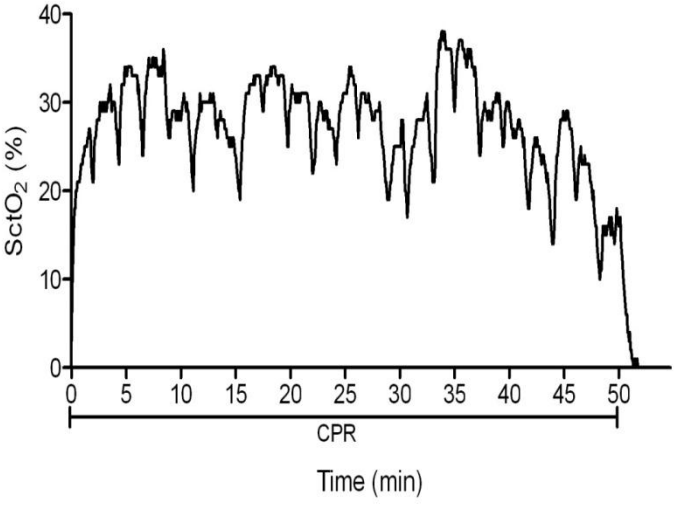

Figure 4.4:Cerebral tissue oxygen saturation ($SctO_2$ (%)) (monitored with EQUANOX Advance® technology) during out-of-hospital cardiac arrest (patient 7). The starting $SctO_2$ value (after 20 min of BLS) was 3%, but rose quickly to 21%. The highest measured value during CPR was 38%. A decrease in $SctO_2$ was observed during rhythm assessment (every 2 min.). CPR was stopped 50 minutes after arrival of the medical emergency team, without obtaining ROSC. After termination of CPR, $SctO_2$ decreased rapidly. CPR: cardiopulmonary resuscitation

4.1.5 Discussion

This is the first report on the use of the ForeSight® and EQUANOX Advance® technology during in- and out-of-hospital CPR. Both technologies use 4 precise infrared wavelengths to maximize the accuracy of oxyhemoglobin and de-oxyhemoglobin measurement and to enable absolute oxygen saturation monitoring (and not just trend-only monitoring). In a recent comparison of accuracy performance (referring to weighted CO-oximeter reference values), the FORE-SIGHT® monitor measured cerebral oxygenation most precisely, followed by the EQUANOX Advance® monitor (39), providing increased confidence in the utilization of this technology in the CPR setting.
Due to the continuous, pulseless wave analysis of both technologies, we were able to monitor the cerebral oxygen saturation in 9 OHCA-patients and 5 IHCA-patients during CPR with two different NIRS-devices. The most important difference between both technologies is the respective weight of both monitors. The EQUANOX® monitoring device is light (0.8kg) and therefore, the most suited for use during out-of-hospital CPR.
Newman *et al*. already assessed the feasibility of NIRS to measure cerebral perfusion during OHCA (180). However, they rarely detected cerebral perfusion or cerebral oxygen saturation using the Invos-3000® technology during CPR. A longer time interval from arrest to initial cerebral oxygen saturation measurements may partially explain the difference between their OHCA-report and previous experience during in-hospital CPR (221, 222).
Recently, several papers were dedicated to the use of INVOS®-NIRS technology in the post-CA area, indicating its potential role in predicting survival and neurological outcome after CA. One of the earliest, although small, OHCA studies demonstrated that all patients surviving for one week achieved a significantly higher median rSO_2 (regional brain oxygen saturation) during CPR efforts than non-survivors (223). Also, Ito *et al.* monitored rSO_2 (INVOS® technology) and noted that any rSO_2 value below 25%, observed on hospital admission in a post-CA patient without ROSC (despite continued CPR efforts), could be interpreted as a potential indicator of futile resuscitation attempts (224). Kämäräinen *et al.* reported on rSO_2 (INVOS® technology) and concluded that improving CPR quality did not result in a significant increase in rSO_2 (179). It should be noted that they described substantial difficulties in reliable recordings of rSO_2 data with INVOS 5100C® technology as 59% of their 30 seconds data had artifacts making quantification of rSO_2 impossible. Most recently, Parnia *et al* (using INVOS®) concluded that IHCA-patients with ROSC had an rSO_2 above 30% for > 50% of their CPR duration, whereas non-survivors had an rSO_2 that was below 30% for > 50% of their CPR period (181, 225). It therefore stands to reason that cerebral oximetry may have a role in predicting ROSC and the optimization of cerebral oxygenation during cardiac arrest.

In our 14 patients, starting $SctO_2$ values were between 0% and 52%. This high

variability could be explained by the fact that we measured both IHCA and OHCA patients and that there was a high variability in time from collapse to first monitored $SctO_2$ value in both groups. Furthermore, not all CPR characteristics were available for all patients. Surprisingly, when using the EQUANOX Advance® monitor, a starting value of 0% $SctO_2$ was observed in one patient and an end-of-CPR value of 0% in another patient. Whereas the EQUANOX Advance® monitor displays these $SctO_2$ values of 0%, the lowest $SctO_2$ value observed with the FORE-SIGHT™ monitor was around 30%. Due to the proprietary algorithms behind both cerebral oximetry monitors it is impossible to provide any further explanation at present. More data are needed to elucidate the exact significance of these extremely low values, and to exclude any possible interference from technical artifacts.
We observed an immediate increase in $SctO_2$ after ROSC and found significantly higher $SctO_2$ values in patients with permanent ROSC compared to patients in whom no further CPR effort was continued. Furthermore, in 4 of our patients, new episodes of ventricular fibrillation were immediately noted on the $SctO_2$ monitoring, as an extra monitoring device indicated this life-threatening situation with urgent need for CPR.
$SctO_2$ monitoring provides not only a tool for continuous estimation of cerebral oxygenation during the status of no ROSC, but also the ability to assess the efficacy of CPR efforts. We observed parallel increases in systolic arterial pressure during CPR (in patient 3) and in $SctO_2$, illustrating the positive effect of CPR on systolic blood pressure and on cerebral oxygenation. Switch of caregivers during mechanical chest compression, resulted in increased systolic blood pressure and $SctO_2$ (figure 4.2). The immediate effect of efficient CPR on cerebral oxygenation is illustrated in the rapid decrease in $SctO_2$ during rhythm analysis (and consequent interruption of CPR) (figure 4.4).

Limitations of this study include the small number of patients, which makes it difficult to conclude on the exact value of $SctO_2$ in CA patients. A second limitation is the fact that we used two different technologies (FORE-SIGHT® and EQUANOX Advance®). Although both technologies use 4 wavelengths and display absolute saturation values (without need for calibration), they do use different (proprietary) algorithms to display their calculated $SctO_2$ values. The EQUANOX Advance® oximeter is shown to have less contamination of extracranial vessels compared with the FORE-SIGHT® oximeter (35), but for both oximeters, accuracy is without doubt acceptable (39). These differences in algorithms can probably be used to explain the different values displayed in extreme conditions. The major limitation of this study was that it was designed as a pilot feasibility study and that not all patient or CPR characteristics are available. A future, randomized, multicenter study will be initiated on the use of NIRS during CPR with the inclusion of all CPR data following the Utstein CPR data registration. Finally, larger and properly designed studies will have to elucidate the potential role of $SctO_2$ monitoring during CPR.

4.1.6 Conclusion

In conclusion, using FORE-SIGHT® and EQUANOX® technology, it is possible to monitor the absolute cerebral tissue oxygen saturation during CPR after IHCA and OHCA. Moreover, changes in cerebral oxygen saturation seem to vary with the quality of chest compressions reflecting changes in cerebral oxygenation. Future studies on the prognostic role of cerebral oximetry during CPR are needed.

CHAPTER 5

General discussion

5.1 Cerebral oxygen saturation and neurocognitive outcome

We conducted two observational studies with patients undergoing arthroscopic shoulder surgery in the beach chair position (BCP) or lateral decubitus position (LDP). In concordance with others (46, 47, 50, 54), we observed cerebral desaturation events when patients were operated in the sitting position (Chapter 2.2 and 2.3). With the use of data of healthy volunteers, we determined a lower threshold value for cerebral oxygenation (measured with FORE-SIGHT®) of 60%, as safe for patients undergoing surgery in the BCP (Chapter 2.2). However, desaturation events (<60% or < 55%) were not associated with neurocognitive impairment after surgery (Chapter 2.3).

Could we therefore conclude that noninvasive cerebral oxygenation monitoring during surgery in the BCP is rather a toy than a helpful tool? We do not believe it is.
There are several possible explanations why we could not find an association between cerebral desaturation and neurocognitive outcome.
First, our patients in de BCP showed mean lowest $SctO_2$-values of 55% (Chapter 2.2) and 59% (Chapter 2.3), without a correlation with neurocognitive outcome. The ischemic threshold of jugular venous oxygen saturation was suggested to be 45% (226). It is believed that the ischemic threshold of $SctO_2$ would be 10% higher. Hypoxic-ischemic piglet studies showed that neurological injury depends on the severity (73) and duration (74) of cerebral desaturations. Furthermore, McCulloch *et al*. observed a mean 22% (range 6-33%) decrease in middle cerebral artery blood flow velocity when position was changed to the BCP (52). During awake carotid endarterectomy, is was proposed that 50% reduction in mean flow velocity lead to detectable ischemic symptoms (100% sensitivity, 85% specificity) (227). Although these studies were not all conducted in the same patient population as ours, this could indicate that desaturation events in our patients might just be not severe enough to cause cerebral ischemia or that a short period of ischemia is well tolerated. Consequently, the lower safe threshold of 60%, that we proposed (in Chapter 2.2), might be overestimated. It stands to reason that it is difficult and unethical to induce different degrees of desaturation to investigate the critical threshold in $SctO_2$-values for neurological damage in patients. We therefore used data from a group of volunteers to detect the body's natural response in maintaining $SctO_2$-values in the BCP. However, comparison between (awake) volunteers and patients (under general anesthesia) should be interpreted with some caution. The difference in age, co-morbidities and ventilator management between volunteers and patients should be kept in mind. Furthermore, anesthesia reduces the brains' metabolism with 57% (propofol-anesthesia) compared to the awake brain (81), which might protect patients for ischemia to some extent. This could imply that $SctO_2$ values below 60% are well tolerated in anesthetized patients. However, in cardiac,

thoracic or abdominal surgery patients, postoperative neurocognitive decline and complications were related to cerebral oxygenation values < 60% (2-4, 71, 86, 107). This could imply that not all patients have the same response to desaturation events, which leads us to the second possible explanation for the lack in association between cerebral oxygenation and neurocognitive outcome. Longer exposure times, which is more likely in longer cardiac surgeries, could increase the risk for postoperative cognitive dysfunction (3) and extended hospital stay (2). Furthermore, patients undergoing shoulder surgery are often younger than patients with need for cardiac, thoracic of abdominal surgery, which makes the risk for long-term cognitive problems after surgery lower (115). Additionally, Schoen *et al*. observed that patients with pre-operatively impaired cognitive function and low cerebral oxygenation values before induction of anesthesia may be at risk for developing cerebral desaturation events (114). Low pre-operative $SctO_2$-values were also associated with post-operative delirium (228). Our relatively young, healthy population might therefore have a higher cognitive reserve than patients in need for cardiac, thoracic or abdominal surgery (229).

Third, the used technology. The accuracy of the NIRS technology in detecting cerebral ischemia in the BCP has been questioned. As described in Chapter 1, values for cerebral oxygenation are calculated based on the assumption of a fixed arterial/venous ratio (31). This arterial/venous ratio can considerable differ between individuals (32) and can dynamically change during hypoxia (39). Furthermore, this ratio could potentially alter when position is changed to the BCP. Any difference in cerebral oxygenation could therefore be caused by a real changes in oxygen saturation levels or be the results of a change in the cerebral arterial/venous ratio. However, in volunteers or patients under regional anesthesia, cerebral oxygen saturation was independent of body position and changed only minimally with a change to the sitting position (48-50). Additionally, although most NIRS monitors are provided with an algorithm to remove the signal of extracerebral tissues from the actual value, this still might contribute significantly to the signal (35). However, changes in jugular venous bulb oxygenation (51) and middle cerebral artery blood velocity (52) were reported in patients in the upright position, which could indicate reduced cerebral blood flow. We could therefore assume a large intracranial contribution to the NIRS signal. As with jugular bulb oximetry, NIRS is believed to serve as an indirect measurement of cerebral blood flow. But, no large clinical studies were conducted to validate this. Taussky *et al*. performed a small, retrospective study in brain-injured patients and reported a linear correlation between cerebral NIRS and regional cerebral blood flow on CT perfusion imaging (33). Therefore, the authors concluded that NIRS may serve as a useful tool to assess brain oxygenation. Unlike CT imaging, NIRS only measures cerebral oxygenation in the prefrontal cortex of the brain. Desaturation events in other parts of the brain may therefore be unnoticed. Fortunately, the prefrontal cortex is important for, among others, executive functioning (230), a major target in our

neurocognitive tests. If the desaturation events observed in our study caused neurocognitive deficits, we should have been able to detect it with our highly sensitive tests.
In arthroscopic shoulder surgery, NIRS is the most recommended technology to monitor the brain; jugular bulb oximetry is invasive, difficult to use and may overlook regional differences in cerebral oxygenation, transcranial doppler sonography is not applicable in all (especially older) patients and not so easy to use correctly, CT imaging is not continuously and involves X-ray exposure.

In conclusion, cerebral oxygen saturation monitoring using NIRS is a non-invasive, continuous and easy to use technology in patients undergoing (shoulder)surgery. Although we did not observe an association between cerebral desaturation events and neurocognitive outcome in our patient population, more and larger studies should be performed on this topic. Furthermore; other patient groups (older patients, major surgery, high risk patients, …) might be more vulnerable during surgery and benefit from cerebral oxygenation monitoring.

Future directions:

1. Our results concerning a lack in association between cerebral desaturation events and early post-operative neurological impairment should be evaluated in larger studies. In the meantime, cerebral oxygenation monitoring during shoulder surgery in the BCP should be applied to detect and resolve desaturation events.

2. More research should be done in high risk patients undergoing surgery in the BCP. These patients are more likely older (>60 years) with lower cognitive reserve. These patients have often no problems in daily life, routine circumstances and therefore difficult to select. However, they could be more vulnerable to desaturation events. Cerebral oxygenation monitoring could help to identify these patients (low pre-operative values) and detect intra-operative cerebral hypoperfusion early.

3. It is very difficult to specify a threshold for cerebral ischemia/hypoxia during shoulder surgery. However, effort should be made to define these threshold values for cerebral ischemia, either absolute values or relative changes.

5.2 Cerebral oxygen saturation during hypothermia

Several factors can potentially compromise cerebral oxygen delivery and induce secondary cerebral injury in the hours to days after cardiac arrest (CA) (e.g. hypotension, hypoxemia and impaired autoregulation). Early detection and treatment of cerebral hypoxia/ischaemia in this critical phase could contribute to a better neuroprotective approach. We therefore performed an observational study in post-CA patients treated with therapeutic hypothermia (TH)(202). We showed a decrease in cerebral oxygenation in the first hours after the start of hypothermia. Three hours after start of TH, non-survivors showed significantly lower cerebral oxygenation values compared to survivors.

Early prognostication is important to inform family members and to prevent futile treatment and prolonged suffering, but is also very challenging (231). Due to hypothermia and the use of sedatives and analgesics, accurate assessment by clinical and neurophysiological examination is suggested to be postponed until at least 72 hours after return to normothermia (232). Could NIRS have the potential to predict outcome in post-CA patients treated with TH? In our study, we observed a difference between survivors and non-survivors in cerebral oxygenation values, three hours after the start of TH (202). Our study was not designed to nor had the power to conclude on the ability of NIRS to predict outcome. Ahn *et al*. included 21 post-CA patients and analyzed the median cerebral oxygenation values over the first 24 hours and 24-48 hours following return of spontaneous circulation (ROSC) (233). They observed significantly lower median cerebral oxygenation values for non-survivors in the first 24 hours after ROSC compared to survivors (63% versus 68%). In the subsequent 24-48 hours following ROSC, the difference between survivors and non-survivors was non-significant. However, also this study was not designed to determine the role of NIRS as predictor of outcome. Storm *et al*. used NIRS to measure cerebral oxygenation in 60 post-CA patients treated with TH, in order to investigate its role as predictor of outcome (12). Patients with good outcome (CPC 1-2) had significantly higher median cerebral oxygenation values during the first 40 hours after ROSC, compared with patients with a poor outcome (CPC 3-5). ROC analysis showed a threshold value for cerebral oxygenation of 50% as a predictor for poor outcome (70% specificity and 86% sensitivity). However, the high overlap in oxygenation values between survivors and non-survivors led to the authors' conclusion that there is limited potential for cerebral NIRS monitoring in the prediction of poor outcome in these patients (12).
To avoid patients with a favorable prognosis being falsely assigned to the patient group with an unfavorable prognosis, with the ethically unacceptable consequence of possible withdrawal in their medical treatment strategy, a prognostic parameter should achieve a very high specificity. The bispectral index (BIS), a value calculated from raw EEG information, might be a promising tool

for prognostication in post-CA patients. The non-invasive monitoring system was initially developed to assess the patient's level of consciousness during anesthesia (234) and provides a number between 0 (EEG silence) and 100 (awake). We evaluated BIS in 57 post-CA patients and observed that, 12 hours after admission, a BIS value ≤ 25.5 predicted mortality with a specificity of 100% and a sensitivity of 61% (*article submitted*). Furthermore, a BIS value of 0 was associated with 100% mortality. This promising technology in the prediction of neurological outcome was also described by others (235-238), and should be studied more extensively. However, a multimodal approach, with a combination of neurological examination and tools like BIS and NIRS, is probably the best way to improve outcome prediction in these patients (239).

Improving cerebral perfusion after CA is of great importance. Denault *et al*. proposed an algorithm to optimize those factors ($PaCO_2$, blood pressure, cardiac output, …) that can affect cerebral oxygen supply and/or demand during surgery (240). Early hemodynamic optimization may also improve outcome after CA (241, 242). Current American Heart Association guidelines for hemodynamic optimization are based on the assumption that the post-cardiac arrest syndrome is a sepsis like syndrome (201). However, the post-CA syndrome is a far more complex entity than a sepsis like syndrome alone. The cerebrovascular reactivity to changes in $PaCO_2$ is probably preserved (67, 187, 188). The regulatory system to counteract imbalances in oxygen supply caused by a change in blood pressure might be disturbed in the early post-CA phase (243). Aiming for the same hemodynamic goals as in sepsis patients might therefore not be sufficient (244). But how should these optimal targets be defined? Perhaps, optimization of hemodynamic and blood gas values in the post-CA patients to obtain or maintain cerebral perfusion can be guided by NIRS? The correlation between global hemodynamics, blood gas values, cerebral oxygenation and survival are poorly investigated (245). Recently, our research group analyzed these parameters in our prospectively monitored group of post-CA patients in order to identify the most optimal MAP, mixed venous oxygen saturation (SvO_2), $PaCO_2$ and PaO_2 and cerebral oxygenation value in the first 24 hours of admission (*article submitted/in preparation*). We showed a correlation of a MAP of 87 mmHg, SvO_2 of 72% and $PaCO_2$ of 40 mmHg with maximal survival. All of these values corresponded with a cerebral oxygenation value of 67%. However, these values are calculated from data from an observational study, we can therefore only report associations rather than deduce causation. Prospective randomized interventional studies should be performed to investigate if reaching or maintaining these targets could increase survival rates.

A few months ago, the multicenter *targeted temperature trial* created quite a stir among post-CA care physicians and researchers (197). The study showed no significant benefit for a targeted body temperature of 33°C compared to a body temperature of 36°C. Although this study should be interpreted with care, future hypothermia protocols may differ from todays. Therefore, survival,

hemodynamic and ventilator targets will probably need adjustment over time. Future studies will have to demonstrate the role of cerebral NIRS in post-CA care. The known limitations (extracranial contamination, ambient light) of the technology should be taken into account when evaluating cerebral oximetry.

In conclusion, post-CA patients are vulnerable and would benefit from a tool that could detect or improve their outcome. Cerebral oximetry is a promising technology but research is still in its infancy in this patient population. More research and large studies are needed to elucidate the potential role of NIRS, which could be as a predictor of outcome or to guide patients' therapy.

Future directions:

1. Large prospective observational trials should be performed to determine if NIRS could play a role in the prediction of outcome. The level of desaturation that is associated with poor outcome should also be assessed. Neurocognitive testing in discharged post-CA patients could help to differentiate in neurological outcome.

2. Large randomized controlled clinical trials should investigate the role of NIRS to guide goal-directed treatment in post-CA patients treated with TH.

5.3 Cerebral oxygen saturation during cardiac arrest

Current monitoring during cardiopulmonary resuscitation (CPR) is limited to the clinical observation of consciousness, breathing pattern, the presence of a pulse and, in the best case, monitoring of end-tidal carbon dioxide ($EtCO_2$). Although the adequacy of cerebral oxygenation during CPR is critical for neurological outcome and thus survival, none of the aforementioned monitoring techniques are able to give information on brain perfusion. We therefore assessed the feasibility of cerebral NIRS during CPR. In our small observational study, 14 out of 16 cardiac arrest patients undergoing in-hospital or out-of-hospital CPR were successfully monitored by either FORE-SIGHT® or EQUANOX Advance® technology. The feasibility of NIRS during CPR was confirmed by other investigators. The power in our study was too small to draw conclusions on the exact role of cerebral oxygenation in this situation. However, several papers were dedicated to the use of NIRS during CPR, most of them published in the last two years.

Cerebral NIRS monitoring might be helpful in answering some vital question during CPR.
First, can cerebral oximetry predict outcome? Several papers suggested that NIRS could play a meaningful role in this critical question (178, 181, 224, 246-249). Not all of these papers used the same value of cerebral oxygenation to predict outcome. Ito *et al*. used initial values of cerebral oxygenation (more specifically, the lowest value measured during a 1 minute monitoring period during CPR at hospital arrival) to predict outcome (224, 246). They observed higher values for patients with a good outcome at hospital discharge (224) and 90 days after cardiac arrest (246). Patients who survived with good neurological outcome showed initial cerebral oxygenation levels of more than 40% (224, 246). Others showed that mean cerebral oxygenation values during CPR were higher in survivors of cardiac arrest compared to non-survivors and therefore a good predictor of outcome (181, 247). However, the study of Ahn *et al*. suggested that these mean values during CPR are only higher in survivors with pulseless electrical activity or asystole as initial rhythm (249). This could imply that cerebral oxygenation measurement has no utility in determining survival in patients with an initial shockable rhythm. More studies are needed to confirm this.
Cerebral oxygen saturation monitoring could probably be more useful as a dynamic measurement instead of a static (225, 250). In this way, low initial cerebral oxygenation values could be interpreted as a need for interventions aiming at improved cerebral oxygenation during CPR. When cerebral oxygenation remains low, despite of maximal interventions, CPR efforts might become futile. Parnia *et al*. (181) and Ahn *et al*. (249) suggested time above or below a certain oxygenation threshold during resuscitation as predictor for

survival. In this way, persisted low (<30%) cerebral oxygenation values, during optimal resuscitation, could indicate futility of CPR effort (249). Not surprisingly, survivors spent more time above cerebral oxygenation values of 40% during CPR compared to non-survivors (181). Furthermore, patients with return of spontaneous circulation also show a higher increase in cerebral oxygenation throughout resuscitation compared to non-survivors (181, 248). All these results show a potential role for cerebral oximetry in the prediction of outcome during resuscitation.

Second, quality of chest compression is of prime importance during cardiac arrest resuscitation. Can NIRS serve as a guidance to optimize these chest compressions? Automated mechanical chest compression devices were developed to perform CPR with the recommended depth and rate. Parnia *et al*. observed significant higher values for cerebral oxygenation during mechanical compared to manual chest compression (251). As Parnia *et al*. described in another study (181), we also observed increased cerebral oxygenation when CPR efforts were optimized (in parallel with an increase in blood pressure in one patient). This could imply that cerebral oximetry has the potential to measure the quality of chest compression during CPR. In this way, effort could be made the optimize chest compressions and therefore cerebral oxygenation. As stated previously, when cerebral oxygenation remains low, despite of optimized compression and interventions, any further effort might be futile.

Third, these results indicate the possibility to monitor quality and utility of resuscitation. But when should cerebral oximetry be applied? All of the studies mentioned in this discussion were conducted when the patient (still undergoing CPR) arrived at the emergency room. However, in our country, decision on the utility or futility of CPR efforts is often made outside the hospital, where limited medical staff is present and a tool for early determination on patient's outcome could be of great value. We showed that it is possible to monitor cerebral oxygenation out-of-hospital, at arrival of the medical team, without losing critical time (chapter 4). Our research group started an observational multicenter study to monitor cerebral oxygenation during CPR in out-of-hospital resuscitations (NCT01806844). In combination with the collection of other variables (no-flow time, low-flow time, bystander CPR, …), it is the goal to define if cerebral oximetry has an additive value to predict outcome during out-of-hospital CPR. Another possible benefit of applying cerebral oximetry in the out-of-hospital situation is its ability to monitor the transport of the patient (regardless of whether spontaneous circulation is achieved or CPR is still ongoing). Patients are often hemodynamically instable and standard monitoring might not always be reliable during transport. Weatherall *et al*. showed no impact of patient or transport movements on the signal during road and helicopter transport in healthy volunteers (252). In comparison with the case series of Frisch et al. (13), we noticed fast decline in cerebral oxygenation when re-arrest occurred and rapid increase when circulation was once again restored

during transport in our patients (chapter 4). In this, often difficult situation, NIRS could provide reliable monitoring of cerebral oxygenation.

As in other circumstances where NIRS has been used, the limitations of the technology and devices should be kept in mind. We used the FORE-SIGHT® and EQUANOX® Advanced technology. Both devices performed well during CPR. However, the FORE-SIGHT® device that we used has a weight of almost 10 kg, which limits its use in the out-of-hospital setting. The new FORE-SIGHT® Elite is more compact and less heavy, but its use in these circumstances has not been tested yet. The EQUANOX® Advance was, with its weight of less than one kg, easier to use out-of-hospital. However, we noticed cerebral oxygenation values of 0% with EQUANOX® at the start or end of CPR. Such a value was never measured with FORE-SIGHT® in our population. Other studies used the INVOS® technology, in which values below 15% are not displayed (180, 181). Future research should point out if this 0% (with EQUANOX®) is a reliable value or a technical artifact. Also, the impact of extracranial contamination (35) and ambient light (36) should be considered in the interpretation of cerebral oximetry results.

In conclusion, cerebral NIRS monitoring is feasible during resuscitation, even in out-of-hospital situations. There are promising results suggesting that this technology could be of additive value to guide quality of chest compressions and predict outcome during CPR. However, more research should be done before cerebral oximetry can be recommended as standard monitoring technique during resuscitation.

Future directions:

1. Large multicenter studies should be conducted to elucidate the potential role of cerebral NIRS during resuscitation. Other information, such as time of arrest, no-flow and low-flow time, end-tidal carbon dioxide, bystander CPR, time before first cerebral oxygenation value, … should be used in the interpretation of the results. Especially in out-of-hospital situations, $EtCO_2$ and NIRS should be compared and evaluated.
   (Genbrugge et al. NCT01806844)

2. The detection of an increase in cerebral oxygenation during optimal resuscitation efforts are probably the most promising to predict outcome. More studies should be conducted to confirm these results.

3. There is growing evidence that extracorporeal CPR can increase survival rates (253, 254). However, this is a highly invasive and resource-consuming procedure and therefore impossible to apply it to all patients with OHCA. An increase in cerebral oxygenation during resuscitation

could perhaps be an indication that a patient would be eligible for extracorporeal CPR. Cerebral oxygenation monitoring should therefore be considered in future research on extracorporeal CPR in OHCA-patients.

4. Quality of chest compression is of vital importance. Future studies could compare quality of compression with values for cerebral oxygenation and neurological outcome, perhaps based on CPC-scores.

5.4 In general

Near-infrared spectroscopy is a non-invasive technology which allows continuous monitoring of regional cerebral oxygen saturation. The technology has a promising future but research is still relatively young. Regardless of its use in the operating room, intensive care unit or in situations out of the hospital, large prospective observational trials should be performed to determine the association between outcome and cerebral desaturation. Randomized controlled trials to define algorithms, aiming at maintaining or restoring cerebral oxygen saturation could then be initiated. As with other available tools, the results of these trials should be interpreted with the limitations of the several NIRS devices in mind.

References

1. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science. 1977;198(4323):1264-7.
2. Fischer GW, Lin H-M, Krol M, Galati MF, Di Luozzo G, Griepp RB, et al. Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. The Journal of thoracic and cardiovascular surgery. 2011;141(3):815-21.
3. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. Br J Anaesth. 2012;108(4):623-9.
4. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesthesia & Analgesia. 2007;104(1):51-8.
5. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. The heart surgery forum. 2004;7(5):E376-E81.
6. Mille T, Tachimiri ME, Klersy C, Ticozzelli G, Bellinzona G, Blangetti I, et al. Near infrared spectroscopy monitoring during carotid endarterectomy: which threshold value is critical? European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2004;27(6):646-50.
7. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. Journal of clinical anesthesia. 2005;17(6):463-9.
8. Bhatti MT, Enneking FK. Visual loss and ophthalmoplegia after shoulder surgery. Anesth Analg. 2003;96(3):899-902.
9. Smith JJ, Porth CM, Erickson M. Hemodynamic response to the upright posture. Journal of clinical pharmacology. 1994;34(5):375-86.
10. Alperin N, Lee SH, Sivaramakrishnan A, Hushek SG. Quantifying the effect of posture on intracranial physiology in humans by MRI flow studies. Journal of Magnetic Resonance Imaging. 2005;22(5):591-6.
11. Greisen G, Leung T, Wolf M. Has the time come to use near-infrared spectroscopy as a routine clinical tool in preterm infants undergoing intensive care? Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2011;369(1955):4440-51.
12. Storm C, Leithner C, Krannich A, Wutzler A, Ploner C, Trenkmann L, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients—A prospective outcome study. Resuscitation. 2014;85(5):1037-41.

13. Frisch A, Suffoletto BP, Frank R, Martin-Gill C, Menegazzi JJ. Potential utility of near-infrared spectroscopy in out-of-hospital cardiac arrest: an illustrative case series. Prehospital Emergency Care. 2012;16(4):564-70.
14. Suffoletto B, Kristan J, Rittenberger JC, Guyette F, Hostler D, Callaway C. Near-infrared spectroscopy in post-cardiac arrest patients undergoing therapeutic hypothermia. Resuscitation. 2012;83(8):986-90.
15. Elwell C, Phil E. A practical users guide to near infrared spectroscopy. Hamamatsu Phonotonics KK, London1995.
16. Madsen PL, Secher NH. Near-infrared oximetry of the brain. Progress in neurobiology. 1999;58(6):541-60.
17. Horecker BL. The absorption spectra of hemoglobin and its derivatives in the visible and near infra-red regions. Journal of biological chemistry. 1943;148(1):173-83.
18. Pellicer A, Bravo Mdel C. Near-infrared spectroscopy: a methodology-focused review. Seminars in fetal & neonatal medicine. 2011;16(1):42-9.
19. Palmer KF, Williams D. Optical properties of water in the near infrared. JOSA. 1974;64(8):1107-10.
20. Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EOR. Characterization of the near infrared absorption spectra of cytochrome aa3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1988;933(1):184-92.
21. Strangman G, Boas DA, Sutton JP. Non-invasive neuroimaging using near-infrared light. Biological psychiatry. 2002;52(7):679-93.
22. Siggaard-Andersen O, Nørgaard-Pedersen B, Rem J. Hemoglobin pigments. Spectrophotometric determination of oxy-, carboxy-, met-, and sulfhemoglobin in capillary blood. Clinica Chimica Acta. 1972;42(1):85-100.
23. Heekeren HR, Kohl M, Obrig H, Wenzel R, von Pannwitz W, Matcher SJ, et al. Noninvasive assessment of changes in cytochrome-c oxidase oxidation in human subjects during visual stimulation. Journal of Cerebral Blood Flow & Metabolism. 1999;19(6):592-603.
24. Matcher S, Cooper C. Absolute quantification of deoxyhaemoglobin concentration in tissue near infrared spectroscopy. Physics in medicine and biology. 1994;39(8):1295-312.
25. Cope M. The application of near infrared spectroscopy to non invasive monitoring of cerebral oxygenation in the newborn infant 1991.
26. Cope M, Delpy DT, Reynolds EO, Wray S, Wyatt J, van der Zee P. Methods of quantitating cerebral near infrared spectroscopy data. Adv Exp Med Biol. 1988;222:183-9.
27. Madsen PL, Skak C, Rasmussen A, Secher NH. Interference of cerebral near-infrared oximetry in patients with icterus. Anesthesia & Analgesia. 2000;90(2):489-93.

28. Doornbos R, Lang R, Aalders M, Cross F, Sterenborg H. The determination of in vivo human tissue optical properties and absolute chromophore concentrations using spatially resolved steady-state diffuse reflectance spectroscopy. Physics in medicine and biology. 1999;44(4):967-81.
29. Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. Canadian Journal of Applied Physiology. 2004;29(4):463-87.
30. Germon T, Evans P, Barnett N, Wall P, Manara A, Nelson R. Cerebral near infrared spectroscopy: emitter-detector separation must be increased. British journal of anaesthesia. 1999;82(6):831-7.
31. McCormick PW, Stewart M, Goetting MG, Balakrishnan G. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. Stroke. 1991;22:596-602.
32. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology. 2000;93(4):947-53.
33. Taussky P, O'Neal B, Daugherty WP, Luke S, Thorpe D, Pooley RA, et al. Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients. Neurosurgical focus. 2012;32(2):E2.
34. Dunham CM, Sosnowski C, Porter JM, Siegal J, Kohli C. Correlation of noninvasive cerebral oximetry with cerebral perfusion in the severe head injured patient: a pilot study. Journal of Trauma-Injury, Infection, and Critical Care. 2002;52(1):40-6.
35. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. Anesthesiology. 2012;116(4):834-40.
36. Zaouter C, Arbeid E. Influence of ambient light on cerebral oximeters. Br J Anaesth. 2010;105(6):873-4.
37. MacLeod D, Ikeda K, Keifer J, Moretti E, Ames W. Validation of the CAS adult cerebral oximeter during hypoxia in healthy volunteers. Anesth Analg. 2006;102(2S):S162.
38. Ikeda K, MacLeod D, Grocott H, Moretti E, Ames W, Vacchiano C. The Accuracy of a Near-Infrared Spectroscopy Cerebral Oximetry Device and Its Potential Value for Estimating Jugular Venous Oxygen Saturation. Anesth Analg. 2014. Epub 10/13/2014.
39. Bickler PE, Feiner JR, Rollins MD. Factors Affecting the Performance of 5 Cerebral Oximeters During Hypoxia in Healthy Volunteers. Anesthesia and analgesia. 2013;117(4):813-23.
40. MacLeod DB, Ikeda K, Vacchiano C, Lobbestael A, Wahr JA, Shaw AD. Development and validation of a cerebral oximeter capable of absolute accuracy. Journal of cardiothoracic and vascular anesthesia. 2012;26(6):1007-14.

41. Skyhar MJ, Altchek DW, Warren RF, Wickiewicz TL, O'Brien SJ. Shoulder arthroscopy with the patient in the beach-chair position. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 1988;4(4):256-9.
42. Peruto CM, Ciccotti MG, Cohen SB. Shoulder arthroscopy positioning: lateral decubitus versus beach chair. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2009;25(8):891-6.
43. Provencher CMT, McIntire ES, Gaston TM, Frank RM, Solomon CDJ. Avoiding complications in shoulder arthroscopy: pearls for lateral decubitus and beach chair positioning. Techniques in Shoulder & Elbow Surgery. 2010;11(1):1-3.
44. Rains DD, Rooke GA, Wahl CJ. Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2011;27(4):532-41.
45. Morandi X, Riffaud L, Amlashi SF, Brassier G. Extensive spinal cord infarction after posterior fossa surgery in the sitting position: case report. Neurosurgery. 2004;54(6):1512-6.
46. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, et al. Cerebral oxygen desaturation events assessed by near-infrared spectroscopy during shoulder arthroscopy in the beach chair and lateral decubitus positions. Anesthesia & Analgesia. 2010;111(2):496-505.
47. Moerman AT, De Hert SG, Jacobs TF, De Wilde LF, Wouters PF. Cerebral oxygen desaturation during beach chair position. European Journal of Anaesthesiology (EJA). 2012;29(2):82-7.
48. YaDeau JT, Liu SS, Bang H, Shaw PM, Wilfred SE, Shetty T, et al. Cerebral oximetry desaturation during shoulder surgery performed in a sitting position under regional anesthesia. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2011;58(11):986-92.
49. Koh JL, Levin SD, Chehab EL, Murphy GS. Neer Award 2012: cerebral oxygenation in the beach chair position: a prospective study on the effect of general anesthesia compared with regional anesthesia and sedation. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2013;22(10):1325-31.
50. Closhen D, Berres M, Werner C, Engelhard K, Schramm P. Influence of Beach Chair Position on Cerebral Oxygen Saturation: A Comparison of INVOS and FORE-SIGHT Cerebral Oximeter. Journal of neurosurgical anesthesiology. 2013;25(4):414-9.
51. Jeong H, Jeong S, Lim HJ, Lee J, Yoo KY. Cerebral oxygen saturation measured by near-infrared spectroscopy and jugular venous bulb oxygen saturation during arthroscopic shoulder surgery in beach chair position under sevoflurane-nitrous oxide or propofol-remifentanil anesthesia. Anesthesiology. 2012;116(5):1047-56.

52. McCulloch TJ, Liyanagama K, Petchell J. Relative hypotension in the beach-chair position: effects on middle cerebral artery blood velocity. Anaesthesia and intensive care. 2010;38(3):486-91.
53. Samra SK, Dy EA, Welch K, Dorje P, Zelenock GB, Stanley JC. Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. Anesthesiology. 2000;93(4):964-70.
54. Murphy G, Szokol J, Avram M, Greenberg S, Shear T, Vender J, et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomized controlled trial. British journal of anaesthesia. 2014;113(4):618-27.
55. Lee JH, Min KT, Chun Y-M, Kim EJ, Choi SH. Effects of beach-chair position and induced hypotension on cerebral oxygen saturation in patients undergoing arthroscopic shoulder surgery. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2011;27(7):889-94.
56. Salazar D, Sears BW, Aghdasi B, Francois A, Tonino P, Marra G. Cerebral desaturation events during shoulder arthroscopy in the beach chair position: patient risk factors and neurocognitive effects. Journal of Shoulder and Elbow Surgery. 2013;22(9):1228-35.
57. Ko S-H, Cho YW, Park SH, Jeong J-G, Shin S-M, Kang G. Cerebral oxygenation monitoring of patients during arthroscopic shoulder surgery in the sitting position. Korean journal of anesthesiology. 2012;63(4):297-301.
58. Salazar D, Sears BW, Andre J, Tonino P, Marra G. Cerebral desaturation during shoulder arthroscopy: A prospective observational study. Clinical Orthopaedics and Related Research®. 2013;471(12):4027-34.
59. Porter JM, Pidgeon C, Cunningham AJ. The sitting position in neurosurgery: a critical appraisal. Br J Anaesth. 1999;82(1):117-28.
60. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology. 1997;86(6):1431-3.
61. Murphy GS, Szokol JW. Blood pressure management during beach chair position shoulder surgery: what do we know? Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2011;58(11):977-82.
62. Reinsfelt B, Westerlind A, Ricksten S. The effects of sevoflurane on cerebral blood flow autoregulation and flow-metabolism coupling during cardiopulmonary bypass. Acta Anaesthesiologica Scandinavica. 2011;55(1):118-23.
63. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesthesia & Analgesia. 1990;71(1):49-54.
64. Yoshitani K, Kawaguchi M, Iwata M, Sasaoka N, Inoue S, Kurumatani N, et al. Comparison of changes in jugular venous bulb oxygen saturation and cerebral oxygen saturation during variations of haemoglobin concentration under propofol and sevoflurane anaesthesia. British journal of anaesthesia. 2005;94(3):341-6.

65. Iwata M, Inoue S, Kawaguchi M, Takahama M, Tojo T, Taniguchi S, et al. Jugular bulb venous oxygen saturation during one-lung ventilation under sevoflurane-or propofol-based anesthesia for lung surgery. Journal of cardiothoracic and vascular anesthesia. 2008;22(1):71-6.
66. Kaisti KK, Långsjö JW, Aalto S, Oikonen V, Sipilä H, Teräs M, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology. 2003;99(3):603-13.
67. Bisschops LL, Hoedemaekers CW, Simons KS, van der Hoeven JG. Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest*. Critical care medicine. 2010;38(7):1542-7.
68. Ide K, Eliasziw M, Poulin MJ. Relationship between middle cerebral artery blood velocity and end-tidal PCO2 in the hypocapnic-hypercapnic range in humans. Journal of Applied Physiology. 2003;95(1):129-37.
69. Meng L, Mantulin WW, Alexander BS, Cerussi AE, Tromberg BJ, Yu Z, et al. Head-up tilt and hyperventilation produce similar changes in cerebral oxygenation and blood volume: an observational comparison study using frequency-domain near-infrared spectroscopy. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2012;59(4):357-65.
70. Picton P, Shanks A, Dorje P, Mashour GA. The influence of basic ventilation strategies on cerebral oxygenation in anesthetized patients without vascular disease. Journal of clinical monitoring and computing. 2010;24(6):421-5.
71. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown III JM, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. The Annals of thoracic surgery. 2009;87(1):36-45.
72. Drummond JC. A beach chair, comfortably positioned atop an iceberg. Anesthesia & Analgesia. 2013;116(6):1204-6.
73. Hou X, Ding H, Teng Y, Zhou C, Tang X, Li S, et al. Research on the relationship between brain anoxia at different regional oxygen saturations and brain damage using near-infrared spectroscopy. Physiological measurement. 2007;28(10):1251-65.
74. Kurth CD, McCann JC, Wu J, Miles L, Loepke AW. Cerebral oxygen saturation-time threshold for hypoxic-ischemic injury in piglets. Anesthesia & Analgesia. 2009;108(4):1268-77.
75. Casati A, Spreafico E, Putzu M, Fanelli G. New technology for noninvasive brain monitoring: continuous cerebral oximetry. Minerva anestesiologica. 2005;72(7-8):605-25.
76. Kurihara K, Kikukawa A, Kobayashi A. Cerebral oxygenation monitor during head-up and-down tilt using near-infrared spatially resolved spectroscopy*. Clinical physiology and functional imaging. 2003;23(4):177-81.

77. Mehagnoul-Schipper DJ, Vloet LC, Colier WN, Hoefnagels WH, Jansen RW. Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. Stroke. 2000;31(7):1615-20.
78. Fuchs G, Schwarz G, Kulier A, Litscher G. The influence of positioning on spectroscopic measurements of brain oxygenation. Journal of neurosurgical anesthesiology. 2000;12(2):75-80.
79. Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Stoddart HF. Validation in volunteers of a near-infrared spectroscope for monitoring brain oxygenation in vivo. Anesthesia & Analgesia. 1996;82(2):269-77.
80. Sia S. Hypotensive technique and sitting position in shoulder surgery. Anesthesia & Analgesia. 2003;97(4):1198-9.
81. Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao JY. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology. 1995;82(2):393-403.
82. Gelber PE, Reina F, Caceres E, Monllau JC. A comparison of risk between the lateral decubitus and the beach-chair position when establishing an anteroinferior shoulder portal: a cadaveric study. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2007;23(5):522-8.
83. Friedman DJ, Parnes NZ, Zimmer Z, Higgins LD, Warner JJ. Prevalence of cerebrovascular events during shoulder surgery and association with patient position. Orthopedics. 2009;32(4).
84. Dippmann C, Winge S, Nielsen HB. Severe cerebral desaturation during shoulder arthroscopy in the beach-chair position. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2010;26(9 Suppl):S148-50.
85. Fischer GW, Torrillo TM, Weiner MM, Rosenblatt MA. The use of cerebral oximetry as a monitor of the adequacy of cerebral perfusion in a patient undergoing shoulder surgery in the beach chair position. Pain Practice. 2009;9(4):304-7.
86. Yao F-SF, Tseng C-CA, Ho C-YA, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. Journal of cardiothoracic and vascular anesthesia. 2004;18(5):552-8.
87. Rigamonti A, Scandroglio M, Minicucci F, Magrin S, Carozzo A, Casati A. A clinical evaluation of near-infrared cerebral oximetry in the awake patient to monitor cerebral perfusion during carotid endarterectomy. Journal of clinical anesthesia. 2005;17(6):426-30.
88. Strauss E, Sherman E, Spreen O. A compendium of neuropsychological tests; administartion, norms and commentary. third ed. New York: Oxford University Press, Inc.; 2006.

89. Mitrushina M, Satz P. Effect of repeated administration of a neuropsychological battery in the elderly. Journal of Clinical Psychology. 1991;47(6):790-801.
90. Buschke H. Selective reminding for analysis of memory and learning. Journal of Verbal Learning and Verbal Behavior. 1973;12(5):543-50.
91. Aldenkamp AP, Alpherts WC. FEPSY. Amsterdam: The Psychology Company; 1997.
92. Ruff R, Light R, Parker S, Levin H. Benton controlled oral word association test: Reliability and updated norms. Archives of Clinical Neuropsychology. 1996;11(4):329-38.
93. Smith A. Symbol Digit Modalities Test, manual. Los Angeles, CA: Western Psychological Services; 1982.
94. Stroop JR. Studies of interference in serial verbal reactions. Journal of experimental psychology. 1935;18(6):643-62.
95. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica. 1983;67(6):361-70.
96. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. Journal of psychosomatic research. 1993;37(2):147-53.
97. McCormack HM, de L Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychological medicine. 1988;18(04):1007-19.
98. Spielberger CD, Gorssuch RL, Lushene PR, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory: Consulting Psychologists Press, Inc.

; 1983.
99. Smith RL, Goode KT, La Marche JA, Boll TJ. Selective Reminding Test short form administration: A comparison of two through twelve trials. Psychological assessment. 1995;7(2):177-82.
100. Chafetz MD, Matthews LH. A new interference score for the Stroop test. Archives of Clinical Neuropsychology. 2004;19(4):555-67.
101. Tange K, Kinoshita H, Minonishi T, Hatakeyama N, Matsuda N, Yamazaki M, et al. Cerebral oxygenation in the beach chair position before and during general anesthesia. Minerva Anestesiol. 2010;76(7):485-90.
102. Sia S. Hypotensive technique and sitting position in shoulder surgery. Anesthesia & Analgesia. 2003;97:1159-207.
103. Cullen DJ, Kirby RR. Beach chair position may decrease cerebral perfusion; catastrophic outcomes have occured. APSF Newsletter. 2007;22(2):27.
104. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning C, Moller J. The assessment of postoperative cognitive function. Acta Anaesthesiologica Scandinavica. 2001;45(3):275-89.
105. Perouansky M. Liaisons dangereuses? General anaesthetics and long-term toxicity in the CNS. European journal of anaesthesiology. 2007;24(02):107-15.

106. Zywiel MG, Prabhu A, Perruccio AV, Gandhi R. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. Clinical Orthopaedics and Related Research®. 2014;472(5):1453-66.
107. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesthesia & Analgesia. 2005;101(3):740-7.
108. Riedel B, Browne K, Silbert B. Cerebral protection: inflammation, endothelial dysfunction, and postoperative cognitive dysfunction. Current Opinion in Anesthesiology. 2014;27(1):89-97.
109. Van Harten A, Scheeren T, Absalom A. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia. 2012;67(3):280-93.
110. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesthesia & Analgesia. 2005;100(1):4-10.
111. Lindholm M-L, Träff S, Granath F, Greenwald SD, Ekbom A, Lennmarken C, et al. Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. Anesthesia & Analgesia. 2009;108(2):508-12.
112. Radtke F, Franck M, Lendner J, Krüger S, Wernecke K, Spies C. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. British journal of anaesthesia. 2013;110(suppl 1):i98-i105.
113. Willingham M, Abdallah AB, Gradwohl S, Helsten D, Lin N, Villafranca A, et al. Association between intraoperative electroencephalographic suppression and postoperative mortality. British journal of anaesthesia. 2014. Epub 05/22/2014.
114. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger K-U, et al. Cognitive function after sevoflurane-vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. British journal of anaesthesia. 2011;106(6):840-50.
115. Monk TG, Weldon BC, Garvan CW, Dede DE, Van Der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108(1):18-30.
116. Reichenbach DD, Moss NS, Meyer E. Pathology of the heart in sudden cardiac death. The American journal of cardiology. 1977;39(6):865-72.
117. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJ, Houben LG, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. Journal of the American College of Cardiology. 1997;30(6):1500-5.

118. Gräsner J, Herlitz J, Koster R, Rosell-Ortiz F, Stamatakis L, Bossaert L. Quality management in resuscitation–towards a European cardiac arrest registry (EuReCa). Resuscitation. 2011;82(8):989-94.
119. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive care medicine. 2004;30(11):2126-8.
120. Reinikainen M, Oksanen T, Leppänen P, Torppa T, Niskanen M, Kurola J. Mortality in out-of-hospital cardiac arrest patients has decreased in the era of therapeutic hypothermia. Acta Anaesthesiologica Scandinavica. 2012;56(1):110-5.
121. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Bbttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke (part 1). International emergency nursing. 2009;17(4):203-25.
122. Kocjancic ST, Jazbec A, Noc M. Impact of intensified postresuscitation treatment on outcome of comatose survivors of out-of-hospital cardiac arrest according to initial rhythm. Resuscitation. 2014;85(10):1364-9.
123. Benson DW, WILLIAMS GR, SPENCER FC, YATES AJ. The use of hypothermia after cardiac arrest. Anesthesia & Analgesia. 1959;38(6):423-8.
124. Williams GJ, Spencer F. The clinical use of hypothermia following cardiac arrest. Ann surg. 1958;148(3):462-8.
125. Bernard SA, Jones B, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Annals of emergency medicine. 1997;30(2):146-53.
126. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. New England Journal of Medicine. 2002;346(8):557-63.
127. Group HACAS. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. New England Journal of Medicine. 2002;346:549-65.
128. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck W, Billi J, et al. Therapeutic hypothermia after cardiac arrest. Circulation. 2003;108(1):118-21.
129. Arrich J, Group. ERCHACARS. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med. 2007;35(4):1041-7.
130. Oddo M, Ribordy V, Feihl F, Rossetti A, Schaller M, Chioléro R, et al. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. Crit Care Med. 2008;36(8):2296-301.
131. Don C, Longstreth WJ, Maynard C, Olsufka M, Nichol G, Ray T, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-

hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. Crit Care Med. 2009;37(12):3062-9.
132. Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, et al. Is Hypothermia After Cardiac Arrest Effective in Both Shockable and Nonshockable Patients? Clinical Perspective Insights From a Large Registry. Circulation. 2011;123(8):877-86.
133. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation. 2001;51(3):275-81.
134. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche J-D, Ohanessian A, et al. High-Volume Hemofiltration After Out-of-Hospital Cardiac ArrestA Randomized Study. Journal of the American College of Cardiology. 2005;46(3):432-7.
135. Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. Resuscitation. 2011;82(9):1162-7.
136. Soga T, Nagao K, Sawano H, Yokoyama H, Tahara Y, Hase M, et al. Neurological benefit of therapeutic hypothermia following return of spontaneous circulation for out-of-hospital non-shockable cardiac arrest. Circ J. 2012;76(11):2579-85.
137. Lundbye JB, Rai M, Ramu B, Hosseini-Khalili A, Li D, Slim HB, et al. Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. Resuscitation. 2012;83(2):202-7.
138. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. The Lancet. 2005;365(9460):663-70.
139. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. New England Journal of Medicine. 2005;353(15):1574-84.
140. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood Outcomes after Hypothermia for Neonatal Encephalopathy. New England Journal of Medicine. 2012;366(22):2085-92.
141. Lin J-J, Hsia S-H, Wang H-S, Chiang M-C, Lin K-L. Therapeutic Hypothermia Associated With Increased Survival After Resuscitation in Children. Pediatric Neurology. 2013;48(4):285-90.
142. Resuscitation ILCo. The international Liaison committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: Pediatric basic and advanced life support. Pediatrics. 2005;117:e955-77.
143. Kuboyama K, Safar P, Radovsky A, Tisherman S, Stezoski S, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral

hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit care Med. 1993;1993(21):9.
144. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol. 2009;133(2):223-8.
145. Sendelbach S, Hearst M, Johnson P, Unger B, Mooney M. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. Resuscitation. 2012;83(7):829-34.
146. Kämäräinen A, Hoppu S, Silfvast T, Virkkunen I. Prehospital therapeutic hypothermia after cardiac arrest--from current concepts to a future standard. Scand J Trauma Resusc Emerg Med. 2009;17:53-9.
147. Bernard S, Smith K, Cameron P, Masci K, Taylor D, Cooper D, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737-42.
148. Castrén M, Nordberg P, Svensson L, Taccone F, Vincent J-L, Desruelles D, et al. Intra-arrest transnasal evaporative cooling a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation. 2010;122(7):729-36.
149. Merchant RM, Abella BS, Peberdy MA, Soar J, Ong ME, Schmidt GA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Critical care medicine. 2006;34(12):S490-S4.
150. Kämäräinen A, Virkkunen I, Tenhunen J, YLI-HANKALA A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta anaesthesiologica scandinavica. 2009;53(7):900-7.
151. Kliegel A, Losert H, Sterz F, Kliegel M, Holzer M, Uray T, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest—a feasibility study. Resuscitation. 2005;64(3):347-51.
152. Gillies MA, Pratt R, Whiteley C, Borg J, Beale RJ, Tibby SM. Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. Resuscitation. 2010;81(9):1117-22.
153. Finley Caulfield A, Rachabattula S, Eyngorn I, Hamilton S, Kalimuthu R, Hsia A, et al. A comparison of cooling techniques to treat cardiac arrest patients with hypothermia. Stroke Res Treat. 2011. Epub 07/25/2011.
154. Heard KJ, Peberdy MA, Sayre MR, Sanders A, Geocadin RG, Dixon SR, et al. A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. Resuscitation. 2010;81(1):9-14.

155. Tømte Ø, Drægni T, Mangschau A, Jacobsen D, Auestad B, K S. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. Crit Care Med. 2011;39(3):443-9.
156. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods*. Critical care medicine. 2009;37(3):1101-20.
157. Kim JJ, Yang HJ, Lim YS, Kim JK, Hyun SY, Hwang SY, et al. Effectiveness of each target body temperature during therapeutic hypothermia after cardiac arrest. The American journal of emergency medicine. 2011;29(2):148-54.
158. Lopez-de-Sa E, Rey JR, Armada E, Salinas P, Viana-Tejedor A, Espinosa-Garcia S, et al. Hypothermia in Comatose Survivors From Out-of-Hospital Cardiac ArrestClinical Perspective Pilot Trial Comparing 2 Levels of Target Temperature. Circulation. 2012;126(24):2826-33.
159. Nielsen N, Wetterslev J, al-Subaie N, Andersson B, Bro-Jeppesen J, Bishop G, et al. Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. American Heart Journal. 2012;163(4):541-8.
160. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Watanabe E, et al. Duration of well-controlled core temperature correlates with neurological outcome in patients with post-cardiac arrest syndrome. American Journal of Emergency Medicine. 2012;30(9):1838-44.
161. Bouwes A, Robillard L, Binnekade J, de Pont A, Wieske L, Hartog A, et al. The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. Resuscitation. 2012;83(8):996-1000.
162. Benz-Woerner J, Delodder F, Benz R, Cueni-Villoz N, Feihl F, Rossetti AO, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. Resuscitation. 2012;83(3):338-42.
163. Grigore AM, Grocott HP, Mathew JP, Phillips-Bute B, Stanley TO, Butler A, et al. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. Anesthesia & Analgesia. 2002;94(1):4-10.
164. Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med. 2001;161(16):2007-12.
165. Gebhardt K, Guyette F, Doshi A, Callaway C, Rittenberger JC, Service PCA. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. Resuscitation. 2013;84(8):1062-7.
166. Pichon N, Amiel J, François B, Dugard A, Etchecopar C, Vignon P. Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Critical Care. 2007;11(3):R71.
167. Winters S, Wolf K, Kettinger S, Seif E, Jones J, Bacon-Baquley T. Assessment of risk factors for post-rewarming "rebound hyperthermia" in cardiac

arrest patients undergoing therapeutic hypothermia. Resuscitation. 2013;84(9):1245-9.
168. Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer F, Povey C, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation. 2013;84(8):1056-61.
169. Lim C, Alexander M, LaFleche G, Schnyer D, Verfaellie M. The neurological and cognitive sequelae of cardiac arrest. Neurology. 2004;63(10):1774-8.
170. Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. Resuscitation. 2009;80(10):1119-23.
171. Group HaCAS. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549-56.
172. Daubeney PE, Pilkington SN, Janke E, Charlton GA, Smith DC, Webber SA. Cerebral oxygenation measured by near-infrared spectroscopy: comparison with jugular bulb oximetry. Ann Thorac Surg. 1996;61(3):930-4.
173. MacLeod D, Ikeda K, Vacchiano C. Simultaneous comparison of FORE-SIGHT and INVOS cerebral oximeters to jugular bulb and arterial co-oximetry measurements in healthy volunteers. Anesth Analg. 2009;108(SCA suppl):1-104.
174. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. Neurocritical care. 2009;10(1):122-8.
175. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke. 2010;41(9):1963-8.
176. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke. 2010;41(9):1951-6.
177. Buunk G, Van Der Hoeven J, Meinders A. A comparison of near-infrared spectroscopy and jugular bulb oximetry in comatose patients resuscitated from a cardiac arrest. Anaesthesia. 1998;53(1):13-9.
178. Müllner M, Sterz F, Binder M, Hirschl M, Janata K, Laggner A. Near infrared spectroscopy during and after cardiac arrest--preliminary results. Clinical intensive care: international journal of critical & coronary care medicine. 1995;6(3):107-11.
179. Kämäräinen A, Sainio M, Olkkola KT, Huhtala H, Tenhunen J, Hoppu S. Quality controlled manual chest compressions and cerebral oxygenation during in-hospital cardiac arrest. Resuscitation. 2012;83(1):138-42.
180. Newman DH, Callaway CW, Greenwald IB, Freed J. Cerebral oximetry in out-of-hospital cardiac arrest: standard CPR rarely provides detectable

hemoglobin–oxygen saturation to the frontal cortex. Resuscitation. 2004;63(2):189-94.
181. Parnia S, Nasir A, Shah C, Patel R, Mani A, Richman P. A feasibility study evaluating the role of cerebral oximetry in predicting return of spontaneous circulation in cardiac arrest. Resuscitation. 2012;83(8):982-5.
182. Leyvi G, Bello R, Wasnick JD, Plestis K. Assessment of cerebral oxygen balance during deep hypothermic circulatory arrest by continuous jugular bulb venous saturation and near-infrared spectroscopy. Journal of cardiothoracic and vascular anesthesia. 2006;20(6):826-33.
183. Tobias JD, Russo P, Russo J. Changes in near infrared spectroscopy during deep hypothermic circulatory arrest. Annals of cardiac anaesthesia. 2009;12(1):17-21.
184. Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. Anesthesia & Analgesia. 2010;110(2):321-8.
185. Meng L, Cannesson M, Alexander B, Yu Z, Kain Z, Cerussi A, et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. British journal of anaesthesia. 2011;107(2):209-17.
186. Meng L, Gelb AW, Alexander BS, Cerussi AE, Tromberg BJ, Yu Z, et al. Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. British journal of anaesthesia. 2012;108(5):815-22.
187. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke. 1997;28(8):1569-73.
188. Lavinio A, Timofeev I, Nortje J, Outtrim J, Smielewski P, Gupta A, et al. Cerebrovascular reactivity during hypothermia and rewarming. British journal of anaesthesia. 2007;99(2):237-44.
189. Pynnönen L, Falkenbach P, Kämäräinen A, Lönnrot K, Yli-Hankala A, Tenhunen J. Therapeutic hypothermia after cardiac arrest–cerebral perfusion and metabolism during upper and lower threshold normocapnia. Resuscitation. 2011;82(9):1174-9.
190. Lemiale V, Huet O, Vigué B, Mathonnet A, Spaulding C, Mira J-P, et al. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. Resuscitation. 2008;76(1):17-24.
191. Edgren E, Enblad P, Grenvik Å, Lilja A, Valind S, Wiklund L, et al. Cerebral blood flow and metabolism after cardiopulmonary resuscitation. A pathophysiologic and prognostic positron emission tomography pilot study. Resuscitation. 2003;57(2):161-70.
192. Beckstead J, Tweed W, Lee J, MacKeen W. Cerebral blood flow and metabolism in man following cardiac arrest. Stroke. 1978;9(6):569-73.

193. Peskine A, Picq C, Pradat-Diehl P. Cerebral anoxia and disability. Brain Injury. 2004;18(12):1243-54.
194. Sokol D, Markand O, Daly E, Luerssen T, Malkoff M. Near infrared spectroscopy (NIRS) distinguishes seizure types. Seizure. 2000;9(5):323-7.
195. Gupta A, Al-Rawi P, Hutchinson P, Kirkpatrick P. Effect of hypothermia on brain tissue oxygenation in patients with severe head injury. British journal of anaesthesia. 2002;88(2):188-92.
196. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post–Cardiac Arrest Syndrome Epidemiology, Pathophysiology, Treatment, and Prognostication A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation. 2008;118(23):2452-83.
197. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 C versus 36 C after cardiac arrest. New England Journal of Medicine. 2013;369(23):2197-206.
198. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between Post-Resuscitation Partial Pressure of Arterial Carbon Dioxide and Neurological Outcome in Patients with Post-Cardiac Arrest Syndrome. Circulation. 2013;127(21):2107-13.
199. Falkenbach P, Kämäräinen A, Mäkelä A, Kurola J, Varpula T, Ala-Kokko T, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation. 2009;80(9):990-3.
200. Lee BK, Jeung KW, Lee HY, Lee SJ, Jung YH, Lee WK, et al. Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. The American Journal of Emergency Medicine. 2014;32(1):55-60.
201. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: Post–Cardiac Arrest Care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 suppl 3):S768-S86.
202. Meex I, Dens J, Jans F, Boer W, Vanhengel K, Vundelinckx G, et al. Cerebral tissue oxygen saturation during therapeutic hypothermia in post-cardiac arrest patients. Resuscitation. 2013;84(6):788-93.

203. Schneider AG, Eastwood GM, Bellomo R, Bailey M, Lipcsey M, Pilcher D, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation. 2013;84(7):927-34.
204. Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Acta neurochirurgica Supplementum. 1989;49:1-64.
205. Yundt KD, Diringer MN. The use of hyperventilation and its impact on cerebral ischemia in the treatment of traumatic brain injury. Critical care clinics. 1997;13(1):163-84.
206. Hino JK, Short BL, Rais-Bahrami K, Seale WR. Cerebral blood flow and metabolism during and after prolonged hypercapnia in newborn lambs. Critical care medicine. 2000;28(10):3505-10.
207. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat. Pediatric research. 1997;42(1):24-9.
208. Dessap AM, Charron C, Devaquet J, Aboab J, Jardin F, Brochard L, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive care medicine. 2009;35(11):1850-8.
209. Brian Jr JE. Carbon dioxide and the cerebral circulation. Anesthesiology. 1998;88(5):1365-86.
210. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, et al. Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurologic Outcome*. Critical care medicine. 2014;42(6):1463-70.
211. Zhou Q, Cao B, Niu L, Cui X, Yu H, Liu J, et al. Effects of permissive hypercapnia on transient global cerebral ischemia–reperfusion injury in rats. Anesthesiology. 2010;112(2):288-97.
212. Voicu S, Deye N, Malissin I, Viqué B, Brun P, Haik W, et al. Influence of α-Stat and pH-Stat Blood Gas Management Strategies on Cerebral Blood Flow and Oxygenation in Patients Treated With Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest: A Crossover Study. Critical care medicine. 2014;42(8):1849-61.
213. Hoover LR, Dinavahi R, Cheng W-P, Cooper Jr JR, Marino MR, Spata TC, et al. Jugular venous oxygenation during hypothermic cardiopulmonary bypass in patients at risk for abnormal cerebral autoregulation: influence of α-stat versus pH-stat blood gas management. Anesthesia & Analgesia. 2009;108(5):1389-93.
214. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. Jama. 2010;303(21):2165-71.
215. Janz DR, Hollenbeck RD, Pollock JS, McPherson JA, Rice TW. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic

hypothermia after sudden cardiac arrest. Critical care medicine. 2012;40(12):3135-9.
216. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care. 2011;15(2):R90.
217. Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. Resuscitation. 2010;81(10):1219-76.
218. Benni PB, Chen B, Dykes FD, Wagoner SF, Heard M, Tanner AJ, et al. Validation of the CAS neonatal NIRS system by monitoring vv-ECMO patients: preliminary results. Adv Exp Med Biol. 2005;566:195-201.
219. Owen-Reece H, Smith M, Elwell CE, Goldstone JC. Near infrared spectroscopy. Br J Anaesth. 1999;82(3):418-26.
220. Fischer GW. Recent advances in application of cerebral oximetry in adult cardiovascular surgery. Seminars in cardiothoracic and vascular anesthesia. 2008;12(1):60-9.
221. Paarmann H, Heringlake M, Sier H, Schön J. The association of non-invasive cerebral and mixed venous oxygen saturation during cardiopulmonary resuscitation. Interact Cardiovasc Thorac Surg. 2010;11(3):371-3.
222. Nagdyman N, Fleck T, Ewert P, Abdul-Khaliq H, Redlin M, Lange P. Cerebral oxygenation measured by near-infrared spectroscopy during circulatory arrest and cardiopulmonary resuscitation. Br J Anaesth. 2003;91(3):438-42.
223. Müllner M, Sterz F, Binder M, Hirschl M, Janata K, Laggner A. Near infrared spectroscopy during and after cardiac arrest--preliminary results. Clinical intensive care: international journal of critical & coronary care medicine. 1995;6(3):107.
224. Ito N, Nanto S, Nagao K, Hatanaka T, Nishiyama K, Kai T. Regional cerebral oxygen saturation on hospital arrival is a potential novel predictor of neurological outcomes at hospital discharge in patients with out-of-hospital cardiac arrest. Resuscitation. 2012;83(1):46-50.
225. Parnia S. Cerebral oximetry–The holy grail of non-invasive cerebral perfusion monitoring in cardiac arrest or just a false dawn? Resuscitation. 2012;83(1):11-2.
226. Chan M, Ng S, Lam J, Poon W, Gin T. Re-defining the ischemic threshold for jugular venous oxygen saturation—a microdialysis study in patients with severe head injury. Acta neurochirurgica Supplementum. 2005;95:63-6.
227. Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology. 2007;107(4):563-9.

228. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger K-U. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. Critical Care. 2011;15(5):R218.
229. Stern Y. Cognitive reserve. Neuropsychologia. 2009;47(10):2015-28.
230. Miller EK, Freedman DJ, Wallis JD. The prefrontal cortex: categories, concepts and cognition. Philosophical Transactions of the Royal Society of London Series B: Biological Sciences. 2002;357(1424):1123-36.
231. Madl C, Kramer L, Domanovits H, Woolard RH, Gervais H, Gendo A, et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. Critical care medicine. 2000;28(3):721-6.
232. Blondin NA, Greer DM. Neurologic prognosis in cardiac arrest patients treated with therapeutic hypothermia. The neurologist. 2011;17(5):241-8.
233. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. Resuscitation. 2014;85(4):522-6.
234. Rosow C, Manberg PJ. Bispectral index monitoring. Anesthesiology Clinics of North America. 2001;19(4):947-66.
235. Leary M, Fried DA, Gaieski DF, Merchant RM, Fuchs BD, Kolansky DM, et al. Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest. Resuscitation. 2010;81(9):1133-7.
236. Seder DB, Fraser GL, Robbins T, Libby L, Riker RR. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive care medicine. 2010;36(2):281-8.
237. Stammet P, Werer C, Mertens L, Lorang C, Hemmer M. Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. Resuscitation. 2009;80(4):437-42.
238. Burjek NE, Wagner CE, Hollenbeck RD, Wang L, Yu C, McPherson JA, et al. Early Bispectral Index and Sedation Requirements During Therapeutic Hypothermia Predict Neurologic Recovery Following Cardiac Arrest. Critical care medicine. 2013;42(5):1204-12.
239. Taccone FS, Cronberg T, Friberg H, Greer D, Horn J, Oddo M, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. Critical Care. 2014;18(1):202-14.
240. Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Seminars in cardiothoracic and vascular anesthesia. 2007;11(4):274-81.

241. Tagami T, Tosa R, Omura M, Yokota H, Hirama H. Implementation of the fifth link of the chain of survival concept for out-of-hospital cardiac arrest. Critical Care. 2012;16(Suppl 1):P266.
242. Gaieski DF, Band RA, Abella BS, Neumar RW, Fuchs BD, Kolansky DM, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2009;80(4):418-24.
243. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001;32(1):128-32.
244. Beylin ME, Perman SM, Abella BS, Leary M, Shofer FS, Grossestreuer AV, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive care medicine. 2013;39(11):1981-8.
245. Jones AE, Shapiro NI, Kilgannon JH, Trzeciak S. Goal-directed hemodynamic optimization in the post-cardiac arrest syndrome: A systematic review. Resuscitation. 2008;77(1):26-9.
246. Ito N, Nishiyama K, Callaway CW, Orita T, Hayashida K, Arimoto H, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: A prospective multicenter observational study. Resuscitation. 2014;85(6):778-84.
247. Singer AJ, Ahn A, Inigo-Santiago LA, Thode HC, Henry MC, Parnia S. Cerebral oximetry levels during CPR are associated with return of spontaneous circulation following cardiac arrest: an observational study. Emergency Medicine Journal. 2014. Epub 03/24/2014.
248. Asim K, Gokhan E, Ozlem B, Ozcan Y, Deniz O, Kamil K, et al. Near infrared spectrophotometry (cerebral oximetry) in predicting the return of spontaneous circulation in out-of-hospital cardiac arrest. The American Journal of Emergency Medicine. 2014;32(1):14-7.
249. Ahn A, Nasir A, Malik H, D'Orazi F, Parnia S. A pilot study examining the role of regional cerebral oxygen saturation monitoring as a marker of return of spontaneous circulation in shockable (VF/VT) and non-shockable (PEA/Asystole) causes of cardiac arrest. Resuscitation. 2013;84(12):1713-6.
250. Genbrugge C, Dens J, Meex I, Boer W, Jans F, De Deyne C. Cerebral saturation monitoring during cardiopulmonary resuscitation should be used as dynamic, rather than static, information. Resuscitation. 2013;84(9):e111-e2.
251. Parnia S, Nasir A, Ahn A, Malik H, Yang J, Zhu J, et al. A Feasibility Study of Cerebral Oximetry During In-Hospital Mechanical and Manual Cardiopulmonary Resuscitation*. Critical care medicine. 2014;42(4):930-3.
252. Weatherall A, Skowno J, Lansdown A, Lupton T, Garner A. Feasibility of cerebral near-infrared spectroscopy monitoring in the pre-hospital environment. Acta Anaesthesiologica Scandinavica. 2012;56(2):172-7.

253. Wang C-H, Choua N-K, Beckerb LB, Linc J-W, Yu H-Y, Chi N-H, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest – A comparison with that for extracorporeal rescue for in-hospital cardiac arrest Resuscitation. 2014;85(9):1219-24.
254. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: A prospective observational study. Resuscitation. 2014;85(6):762-8.

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aEEG: amplitude-integrated electroencephalography
ALS: advanced life support
A_{rms}: root mean square error
BCP: beach chair position
BIS: bispectral index
°C: degrees Celsius
CA: cardiac arrest
CBF: cerebral blood flow
CCU: coronary care unit
CDE: cerebral desaturation event
CEO_2: cerebral oxygen extraction
CI: cardiac index
$CMRO_2$: cerebral metabolic rate for oxygen
CO_2: carbon dioxide
COWAT: controlled oral word association test
CPC: cerebral performance category
CPR: cardiopulmonary resuscitation
CVST: computerized visual searching task
DD: dorsal decubitus
DPF: differential pathlength factor
ECG: electrocardiography
EEG: electroencephalogaphy
EMT: emergency medical team
ER: emergency room
$EtCO_2$: end-tidal carbon dioxide
FAS: fatigue assessment scale
FiO_2: inspired fraction of oxygen
HACA: hypothermia after cardiac arrest
HADS: hospital anxiety and depression scale
Hb: deoxyhemoglobin
HbO_2: oxyhemoglobin
ICU: intensive care unit
HR: heart rate
IHCA: in-hospital cardiac arrest
ILCOR: international liaison committee on resuscitation
IPPV: intermittent positive pressure ventilation
IQR: interquartile range
LDP: lateral decubitus position
MAP: mean arterial pressure
NIRS: Near-infrared spectroscopy

OHCA: out-of-hospital cardiac arrest
$PaCO_2$: partial pressure of carbon dioxide
PaO_2: partial pressure of oxygen
PCI: percutaneous coronary intervention
PEA: pulseless electrical activity
RBANS: Repeatable battery for the assessment of neuropsychological status
rSO_2: regional blood oxygen saturation
ROSC: return of spontaneous circulation
SAP: systolic arterial pressure
$SctO_2$: absolute cerebral tissue oxygen saturation
SD: standard deviation
SpO_2: arterial oxygen saturation
SRT: selective reminding test
STAI: state-trait anxiety inventory
TH: therapeutic hypothermia
VAS: visual analogue scale
VF: ventricular fibrillation
VT: ventricular tachycardia

Curriculum Vitae

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Publications

Cerebral tissue oxygen saturation during therapeutic hypothermia in post-cardiac arrest patients
***Ingrid Meex**, Jo Dens, Frank Jans, Willem Boer, Kristof Vanhengel, Guy Vundelinckx, René Heylen, Cathy De Deyne*
Resuscitation 2013 Jun;84(6):788-93

Feasibility of absolute cerebral tissue oxygen saturation during cardiopulmonary resuscitation
***Ingrid Meex**, Cathy De Deyne, Jo Dens, Simon Scheyltjens, Kevin Lathouwers, Willem Boer, Guy Vundelinckx, René Heylen and Frank Jans*
Critical Care 2013 Mar 1;17(2):R36

Therapeutic hypothermia after cardiac arrest; yes, but who, when and how?
***Ingrid Meex**, Jo Dens, Cornelia Genbrugge, Frank Jans, Cathy De Deyne*
International Journal of Intensive Care 2013;20(3):93-98

Koorts na therapeutische hypothermie toegepast ter neuroprotectie na hartstilstand
*Kristof Vanhengel, Cathy De Deyne, **Ingrid Meex**, Frank Jans, Jo Dens*
Bloedvaten-Hart-Longen 2013;18:6-10

Out-of-hospital cardiac arrest: implementatie van 'cardio-brain goal directed management'
*Philippe Vandyunhoven, Cornelia Genbrugge, **Ingrid Meex**, Cathy De Deyne, Jo Dens*
Tijdschrift voor Cardiologie 2013; 25(5): 255-263

Accuracy of continuous thermodilution cardiac output monitoring by pulmonary artery catheter during therapeutic hypothermia in post-cardiac arrest patients
*Koen Ameloot, **Ingrid Meex**, Cornelia Genbrugge, Frank Jans, Manu Malbrain, Wilfried Mullens, Jo Dens, Cathy De Deyne, Mathias Dupont*
Resuscitation 2014 Sep;85(9):1263-8

Submitted publications

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American Journal of Cardiology 2013 Jan 15;111(2):302

Role of intra-aortic balloon pumping on cerebral perfusion after cardiac arrest
*Cathy De Deyne, **Ingrid Meex**, Jo Dens*
Resuscitation 2013 Jan;84(1):e5

Association of serum lactate and survival outcomes after cardiac arrest
***Ingrid Meex**, Cathy De Deyne, Cornelia Genbrugge, Frank Jans, Jo Dens*
Resuscitation 2013 Aug;84(8):e89

Uneventful neurological outcome in case of late awakening after cardiac arrest treated with hypothermia
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LCRP Symposium – ZOL, Genk – November 2012

Neuromonitoring na hartstilstand
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Cerebral desaturation during shoulder surgery: should we be worried?
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Cerebrale zuurstofsaturatie tijdens therapeutische hypothermie
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***Ingrid Meex**, Francis Deburggraeve, Kevin Lathouwers, Joris Vundelinckx, Veerle De Sloovere, René Heylen, Frank Jans, Cathy De Deyne*
BIOMEDICA – EINDHOVEN, THE NETHERLANDS – April 2011

Cerebral oxygenation measured by NIRS Fore-Sight technology reveals adequacy of cerebral perfusion during cardiopulmonary resuscitation
***Ingrid Meex**, Cathy De Deyne, Frank Jans, Jo Dens, Kevin Lathouwers, René Heylen*
SNACC - CHICAGO, USA - October 2011

Shivering during induced hypothermia after cardiac arrest results in significant decrease in non-invasive cerebral oxygen saturation, as measured by near infrared spectroscopy
***Ingrid Meex**, Cathy De Deyne, Frank Jans, Jo Dens, Kevin Lathouwers, René Heylen*
SNACC - CHICAGO, USA - October 2011

Non-invasive monitoring reveals a decrease in cerebral oxygenation during therapeutic hypothermia after cardiac arrest
***Ingrid Meex**, Jo Dens, Frank Jans, René Heylen, Cathy De Deyne*
EURONEURO – VIENNA, AUSTRIA – February 2012
Abstract published in European Journal of Anaesthesiology

Can cerebral oxygenation after cardiac arrest be correlated to outcome?
***Ingrid Meex**, Jo Dens, Frank Jans, René Heylen, Cathy De Deyne*
EURONEURO – VIENNA, AUSTRIA – February 2012
Abstract published in European Journal of Anaesthesiology

Decrease in arterial CO_2 tension and cerebral oxygenation during induction of therapeutic hypothermia
***Ingrid Meex**, Jo Dens, Frank Jans, René Heylen, Cathy De Deyne*
EURONEURO – VIENNA, AUSTRIA – February 2012
Abstract published in European Journal of Anaesthesiology

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EURONEURO – ISTANBUL, TURKEY – April 2014

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