Stichting transnationale Universiteit Limburg (tUL) is a cooperation between Hasselt University (Belgium) and Maastricht University (the Netherlands) and can be considered as one university with a home base in each country.

UHASSELT
KNOWLEDGE IN ACTION

www.uhasselt.be
Hasselt University
Martelarenlaan 42 |BE-3500 Hasselt

Non-invasive cerebral monitoring in predicting neurological outcome in out-of-hospital cardiac arrest and cardiac surgery patients

Ward Eertmans

2018 | Faculty of Medicine and Life Sciences

UHASSELT
KNOWLEDGE IN ACTION

Maastricht University

Doctoral dissertation submitted to obtain the degree of
Doctor of Biomedical Sciences, to be defended by

Ward Eertmans

DOCTORAL DISSERTATION

Non-invasive cerebral monitoring in predicting neurological outcome in out-of-hospital cardiac arrest and cardiac surgery patients

Promoter: Prof. Dr Cathy De Deyne
Co-promoter: Prof. Dr Frank Jans

2018 | Faculty of Medicine and Life Sciences

UHASSELT

KNOWLEDGE IN ACTION

Maastricht University

Doctoral dissertation submitted to obtain the degree of
Doctor of Biomedical Sciences, to be defended by

Ward Eertmans

DOCTORAL DISSERTATION

Non-invasive cerebral monitoring in predicting neurological outcome in out-of-hospital cardiac arrest and cardiac surgery patients

Promoter: Prof. Dr Cathy De Deyne

Co-promoter: Prof. Dr Frank Jans

D/2018/2451/62

Promoter: Prof. Dr. Cathy De Deyne | Hasselt University, BE

Co-promoters: Prof. Dr. Frank Jans | Hasselt University, BE

Chair: Prof. Dr. Sven Hendrix| Hasselt University, BE

Jury members: Prof. Dr. Bert Brône | Hasselt University, BE

Prof. Dr. Pascal Vanelderen | Hasselt University, BE

Prof. Dr. Alain Cariou | Cochin University Hospital, Paris Descartes University, FR

Dr. Astrid Hoedemaekers | Radboud UMC, NL

Prof. Dr. Annelies Moerman | Ghent University, BE

Dr. Pascal Stammet | Corps Grand-Ducal d'Incendie et de Secours, Direction médicale et de la santé, LUX

Prof. Dr. Fabio Taccone | Erasme Hospital, ULB, BE

October 2, 2018

Ward Eertmans was supported by the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

Michèle

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

aEEG	Amplitude-integrated electro-encephalography
ALS	Advanced life support
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
BAV	Balloon aortic valvuloplasty
BIS	Bispectral index
BIS 0	BIS values equal to zero
BIS EEG	Simplified EEG obtained from the BIS monitor
BLS	Basic life support
CA	Cardiac arrest
CABG	Coronary artery bypass graft surgery
CAM-ICU	Confusion assessment method for ICU
CBF	Cerebral blood flow
CCU	Coronary Care Unit
cEEG	Continuous electro-encephalography
CEO_2	Oxygen extraction rate
CI	Confidence Interval
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation

CKI	Chronic kidney insufficiency
DWI-MRI	Diffusion-weighted Magnetic Resonance Imaging
ECMO	Extra-corporal membrane oxygenation
EEG	Electro-encephalography
EMG	Electromyographic power
FPR	False-positive range
Hb	Haemoglobin
HbO_2	Oxygenated haemoglobin
IABP	Intra-aortic balloon pump
ICU	Intensive Care Unit
IHCA	In-hospital cardiac arrest
IQR	Interquartile range
MAP	Mean arterial pressure
MMSE	Mini-mental state examination
NIR	Near-infrared
NIRS	Near-Infrared Spectroscopy
NMB	Neuromuscular blockers
NPV	Negative predictive value
NSE	Neuron-specific enolase
OHCA	Out-of-hospital cardiac arrest
$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure
PCI	Percutaneous coronary intervention

PEA	Pulseless electrical activity
PED	Periodic epileptic discharges
POD	Postoperative delirium
PPV	Positive predictive value
RASS	Richmond agitation sedation scale
ROC	Receiver operating curve
ROSC	Return of spontaneous circulation
RR	Risk ratio
RVP	Rapid ventricular pacing
SAVR	Surgical aortic valve replacement
SE	Status epilepticus
$SctO_2$	Regional cerebral tissue oxygen saturation
SQI	Signal Quality Index
SR	Suppression ratio
SSEP	Somatosensory-evoked potential
SvO_2	Mixed venous blood oxygen saturation
TA	Transapical
TAVI	Transcatheter Aortic Valve Implantation
TF	Transfemoral
TTM	Targeted Temperature Management
VF	Ventricular fibrillation

GENERAL INTRODUCTION

The human brain represents only 2% of total body weight, yet more than 20% of the oxygen supplied to the body is required to ensure adequate cerebral functioning. Any persisting deprivation in oxygen, if not restored, will rapidly induce irreversible brain injury. In contrast to the abundance of hemodynamic monitoring options that have been introduced over the past two decades, the brain remains an organ that is rarely being monitored in the operating theatre and on the ICU (1).

Especially in patients suffering from an out-of-hospital cardiac arrest (OHCA) or in elderly patients undergoing cardiac surgery, the interest to monitor brain functioning and perfusion has intensified in recent years (2-4). Even though these two patient populations are rather different, the extent to which their brain is being exposed to hypoxemia is commonly recognized to impact neurological outcome and survival (5, 6). Therefore, monitoring the brain during the acute care of a patient with/or at risk of neurological injury is pivotal. In the most ideal situation, neuromonitoring should be targeted at the early identification of hypoxic/ischemic cerebral insults before the manifestation of irreversible brain damage, or should at least enable the preservation of cerebral integrity. Additionally, cerebral monitoring could guide patient-tailored treatment or provide assistance during the process of neuroprognostication (7-11).

In part I of this PhD thesis, the prognostic role of two non-invasive, bedside available and readily interpretable monitoring techniques will be discussed in the post-cardiac arrest (CA) setting, i.e. Near-Infrared Spectroscopy (NIRS) and Bispectral Index (BIS) monitoring. Next, the added value of cerebral oxygen saturation, as assessed by NIRS technology, will be explored in elderly patients undergoing (high-risk) cardiac surgery and will be discussed in part II of this thesis.

CARDIAC ARREST

Sudden CA is the abrupt loss of cardiac pump function resulting in a hemodynamic collapse. Approximately 38-55 per 100 000 habitants suffer yearly from an OHCA in Europe and in the United States (12-14). In Belgium, it was estimated that about 9000 persons experience an OHCA each year (15). Despite substantial improvements in advanced life support and post-CA management, the overall mortality of OHCA still peaks above 90% (16, 17). This poor survival rate can be mainly attributed to a two-step brain injury process, which is part of the so-called post-CA syndrome (18). First, global

(cerebral) ischemia arises during CA itself. This so-called no-flow period accounts for the primary neurological injury through which about 60-70% will eventually not achieve return of spontaneous circulation (ROSC). Secondly, a combination of pathophysiological processes develops within the initial 24-72 hours following ICU admission. More specifically, the brain encounters a short-lasting cerebral hyperaemic phase from the moment ROSC is achieved. Subsequently, a delayed hypoperfusion period develops, characterized by an imbalance between cerebral oxygen demand and supply, typically lasting for several hours to days (18). Not surprisingly, about 50% of these CA survivors will eventually succumb to neurological sequelae of the post-ischemic brain injury (6, 19). In terms of outcome prediction, it has become of vital importance to distinguish between delayed awakening and irreversible brain injury within the initial days following the arrest. Nonetheless, early and adequate prognostication remains challenging in this setting. Recently, a sequential neuroprognostication strategy was proposed by current guidelines which included five neuromonitoring modalities that – whenever possible – should be bundled with each other, i.e. clinical neurological examination, somatosensory evoked potentials (SSEPs), electro-encephalography (EEG), blood biomarkers and cerebral imaging. These guidelines strongly recommended to postpone any decisive evaluation concerning prognosis beyond 72 hours following CA (10, 20-22). However, any earlier indication of neurological outcome would allow clinicians to maximize (cost-effective) therapy in patients with a likely favourable outcome. Likewise, this would also avoid futile and expensive treatment efforts in those with no reasonable chances of recovery. Unfortunately, most of the aforementioned prognostic tools are not continuously available, rather labour-intensive and above all, they often require trained personnel for a correct interpretation. Over the years, NIRS and BIS monitoring have rapidly gained interest in the post-CA setting through their ease-of-use, non-invasiveness, and bedside availability.

CEREBRAL TISSUE OXYGEN SATURATION, AS ASSESSED BY NEAR- INFRARED SPECTROSCOPY, IN THE OUT-OF-HOSPITAL CARDIAC ARREST PATIENT

NIRS technology relies on (1) the existence of near-infrared (NIR) light and its ability to penetrate through skin, bone and biological tissue, (2) the amount of NIR light absorbed by haemoglobin, which is dependent on its oxygenation status and (3) the Beer-Lambert principle stating that the quantity of NIR light absorbed by a chromophore is directly proportional to its concentration (23, 24).

NIRS monitors emit photons at minimally two wavelengths in the NIR spectrum (700 – 1000nm) facilitating the estimation of the ratio of oxygenated (HbO_2) to total haemoglobin (Hb), which is then expressed as the cerebral tissue oxygen saturation ($SctO_2$ (in %)). The NIR light emitted from the light source travels towards the light detectors via a banana-shaped pathway, with a penetration depth that is being determined by the distance between light source and detector (25, 26). Given a source-detector separation of approximately 3cm, the penetration depth of adult NIRS sensors is typically around 1.5cm (27). Usually, two light detectors are placed at different distances from the light source with the proximal one detecting NIR light reflected from superficial tissues and the distal one also detecting light from deeper tissues. To eliminate any interference of extracerebral compartments – which are not of interest – a subtraction algorithm is applied to provide a value representative for the oxygenation of deeper tissues (28). In clinical practice, NIRS sensors are usually placed bilaterally about 2cm above the eye brows in order to avoid the sagittal sinus (27). Consequently, the calculated $SctO_2$ is representing microcirculatory oxygenation (venules, arterioles and capillaries) in the frontal cortex, a part of the brain particularly vulnerable to hypoxemia (29). The cerebral oximeters used in this thesis, the first and second generation FORE-SIGHT™ monitors (CAS Medical Systems, Inc., Branford, CT, USA) assume a fixed venous to arterial blood (70:30) volume ratio when $SctO_2$ is calculated (30, 31).

Over the past decades, NIRS technology was mainly promoted as brain monitor in the field of cardiac surgery (29). Yet, the role of cerebral oximetry in the OHCA patient has been investigated extensively in recent years, either during CA itself or in the post-CA setting (3). While some studies suggested the use of cerebral oximetry for monitoring the quality of cardiopulmonary resuscitation (CPR), multiple studies showed that higher $SctO_2$ levels during CPR efforts were strongly associated with ROSC and even a favourable neurological outcome (32-36). Others even proposed an ambitious role for $SctO_2$ monitoring in the prediction of ROSC itself (37).

In recent years, others also suggested a prognostic role of cerebral oximetry in the post-CA setting. Based on these studies with a rather small sample size, higher $SctO_2$ values within the period of targeted temperature management (TTM) at 33°C appeared to be associated with a favourable neurological outcome (38-40). Although observations like these are promising, larger studies are warranted to investigate the association between $SctO_2$, measured upon ICU admission, and long-term neurological outcome. Still, the

abundance of neuromonitoring devices used in the post-CA setting mainly focus on the prediction of neurological outcome instead of focusing on potential therapeutic strategies. Nonetheless, two landmark studies, published in NEJM in 2002, revealed at first the existence of a potential therapeutic window after CA. Within the initial 24 hours following CA, it seemed possible to improve long-term neurological outcome substantially when core temperatures between 32 and 34°C were aimed for (41, 42). Alongside a prognostic role, the ability of NIRS to detect subtle hemodynamic disturbances might allow this technology to be used for therapeutic implications as well. In fact, fundamental knowledge gained by using cerebral oximetry within the period of TTM might eventually result in patient-tailored strategies to avoid cerebral hypoperfusion.

> *In this thesis, an attempt will be made to obtain a thorough understanding of using cerebral oximetry in the post-CA setting and assess its role in outcome prognostication.*

BISPECTRAL INDEX (EEG) MONITORING IN THE OUT-OF-HOSPITAL CARDIAC ARREST

Any instrument intended to support outcome prediction following OHCA should ideally be based on frequent evaluations of the post-ischemic status of the brain. Over the years, EEG has emerged as one of the most valuable tools to assist with neuroprognostication in patients successfully resuscitated from OHCA (43). Others previously demonstrated that specific EEG patterns, observed within the initial 24 hours following ICU admission, bare a remarkable prognostic power for both good and poor neurological outcome. Current research is now focusing on the temporal evolution of these EEG patterns which might be more valuable than single EEG assessments in terms of outcome prediction (44-47). Based on these observations, resuscitation guidelines nowadays advise to perform EEG assessments more frequently in all post-CA patients, and preferably in a continuous manner (20, 48). However, continuous EEG (cEEG) is rather expensive, often unavailable in a general ICU setting, and above all, the continuous presence of trained neurophysiologists becomes crucial when these serial EEG measurements need interpretation. These limitations, more or less intrinsic to cEEG, have intensified the quest towards more simplified and accurate EEG systems, either for the identification of seizures and other malignant EEG patterns or for prognostic implications. In this context, amplitude-integrated EEG (aEEG) as alternative for full EEG has already been investigated by others (49-52).

Another simplified EEG monitoring system is the BIS monitor which relies on the bispectral analysis of raw sampled frontotemporal EEG measurements. Originally designed to assess the depth of anaesthesia in the operating theatre, a proprietary algorithm automatically converts several EEG components into a dimensionless BIS number, ranging from 0 to 100 (53). In the operating room, BIS values between 40 and 60 correlate well with an adequate depth of surgical anaesthesia. Another parameter observed on the BIS monitor, is the suppression ratio (SR) which represents the percentage of iso-electric or suppressed EEG in the previous 63 seconds of monitoring. Suppression ratio values also range from 0 (no EEG suppression) to 100 (full EEG suppression). In fact, SR values above 40% have been shown to be linearly correlated with BIS values ranging from 30 to 0 (54-56). Aside from BIS and SR values, raw EEG traces, originally being used for the estimation of BIS and SR, are displayed on the commercially available BIS VISTA™ monitor, and therefore are at the disposition of the user. Up to now, its use as a simplified EEG monitor in successfully resuscitated OHCA patients remains to be elucidated.

> *In this thesis, efforts were made to validate raw EEG traces, displayed on the BIS device, against standard EEG monitoring. Secondly, we attempted to determine the prognostic value of these raw BIS EEG traces in OHCA patients. It has to be noted that these were retrospective analyses based on prospectively gathered (numerical) BIS data.*

In contrast to the raw BIS EEG traces, other research groups mainly focused on the numeric BIS and SR values as potential prognostic targets in the post-CA setting (57-59). During the first four hours following CPR, mean BIS values below 40 or mean SR values above 40 were suggested as early indicators for poor neurological outcome (60). In another study, a mean BIS value of 23 calculated over the initial 12.5 hours following ICU admission was pointed out as the optimal threshold to predict poor outcome (61). Others rather focused on the prognostic value of a BIS value equal to zero (BIS 0), equivalent to a flat or low-voltage EEG, and showed that its presence at any time point was strongly indicative for a poor neurological outcome (59, 62, 63). Despite these promising results in terms of outcome prediction, neither of the suggested BIS thresholds univocally reached a specificity of 100% on their own and more importantly, the reported range of false positive ratios (FPR) ranges was relatively high across studies (64). Therefore, resuscitation guidelines did not support the use of BIS monitoring within the process of

neuroprognostication after OHCA (20, 21). In fact, the fundamental reason for this advice was that BIS monitoring in general is subjective to several confounding factors. One of the predominant confounders in the post-CA setting is a high electromyographic (EMG) activity interference which results in an overestimation of the BIS value (65). Only by administering neuromuscular blockers (NMBs), one is able to eliminate the influencing component of EMG on the BIS value. It is for this reason that previous studies examining the prognostic performance of BIS monitoring after OHCA consistently used NMBs in all study patients. Nonetheless, the routine use of NMBs has been previously associated with an increased incidence of side effects such as pneumonia and ICU-acquired weakness. Moreover, the continuous blockade of muscle activity delays clinical neurological examination and will mask clinically overt seizures, thereby possibly affecting neurological outcome (66-68). Hence, the continuous administration of NMBs is not in accordance with current post-CA guidelines, specifically stating that only patients who experience shivering are allowed to be treated with NMBs (69). As such, the prognostic role of BIS monitoring in OHCA patients fully treated according to ICU guidelines has not been investigated up to now.

In this thesis, the prognostic role of BIS and SR monitoring was prospectively explored in post-CA patients, who were fully treated according to post-CA guidelines (i.e. without the continuous administration of NMBs). First, an attempt was made to determine the optimal BIS and SR threshold to predict poor neurological outcome in the first 36 hours following the initiation of TTM at 33°C. Secondly, we retrospectively investigated whether characteristics of BIS 0 values, other than solely their presence (i.e. duration and/or uni versus bilateral presence), were indicative for poor neurological outcome.

POSTOPERATIVE DELIRIUM IN THE PERIOPERATIVE PERIOD FOLLOWING CARDIAC SURGERY: IS THERE ANY ROLE FOR CEREBRAL OXIMETRY?

With an incidence up to 46%, postoperative delirium (POD) is recognized as one of the most frequently observed postoperative (neurological) complications in elderly patients undergoing cardiac surgery (70). Delirium is an etiological nonspecific brain syndrome characterized by disturbances in consciousness, periods of inattention and changes in cognition, emotion, behaviour, and the sleep-wake schedule. Episodes of delirium have been associated with a prolonged hospital stay, functional and cognitive dysfunction and

an increased mortality (71-75). Therefore, identifying risk factors for the development of POD becomes key in the prevention and treatment of this condition. Even though the exact pathophysiological mechanisms involved in the manifestation of POD are poorly understood, cerebral hypoperfusion and hypoxia have been widely suggested as one of the underlying causes (76, 77). Recently, Hori et al. even showed that excursions above the upper limit of cerebral autoregulation – suggestive for cerebral hyperperfusion – were independently associated with POD development (78).

Over the past decades, NIRS technology has emerged as a promising tool due to its ability to detect subtle mismatches between cerebral oxygen supply and uptake at the microvascular level (30, 79). Several studies delivered observational evidence that prolonged cerebral desaturations during cardiac as well as during thoracic surgery increased the risk to develop neurological complications, thereby concluding that these should be avoided at all costs (80-84). Subsequently, others have assessed the clear benefit of using cerebral oximetry intraoperatively for both the detection and reversal of potentially harmful cerebral desaturations using NIRS-guided interventions, with so far inconclusive results (79, 82, 85-92). This might imply that future research should surpass the idea that cardiac surgery patients are solely at risk to develop potentially harmful cerebral desaturations within the intraoperative period. Others previously showed that cerebral desaturations continue to occur in the early postoperative period (93). The paucity of data linking postoperative cerebral desaturations to the development of POD asks for observational studies to determine the clinical value of cerebral oximetry in the postoperative setting (94).

In this way, this thesis might shed another light on the use of cerebral oximetry on the ICU for elderly cardiac surgery patients at risk to develop POD.

RESEARCH OBJECTIVES

Main Objective I : To explore the clinical value of two non-invasive, bedside available neuromonitoring tools in the post-CA setting, i.e. Near-Infrared Spectroscopy (NIRS) and Bispectral index (BIS) monitoring. **(PART I)**

(i) *To gain knowledge concerning the use of cerebral oximetry in the post-CA setting and assess its role in outcome prognostication* ***(Chapter 1)****;*

(ii) *To determine the optimal BIS and SR threshold within the period of TTM at 33°C for the prediction of poor neurological outcome* ***(Chapter 2)****;*

(iii) *To investigate whether characteristics of a BIS value equal to zero, other than solely its presence, are more predictive for poor neurological outcome* ***(Chapter 3)****;*

(iv) *To validate raw BIS EEG traces against standard EEG, and assess the prognostic value of BIS EEG* ***(Chapter 4-5)****;*

(v) *To construct a multivariate prediction model for the prediction of good neurological outcome using these bedside available non-invasive cerebral parameters in conjunction with other variables readily available at the ICU* ***(Chapter 6)***.

Main objective II: To assess the potential role of NIRS monitoring in the setting of (high-risk) cardiac surgery **(PART II)**

*(i) To evaluate the influence of the evolution in Transcatheter Aortic Valve Implantation (TAVI) technology on the adequacy of cerebral oxygenation **(Chapter 7)**;*

*(ii) To investigate the potential association between postoperative delirium and postoperative cerebral desaturations **(Chapter 8)**.*

PART I

Cerebral tissue oxygen and bispectral index monitoring in the post-cardiac arrest setting

CHAPTER 1

What is the value of regional cerebral saturation in post-cardiac arrest patients? A prospective observational study

Genbrugge C, **Eertmans W***, Meex I, Van Kerrebroeck M, Daems N, Creemers A, Jans F, Boer W, Dens J, De Deyne C

* Equally contributed

Critical Care (2016) 20:327

ABSTRACT

Background: The aim of this study was to elucidate the possible role of cerebral saturation monitoring in the post-cardiac arrest setting.

Methods: Cerebral tissue saturation ($SctO_2$) was measured in 107 successfully resuscitated out-of-hospital cardiac arrest patients for 48 hours between 2011 and 2015. All patients were treated with targeted temperature management, 24 hours at 33°C and rewarming at 0.3°C per hour. A threshold analysis was performed as well as a linear mixed models analysis for continuous $SctO_2$ data to compare the relation between $SctO_2$ and favourable (cerebral performance category (CPC) 1-2) and unfavourable outcome (CPC 3-4-5) at 180 days post-cardiac arrest in OHCA patients.

Results: Of the 107 patients, 50 (47%) had a favourable neurological outcome at 180 days post-cardiac arrest. Mean $SctO_2$ over 48 hours was 68% ± 4 in patients with a favourable outcome compared to 66% ± 5 for patients with an unfavourable outcome (p = 0.035). No reliable $SctO_2$ threshold was able to predict favourable neurological outcome. A significant different course of $SctO_2$ was observed, represented by a logarithmic and linear course of $SctO_2$ in patients with favourable outcome and unfavourable outcome, respectively ($p < 0.001$). During the rewarming phase, significant higher $SctO_2$ values were observed in patients with a favourable neurological outcome (p = 0.046).

Conclusion: This study represents the largest post-resuscitation cohort evaluated using NIRS technology, including a sizeable cohort of balloon-assisted patients. Although a significant difference was observed in the overall course of SctO2 between OHCA patients with a favourable and unfavourable outcome, the margin was too small to likely represent functional outcome differentiation based on SctO2 alone. As such, these results given such methodology as performed in this study suggest that NIRS is insufficient by itself to serve in outcome prognostication, but there may remain benefit when incorporated into a multi-neuromonitoring bedside assessment algorithm.

INTRODUCTION

During a cardiac arrest (CA), the brain is exposed to hypoxia resulting in neurological injury and determining survival in the majority of the post-CA patients. The brain is namely a highly aerobic organ with a limited capacity to store energy, necessitating a constant delivery of oxygen and glucose. Regardless of the recent advances in cardiopulmonary resuscitation and post-resuscitation care, neurological injury still remains a major problem. Almost 70% of patients who die during their hospital stay after out-of-hospital cardiac arrest (OHCA), decease due to post-anoxic neurological injury (19). This may be explained by the fact that the brain of an OHCA patient is subjected to a sequence of pathophysiological changes during the arrest itself, but also during the return of spontaneous circulation (ROSC) and in the post-resuscitation phase. First, global ischemia of the brain occurs during the arrest which accounts for the primary neurological injury. Next, after ROSC is achieved a post-CA syndrome develops which is characterized by a short-lasting cerebral hyperaemia followed by an increase in cerebrovascular resistance finally resulting in a decrease in cerebral blood flow (CBF) (18). During this post-CA phase, there is an imbalance between oxygen delivery relative to oxygen requirements which can last for several hours to days. These pathophysiological changes may cause progressive and irreversible brain injury responsible for the so-called secondary neurological injury. Thus far, targeted temperature management (TTM) is the only treatment with proven efficacy on neurological outcome after OHCA (16, 20).

Current brain monitoring techniques applied in post-CA patients, focus on the prediction of cerebral outcome rather than on possible therapeutic implications (9). Hence, cerebral hemodynamics could have an influence on outcome in the post-CA phase. Therefore a better understanding of cerebral hemodynamic disturbances via cerebral monitoring could have an impact on the post-CA management. Near-infrared spectroscopy (NIRS) provides information on brain oxygenation by monitoring the regional cerebral oxygen saturation ($SctO_2$) at the microvascular level. It is a non-invasive monitoring tool to measure the difference between oxygenated and deoxygenated haemoglobin in venous, arterial and capillary blood. The aim of this study was to improve our knowledge and to elucidate the possible role of non-invasive $SctO_2$ during the first 48 hours after an OHCA (with use of TTM at 33 °C) and to assess its possible relationship to outcome.

MATERIAL AND METHODS

STUDY POPULATION

All comatose survivors after OHCA with presumed cardiac origin treated in our tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium) were prospectively enrolled between March 2011 and May 2015 (n = 107). Exclusion criteria were patients < 18 year and an obviously non-cardiac cause of OHCA. If a fall was mentioned in the hetero-anamnesis, or if any clinical signs of a fall were present (e.g. bruises) a CT was performed prior to CCU admission. If no clear cause of the arrest was determined at arrival at the emergency department a head CT scan was performed to exclude cerebral causes of CA. None of the included patients had intracerebral pathologies. All patients were treated uniformly according to the institutional post-CA protocol (38). As part of this protocol, $SctO_2$ monitoring was routinely applied on arrival at the coronary care unit (CCU). The study protocol was approved by the local medical ethics committee (Comité Medische Ethiek Ziekenhuis Oost-Limburg 11/066). Written informed consent was obtained from a next of kin.

GENERAL MANAGEMENT

Our institutional post-CA protocol has been described previously (38). In summary, all patients were intubated, mechanically ventilated and sedated with propofol and remifentanil (if hemodynamically tolerated). Cisatracurium was administrated in case of shivering (bolus or continuous infusion). Patients underwent urgent coronary angiography followed by percutaneous coronary intervention when indicated. TTM at 33°C was induced as soon as possible after hospital admission by cold saline (4°C – 30 ml/kg) and was further mechanically induced and maintained in the CCU by endovascular (Icy-catheter, CoolGard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGel™ pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems at 33°C for 24h. Both systems are equipped with a feedback loop controlling target temperature using an oesophageal temperature probe. Oesophageal temperature was recorded every minute during hypothermia and rewarming. After rewarming (0.3°C/h for 12 hours) sedation was titrated towards patient's comfort with efforts to minimize sedation. Patients were extubated when their neurological, respiratory and hemodynamic status had recovered sufficiently. During the first 48 hours post-CA, an hourly blood gas was taken.

CEREBRAL SATURATION MONITORING

Cerebral tissue oxygen saturation was continuously measured with NIRS, using the FORE-SIGHT™ technology (CAS Medical systems, Branford, CT, USA). Sensors were bilaterally applied to the frontotemporal area at CCU admission, before the start of mechanically induced hypothermia. Data were transmitted to a personal computer together with all hemodynamic data with a 2s time interval. We also calculated the area below a pre-set $SctO_2$ threshold. This value encompasses both duration and severity of a desaturation below a pre-set $SctO_2$ threshold during the first 48 h after CA. Since this was an observational study, treatment was guided according to the guidelines of the European Resuscitation Council and was not affected in any way by the collected NIRS data although the $SctO_2$ data were not blinded for the treating physician (95).

HEMODYNAMIC MONITORING AND MANAGEMENT

Patients were treated according to the guidelines with the main focus on achieving a mean arterial pressure (MAP) above 65 mmHg (96). If signs of inadequate circulation persisted despite correct fluid resuscitation (wedge pressure >18 mmHg), norepinephrine was infused first with a target MAP of 65 mmHg and subsequently dobutamine was given with a target cardiac index of >2.2l/min/m^2. An intra-aortic balloon pump (IABP) was installed as deemed necessary by the treating physicians. Blood pressures were obtained by a radial artery line while a Swan–Ganz catheter provided information about CO, cardiac index and continuous mixed venous blood oxygen saturation (SvO_2).

OUTCOME MEASUREMENT

The Cerebral Performance Category (CPC) scale was used to define patient's outcome (97-99). According to the scale classification, CPC 1 indicates good cerebral performance, CPC 2 implies a 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 180 days after the CA.

STATISTICAL METHODS

Patients' characteristics were compared using Student's t-test if normally distributed and expressed as mean ± standard deviation. The Chi-square test and Fisher's exact test (when expected frequency of five or less) were used to compare categorical values.

Descriptive statistics were used for continuously measured $SctO_2$ values and are expressed as mean ± standard deviation.

The data as collected are longitudinal in nature: $SctO_2$ was measured repeatedly over time. By averaging $SctO_2$ values per hours, the data yields 48 measurements per patient. To take the longitudinal nature of the data into account, a linear mixed model with a random intercept and a random slope was used (100). The comparison of the evolution of $SctO_2$ for the survivors versus non-survivors was of primary interest. To take possible confounders into account, an effect of gender and age, together with a quadratic effect of time, and all interactions with gender and survival were considered in a first, elaborated model. A backward selection procedure was performed to exclude non-significant effects. This resulted in the following model:

$$Sat_{ij} =$$

$$(\beta_0^{ms} + b_{0i}) + (\beta_1^{ms} + b_{1i})t_{ij} + \beta_2^{s}t_{ij}^2 + \beta_3^{ms}age_i + \beta_4^{m}t_{ij}age_i + \epsilon_{ij} \quad \text{Male survivors}$$

$$(\beta_0^{mn} + b_{0i}) + (\beta_1^{mn} + b_{1i})t_{ij} + \beta_2^{n}t_{ij}^2 + \beta_3^{mn}age_i + \beta_4^{m}t_{ij}age_i + \epsilon_{ij} \quad \text{Male non-survivors}$$

$$(\beta_0^{fs} + b_{0i}) + (\beta_1^{fs} + b_{1i})t_{ij} + \beta_2^{s}t_{ij}^2 + \beta_3^{fs}age_i + \beta_4^{f}t_{ij}age_i + \epsilon_{ij} \quad \text{Female survivors}$$

$$(\beta_0^{fn} + b_{0i}) + (\beta_1^{fn} + b_{1i})t_{ij} + \beta_2^{n}t_{ij}^2 + \beta_3^{fn}age_i + \beta_4^{f}t_{ij}age_i + \epsilon_{ij} \quad \text{Female non-survivors.}$$

Where Sat_{ij} and t_{ij} are $SctO_2$ measurement and the corresponding time of this measurement for patient i on hour j, age_i is the age of patient i, and $(b_{0i}, b_{1i}) \sim N\left(\binom{0}{0}, \begin{pmatrix} d_{11} & d_{12} \\ d_{12} & d_{22} \end{pmatrix}\right)$, are the random intercept and random slope respectively. All parameters in this model were significant, and no further reduction could be obtained.

A p-value < 0.05 was considered to be statistically significant. Tests were performed using SPSS 20.00 (SPSS, Chicago, IL, USA) and SAS Software version 13.2 (SAS, Cary, NC, USA). Figures were made using GraphPad Prism 5.01 (GraphPad Software, CA, USA).

RESULTS

Hundred and seven consecutive OHCA patients were included in this study. Baseline characteristics are summarized in Table 1. Fifty patients (47%) survived with a good neurological outcome (CPC1-2) at 180 days post-CA. A significant difference in initial rhythm was observed, 84% of the survivors had ventricular fibrillation in contrast to 41% of the non-survivors ($p < 0.001$). Significantly more survivors underwent urgent coronary angiography (92% versus 71%, p = 0.008) and received a percutaneous coronary intervention (71% versus 39%, $p = 0.001$). We observed no significant difference in the use of IABP between both groups ($p = 0.969$). Within the group of survivors, 39 (78%) patients had a CPC 1 and 11 (22%) had a CPC 2 at 180 days post-CA. None of the survivors had a CPC 3 or CPC 4. Twelve patients died within 48 hours, with a mean age of 67 years ± 11, of whom four (33%) were women. The mean $SctO_2$ of these patients was 65% ± 7. In Figure 1 the course of the hourly mean MAP, arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$), SvO_2 and lactate during the first 48 hours is shown for survivors and non-survivors.

Table 1. Patient demographics.

	All patients	Survivors	Non-survivors	P-value
Patients, n (%)	107	50 (47)	57 (53)	/
Age, mean (±SD)	63 (13)	61 (13)	65 (13)	0.084
Gender, male/female, n (%)	75 (70) / 32 (30)	40 (78) / 11 (22)	35 (63) / 21 (37)	0.072
Witnessed, n (%)	91 (85)	46 (92)	45 (79)	0.182
Bystander BLS, n (%)	59 (55)	28 (55)	31 (55)	0.962
Initial rhythm				
VF, n (%)	66 (62)	42 (84)	24 (42)	**<0.001**
PEA, n (%)	11 (10)	4 (8)	7 (12)	0.374
Asystole, n (%)	25 (23)	4 (8)	21 (37)	**<0.001**
Time emergency call – ROSC (min)	30 ± 19	27 ± 17	34 ± 20	0.099
Cooling, endovascular/surface, n (%)	46 (43) / 61(57)	26 (51) / 25 (49)	20 (36) / 36 (64)	0.111
Coronary angiography	87 (81)	46 (92)	41 (71)	**0.008**
PCI, n (%)	58 (54)	36 (72)	22 (39)	**0.001**
IABP, n (%)	25 (23)	12 (24)	13 (23)	0.969

BLS = Basic Life Support; VF = Ventricular Fibrillation; PEA = Pulseless Electrical Activity; ROSC = Return Of Spontaneous Circulation; PCI = Percutaneous Coronary Intervention; IABP = Intra-aortic Balloon Pump.

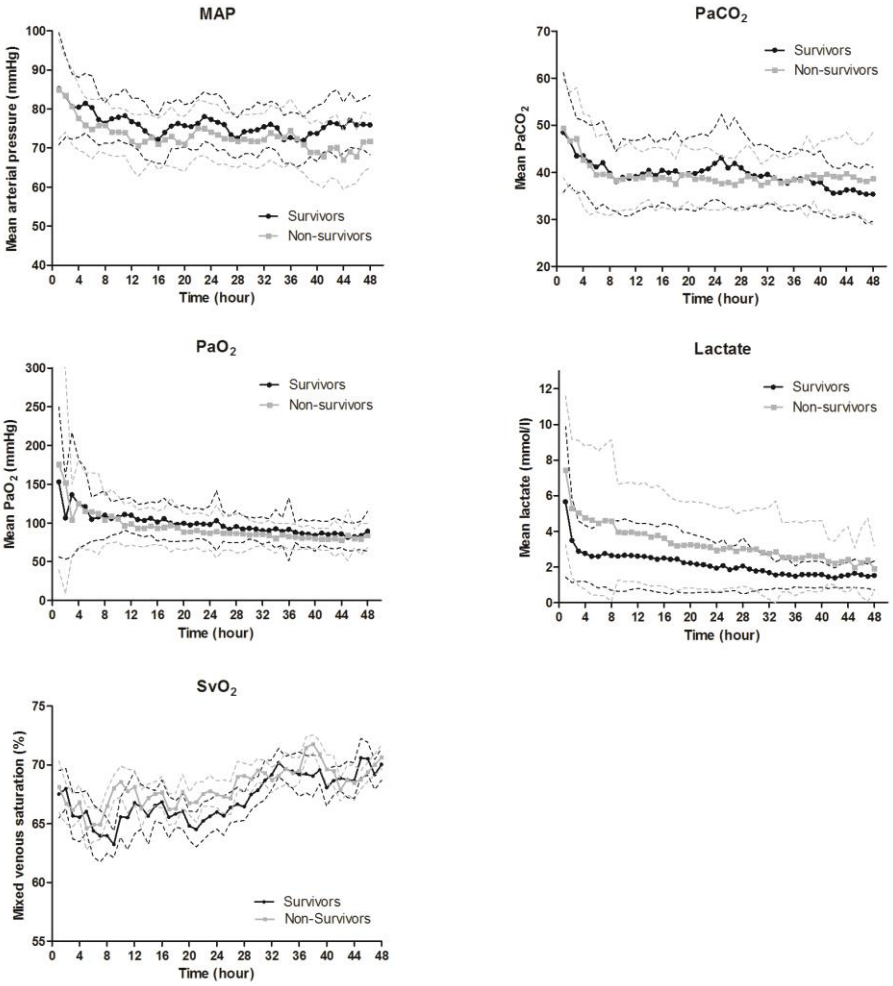


Figure 1. Course of hemodynamic parameters, mean arterial pressure, arterial carbon dioxide pressure, arterial oxygen pressure, lactate and mixed venous saturation. In this figure, the course for 48 hours of different hemodynamic parameters is shown as mean ± standard deviation. Overall p-values: MAP: p = 0.020; $PaCO_2$: p = 0.842; PaO_2: p = 0.370; lactate: p = 0.002; SvO_2: p = 0.649. MAP = mean arterial pressure, $PaCO_2$ = arterial carbon dioxide; PaO_2 = arterial oxygen tension; SvO_2 = mixed venous saturation.

The mean $SctO_2$ of the first hour after admission at the coronary care unit was 64% ± 7 in survivors compared to 66% ± 6 in non-survivors (p = 0.184). The mean $SctO_2$ over 48 hours was significantly higher in the survivors (68% ± 4) compared to non-survivors (66% ± 5; p = 0.035). The mean course of $SctO_2$ in both groups is given in Figure 2. An initial decrease was observed after initiation of TTM until hour 3 in survivors (-5% ± 6) and until hour 5 in non-survivors (-3% ± 12; p = 0.432) followed by a progressive increase in both groups.

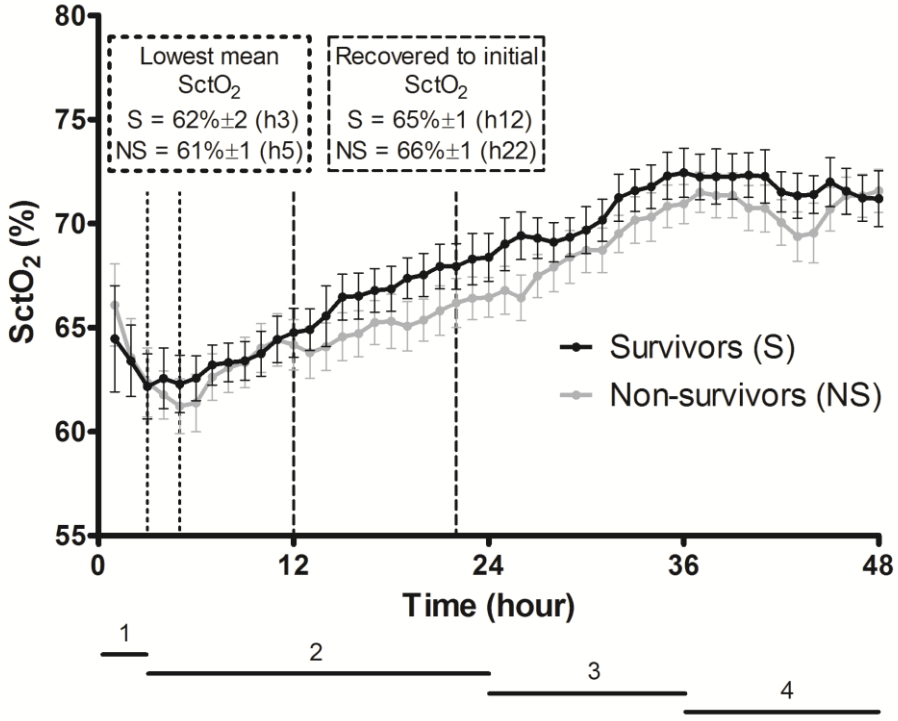


Figure 2. Cerebral saturation course (mean ± standard deviation). 1 = time to target temperature; 2 = therapeutic hypothermia; 3 = rewarming; 4 = normothermia. $SctO_2$ = cerebral tissue oxygen saturation.

The first 48 hours of TTM at 33°C after CA can be divided in four different phases: the cooling phase, followed by the hypothermia phase at 33°C, the rewarming phase and finally the normothermia phase. The mean time to target temperature (cooling phase) was 183min ± 160 in both groups. The hypothermia phase took 21 hours followed by a 12 hours rewarming phase and a 12 hours normothermia phase. The results of the mean

$SctO_2$ in each phase are listed in Table 2. We observed a significant difference in the mean $SctO_2$ in the rewarming phase between survivors and non-survivors (70% ± 1 versus 68% ± 1, p = 0.046). No significant differences were observed in the other phases.

Table 2. Cerebral saturation values phase by phase.

	Survivors	**Non-survivors**	**p-value**
Cerebral saturation (%)			
Time to target temperature (0-3h)	63 ± 2	64 ± 2	0.509
Therapeutic hypothermia (3-24h)	65 ± 1	64 ± 1	0.076
Rewarming (24-36h)	70 ± 1	68 ± 1	**0.046**
Normothermia (36-48h)	72 ± 1	71 ± 1	0.217

If $SctO_2$ values during the four different cooling phases were compared between patients with and without IABP, a difference was observed during the cooling and hypothermia phase with higher $SctO_2$ values in the no-IABP group (p = 0.009 and p = 0.042). In the next two phases, the rewarming (phase 3) and normothermia phase (phase 4), no significant difference in $SctO_2$ values was observed between both groups (phase 3 - p = 0.722; phase 4 - p = 0.827).

The area below a pre-set $SctO_2$ threshold was calculated as well. Receiver operating curve (ROC) analysis revealed the highest AUC for a $SctO_2$ threshold of 55% (AUC 0.58; specificity 52% and sensitivity 62%).

If data were fitted in an optimal mixed model, a significant difference was observed between survivors and non-survivors concerning the course of $SctO_2$ after adjustment for age and gender (p < 0.001) (Fig. 3). Between female survivors and non-survivors we observed a significant difference already from the start of TTM at 33°C with a logarithmic course of $SctO_2$ in the survivors group versus a linear one in the non-survivor group. Male survivors and non-survivors had initially similar $SctO_2$ values but during induction of hypothermia, $SctO_2$ increased more rapidly in the male survivors (logarithmic) compared to male non-survivors (linear).

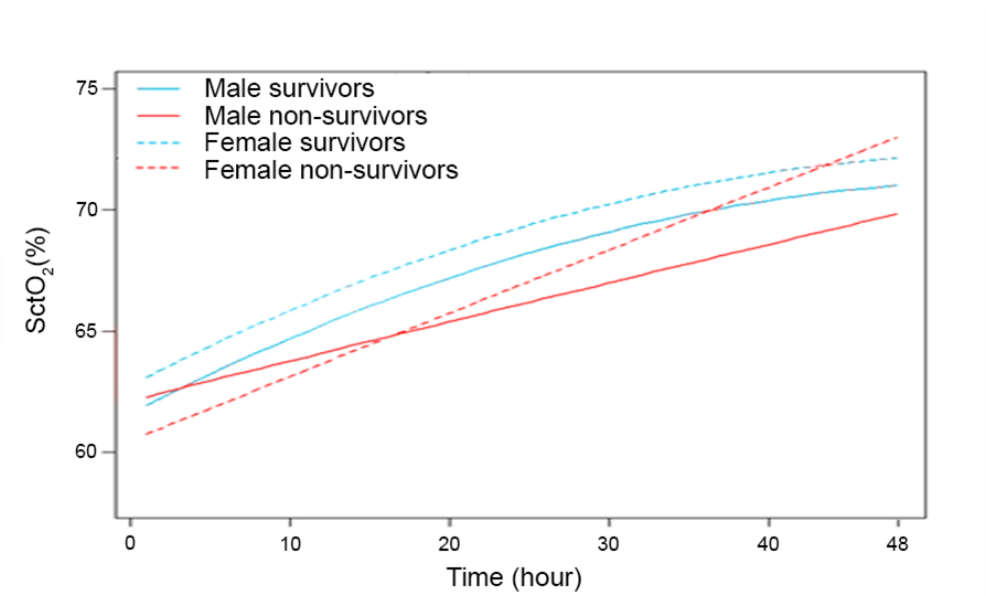


Figure 3. Fitted cerebral saturation by linear mixed models. $SctO_2$ = cerebral tissue oxygen saturation.

DISCUSSION

In this study, $SctO_2$ was prospectively monitored in OHCA patients with a presumed cardiac cause during the initial 48 hours after admission to the CCU. This is currently the largest post-resuscitation patient cohort evaluated using $SctO_2$ to prognosticate outcome. In all patients TTM at 33°C was applied for 24 hours, followed by an active rewarming at 0.3°C/hour. Within this timeframe, we observed a significant different course of $SctO_2$ between survivors (CPC 1-2) and non-survivors (CPC 5). In the rewarming phase, significant higher $SctO_2$ values were observed in patients with a favourable neurological outcome. However the clinical significant difference we observed in $SctO_2$ course is of unlikely clinical meaning since this information is not available at the bedside and moreover it is so small that at present clinicians will not be able to use any $SctO_2$ cut-off value to predict outcome.

Experimental studies on CA and outcome revealed that the severity of brain damage is mainly influenced by the duration of the CA, and by the mismatch in the oxygen extraction rate (CEO_2) to CBF during the post-resuscitation period (101). A better understanding of cerebral hemodynamic disturbances may have an impact on the post-CA

management and may also allow a better prognostication. Monitoring of $SctO_2$ could provide a non-invasive assessment of these cerebral hemodynamic disturbances.

In recent years, several studies investigated whether NIRS could be used during the post-CA stage to assist with the neuroprognostication and as a therapeutic target (38-40). Overall, significant higher $SctO_2$ were observed at different time points in the post-CA phase between patients with a favourable compared to unfavourable outcome. Nevertheless, the included patient populations were inhomogeneous (mix of OHCA and in-hospital cardiac arrest (IHCA) patients), rather small in sample size and mean $SctO_2$ values over several hours were used.

In our patient cohort, we found the best AUC for a threshold value of 55%. However, this AUC had a very low sensitivity and specificity. In contrast, Storm et al. found the highest AUC for outcome prediction at a $SctO_2$ threshold of 50% with a far more higher sensitivity and specificity (AUC 0.80; specificity 70% and sensitivity 86%) (39). We should remark that they included 60 both IH- and OHCA patients of which 38% had a good neurological outcome compared to 47% in our exclusively OHCA patient population. In the setting of aortic arch surgery, Fischer et al. showed that the time under $SctO_2$ thresholds of 55%, 60% and 65% was associated with poor outcome (102). In contrast to the perioperative setting where treatment algorithms are proposed to treat cerebral desaturations, no target $SctO_2$ values are currently recommended in the post-CA phase.

In contrast to previous mentioned studies which applied an hour by hour analysis, we performed a linear mixed model analysis using continuous $SctO_2$ data to investigate whether the $SctO_2$ course over time was different between survivors versus non-survivors (38-40). If all $SctO_2$ values were fitted in a linear mixed model, a significant time effect was observed during the $SctO_2$ course. More specifically, survivors followed a logarithmic $SctO_2$ course over time compared to a more linear one for non-survivors. Based on these findings, it seems possible that the balance between oxygen supply and demand in survivors recovered more rapidly and that non-survivors have longer-lasting disturbances in cerebrovascular autoregulation. This implies that $SctO_2$ in non-survivors could be more dependent on hemodynamic parameters such as MAP, CO and $PaCO_2$. Despite this significant discordance in time course which probably indicates different underlying pathophysiologic mechanisms between both patient groups, we should take into account that this represents post-hoc information, not available at the bedside. The $SctO_2$ course of both, male and female patients with good favourable neurological outcome, follow the

same shape compared to the patients with unfavourable outcome. However the overall course of female survivors is higher compared to the male survivors, which is more or less also the case in the non-survivor group. Bickler et al. observed no difference in gender using the FORE-SIGHT technology to measure cerebral saturation in healthy volunteers (103). In this way a bias by the used technology can be excluded. In healthy volunteers, regional cerebral blood flow is higher in female volunteers compared to male volunteers (104, 105). In animal studies a greater cerebral cortical blood flow and lower cerebral oxygen extraction ratio was observed after severe cerebral haemorrhage and ventricular fibrillation in females (106). However, these studies were performed without the use of TTM at 33°C. All previous described findings might explain the higher observed $SctO_2$ in female patients if we assume that TTM at 33°C has a similar effect on both sexes. Another explanation could be the number of included female patients which is only one third of the total included population.

At the initiation of TTM at 33°C, a decrease in mean $SctO_2$ was observed followed by a progressive increase in mean $SctO_2$ in both survivors and non-survivors. This decrease could be explained by the onset of different pathophysiological mechanisms after CA. A period of delayed cerebral hypoperfusion occurs which is associated with an increase in cerebrovascular resistance, a drop in CBF and cerebral metabolic oxygen consumption (107, 108). Moreover, it has been shown that blood viscosity is higher during the initial hours after a CA (109-112). As a significant negative correlation exists between blood viscosity and the mean flow velocity of the middle cerebral artery, this could explain the observed decrease in $SctO_2$ (112). Thirdly, hemodynamic parameters such as $PaCO_2$, MAP and CO influence $SctO_2$ (113). Especially our observed decrease in $PaCO_2$ (50mmHg until 40mmHg) with its subsequent effects on cerebral vasculature and CBF could influence $SctO_2$ values (114). Additionally, we observed a simultaneous decrease in MAP until 5-6 hours after the induction of TTM at 33°C together with a decrease in $SctO_2$ suggesting an impaired autoregulation. Cerebrovascular autoregulation is known to be disturbed or right shifted after a CA which can influence $SctO_2$ (107, 115). Finally, CO, in the initial phase after a CA, is relatively low due to myocardial dysfunction (116). We observed a decrease in SvO_2, and as SvO_2 is highly correlated with CO, our observed decrease in $SctO_2$ can therefore be partially explained by a drop in CO (108, 116-118). The hemodynamic variability in the initial hours after CA as described above suggest the presence of a therapeutic window. Therefore, hemodynamic parameters such as MAP and CO could be

optimized using an interventional protocol which may prevent the potential harming cerebral desaturation in the early post-CA hours.

After the initial drop in mean $SctO_2$, a progressive increase in mean $SctO_2$ was observed reaching stable values around hour 12 and 22 in survivors and non-survivors, respectively. This ten hour delay in $SctO_2$ recovery in non-survivors may implicate once more that brain recovery from ischemia after CA is not similar in survivors versus non-survivors. Since others described a low CEO_2 together with a gradual increase in mean flow velocity until 48 hours after CA, our observed increase in $SctO_2$ six hours after the start of TTM at 33°C is supported by these findings (101, 119). In addition, TTM at 33°C induces a leftward shift of the oxygen dissociation curve. This results in an enhanced affinity of oxygen to haemoglobin, a phenomenon which may explain the progressive increase in $SctO_2$ as well.

During the rewarming phase, using a rewarming rate of 0.3°C/h, we observed significant higher $SctO_2$ values in survivors compared to non-survivors (p = 0.046). This finding has probably an influence on the statistical difference we observed in the overall course of $SctO_2$. The optimal rewarming rate in post-CA patients (after TTM at 33°C) is not known thus far. But both animal and human studies performed during cardiac surgery suggest a detrimental effect of rapid rewarming at the expense of potential neuroprotective effects of TH (120-123). Therefore, our results can only indicate that rewarming has a different influence on cerebral hemodynamics in survivors versus non-survivors.

If a sub-analysis is performed comparing patients with and without an IABP, significant higher $SctO_2$ values are observed during cooling and hypothermia in the no-IABP group. This represents probably the higher hemodynamic instability of patients receiving an IABP.

Our study has several limitations. First, we did not assess cerebral hemodynamic parameters by Transcranial Doppler. The continuous measurement of both $SctO_2$ and cerebral hemodynamic parameters could have allowed a better understanding of cerebral hemodynamic changes in post-CA patients. Secondly, $SctO_2$ was measured using NIRS technology on the forehead. This is a regional measurement with the disadvantage that we do not had any information other than the frontal region. The number of patients included was rather limited but as far as we know, this study is currently the largest in which $SctO_2$ is prospectively measured in post-CA patients. Nevertheless, we suppose that extending the number of patients will be of no added value for a better understanding of

the underlying pathophysiologic mechanism responsible for the observed $SctO_2$ course. For this purpose, an experimental setting using non-invasive as well as invasive cerebral hemodynamic measurements could provide more valuable information. At last, in this study $SctO_2$ was measured during TTM at 33°C. Consequently these findings might not be applicable to patients treated with TTM at 36°C. More importantly, significant higher $SctO_2$ values were measured in the favourable neurological outcome group during the rewarming phase, which is absent in post-CA patients treated with TTM at 36°C.

CONCLUSION

This study represents the largest post-resuscitation cohort evaluated using NIRS technology, including a sizeable cohort of balloon-assisted patients. Although a significant difference was observed in the overall course of $SctO_2$ between OHCA patients with a favourable and unfavourable outcome, the margin was too small to likely represent functional outcome differentiation based on $SctO_2$ alone. As such, these results given such methodology as performed in this study suggest that NIRS is insufficient by itself to serve in outcome prognostication, but there may remain benefit when incorporated into a multi-neuromonitoring bedside assessment algorithm.

CHAPTER 2

The prognostic value of bispectral index and suppression ratio monitoring after out-of-hospital cardiac arrest. A prospective observational study

Eertmans W, Genbrugge C, Vander Laenen M, Boer W, Mesotten D, Dens J, Jans F, De Deyne C

Ann Intensive Care (2018) 8:34.

ABSTRACT

Background: We investigated the ability of bispectral index (BIS) monitoring to predict poor neurological outcome in OHCA patients fully treated according to guidelines.

Results: In this prospective, observational study, 77 successfully resuscitated OHCA patients were enrolled in whom bispectral index (BIS), suppression ratio (SR) and electromyographic (EMG) values were continuously monitored during the first 36 hours after the initiation of targeted temperature management at 33°C. The Cerebral Performance Category (CPC) scale was used to define patients' outcome at 180 days after OHCA (CPC 1-2: good - CPC 3-5: poor neurologic outcome). Using mean BIS and SR values calculated per hour, receiver operator characteristics curves were constructed to determine the optimal time point and threshold to predict poor neurological outcome. At 180 days post-cardiac arrest, 39 patients (51%) had a poor neurological outcome. A mean BIS value ≤ 25 at hour 12 predicted poor neurological outcome with a sensitivity of 49% (95% CI:30-65%), a specificity of 97% (95% CI:85-100%) and false positive rate (FPR) of 6% (95% CI: 0-29%) (AUC: 0.722 (0.570-0.875); p=0.006). A mean SR value ≥ 3 at hour 23 predicted poor neurological outcome with a sensitivity of 74% (95% CI:56-87%), a specificity of 92% (95% CI:78-98%) and FPR of 11% (95% CI: 3-29%) (AUC: 0.836 (0.717-0.955); p<0.001). No relationship was found between mean EMG and BIS<25 (R^2=0.004; p=0.209).

Conclusion: This study found that mean BIS≤25 at hour 12 and mean SR≥3 at hour 23 might be used to predict poor neurological outcome in an OHCA population with a presumed cardiac cause. Since no correlation was observed between EMG and BIS<25, our calculated BIS threshold might assist with poor outcome prognoscitation following OHCA.

INTRODUCTION

Once admitted to the Intensive Care Unit (ICU), post-anoxic brain injury is considered as the predominant cause of death in patients admitted after cardiac arrest (CA) (6, 19). The implementation of targeted temperature management (TTM) in the post-CA setting improved neurological outcome substantially, but delayed neuroprognostication until at least 72 hours after CA (16, 20, 21, 41, 42). Nevertheless, early and reliable prognostication is most appreciated to inform relatives. Moreover, it could avoid futile and expensive treatment efforts in out-of-hospital cardiac arrest (OHCA) patients with irreversible brain damage.

Current guidelines recommend the use of a neuroprognostication algorithm including four main modalities which should be used in conjunction with each other whenever possible, i.e. clinical neurological examination, electrophysiology, biomarkers and brain imaging (10, 20, 21). Unfortunately, most of the recommended prognostic markers are labour-intensive and above all require trained experts for correct interpretation. In recent years, the potential use of Bispectral Index (BIS) and to a lesser extent suppression ratio (SR) monitoring has been investigated in the post-CA setting (58, 59, 61-63, 124, 125). Although these studies demonstrated that BIS and SR values could be used to predict poor neurological outcome, this monitoring option was not yet implemented in the neuroprognostication algorithm proposed by current guidelines (20). Its use in brain-injured CA patients is namely associated with certain limitations. The BIS monitor was originally designed to monitor intraoperative awareness during anaesthesia, possibly implying that physicians treating post-CA patients are unfamiliar with its use (54). Additionally, BIS monitoring is exposed to potential confounders of which high electromyographic (EMG) activity is acknowledged as the predominant one within CA research, causing falsely elevated BIS values (65). In previous BIS studies, neuromuscular blockers (NMB) were administered continuously in all patients to minimize EMG activity interference although its constant use is not in line with current guidelines (69). Altogether, these limitations question the clear benefit of this user-friendly monitoring option to assist with neuroprognostication. Therefore, this prospective, observational study aimed to assess the ability of BIS monitoring to predict poor neurological outcome in OHCA patients fully treated according to guidelines.

MATERIAL AND METHODS

STUDY POPULATION

A prospective, observational study was performed between March 2011 and May 2015 in a Belgian tertiary care hospital (Ziekenhuis Oost-Limburg, Genk). All adult comatose survivors successfully resuscitated from OHCA with a presumed cardiac cause were admitted to the coronary care unit (CCU) and were considered as eligible for this study. According to the institutional post-CA care protocol, all patients were treated uniformly and BIS monitoring was started immediately after admission to CCU (38). Approval from the local Committee for Medical Ethics was obtained prior to study onset (11/06) and written informed consent was obtained from patient's next of kin.

PATIENT MANAGEMENT

The institutional post-resuscitation protocol has been described previously (38, 126). To summarize, TTM at 33°C was initiated immediately after arrival at the emergency department by administering cold saline intravenously (4°C – 15-30ml/kg). Urgent coronary angiography was performed followed by a percutaneous coronary intervention when indicated. TTM was further mechanically induced after CCU admission and maintained at 33°C for 24 hours using either endovascular (Icy-Cathether, Coolgard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGel™ pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems. Subsequently, patients were rewarmed over the following 12 hours (0.3°C/hour). Both cooling systems were equipped with a feedback loop system to control target temperature using an oesophageal temperature probe. All patients were intubated, mechanically ventilated and sedated with propofol, midazolam and remifentanil. Within the period of TTM, sedation doses were titrated to obtain values between -3 and -5 on the Richmond Agitation-Sedation scale. According to current guidelines, cisatracurium was only administered in case of shivering (69). After the return to normothermia, sedation was reduced to evaluate patients' neurological status properly. Patients not ready for extubation owing to circulatory or respiratory issues or due to persisting coma were kept sedated under the lowest dose needed to tolerate the endotracheal tube. EEGs were performed on clinical indication and anti-epileptic drugs were given in case of epileptic activity. Every EEG was characterized by a description of the posterior dominant rhythm (or absence thereof) and amplitude as well as the presence of non-dominant rhythms. Lateralization and the presence of artefacts was described where applicable. If present, epileptic activity was described as interictal, ictal or

as status epilepticus. A status epilepticus was defined as continuous epileptic activity including rhythmic focal or generalized spikes lasting for more than five minutes, and was considered as therapy-refractory in case of persistent epileptic activity in spite of at least two lines of antiepileptic drugs. Once the neurological, hemodynamic and respiratory status had been recovered sufficiently, patients were extubated.

BISPECTRAL INDEX AND SUPPRESSION RATIO MONITORING

Bilateral BIS monitoring was initiated as soon as possible after CCU admission using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA). A six-electrode frontotemporal bilateral sensor was applied to the patient's forehead. The BIS monitor is a simplified EEG monitor that uses Fast Fourier transformation to convert raw frontal EEG signals into simple and real-time BIS numbers ranging from 0 (iso-electric EEG) to 100 (normal electrical activity in awake subjects). Additionally, a SR is calculated, representing the percentage of each 63 second period that is iso-electric (55). Finally, EMG activity is another parameter calculated by the BIS monitor describing the electromyographic content of the EEG signal and ranges from 0 (no EMG activity) to 100 (large EMG activity). BIS, SR and EMG values were continuously recorded and stored during the hypothermic and rewarming phase (i.e. 36 hours). Although treating physicians (cardiologists) were not blinded to values displayed on the BIS monitor, decisions to withdraw life-support were never based on these parameters and the dosage of sedatives was not titrated based on BIS values.

WITHDRAWAL OF TREATMENT POLICY

In patients not regaining consciousness despite complete cessation of sedation, maximal supportive treatment was provided until at least 72 hours after normothermia was reached. Together with clinical neurological examination, malignant EEG patterns (i.e. status epilepticus, persisting burst suppression rhythms or long-lasting cerebral inactivity) were considered as the first-line support for the decision to withdraw therapy, and in specific, when seizures remained therapy-refractory or if other EEG rhythms with a poor prognosis remained present on subsequent EEG assessments. In case subsequent EEGs were inconclusive or when patients failed to wake up after the end of active temperature control, SSEPs and/or brain CT were performed. In line with international guidelines, absent corneal and pupillary reflexes, bilateral absence of the N20 component of SSEPs and refractory epileptic activity were considered to support this decision to withdraw therapy (96).

OUTCOME ASSESSMENT

The primary endpoint was neurological outcome defined by the Cerebral Performance Category (CPC) at 180 days post-CA. According to the scale classification, CPC1 is indicative for good cerebral performance; CPC2 implies moderate disability with sufficient cerebral functioning for independent daily-life activity; CPC3 indicates severe neurological sequelae; CPC4 implies coma or vegetative state and CPC5 stands for death (99). In this study, a CPC1-2 and CPC3-5 was considered as good and poor neurological outcome, respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Version 22.0 (SPSS Inc, Chicago, USA). Equal distribution was tested with a Kolmogorov-Smirnov test. Depending on normality, categorical data were compared between patients with a good and poor neurological outcome using Fisher exact or Chi-Square tests, while unpaired T-tests or Mann-Whitney U tests were used to compare continuous data. BIS, SR and EMG values were stored per second and left and right values were averaged. Mean BIS, SR and EMG values were then calculated per hour from initiation of TTM onwards and were used for data analysis. To assess the predictive ability of BIS and SR, receiver operating characteristic (ROC) curves were constructed at each hour using mean BIS and SR values and the Youden index was calculated for each ROC curve (Youden index = sensitivity + specificity − 1). The optimal time point and threshold to predict poor neurological outcome was determined based on the highest Youden index across all ROC curves. Relative risk ratios of poor neurological outcome were computed for the presence of single BIS and SR values between given intervals on the respective optimal time points. In addition, regression curves were fitted (including the calculation of the Pearson correlation coefficient) to describe the relationship between mean EMG and BIS values below and above our calculated (optimal) BIS threshold. Survival analyses were executed using Kaplan-Meier curves and log-rank statistic. P-values < 0.05 were considered as significant.

RESULTS

Between March 2011 and May 2015, 121 eligible OHCA patients were consecutively enrolled in this study. Forty-four patients were excluded from further analysis for following reasons: no recording of BIS values (n = 34), initiation of BIS monitoring at day 2 (n = 4) and incoherence between time stamp and start of BIS monitoring (n = 6). In total, 77 successfully resuscitated OHCA survivors were prospectively included. At 180 days post-

CA, 38 patients (49%) had a good (CPC1-2), while 39 patients (51%) had a poor neurological outcome (CPC5). There were no patients with a CPC 3 or 4 at 180 days following CA. Baseline characteristics, patient's severity at admission and complications within the post-resuscitation management phase are summarized in table 1 for both outcome groups. Sedation doses were in general higher in patients with a good neurological outcome. In total, 44 (57%) patients received NMB during the period of TTM, with no difference in the NMB dosage between both outcome groups (p=0.804; table 2).

Table 1. Baseline characteristics and post-resuscitation management and complications.

Characteristic	Good neurological outcome (N = 38)	Poor neurological outcome (N = 39)	P
Age	67 ± 13	61 ± 13	**0.034**
Male	31 (82)	31 (80)	0.817
Co-morbidities			
Diabetes	2 (5)	10 (26)	**0.025**
Chronic kidney insufficiency	2 (5)	6 (15)	0.263
Cerebrovascular disease	2 (5)	2 (5)	1.000
Acute myocardial infarction	6 (16)	5 (13)	0.755
Arterial hypertension	16 (42)	17 (44)	1.000
Hyperlipidaemia	15 (39)	16 (41)	1.000
Cardiac arrest variables			
Initial Rhythm			**0.003**
Shockable	33 (87)	20 (56)	
Non-shockable	5 (13)	16 (44)	
Witnessed arrest	34 (92)	33 (87)	0.479
Bystander CPR	18 (47)	20 (51)	0.821
BLS duration (min)	8 (0 – 14)	10 (0 – 12)	0.561
ALS duration (min)	12 (8 – 21)	15 (10 – 28)	0.348
Number of shocks	2 (1 – 5)	1 (0 – 4)	0.111
Time Emergency call – ROSC (min)	28 ± 19	32 ± 15	0.388
Post-resuscitation management			
Percutaneous Coronary Intervention	27 (71)	17 (44)	**0.015**
Cooling, endovascular/surface	20 (53) / 18 (47)	15 (38) / 24 (62)	0.256

Table 1 continued

Time to target temperature (min)	140 (73 – 295)	141 (107 – 195)	0.652
Intra-aortic balloon pump	11 (29)	6 (15)	0.178
Post-resuscitation complications			
Post-resuscitation shock	16 (42)	21 (54)	0.365
ARDS	4 (11)	7 (18)	0.517
Pneumonia	21 (55)	17 (44)	0.365
Acute kidney injury	9 (24)	12 (31)	0.610
Renal replacement therapy	3 (8)	3 (8)	1.000
Status Epilepticus	1 (3)	20 (51)	**<0.001**
Burst Suppression	4 (11)	16 (41)	**0.004**
Cause of death			
Neurological injury	/	27 (69)	/
Post cardiac arrest shock	/	10 (26)	/
Other	/	2 (5)	/
CCU days	19 (12 – 32)	9 (6 – 17)	**<0.001**

Data are shown as mean ± SD, median with interquartile range and n (%).

ALS = Advanced Life Support; ARDS = Acute Respiratory Distress Syndrome BLS = Basic Life Support; CCU = Coronary Care Unit; CPR = Cardiopulmonary resuscitation; ROSC = Return of spontaneous circulation.

Table 2. Sedation doses and neuromuscular blockage.

Sedatives	Good neurological outcome	Poor neurological outcome	P-value
Propofol (mg/kg/h)	2.54 ± 0.51	1.35 ± 0.05	0.071
Remifentanil (µg/kg/min)	0.15 ± 0.07	0.10 ± 0.01	0.210
Midazolam (µg/kg/min)	1.45 ± 0.34	0.85 ± 0.21	0.156
Cisatracurium (mg/kg/h)*	0.13 (0.03 – 0.17)	0.10 (0.07 – 0.14)	0.804

Data are presented as mean ± SD and median with interquartile ranges.

* Cisatracurium was administered in 20 and 24 patients with a good and poor neurological outcome, respectively.

In 27 out of the 39 (69%) patients with a poor (neurological) outcome (CPC5), therapy was withdrawn at day 10 (6 – 20) post-CA and died due to extensive neurological injury. First, 19 out of these 27 patients had a therapy-refractory status epilepticus. On top of persistent seizure activity, six and four out of these 19 patients had bilateral absent cortical responses on SSEP and diffuse brain oedema on CT, respectively. One patient with therapy-refractory seizures developed a septic shock after TTM at 33°C ended and died six days after CCU admission. Another patient died two days after admission due to multi-organ failure in addition to persistent epileptic activity. Despite aggressive anti-epileptic therapy, the other seven patients remained in a comatose vegetative state in whom therapy was withdrawn after 10 (9 – 32) days. Second, a bilateral absent cortical response (N20) on SSEP was the main reason for withdrawal of life-sustaining treatment in four out of these 27 patients. Third, two patients did not recover neurologically two to three weeks following CA, and EEGs persistently showed burst-suppression patterns. Finally, two patients had long-lasting cerebral inactivity based on EEG in whom a brain CT showed diffuse cerebral oedema indicative for extensive cerebral swelling.

Figure 1 displays the evolution of mean BIS and SR values over the first 36 hours from the initiation of TTM onwards in patients with a good and poor neurological outcome. After calculating the mean BIS and SR per hour, the optimal time point which provided the best sensitivity and specificity to predict poor neurological outcome was determined. A mean BIS value below or equal to 25 at hour 12 predicted poor neurological outcome with a sensitivity of 49% (95% CI:30-65%) and specificity of 97% (95% CI:85-100%) (AUC: 0.722 (0.570-0.875); p=0.006). Only one patient with a mean BIS≤25 at hour 12 survived with a good neurological outcome. This corresponded to a false positive rate (FPR) of 6% (95% CI: 0-29%). A mean SR value above or equal to 3 at hour 23 predicted poor neurological outcome with a sensitivity of 74% (95% CI:56-87%) and specificity of 92% (95% CI:78-98%) (AUC: 0.836 (0.717-0.955); p<0.001). This corresponded to a FPR of 11% (95% CI: 3-29%). Three patients with a mean SR≥3 at hour 23 had a good neurological outcome.

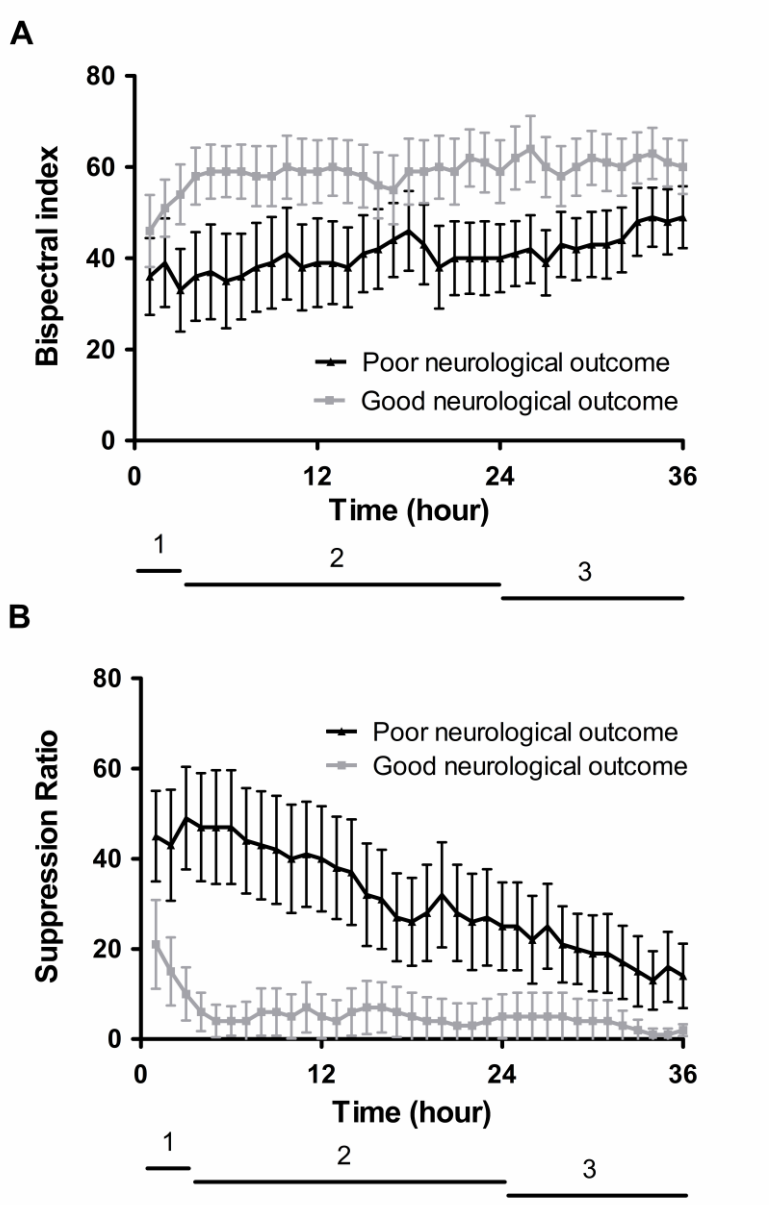


Figure 1. Evolution of mean BIS and SR during Targeted Temperature Management. Hourly mean BIS **(A)** and SR values **(B)** are shown with their 95% CI in patients with a good and poor neurological outcome. Patients with a poor neurological outcome had significantly lower BIS and higher SR values during (1) the induction phase ($p=0.002$ and $p<0.001$, respectively), (2) the hypothermic phase ($p<0.001$ and $p<0.001$, respectively) and (3) rewarming phase ($p<0.001$ and $p<0.001$, respectively).

At these optimal time points, relative risk ratios of poor neurological outcome were calculated for the presence of single BIS and SR values per second between given intervals (Fig. 2). Patients experiencing at least one BIS≤25 at hour 12 had a 2.3-fold higher risk of poor neurological outcome (95% CI:1.38-3.85; p=0.001). On the other hand, the presence of at least a single SR≥3 at hour 23 was associated with a 4.4-fold higher risk of poor neurological outcome (95% CI:2.09-9.30; p<0.001).

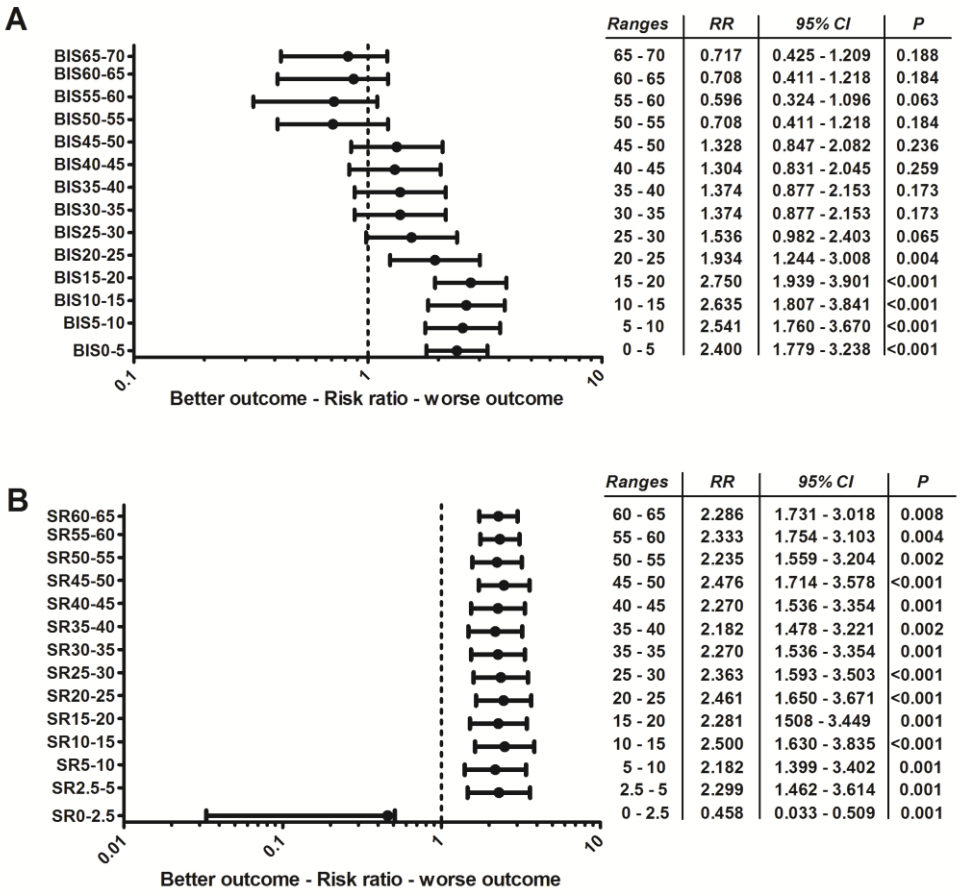


Figure 2. Forest plots. Relative risk ratios for poor neurological outcome at 180 days post-cardiac arrest are presented for the presence between given BIS (A) and SR (B) ranges at hour 12 and 23, respectively.

The overall relationship between mean EMG and BIS was best described by a quadratic regression curve ($Y = 29.64 - 0.228X + 0.007X^2$; $R^2=0.671$; $p<0.001$; Fig. 3). To account for possible EMG interferences on our calculated BIS threshold, regression curves were fitted between mean EMG and BIS values below and above 25. This analysis showed no relationship between mean EMG and BIS values below 25 ($Y = 28.10 + 0.043X$; $R^2 = 0.004$; $p=0.209$), implying that EMG interference below our calculated BIS threshold is rather neglible. In contrast, a significant relationship was observed between mean EMG and BIS values above 25 ($Y = 30.35 - 0.263X + 0.007X^2$; $R^2 = 0.650$; $p<0.001$; Fig. 3).

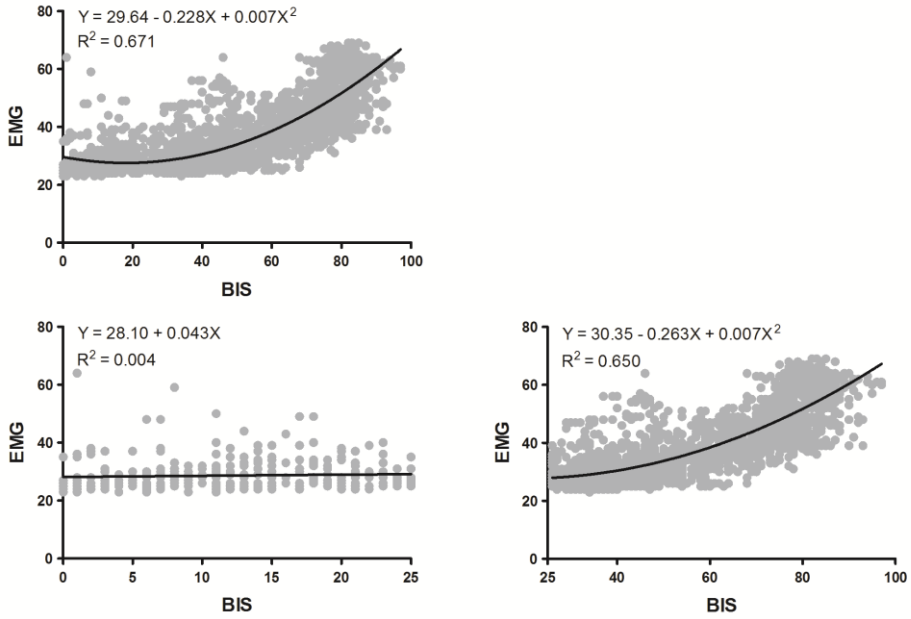


Figure 3. Correlation between EMG and BIS. The overall relationship between mean EMG and BIS is best described by a quadratic regression curve. No correlation is present between mean EMG and BIS below 25.

Survival curves are presented in Figure 4. Patients with a mean BIS≤25 at hour 12 were at high risk of poor neurological outcome (log-rank test $p<0.001$; Fig. 4A). Patients with a mean SR≥3 at hour 23 had a high risk for poor neurological outcome (log-rank test $p<0.001$; Fig. 4B). A mean BIS≤25 at hour 12 together with a mean SR≥3 at hour 23 was associated with poor neurological outcome (log-rank test $p<0.001$; Fig. 4C).

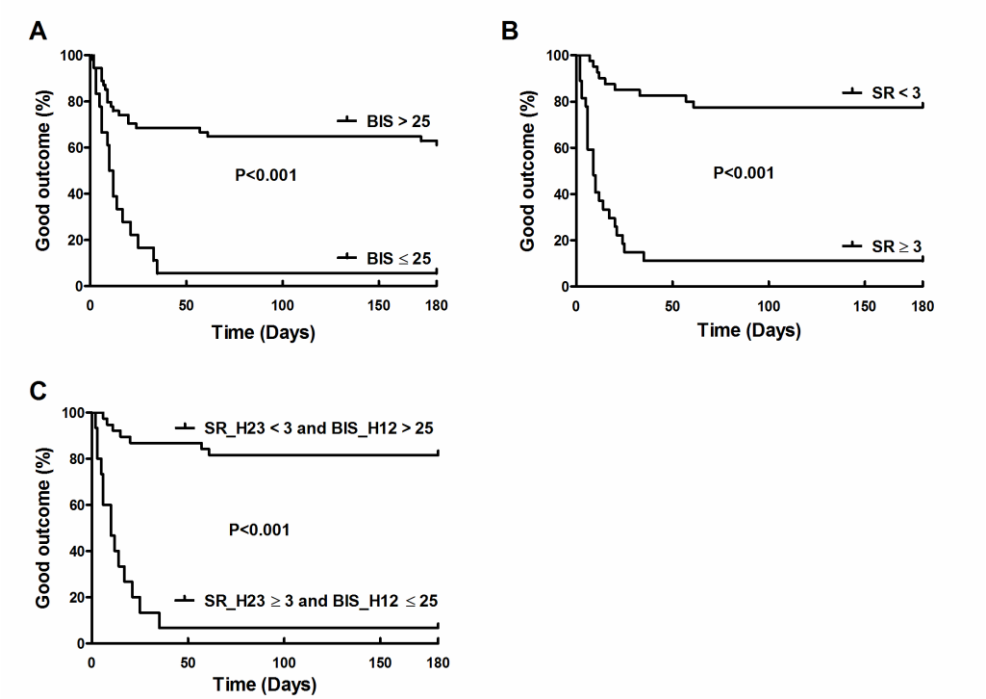


Figure 4. Survival analyses. Kaplan-Meier curves showing survival with a good neurological outcome according to BIS monitoring at hour 12 **(A)**, SR monitoring at hour 23 **(B)** or both **(C)**.

DISCUSSION

This study shows that BIS monitoring might assist with the prediction of poor neurological outcome in OHCA patients fully treated according to current guidelines. Mean BIS values below or equal to 25 at hour 12 and mean SR values above or equal to 3 at hour 23 was associated with poor neurological outcome in OHCA patients.

Consistent with previous studies, patients with a poor neurological outcome had lower BIS and higher SR values during the entire period of TTM. Up to now, the optimal time point and threshold to predict poor neurological outcome remain questionable. In the post-CA setting, mean BIS values below 40 or mean SR values above 40 during the first four hours after cardiopulmonary resuscitation were shown to be early predictors for poor outcome (60). According to Stammet et al., a mean BIS value of 23 calculated over 12.5 hours achieved a specificity and sensitivity of 89% and 86%, respectively (61). In line with these

data, the optimal time point to predict poor neurological outcome in our patient cohort was at hour 12 using a mean BIS value of 25 reaching a specificity of 97%. As such, this is the first study which found a nearly similar BIS threshold to predict poor neurological outcome at a more or less identical time point. Furthermore, we demonstrated that a SR value of 3 at hour 23 had an even higher predictive power for poor outcome and its presence was associated with a 4-fold higher risk to decease. Unfortunately, others did not assess the prognostic performance of SR longitudinally, which prevents us from comparing these results with current literature (59, 60). For that reason, future studies are warranted to validate the value of SR as early prognostic marker in comparison to BIS.

BIS monitoring is known to be subjected to several confounding factors although this study confirms its potential to assist with early neuroprognostication (59-61, 63, 125, 127). One of the predominant confounders is high EMG activity interference which is known to falsely elevate the BIS value (65). In previous BIS studies, any influence of EMG activity on the BIS value was excluded by the continuous administration of NMB in all study patients although several undesirable effects have been associated with its routine use. Besides an increased risk on pneumonia and ICU-acquired weakness, continuous administration of NMB during TTM delays neurological examination and masks seizures (66-68). Our patient cohort, however, was treated according to current guidelines, which suggest to limit the use of NMB to patients who experience shivering (69). This allowed us to assess whether BIS monitoring was still able to predict poor neurological outcome after OHCA even though EMG activity interference was not minimized in all study patients. In fact, no correlation was observed between EMG and BIS values below or equal to our calculated threshold of 25, implying that EMG activity interference below this cut-off value is most likely negligible. Nonetheless, it is plausible to assume that the calculated sensitivity of our BIS threshold would have been higher if NMB were administered continuously.

In general, our results strengthen the hypothesis that BIS monitoring could be used as early prognostic tool after OHCA. Nevertheless, early neuroprognostication has always been challenging. It has become even more complicated within the era of TTM with guidelines currently suggesting to postpone prognostication until at least 72 hours after OHCA (128, 129). Still, it is desirable to identify patients with no prospect of full neurological recovery as early as possible. Therefore, prognostic markers should always achieve a high specificity with narrow confidence intervals. Using mean BIS values at hour

12 and mean SR values at hour 23, we were able to predict poor neurological outcome with a specificity of 97% and 92%, respectively. To compare our results, established neurophysiological tools such as SSEPs and EEGs reach a comparably high specificity (130, 131). However, prognostic markers cannot be used on its own unless they reach a FPR of 0%. A false classification of patients with a favourable prognosis would namely result in an ethically unacceptable decision to withdraw medical treatment. Therefore, our results should be interpreted with caution and we do not advise to use BIS or SR as single parameter for outcome prediction. Currently, the benefit of a multimodal approach using an entire battery of prognostic markers is being investigated (9, 58). Based on our results, future studies are needed to elucidate whether poor neurological outcome can be predicted with a false positive ratio of 0% by combining BIS and SR values with other highly specific parameters. For now, this study only confirmed the value of BIS and SR as potential early outcome predictors.

Several limitations need to be acknowledged. First, this was a single-centre study with a limited sample size. Second, physicians were not blinded since visual confirmation is required to assess signal quality. Nonetheless, BIS and SR values were not used in the decision of withdrawal of life-sustaining therapy. Third, it has been demonstrated that BIS values decrease under hypothermic conditions (132, 133). Nevertheless, TTM at 33°C unlikely influenced our results as all patients were treated uniformly and time to target temperature did not differ between both patient cohorts. Still, the ability of BIS monitoring to predict poor neurological outcome in patients treated with TTM at 36°C remains to be elucidated. Finally, mean BIS and SR values were calculated per hour although these are not available in clinical practice. Nevertheless, Stammet et al. demonstrated that a minute-by-minute analysis did not provide additional prognostic information (61). Therefore, we believe that mean BIS and SR values per hour should be implemented in the current BIS monitor as they might assist with neuroprognostication.

CONCLUSIONS

This study shows that mean BIS values below or equal to 25 at hour 12 and mean SR values above or equal to 3 at hour 23 predicted poor neurological outcome in OHCA patients fully treated according to current guidelines. These results underline the possible potential of BIS monitoring to assist with early neuroprognostication in successfully resuscitated OHCA patients treated with TTM at 33°C. Future studies are now warranted

which should focus on the contribution of BIS and SR values to the multimodal neuroprognostication algorithm advised by current guidelines.

CHAPTER 3

Recorded time periods of bispectral index values equal to zero predict neurological outcome after out-of-hospital cardiac arrest

Eertmans W, Genbrugge C, Haesevoets G, Dens J, Boer W, Jans F, De Deyne C

Crit Care (2017) 21:221.

ABSTRACT

Background: Prognostication in out-of-hospital cardiac arrest (OHCA) survivors is often difficult. Recent studies have shown the predictive ability of bispectral index (BIS) monitoring to assist with early neuroprognostication. The aim of this study was to investigate whether characteristics of BIS values equal to zero (BIS 0) (i.e. duration and/or uni- versus bilateral presence) instead of simply their occurrence are better indicators for poor neurological outcome after OHCA by aiming at a specificity of 100%.

Methods: Between 2011 and 2015, all successfully resuscitated OHCA patients were treated with targeted temperature management (TTM) at 33°C for 24 hours followed by rewarming over 12 hours (0.3°C/h). In total, BIS values were registered in 77 OHCA patients. The occurrence of unilateral (BIS 0 at one hemisphere) and bilateral (BIS 0 at both hemispheres) BIS 0 values as well as their total duration were calculated. Receiver operating characteristic (ROC) curves were constructed using the total duration with BIS 0 values calculated from the initiation of TTM onwards to determine poor neurological outcome.

Results: In 30 of 77 OHCA patients (39%), at least one BIS 0 value occurred during the first 48 hours after admission. Of these 30 patients, six (20%) had a good (cerebral performance category (CPC) 1-2) and 24 (80%) a poor neurological outcome (CPC3-5) at 180 days post-CA. Within these 30 patients, the incidence of bilateral BIS 0 values was higher in patients with poor neurological outcome (CPC1-2: 2 (33%) vs. CPC3-5: 19 (79%); p=0.028). The presence of a BIS 0 value predicted poor neurological outcome with a sensitivity of 62% and specificity of 84% (AUC: 0.729; p=0.001). With a ROC analysis, a total duration of 30,3 minutes with BIS 0 values calculated over the first 48 hours predicted poor neurological outcome with a sensitivity of 63% and specificity of 100% (AUC: 0.861; p=0.007).

Conclusion: This study shows that a prolonged duration with (bilateral) BIS 0 values serves as a better outcome predictor after OHCA as compared to a single observation.

BACKGROUND

Despite improvements in cardiopulmonary resuscitation and intensive care treatment including targeted temperature management (TTM), hypoxic-ischaemic brain injury remains the predominant cause of death in out-of-hospital cardiac arrest (OHCA) patients admitted to the Intensive Care Unit (6, 16, 19). Early and reliable identification of patients with no prospect of favourable outcome avoids futile and expensive treatment prolongation and would be of value informing relatives. Currently, a multimodal strategy is being recommend for reliable neuroprognostication, encompassing modalities such as electro-encephalography (EEG), somatosensory evoked potentials (SSEP) and magnetic resonance imaging (20, 44, 134, 135). Still, most of these robust outcome predictors are labour-intensive, expensive, not continuous and above all require trained specialists for correct interpretation. Recently, the prognostic performance of simple bispectral index (BIS) monitoring has been investigated thoroughly in the post-cardiac arrest (CA) setting (58-63, 124, 125). This monitoring option, originally designed to monitor the degree of awareness during anaesthesia, converts raw sampled frontal EEG signals into a simple and real-time BIS index that ranges from 0 (iso-electric EEG) to 100 (normal electrical activity in awake subjects). The presence of BIS values equal to zero (BIS 0) during TTM at 33°C, equivalent to flat or low-voltage EEG, has been associated with poor neurological outcome (62). However, as it has been shown that the presence of BIS 0 values does not reach a specificity of 100% on its own, it was recommended not to use the presence of low-voltage EEG or BIS 0 values on its own to predict poor outcome after OHCA (21). We investigated whether characteristics of BIS 0 values (duration and/or uni- versus bilateral presence) during the first 48 hours after admission instead of simply their occurrence were indicative for poor neurological outcome after OHCA aiming at a specificity of 100%.

METHODS

In this prospective, observational study, all adult comatose survivors after OHCA with a presumed cardiac origin admitted to the Coronary Care Unit (CCU) of Ziekenhuis Oost-Limburg (Genk, Belgium) were consecutively included between March 2011 and May 2015. Ethical approval was obtained before study onset (CME11/066) and written informed consent was obtained from the patient's next of kin.

The institutional post-resuscitation protocol has been described previously (38, 126). In summary, TTM at 33°C was initiated immediately after admission to the emergency department by administering cold fluids intravenously (4°C, 30 ml/kg). After admission to

the CCU, TTM at 33°C was further induced and maintained for 24 hours using either a surface-cooling (ArcticGel™ pads, Artic Sun System® 5000, Medivance, Louisville, Colorado, USA) or endovascular cooling system (Icy-cathether, CoolGard® 3000; Alsius, Irvine, CA, USA). Both systems were equipped with a feedback loop system to control target temperature using an oesophageal temperature probe. Twenty-four hours after CCU admission, patients were actively rewarmed towards a core temperature of 36,6°C at a rate of 0.3°C per hour. All patients were intubated, mechanically ventilated and sedation was induced and maintained by administering propofol, midazolam and remifentanil intravenously. Within the period of TTM, doses of sedative drugs were titrated to obtain values between -3 and -5 on the Richmond Agitation-Sedation Scale. According to the guidelines, cisatracurium was only administered in case of shivering (69). EEGs were carried out on clinical indication and epileptic activity was treated with anti-epileptic drugs. Patients were extubated once their neurological, hemodynamic and respiratory status was recovered sufficiently.

In patients remaining comatose despite complete cessation of sedation, full supportive treatment was continued until at least 72 hours after rewarming. As such, withdrawal of life-sustaining therapy was never performed before this time point. In accordance with recommendations of international guidelines, signs of brain death (i.e. absent pupillary and corneal reflexes), refractory seizures and the bilateral absence of the N20 component of the SSEPs were taken into account for the decision to withdraw life-support (136).

BIS VISTA™ monitoring with a six-electrode frontotemporal bilateral sensor was initiated after CCU admission (Aspect Medical Systems, Inc. Norwood, USA). BIS values were stored per second during the first 48 hours, resulting in a maximum of 172800 unilateral data points per patient. In addition, the signal quality index (SQI) and electromyographic (EMG) power were recorded continuously. The SQI refers to the signal accuracy where values above 80% are considered as reliable. The EMG power, (measured as dB), describes the electromyographic content of the EEG signal. The BIS VISTA™ device displays EMG bars according to the level of EMG noise where absence of EMG bars is indicative for EMG noise below 30dB (i.e. a good signal quality) and presence of EMG bars means increasing EMG noise (1 bar: 30-38dB up to 4 bars: >55dB). Although physicians were not blinded to values displayed on the BIS monitor, decisions to withdraw life support or limit care were never based on the observed BIS values.

Outcome was assessed at 180 days post-CA using the Cerebral Performance Category (CPC) scale (99). According to the scale classification, CPC1 is indicative for good cerebral performance; CPC2 implies a moderate disability with sufficient cerebral functioning for independent daily-life activity; CPC3 indicates severe neurological sequelae; CPC4 implies coma or vegetative state and CPC5 stands for death. In this study, a CPC1-2 and CPC3-5 was considered as good and poor neurological outcome, respectively.

Statistical analysis was performed using SPSS Version 24.0 (SPSS Inc, Chicago, USA). Equal distribution was tested by means of a Kolmogorov-Smirnov test. Depending on normality, categorical data were compared between patients with a good and poor neurological outcome using a Fisher exact or Chi-Square test while unpaired T-tests or Mann-Whitney U tests were used to compare continuous data. All data are presented as median (interquartile range (IQR)). Raw sampled BIS data were synchronized with the time TTM at 33°C was initiated. The occurrence of unilateral (BIS 0 at left or right hemisphere) and bilateral (BIS 0 at both hemispheres) BIS 0 values was calculated together with their total duration within the first 48 hours from the initiation of TTM at 33°C onwards. The concomitant EMG power and SQI values at the time BIS 0 values were present, were analysed as well. The total duration with any BIS 0 value was calculated within the first 12 and 48 hours after TTM was initiated. Afterwards, receiver operating characteristic (ROC) curves were constructed using the total duration with any BIS 0 value (within the first 12 or 48 hours) to determine poor neurological outcome aiming at a specificity of 100%. P-values < 0.05 are considered as significant.

RESULTS

One-hundred and twenty-one eligible OHCA patients were prospectively enrolled between March 2011 and May 2015. Data of 44 patients were excluded from further analysis due to the following reasons: no registration of BIS values (n=34), start BIS monitoring after day 2 (n=4) and incoherence between time notation and start BIS measurement (n=6). In total, 77 successfully resuscitated OHCA survivors with a cardiac cause of origin were prospectively included (Fig. 1).

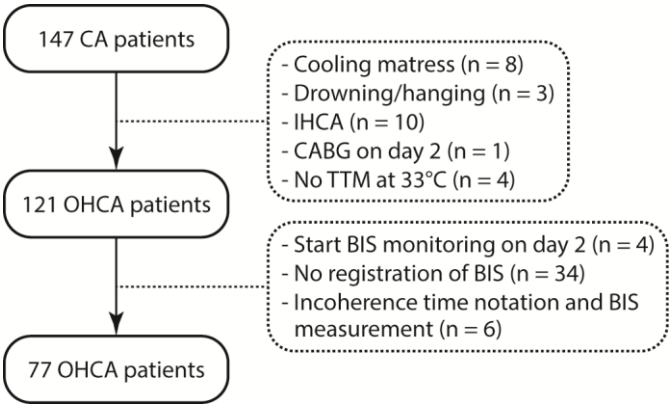


Figure 1. Flowchart of enrolled study patients. CABG = Coronary Artery Bypass Graft Surgery; IHCA = In-Hospital Cardiac Arrest; TTM = Targeted Temperature Management.

Forty-seven out of these 77 patients (61%) never experienced a BIS value of 0 during the first 48 hours after CCU admission of whom 15 had a poor (32%) and 32 (68%) a good neurological outcome at 180 days post-CA. In contrast, at least one BIS 0 value was observed during the first 48 hours after CCU admission in 30 out of 77 patients (39%). At the moment BIS 0 values were recorded, mean SQI was 98±1% and mean EMG was 26±3 dB, indicating an adequate signal quality with insignificant interference. Of these 30 patients, 6 (20%) had a good and 24 (80%) a poor neurological outcome at 180 days post-CA. Baseline characteristics of these 30 patients are summarized in table 1. Also, the incidence of bilateral BIS 0 values was higher in patients with a poor neurological outcome (CPC1-2: 2/6 (33%) vs. CPC3-5: 19/24 (79%); p=0.028). The presence of a BIS 0 value within the first 48 hours predicted poor neurological outcome with a sensitivity of 62% (95% CI: 45-76) and specificity of 84% (95% CI: 68-93) (AUC: 0.729 (0.614–0.844); p=0.001; Fig. 2). This corresponded to a positive predictive value (PPV) of 80% (95% CI: 61-92), a negative predictive value (NPV) of 68% (95% CI: 53-80) and false positive ratio (FPR) of 20% (95% CI: 8-39).

Table 1. Demographics.

	Good neurological outcome (N=6)	Poor neurological outcome (N=24)	P-value
Demographics			
Age	66 (49-70)	67 (56-79)	0.27
Male	5 (83)	21 (88)	0.79
Initial rhythm			0.60
Shockable	4 (67)	17 (77)	
Non-shockable	2 (33)	5 (22)	
Witnessed arrest	6 (100)	20 (87)	0.35
Time to target temperature (min)	174 (90-294)	147 (101-229)	0.85
Time Emergency call – ROSC (min)	38 (30-38)	35 (22-39)	0.48
Neuron-Specific Enolase (µg/l)			
Hour 24	28 (21-57)	86 (55-110)	**0.006**
Hour 48	48 (15-62)	156 (71-278)	**0.003**
Electro-encephalography			
Burst suppression	1 (16)	11(46)	0.36
Status Epilepticus	0 (0)	10(42)	0.07
Use of sedatives and neuromuscular blockage			
Max. dose propofol (mg/kg/hour)	3.30 (1.55-5.78)	2.20 (1.78-2.53)	0.14
Max. dose remifentanil (µg/kg/min)	0.12 (0.07-0.13)	0.10 (0.08-0.13)	0.96
Neuromuscular blockage use	3 (50)	15 (63)	0.66

Values are shown as median with 25 and 75 percentile and n (%).
ROSC=Return of Spontaneous Circulation.

The median recording time in patients with a good and poor neurological outcome was 2880 (IQR: 2728 – 2880) and 2880 (IQR: 2521 – 2880) minutes, respectively (p=0.631). The median duration with unilateral BIS 0 values during the first 48 hours was 3 (IQR: 0 – 21) and 17 (IQR: 8 – 49) minutes in patients with a good and poor neurological outcome, respectively (p=0.052). The median duration with bilateral BIS 0 values was higher in patients with a poor neurological outcome (CPC1-2: 0 (IQR: 0 – 3) vs. CPC3-5: 13 minutes (IQR: 0 – 219); p=0.016). Within the first 48 hours, the total median duration with any BIS 0 value was 8 (IQR: 1 - 21) and 49 (IQR: 23 - 378) minutes in patients with a good and poor neurological outcome, respectively (p=0.007). By means of a ROC

analysis, a total duration of 1820 seconds (i.e. 30,33 minutes) with BIS 0 values calculated over the first 48 hours predicted poor neurological outcome with a sensitivity of 63% (95% CI: 41-81) and specificity of 100% (95% CI: 54-100) (AUC: 0.861 (0.719-1.000); p=0.007; Fig. 2). With this cut-off value, a PPV of 100% (95% CI: 75-100), a NPV of 40% (95% CI: 17-67) and FPR of 0% (95% CI: 0-25) was calculated. An additional ROC analysis was performed using the total duration with BIS 0 values calculated over the first 12 hours to assess the possibility to use the BIS monitor as a triage method after OHCA. A total duration of 1810 seconds (30.17 minutes) with BIS 0 values calculated over the first 12 hours predicted poor neurological outcome with a sensitivity of 57% (95% CI: 34-77) and specificity of 100% (95% CI: 54-100) (AUC: 0.855 (0.703-1.000); p=0.008).

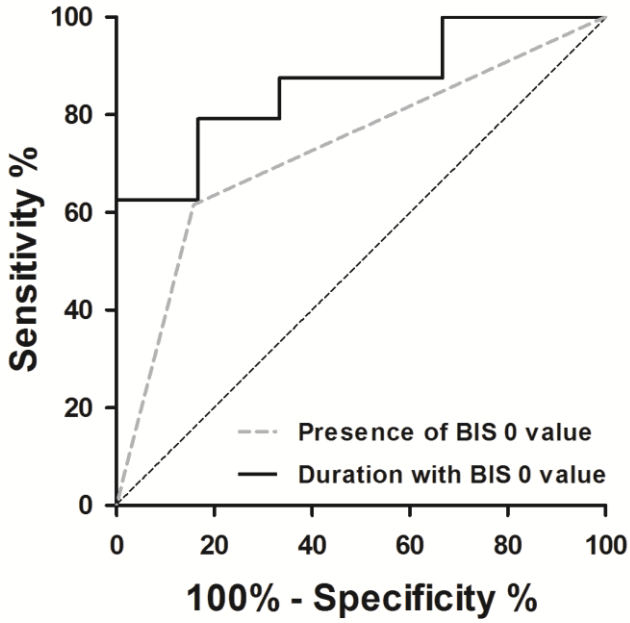


Figure 2. ROC curves of the presence and duration with BIS 0 values. The presence of a BIS 0 value predicted poor neurological outcome with a sensitivity of 62% (95% CI: 45-77) and specificity of 84% (95% CI: 45-77) (AUC: 0.729 (0.614-0.844)). The total duration with any BIS 0 values was calculated within the first 48 hours after TTM was initiated. A duration of 1820 seconds was associated with poor neurological outcome with a sensitivity of 62% (95% CI:41-81) and specificity of 100% (95% CI: 54-100) (AUC: 0.861 (0.719-1.000)).

The first 48 hours after the induction of TTM at 33°C can be subdivided in (1) a hypothermic phase (0-24h), (2) a rewarming phase (24-36h) and (3) the normothermia phase (36-48h). BIS 0 values were observed during hypothermia in all 6 patients with a good and in 23 out of 24 patients (96%) with a poor neurological outcome (Fig. 3). Seven patients had BIS 0 values during the rewarming phase of whom one (16%) with a good and 5 (22%) with a poor neurological outcome. Three patients (13%) with poor neurological outcome experienced BIS 0 values during normothermia in contrast to none of the patients with a good neurological outcome, corresponding to a sensitivity of 13% (95% CI: 3-33) and specificity of 100% (95% CI: 52-100).

DISCUSSION

This study shows that the duration with BIS 0 values rather than a single observation serves as a better outcome predictor after OHCA. Thirty OHCA patients (38%) experienced a BIS 0 value during TTM. Still, six of them attained a good neurological outcome. In contrast, a total duration with BIS 0 values beyond half an hour was uniformly associated with poor neurological outcome at 180 days post-CA. Furthermore, bilateral BIS 0 values seem to be of better prognostic value as compared to unilateral BIS 0 values.

To date, early neuroprognostication in OHCA survivors remains challenging. Current guidelines now recommend the use of a multimodal neuroprognostication algorithm containing prognostic tools such as EEG, SSEP and neuroimaging. Although these robust predictors do reach a high specificity on their own, they require trained physicians for correct interpretation and are often considered as time-consuming and expensive (20, 44, 134, 135). Due to its simple and non-invasive nature, BIS monitoring has been investigated for its potential to assist with early neuroprognostication. The phenomenon that OHCA patients displaying lower BIS values are prone to a worse neurological outcome has gained acceptance in recent years (58-63, 124). Several studies reported that the presence of BIS 0 values at any point up to 24 hours could be considered as an early indicator for poor outcome (specificity: 100%) (59, 62, 63). This was mitigated by a subsequent study in which BIS 0 values predicted poor neurological outcome with a specificity of only 90% (58). This is consistent with our results in which the presence of a BIS 0 value corresponded with a specificity of 84%. In total, six OHCA patients experienced BIS 0 values and attained a good neurological outcome at 180 days post-CA. However, this is the first study showing that the duration of periods with BIS 0 values

rather than a single observation serves as a better outcome predictor after OHCA. Within the first 48 hours after TTM was initiated, all patients who experienced BIS 0 values exceeding half an hour had a poor neurological outcome (sensitivity: 63% and specificity: 100%). Given the described confounding impact of neuromuscular activity on the BIS index, we cannot exclude the possibility that the calculated sensitivity would have been even higher if neuromuscular blockers (NMB) would have been administered continuously (59). Interestingly, a nearly similar predictive accuracy was reached if only the first 12 hours were taken into account. This is in line with Stammet et al. which recently demonstrated that a mean BIS below 2.4 calculated over the first 6.5 hours was a certain predictor for poor outcome (61). In this way, our findings contribute to the concept that a prolonged duration with low BIS values in the early hours after cardiac arrest could be used to guide early post-cardiac arrest triage (59-61, 124, 127).

Another remarkable observation was the lower incidence and shorter duration with bilateral BIS 0 values in the six patients with a good neurological outcome. Since we are the first to report this finding, we can only speculate that most patients with unilateral BIS 0 values might have had sufficient cerebral reserve allowing the contralateral hemisphere to recover from small time periods of cortical inactivity. Another possibility, on the other hand, is that the incidence with bilateral BIS 0 values would have been higher with the continuous administration of NMB. Hence, future studies using bilateral BIS monitoring concomitantly with continuous full EEG are required to confirm these preliminary results and need to elucidate the impact of NMB on the uni- or bilateral appearance of a BIS 0 value.

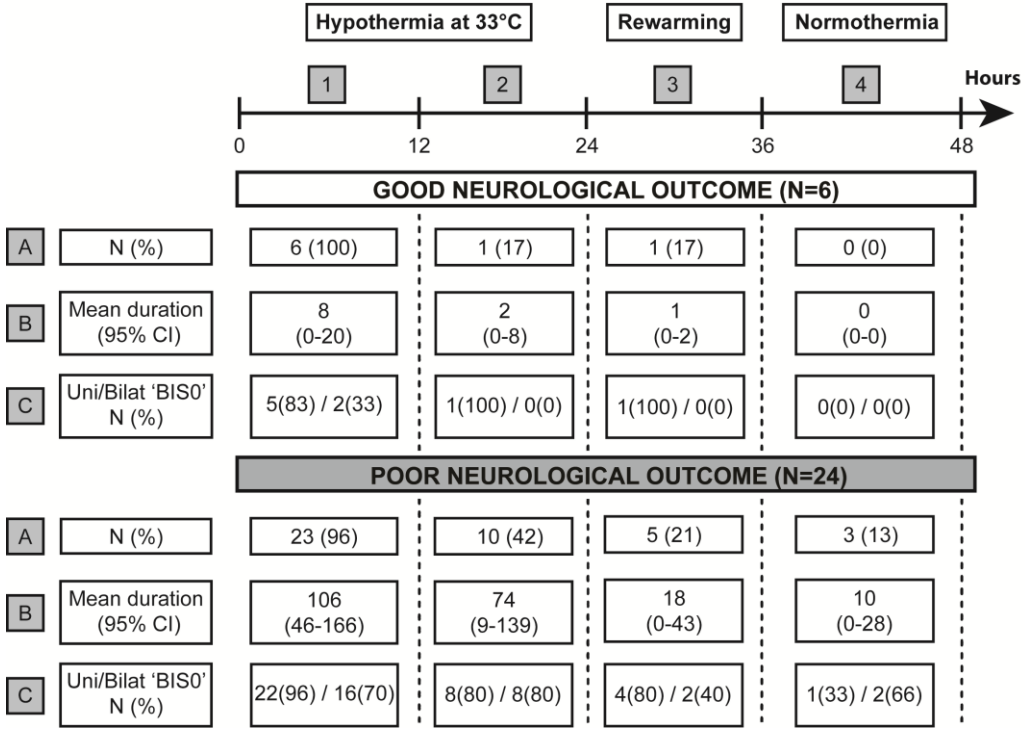


Figure 3. Overview of the characteristics of BIS 0 values within specific time periods. In total, 6 patients with a good and 24 with a poor neurological outcome experienced at least one BIS 0 value within the first 48 hours following CCU admission. After subdividing this 48h-time period into 4 equal time frames (denoted as 1-4 in the figure), the proportion of patients (A) with their respective mean duration of BIS 0 in minutes (B) was calculated per phase for both outcome groups. Additionally, the percentage of patients experiencing unilateral (BIS 0 at one hemisphere) or bilateral (BIS 0 at both hemispheres) BIS 0 values (C) is represented within each phase as well.

Especially during hypothermia, BIS values as low as zero can be observed in patients with good neurological outcome. It has been shown that cerebral ischemia induces an acute failure of synaptic transmission within the first minute following circulatory arrest resulting in a flat EEG (137, 138). Therefore, our results confirmed that iso-electric EEG patterns or BIS values of 0 are not uncommon in the early hours after cardiac arrest, but do not preclude full recovery of brain function. On the other hand, 25 percent of patients with poor neurological outcome experienced BIS 0 values after the hypothermic phase was ended. This is consistent with published data where the presence of an initial flat EEG during TTM at 33°C was shown to be of no prognostic value and more importantly, an EEG pattern evolving from flat towards continuous EEG lines was predictive for good neurological outcome (49, 50, 139-142). In analogy with these results, others demonstrated that the presence of iso-electric or low-voltage EEGs 24 hours after resuscitation, but not earlier, was a strong indicator of poor neurological outcome (specificity: 100%) (44-46, 143). As such, our results strengthen the hypothesis that persisting suppression of cortical activity after the end of TTM at 33°C is associated with an increased mortality risk. Nevertheless, one should be aware that BIS indices remain an automated calculation of frontal EEG activity and, unlike conventional EEG, are not reliable to use for diagnostic purposes (47, 142).

This study has several limitations. First, BIS values were not blinded because signal quality assessments required visual confirmation. Despite this, BIS 0 values were never used in the decision to withdraw life-support. In fact, treating physicians were cardiologists who were most often not familiar with the use of BIS monitoring. Second, previous studies showed that hypothermia lowers the BIS value (132, 133). However, TTM unlikely affected our results as the applied temperature regimen was uniform in all patients and the time to target temperature was not different between both outcome groups. Still, the potency of the duration with BIS 0 values to predict poor neurological outcome in patients treated with TTM at 36°C remains unanswered as TTM at 33°C was applied in our patient cohort. Third, the exact time to return of spontaneous circulation (ROSC) and the specific time span between ROSC and the initiation of BIS monitoring were unknown which could be considered as a limitation. In order to have a similar starting point for all patients, it was therefore decided to synchronize the raw sampled BIS data with the time TTM at 33°C was initiated. Fourth, the total sample size was relatively small although 39% of all patients experienced BIS 0 values. Due to the limited sample size, it is not possible to exclude that in a larger database, OHCA patients presenting with BIS 0 values exceeding

half an hour, might attain a good neurological outcome. Therefore, this (preliminary) study should be considered as a hypothesis-generating one which raised some interesting thoughts that should be confirmed in future large-scale trials. In addition, these studies should focus on the contribution of the duration with BIS 0 values to the standardized neuroprognostication algorithm recommended by current guidelines.

CONCLUSION

This study demonstrated at first that a prolonged duration with BIS 0 values serves as a better outcome predictor after OHCA as compared to a single observation. Although less specific, isolated BIS 0 values remained associated with a poor neurological outcome. Despite these promising results, the validness of this prognostic parameter in clinical practice remains inconclusive due to the small number of patients studied.

CHAPTER 4

The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients

Haesen J, **Eertmans W***, Genbrugge C, Meex I, Demeestere J, Vander Laenen M, Boer W, Mesotten D, Dens J, Jans F, Ernon L, De Deyne C

*Equally contributed.

Resuscitation (2018) 126:179-184.

ABSTRACT

Aims: We aimed to validate retrospectively the accuracy of simplified electroencephalography (EEG) monitoring derived from the bispectral index (BIS) monitor in post-cardiac arrest (CA) patients.

Methods: Successfully resuscitated CA patients were transferred to the Catherization Lab followed by percutaneous coronary intervention when indicated. On arrival at the coronary care unit, bilateral BIS monitoring was started and continued up to 72 hours. Raw simplified EEG tracings were extracted from the BIS monitor at a time point coinciding with the registration of standard EEG monitoring. BIS EEG tracings were reviewed by two neurophysiologists, who were asked to indicate the presence of following patterns: diffuse slowing rhythm, burst suppression pattern, cerebral inactivity, periodic epileptiform discharges and status epilepticus (SE). Additionally, these simplified BIS EEG tracings were analysed by two inexperienced investigators, who were asked to indicate the presence of SE only.

Results: Thirty-two simplified BIS EEG samples were analysed. Compared to standard EEG, neurophysiologists interpreted all simplified EEG samples with a sensitivity of 86%, a specificity of 100% and an interobserver variability of 0.843. Furthermore, SE was identified with a sensitivity of 80% and a specificity of 94% by two unexperienced physicians.

Conclusion: Using a simple classification system, raw simplified EEG derived from a BIS monitoring device is comparable to standard EEG monitoring. Moreover, investigators without EEG experience were capable to identify SE in post-CA patients. Future studies will be warranted to confirm our results and to determine the added value of using simplified BIS EEG in terms of prognostic and therapeutic implications.

INTRODUCTION

Up to one third of the cardiac arrest (CA) survivors develop seizures which often remain underdiagnosed as most of them are classified as non-convulsive ones (144, 145). Multiple studies already showed that the development of seizures is associated with a poor prognosis (146, 147). Moreover, early detection of these seizures is of the utmost importance since mortality increases exponentially with their duration (145, 148, 149). Unfortunately, there is still a delay in the identification of these harmful seizures in most post-CA patients as full or continuous EEG (cEEG) recording is rarely performed in the early hours following CA (150, 151). This emphasizes the need for a simple but accurate EEG tool to identify aggravating neurological conditions and secondary cerebral insults such as epileptic activity. Patients who experience epileptic seizures might benefit the most from a specific treatment in case of early detection (152-155).

The bispectral index (BIS) monitor is an easy to use and rapidly deployable 4-channel quantitative EEG system (55). Although the BIS monitor, with incorporated BIS value calculation (0 – 100), is developed to measure the depth of consciousness during general anaesthesia, several studies have used the BIS value to guide neurological prognostication after CA (61, 124). The overall goal of this study, however, was to validate retrospectively simplified raw EEG tracings derived from the BIS monitor against standard EEG monitoring in order to identify seizures and other ominous patterns often observed in post-CA patients.

METHODS

From March 2011 to April 2014, all adult comatose patients successfully resuscitated CA patients were admitted to the coronary care unit (CCU) in Ziekenhuis Oost-Limburg (Genk, Belgium). This retrospective study, based on prospectively gathered BIS data, aimed to validate the accuracy of simplified EEG obtained from the BIS monitor (BIS EEG) against full intermittent EEG. Therefore, only patients in whom the BIS monitor was still applied at the moment a full intermittent EEG was performed, were retrospectively selected for enrolment in this validation study. Approval of the local ethical committee was obtained before the onset of the study (CME11/066) and written informed consent was obtained from the patient's next of kin and was reconfirmed if patients regained consciousness.

PATIENT MANAGEMENT

According to the institutional protocol, targeted temperature management (TTM) at 33°C was immediately started after admission to the emergency department and was further maintained at the CCU for 24 hours after which patients were gradually rewarmed at a rate of 0.3°C/h over the following 12 hours (38, 126). Sedation was maintained by intravenous administration of propofol, midazolam and remifentanil. In line with current guidelines, patients received cisatracurium only in case of shivering. All patients were intubated and mechanically ventilated. At the end of rewarming, sedation was reduced to facilitate assessment of patients' neurological status. Patients unready for extubation due to respiratory, circulatory complications or due to persisting coma remained sedated with the lowest dose necessary to tolerate endotracheal intubation. Full standard EEG registrations were performed routinely after the return to normothermia (i.e. at about 36 hours after CA) or in case of a clinical indication. These EEG measurements were digitally recorded with a 19-channel system, arranged according to the international 10-20 system. Every EEG was characterized by a description of the posterior dominant rhythm (or absence thereof) and amplitude as well as the presence of non-dominant rhythms. Lateralization and the presence of artefacts was described where applicable. If present, epileptic activity was described as interictal, ictal or as status epilepticus. Patients with epileptic activity, based on standard EEG measurements, were treated with antiepileptic drugs, often in combination with midazolam and propofol. Although treating physicians were not blinded, BIS values were not used for titrating depth of sedation. Furthermore, withdrawal of life support was not based on the simplified EEG measurements displayed on the BIS monitor, but was in line with international guidelines and relied on a clinical evaluation, full EEG measurements and somatosensory evoked potentials (SSEP) instead (20).

BISPECTRAL INDEX MONITORING

On arrival at the CCU, bilateral BIS monitoring using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA) was started as soon as possible and continued up to 72 hours. The BIS monitor provides a real-time number using an easily applicable six-electrode forehead sensor (BIS™ bilateral sensor), which was applied to the frontotemporal area before the start of TTM. Aside from the BIS value itself, the BIS VISTA™ monitor also displays bilateral frontotemporal EEG traces (Fig. 1). To compare these simplified EEG traces derived from the BIS monitor with standard intermittent EEG,

raw BIS EEG traces of at least five consecutive minutes were retrospectively extracted at a time point that coincided with the registration of a standard full EEG using the DATALOGGER Data Review Program for Windows (Aspect Medical Systems inc.;version 0.04.07;1995). Afterwards, these small BIS EEG frames were reviewed by two experienced neurophysiologists (LE and JD) who were blinded to patients' clinical course and neurological outcome. They were asked to indicate the presence of five simple EEG patterns (i.e. diffuse slowing rhythm, burst suppression pattern, cerebral inactivity, epileptic activity/PEDs or status epilepticus (SE)) based on the classification system used by Rundgren et al. (49, 50). After calculating the inter-observer variability, a consensus decision was made by the two neurophysiologists in case of any discrepancies.

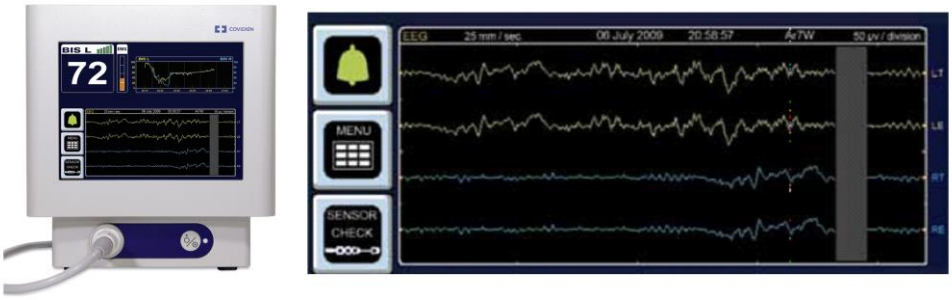


Figure 1. BIS VISTA™ monitor with EEG display. The BIS VISTATM device is able to display bilateral frontotemporal EEG traces in real-time.

In order to further validate the ease of use of the simplified BIS EEG by unexperienced physicians, two investigators (IM and CG) without any experience in the interpretation of EEG, analysed the same simplified BIS EEG frames as were given to the neurophysiologists. They were specifically asked to focus only on the detection of epileptiform activity. Figure 2 was used as an example of typical EEG tracings after CA in order to instruct the non-qualified investigators.

DATA COLLECTION

Baseline demographics including gender, age and information regarding drug administration were extracted from the electronic medical record. Cardiopulmonary resuscitation (CPR) details such as initial rhythm and bystander CPR were extracted from the Utstein data. Time to return to spontaneous circulation (ROSC) was determined as time of collapse to time of ROSC. Patients' outcome was graded according to the Cerebral

Performance Category (CPC) score at 6 months (99). CPC-scores were dichotomized as good (CPC 1-2) or poor neurological outcome (CPC 3-5).

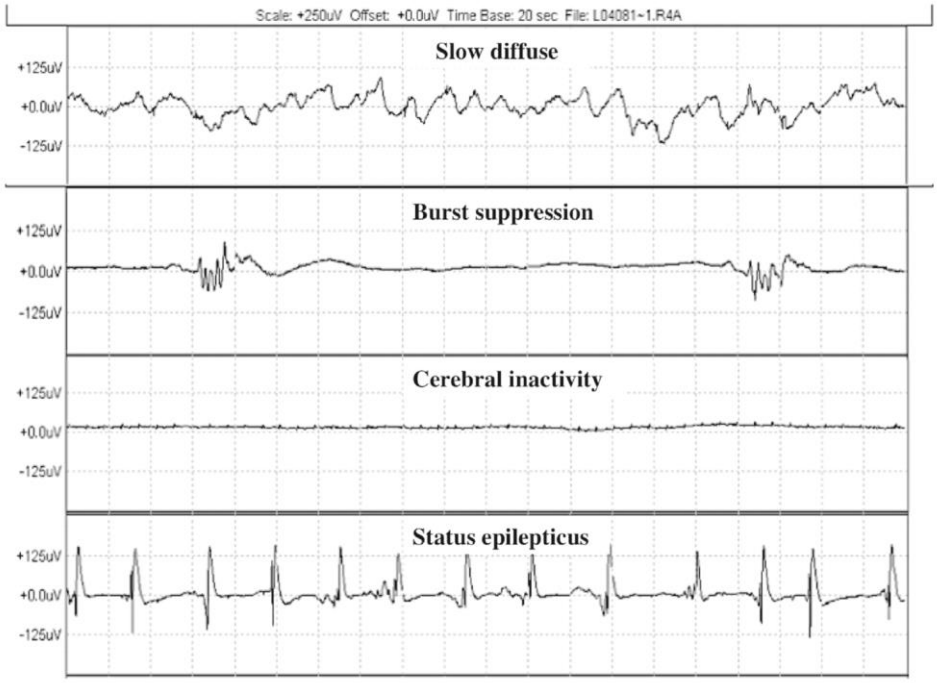


Figure 2. Four typical electro-encephalic patterns after cardiac arrest. These patterns are read-outs from raw simplified frontotemporal EEG traces which can be observed on the BIS monitor.

STATISTICAL ANALYSIS

All analyses were conducted using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean with standard deviation and categorical variables as counts and percentages (%). Equal distribution was tested using a Shapiro-Wilk test. Depending on normality, categorical date were analysed using a Fisher exact or a Pearson Chi-Square test, while an unpaired T-test or Mann-Whitney U test was used for continuous data. Correlations were calculated using Pearson's or Spearman's coefficient of correlation, depending on normality. Sensitivity and specificity were calculated for the correct detection of the aforementioned five EEG patterns. A p-value<0.05 was considered significant.

RESULTS

PATIENT CHARACTERISTICS

Between 2011 and 2014, 115 comatose CA survivors were enrolled in this study and BIS monitoring was started in 88 patients treated with TTM at 33°C (Fig. 3). Thirteen subjects were excluded due to invalid data caused by technical difficulties (n = 12) and hemodynamic instability resulting in death within the initial hours following admission (n = 1). In 32 out of these 75 retained patients, the BIS monitor was still applied at a time point coinciding with the performance of a full standard EEG. At 180 days post-CA, 14 out of these 32 patients (44%) had a good neurological outcome (CPC1-2), while 18 patients (56%) had a CPC of 5. There were no patients with a CPC of 3 or 4 at 180 days post-CA. Baseline characteristics of both outcome groups are summarized in table 1. Interestingly, all patients who experienced a SE had a poor neurological outcome ($p<0.001$).

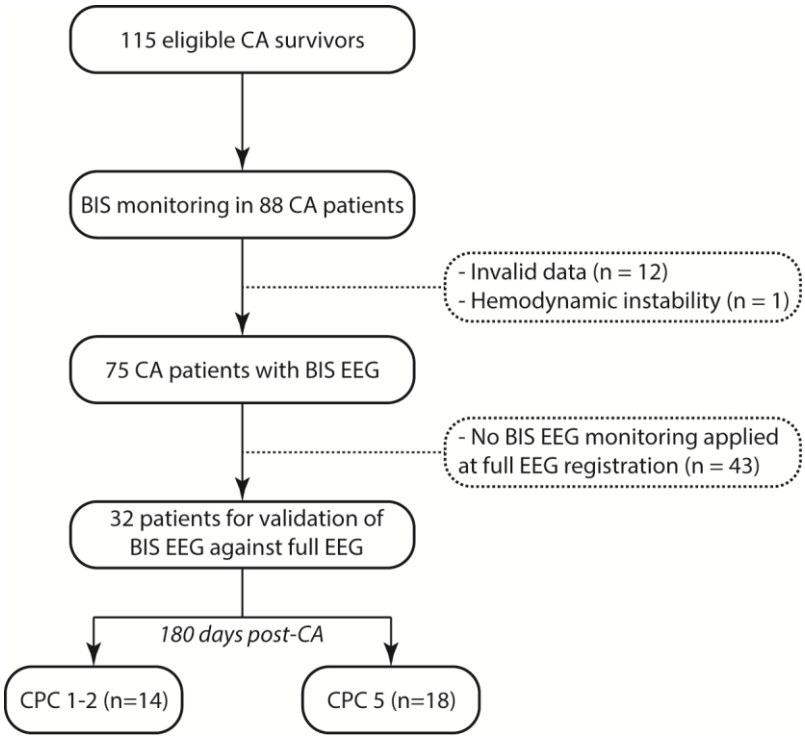


Figure 3. Flowchart of enrolled patients. BIS = bispectral index; CA = cardiac arrest; CPC = Cerebral Performance Category; EEG = electro-encephalography.

Table 1. Patient characteristics.

	All subjects	Good outcome CPC1-2	Poor outcome CPC3-5	P-value
Subjects, n (%)	32 (100)	14 (44)	18 (56)	
Age	61 ± 14	61 ± 14	61 ± 14	0.796
Male sex, n (%)	23 (72)	10 (71)	13 (72)	0.960
Initial rhythm				
Ventricular arrhythmia, n (%)	24 (75)	12 (86)	12 (67)	0.217
Witnessed arrest, n (%)	27 (84)	13 (93)	14 (78)	0.069
Time to ROSC, minutes	32 ± 20	24 ± 23	39 ± 13	**0.045**
CCU stay, days	10 ± 5	10 ± 5	9 ± 8	0.639
SE, n (%)	12 (38)	0 (0)	12 (67)	**<0.001**
Time of validation, in days after cardiac arrest	3 ± 1	2 ± 1	3 ± 2	0.613
Number of full EEGs	3 ± 1	3 ± 1	3 ± 2	0.866

CPC: cerebral performance score – ROSC: return to spontaneous circulation – CCU: coronary care unit – SE: status epilepticus – EEG: electro-encephalogram.

VALIDATION

In total, 32 simplified BIS EEG samples were analysed at a time point coincident with the registration of full standard EEG monitoring, in order to compare the concordance of both EEG options. The time of validation was at day 3±1 after CA and was not different between patients with a good and poor neurological outcome (p=0.613; Table 1). According to the standard EEG measurements, 11 (34%) recordings showed a diffuse slowing pattern, six (19%) a burst suppression pattern, three (9%) recordings showed cerebral inactivity, four (13%) indicated PEDs and 8 (25%) recordings showed a SE (Table 2). As compared to these standard EEG measurements, neurophysiologist I misinterpreted simplified BIS EEG samples, whereas neurophysiologist II misdiagnosed six of them. As such, neurophysiologist I classified all analysed BIS EEG samples with a sensitivity of 86% and a specificity of 91%, while neurophysiologist II reached a sensitivity and specificity of 71% and 100%, respectively. After consensus was actively asked for, all BIS EEG samples were correctly analysed with a sensitivity of 86% and a specificity of 100% (Table 2).

In fact, only one SE was missed by one neurophysiologist. Most other misdiagnosed recordings showed a pattern of PEDs according to the standard EEG measurements, while

the simplified BIS EEG samples were interpreted as a diffuse slowing pattern. Three of them (75%) were misinterpreted by both neurophysiologists. Therefore, sensitivity for the classification of PEDs based on simplified BIS EEG samples is 25%.

Table 2. Validation of simplified BIS EEG.

EEG patterns	Full EEG	Simplified BIS EEG		
		Neurophys I	Neurophys II	Consensus
Slow diffuse (n)	11	10	11	11
Burst suppression (n)	6	6	4	6
Cerebral inactivity (n)	3	3	3	3
PEDs (n)	4	1	1	1
Status epilepticus (n)	8	8	7	8
Total	32	28	26	29
STATISTICS				
Sensitivity (%)		86	71	86
Specificity (%)		91	100	100

EEG: Electroencephalogram – BIS: Bispectral index – PEDs: Periodic epileptic discharges.

A high level of agreement was observed between the two independent neurophysiologists (kappa = 0.843). There was a strong correlation between full and simplified BIS EEG for both neurophysiologists, with a mean correlation of r = 0.810 ($r_{\text{neurophysiologist I}}$ = 0.852 and $r_{\text{neurophysiologist II}}$ = 0.767).

To test whether physicians without any EEG experience would be able to detect epileptic activity using simplified BIS EEG traces, two independent and unexperienced investigators were asked to indicate the presence of a SE on the same BIS EEG samples as were given to the neurophysiologists. One investigator missed only one patient diagnosed with SE, whereas the other investigator missed three patients. Additionally, three patients without SE on full EEG were falsely indicated as at risk for epileptic activity. As such, one investigator identified patients diagnosed with SE with a sensitivity of 90% and a

specificity of 92%, whereas the other one reached a sensitivity of 70% and a specificity of 96%.

DISCUSSION

This was a retrospective validation study showing that: 1) raw simplified EEG traces derived from a BIS monitor correlate well with standard EEG when a simple classification system is being used in a post-CA-setting, and 2) non-experienced investigators are able to detect epileptic activity/SE on the BIS EEG monitor with a high level of accuracy.

To date, it remains to be elucidated whether the treatment of seizures effectively improves neurological outcome, or that seizures are simply a clinical expression of the post-ischemic damage questioning the benefit of any treatment efforts. Nonetheless, guidelines still advocate the use of anti-convulsive therapy in case of seizures, and therefore cEEG monitoring has been recommended in comatose CA patients treated with TTM (20, 48). Unfortunately, cEEG is expensive and labour-intensive but more importantly, most of the available cEEG devices still require continuous availability of expertise for a correct interpretation. In order to become generally applicable, it should be simple, cost-effective and easy to use at the bedside (156-158). A simplified EEG monitor would overcome these limitations and would allow us at the same time to detect non-convulsive seizures in an early stage.

Numerous studies have already investigated BIS monitoring to assist in neurological prognostication after CA (61, 124, 159). Furthermore, it has been suggested that the BIS monitor might be used to detect non-convulsive seizures as their occurrence is accompanied with fluctuations of the BIS value (160-163). In fact, the BIS monitor samples raw EEG tracings to provide the real-time BIS value. Although these raw EEG tracings are displayed in real-time, the potential to use the BIS device as a simplified EEG monitor after OHCA has not been investigated.

Rundgren et al. already investigated in OHCA patients the prognostic role of amplitude-integrated EEG, another simplified EEG tool, although it was not fully validated against standard EEG (49, 50). It is for this reason that we preferred to validate first the accuracy of simplified EEG traces obtained by the BIS monitor before providing prognostic values. As such, a similar classification system, as suggested by Rundgren et al., was used consisting out of five simple EEG patterns, i.e. diffuse slowing, burst suppression, cerebral inactivity, PEDs and SE. Using this simple classification system, this study showed a high

concordance between standard and simplified BIS EEG monitoring (r = 0.810). While other studies were able to detect a SE with a sensitivity ranging from 60% to 100%, this study reached an overall sensitivity of 86%, not only for the diagnosis of SE, but for the detection of the entire classification system (164-167). This strongly indicates that simplified BIS EEG monitoring could be used to detect other ominous EEG patterns aside from a SE as well. In fact, only 9% of all BIS EEG samples were misdiagnosed by both neurophysiologists, all from patients diagnosed with PEDs. It is plausible to assume that these promising results can be partially explained by the combined use of a simplified classification system and simplified EEG monitoring device. Still, early detection of pathologic EEG tracings using a simplified EEG device can only be relevant if it either influences the course of the disease beneficially or if it would assist with the process of neuroprognostication. In this context, our data should be considered as hypothesis-generating since our study results only show that simplified BIS EEG correlate well with standard EEG. Future studies will now be warranted to validate our results and to determine the added value of using simplified BIS EEG in terms of prognostic and therapeutic implications. Unfortunately, our time point of validation was situated approximately three days after CA. As previous studies showed that the prognostic power of EEG lies within the first 24 hours, we acknowledge that the prognostic value of simplified BIS EEG warrants further examination in a similar time window (44, 45, 47, 61, 124).

Aside from experienced neurophysiologists, treating physicians should also be capable of interpreting simplified EEG traces on the BIS monitor as they can play a prominent role in the early identification of epileptic activity. This study showed that even unexperienced investigators were able to indicate the presence of a SE with an adequate sensitivity (mean 80%) and specificity (mean 94%). Three patients, however, were identified as at risk for epileptic activity, although no epileptic activity was present on full EEG. Nevertheless, we believe that in case of uncertainty, it is more important to consider treatment for epileptic activity and/or request full EEG measurements as soon as possible rather than delaying until the patient is undoubtedly diagnosed with SE. Although the benefit of anti-convulsive therapy remains indistinct, this study confirms that electrographic seizures are associated with poor neurological outcome.

In line with our study findings, others already demonstrated the ability of diverse simplified EEG systems with three to seven channels to detect epilepsy accurately (164, 166). In

contrast, Kolls et al. did not confirm the high compliance between a full and simplified hairline EEG system, as only 71% of the samples were correctly interpreted (165). However, the EEGs samples analysed by Kolls et al. consisted out of very specific EEG patterns (e.g. GPEDs, PLEDs), which are far more difficult to diagnose as compared to the more prominent EEG patterns in post-CA patients. Similarly, we tested the accuracy of our simplified BIS EEG tool to detect PEDs and found that the sensitivity for the detection of these specific patterns was only 25%. This could be explained by the fact that these PEDs as well as other focal epileptic discharges might occur outside the frontotemporal range detected by our simplified BIS EEG device. Therefore, we believe that a simplified EEG monitoring tool should preferably be used to screen for generalized ominous patterns such as cerebral inactivity or SE instead of using it to detect very specific EEG patterns (58, 61, 124). However, it has to be stated that a full EEG will always be necessary to confirm the diagnosis based on simplified BIS EEG.

LIMITATIONS

Several limitations should be acknowledged. First, this validation study was a retrospective analysis which is inherently susceptible to limitations such as selection bias and missing data. In addition, a single-centre study could have biased the visual analysis of the EEG findings. Therefore, we asked two independent neurophysiologists blinded to each other's results although it has to be stated that a third neurophysiologist to reach consensus would eliminate the risk of a self-fulfilling prophecy. Nevertheless, this validation study should be considered as a hypothesis-generating one which requires confirmation in future multicentre studies with a larger sample size. Secondly, treating physicians were not blinded to the EEG tracings displayed on the BIS monitor as visual confirmation was needed to assure adequate signal quality. Nevertheless, the recorded BIS EEG tracings were not considered for the withdrawal of treatment policy. Finally, the BIS monitor comprises only the frontotemporal area, which does not provide information about other parts of the brain. Nonetheless, CA generally induces global ischemic brain damage, possibly implying that a frontotemporal sensor might be sufficient to provide valuable electrographic information, especially in the early hours following OHCA where there is often hardly any neuromonitoring present.

CONCLUSION

This retrospective analysis shows that raw simplified EEG derived from a BIS monitoring device might be comparable to standard EEG monitoring when a simple classification system is being used by experienced neurophysiologists. Furthermore, investigators without any EEG experience were also able to identify epileptic activity in post-CA patients with an adequate accuracy. Nevertheless, multicentre studies are warranted to verify our preliminary study findings and should consider validation sessions at time points where EEG encompasses the highest prognostic power. Additionally, these studies should also determine whether BIS EEG monitoring could influence neurological outcome by detecting epileptic activity in an early phase followed by immediate anti-convulsive therapy.

CHAPTER 5

The prognostic value of simplified EEG in out-of-hospital cardiac arrest patients

Eertmans W, Genbrugge G, Haesen J, Drieskens C, Demeestere J, Vander Laenen M, Boer W, Mesotten D, Dens J, Ernon L, Jans F, De Deyne C

Neurocrit Care (2018).

In press

ABSTRACT

Introduction: We previously validated simplified EEG tracings obtained by a bispectral index (BIS) device against standard EEG. This retrospective study now investigated whether BIS EEG tracings can predict neurologic outcome after cardiac arrest (CA).

Methods: Bilateral BIS monitoring (BIS VISTA™, Aspect Medical Systems, Inc. Norwood, USA) was started following ICU admission. Six, 12, 18, 24, 36 and 48hrs after targeted temperature management (TTM) at 33°C was started, BIS EEG tracings were extracted and reviewed by two neurophysiologists for the presence of slow diffuse rhythm, burst suppression, cerebral inactivity and epileptic activity (defined as continuous, monomorphic, >2Hz generalized sharp activity or continuous, monomorphic, <2Hz generalized blunt activity). At 180 days post-CA, neurologic outcome was determined using CPC classification (CPC1-2: good and CPC3-5: poor neurological outcome).

Results: Sixty-three OHCA patients were enrolled for data analysis of whom 32 had a good and 31 a poor neurological outcome. Epileptic activity within 6-12hrs predicted CPC3-5 with a positive predictive value (PPV) of 100%. Epileptic activity within time frames 18-24hrs and 36-48hrs showed a PPV for CPC3-5 of 90% and 93%, respectively. Cerebral inactivity within 6-12hrs predicted CPC3-5 with a PPV of 57%. In contrast, cerebral inactivity between 36-48hrs predicted CPC3-5 with a PPV of 100%. The pattern with the worst predictive power at any time point was burst suppression with PPV of 44%, 57% and 40% at 6-12hrs, at 18-24hrs and at 36-48hrs, respectively. Slow diffuse rhythms at 6-12hrs, at 18-24hrs and at 36-48hrs predicted CPC1-2 with PPV of 74%, 76%, and 80%, respectively.

Conclusion: Based on simplified BIS EEG, presence of epileptic activity at any time and cerebral inactivity after the end of TTM may assist poor outcome prognostication in successfully resuscitated CA patients. A slow diffuse rhythm at any time after CA was indicative for a good neurological outcome.

INTRODUCTION

In spite of beneficial changes in resuscitation and post-cardiac arrest (CA) management, post-ischemic brain injury is the main cause of mortality in patients successfully resuscitated from CA (6, 16, 19). One of the major challenges in the post-CA setting remains early and adequate neuroprognostication. Nowadays, prognostication relies on clinical neurological examination, somatosensory evoked potentials (SSEPs), electro-encephalography (EEG), biomarkers and brain imaging. Guidelines recommend that these prognostic tools – whenever possible – should be bundled and, strongly advise that any decisive evaluation of prognosis needs to be avoided until at least 72 hours following CA (10, 20, 21). Nonetheless, tools providing an earlier indication of neurological outcome would be valuable or would at least facilitate early communication with relatives.

A recent survey revealed that routine (continuous) EEG assessments are widely considered as one of the most useful tools to assist with prognostication in patients successfully resuscitated from out-of-hospital cardiac arrest (OHCA) (43). Continuous EEG yields a remarkable prognostic power within the initial 24 hours following CA, both in terms of good and poor outcome prognostication (44-46, 142). Nevertheless, cEEG is rather expensive, requires trained technicians for correct interpretation, and is unavailable in many ICUs. Others previously demonstrated that simplified EEG systems might also provide valuable prognostic information, especially within the initial hours following admission (49-52). Therefore, these systems may be a valid alternative for a full continuous EEG. Our research group previously showed that mean bispectral index (BIS) values ≤ 25 at hour 12 and mean suppression ratio (SR) values ≥ 3 at hour 23 are highly predictive for a poor neurological outcome after OHCA (168). Based on these prospectively gathered BIS data, we previously validated the accuracy of simplified EEG obtained from the BIS monitor against full intermittent EEG in post-CA patients (169). This retrospective study now aims to determine the prognostic role of BIS EEG monitoring in comatose patients successfully resuscitated from OHCA.

MATERIAL AND METHODS

All adult comatose patients successfully resuscitated from CA and admitted to the emergency department of Ziekenhuis Oost-Limburg (Genk, Belgium) between March 2011 and April 2014 were prospectively enrolled. Exclusion criteria were an in-hospital CA and an obvious non-cardiac cause of arrest. We previously validated the accuracy of simplified EEG samples obtained from the commercially available BIS VISTA™ monitor (BIS EEG) against full intermittent EEG (169). Based on prospectively gathered BIS data, this retrospective analysis aimed to assess the prognostic power of BIS EEG in OHCA patients (including in those patients in whom the validation was performed) (168). The study protocol and consent procedure were approved by the institutional Committee for Medical Ethics (11/066). Following admission to the Coronary Care Unit (CCU), written informed consent was obtained from patient's next of kin by the attending cardiologist and reconfirmed in those who regained consciousness.

PATIENT MANAGEMENT

Our institutional post-resuscitation protocol has been described in detail elsewhere (38, 126). In summary, patients were cooled with cold saline (4°C – 30 ml/kg) after arrival at the emergency department. When indicated, patients were transferred to the catheterization lab where coronary interventions were performed. Afterwards, all patients were admitted to the CCU where targeted temperature management (TTM) at 33°C was mechanically initiated 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 patients received an esophageal temperature probe, connected to the cooling system, to control temperature. A core temperature of 33°C was applied for 24 hours, followed by an active rewarming period (0.3°C/h over 12 hours) until normothermia was achieved. Patients were kept sedated using intravenous propofol, midazolam and remifentanil and doses were titrated to obtain values between -3 and -5 on the Richmond Agitation-Sedation scale. In line with current guidelines, cisatracurium was administered only in case of shivering. All patients were intubated and mechanically ventilated. After achieving normothermia or upon clinical suspicion of epileptic activity, full intermittent EEG registrations were performed routinely using a 19 - channel system, which is in accordance with the international 10-20 system. Patients with EEG evidence of epileptic activity were treated at the discretion of the treating physician and consulting neurophysiologist using anti-epileptic drugs (levetiracetam, diazepam or phenobarbital),

often in combination with propofol or midazolam. Following rewarming, sedation was reduced taking into account patients' neurological, hemodynamic and respiratory status and patients were extubated in case of full recovery.

SIMPLIFIED BIS EEG MONITORING

After admission to the CCU, BIS monitoring using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA) was started as soon as possible. Bilateral BIS sensors were applied to the frontotemporal area before initiation of TTM at 33°C, and remained in place up to 72 hours. The BIS monitor samples frontotemporal EEG that is being digitized, filtered from artefacts and then divided into small time periods, called epochs. Using a fast Fourier analysis, these EEG epochs are being transformed into different frequencies after which the power in each frequency band is estimated. Then, two features are analysed and combined to provide a BIS index, i.e. the beta ratio and sync fast slow. The beta ratio, a frequency domain feature, compares the power in the 11-20Hz frequency band to the 40-47Hz band. The sync fast slow, a bispectral-domain feature, compares the power in the 0.5-47Hz frequency band with the 40-47Hz band. Next, burst-suppression, displayed as the SR on the BIS monitor, is a time-domain feature that combines two algorithms: (1) a Burst Suppression Ratio calculating the degree of iso-electric periods, and (2) a QUAZI suppression index identifying background noise to correct the degree of burst suppression. Aside from BIS and SR values, the BIS VISTA™ monitor is the only BIS device commercially available with the ability to display four channels of raw frontotemporal EEG traces online (Fig. 1).

To validate raw BIS EEG against standard EEG, we previously performed a validation study in which raw BIS EEG traces of 32 CA patients were extracted at a time point coincident with the registration of standard EEG. A high concordance between both systems was demonstrated (r=0.810) (169).

For this data analysis, raw simplified EEG traces of five to ten minutes were retrospectively extracted using DATALOGGER Data Review Program for Windows (Aspect Medical Systems inc.; version 0.04.07;1995) between 6 and 12 hours (initial hypothermic phase), between 18 and 24 hours (end of hypothermic phase) and between 36 and 48 hours (normothermic phase). Unfortunately, intermittent EEG was not standardly performed at these specific time frames. Next, these raw BIS EEG traces were given to two neurophysiologists (LE and JD), blinded for patients' clinical course, previously obtained EEG results as well as neurological outcome. Neurophysiologists were asked to indicate

the presence of the following EEG patterns: (1) Epileptic activity defined as continuous and monomorphic, >2Hz generalized sharp activity or continuous and monomorphic, <2Hz generalized blunt activity; (2) Burst suppression rhythm: alternating low voltage (<10μV) and generalized normal-to-high voltage, non-epileptic cerebral activity; (3) Cerebral inactivity : electrographically silence (<5μV) ; (4) Slow diffuse rhythm: heterogeneous diffuse theta (4-7Hz) and/or delta (1-3Hz) activity. In case of any discrepancies, a consensus decision was made by the two neurophysiologists.

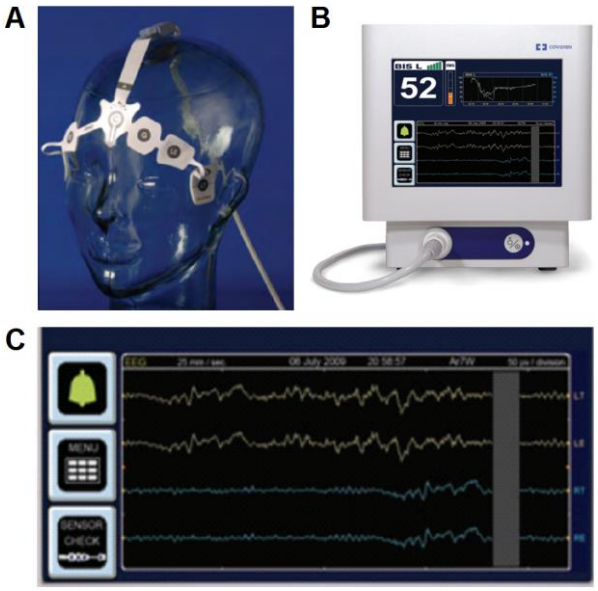


Figure 1. BIS VISTA™ with EEG waveform display. This figure illustrates the positioning of the bilateral BIS sensor (A), the BIS VISTA™ device (B) with its ability to display four channels of raw BIS EEG (C).

OUTCOME ASSESSMENT AND WITHDRAWAL OF TREATMENT POLICY

The primary endpoint was neurological outcome at 180 days post-CA according to the Cerebral Performance Category (CPC) score (99). Surviving patients were interviewed at follow-up by attending cardiologists. Based on the scale classification, CPC1 indicates an adequate cerebral performance; CPC2 signifies moderate disability with satisfactory cerebral function for independent daily-life activity; CPC3 is assigned to patients with

severe neurological sequelae with dependency for daily-life activity; CPC4 is indicative for a comatose or a persistent vegetative state and CPC5 stands for death . In this study, good and poor neurological outcome were defined as CPC1-2 and CPC3-5, respectively.

Maximal supportive therapy was guaranteed in all patients who did not regain consciousness despite complete cessation of sedation upon at least 72 hours after the end of rewarming. Malignant patterns on standard intermittent EEG (i.e. status epilepticus, persisting suppression-burst patterns or long-lasting cerebral inactivity) were considered as first-line support in the decision to withdraw life-sustaining therapy, and in specific, if epileptic activity remained therapy-refractory of when other EEG patterns with a poor prognosis remain present on subsequent EEG assessments. In case subsequent EEGs were inconclusive or when patients failed to wake up, a clinical neurological examination, SSEPs and/or a brain CT were performed. As such, the decision to withdraw life-sustaining treatment efforts was predominantly based on therapy-refractory epileptic activity, and sporadically on the absence of brainstem reflexes or lack of cortical responses (N20 on SSEPs). Epileptic activity was considered as therapy-refractory in case of persistent epileptic activity in spite of at least two lines of anti-epileptic drugs. Although treating physicians were not kept blinded for BIS EEG traces, they were never used to support the decision to withdraw life-sustaining therapy.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS Version 24 (IBM Corp., Armonk, NY, USA). Normality was tested by means of a Kolmogorov-Smirnov test. Continuous data are presented as mean with standard deviation or median with interquartile ranges and categorical variables are presented as counts and percentages. Categorical data were compared using the Fisher exact and Pearson Chi-square test as appropriate. Depending on normality, Student T-tests or Mann-Whitney U tests were used to compare continuous variables. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), accuracy, false positive ratios (FPR) and risk ratios (RR) were calculated for the prediction of neurological outcome using these BIS EEG patterns at the diverse time frames. P-values<0.05 were considered as statistically significant.

RESULTS

Between March 2011 and April 2014, 95 eligible OHCA patients, with a presumed cardiac cause of arrest, were prospectively enrolled (Fig. 2). Thirty-two patients were excluded from retrospective data analysis for the following reasons: no BIS monitoring started (n=20), hemodynamic instability resulting in early death following admission (n=2) and failed to store BIS data (n=10). In total, 63 OHCA patients with a presumed cardiac cause of arrest were retained for further data analysis, of whom 32 (51%) reached a good and 31 (49%) a poor neurological outcome at 180 days post-CA. None of these patients had a CPC 3 or 4 at follow-up. Demographic data of both outcome groups are summarized in table 1. Throughout the entire TTM period, patients were sedated using propofol (median, 1.65 mg/kg/h; IQR, 1.26 – 2.50) and remifentanil (median, 0.10 µg/kg/h; IQR, 0.08 – 0.13). Midazolam was administered in 17 patients (median, 1.40 µg/kg/h; IQR, 1.05 – 1.95), in combination with propofol (median, 1.65 mg/kg/h; IQR, 1.27 – 2.21). Between 36 and 48 hours, 55 (87%) out of 63 OHCA patients were still on sedation.

The level of agreement between both neurophysiologists was adequate at all time frames ($kappa_{6\text{-}12hrs}$ = 0.706; $kappa_{18\text{-}24hrs}$ = 0.624 and $kappa_{36\text{-}48hrs}$ = 0.668, respectively).

The time to death was 9 (5 - 20) days. While seven patients died due to post-resuscitation shock, one patient died on the consequences of heart failure and another one deceased due to sternitis following coronary-artery bypass graft surgery. Life-sustaining therapy was withdrawn in 22 patients due to extensive post-ischemic brain injury (Table 2). First, 15 out of these 22 patients had a therapy-refractory epileptic activity. On top of persistent epileptic activity, one, two and three out of these 15 patients had absent brainstem reflexes, bilateral absent cortical responses on SSEP and diffuse brain oedema on CT, respectively. One patient with therapy-refractory epileptic activity developed a septic shock after TTM at 33°C ended and died six days after CCU admission. Despite aggressive anti-epileptic treatment, the other eight patients remained in a comatose vegetative state in whom therapy was withdrawn after 21 (9 – 32) days. Secondly, a bilateral absent N_{20} response on SSEP was the main reason for withdrawal of life-sustaining treatment in four out of these 22 patients. Two out of these four patients had absent brainstem reflexes in addition to absent cortical responses on SSEP. Third, one patient did not regain consciousness three weeks following CA, and EEGs persistently showed burst-suppression patterns. Finally, two patients had persisting cerebral inactivity based on EEG and in one of them, a brain CT showed diffuse cerebral oedema indicating extensive brain swelling.

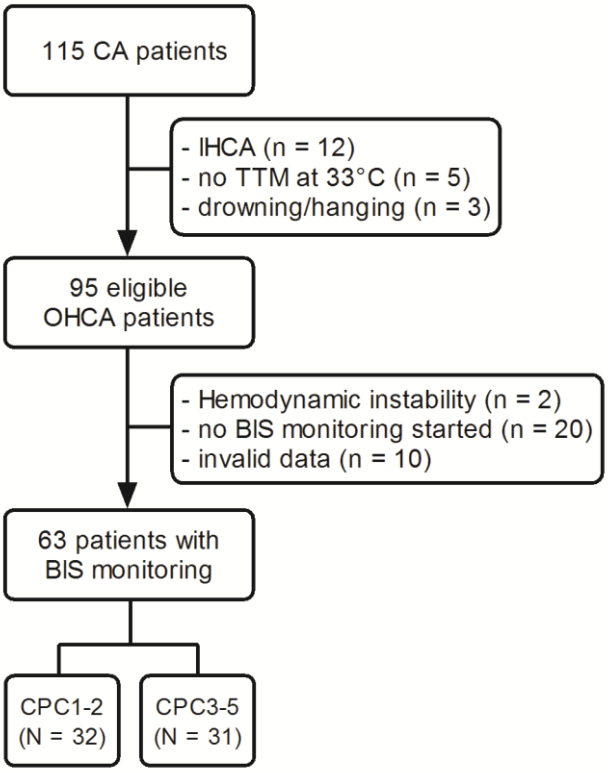


Figure 2. Flowchart of enrolled patients. BIS = bispectral index; CA = cardiac arrest; CPC = cerebral performance category; IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest; TTM = targeted temperature management.

Table 1. Demographics.

Variables	Good neurological outcome (CPC1-2)	Poor neurological outcome (CPC3-5)	P-value
Patients	32 (51)	31 (49)	
Age, years	62 ± 13	66 ± 13	0.173
Male gender	26 (81)	24 (77)	0.763
Arrest variables			
Shockable initial rhythm	28 (88)	17 (55)	**0.010**
Witnessed arrest	29 (91)	25 (81)	0.417
Bystander CPR	17 (53)	18 (58)	0.801
BLS duration (min)	9 (2 – 14)	10 (4 – 14)	0.486
ALS duration (min)	12 (7 – 25)	17 (9 – 30)	0.274
Time $_{\text{emergency call – ROSC}}$ (min)	31 ± 19	35 ± 18	0.172
Post-resuscitation management			
Coronary angiography	30 (94)	23 (74)	**0.043**
Percutaneous coronary intervention	23 (72)	13 (42)	**0.023**
Cooling, $_{\text{endovascular/surface}}$	19 (59) / 13 (41)	14 (45) / 17 (55)	0.317
Intra-aortic balloon pump	10 (31)	6 (19)	0.278
Post-resuscitation complications			
Post-resuscitation shock	14 (44)	14 (45)	0.910
ARDS	3 (9)	5 (16)	0.421
Pneumonia	17 (53)	12 (39)	0.251
Acute kidney injury	9 (28)	10 (32)	0.721
Renal replacement therapy	2 (6)	4 (13)	0.368
Status epilepticus on standard EEG	1 (3)	16 (52)	**<0.001**
CCU length of stay (days)	21 (12 – 30)	9 (5 – 13)	**0.008**

Data are shown as mean ± SD, median with interquartile range and n (%).

ALS = Advanced Life Support; ARDS = Acute Respiratory Distress Syndrome; BLS = Basic Life Support; CCU = Coronary Care Unit; CPR = Cardiopulmonary resuscitation; ROSC = Return of spontaneous circulation.

Table 2. Prognostication in the 22 patients in whom life-sustaining therapy was withdrawn.

Prognostic tool	# patients	Comment
EEG	22 (100%)	• 15 diagnosed with therapy-refractory seizures; • 5 diagnosed with persisting cerebral inactivity
CT	10 (45%)	• 6 diagnosed with diffuse cerebral oedema
SSEPs	15 (68%)	• 6 diagnosed with bilateral absence of N_{20} response
Clinical examination	10 (45%)	• 4 diagnosed with absent brainstem reflexes
BIS EEG at 6-12hrs		
Epileptic activity	6 (27%)	
Burst suppression	3 (14%)	• One patient had no BIS EEG sample at 6-12hrs
Cerebral inactivity	8 (36%)	
Slow diffuse	4 (18%)	
BIS EEG at 18-24hrs		
Epileptic activity	8 (36%)	
Burst suppression	3 (14%)	
Cerebral inactivity	7 (32%)	
Slow diffuse	4 (18%)	
BIS EEG at 36-48hrs		
Epileptic activity	12 (55%)	
Burst suppression	1 (5%)	• One patient had no BIS EEG sample at 36-48hrs
Cerebral inactivity	7 (32%)	
Slow diffuse	3 (14%)	

BIS EEG WITHIN THE INITIAL HYPOTHERMIC PHASE (6 – 12 HOURS)

All seven patients in whom epileptic activity was observed on the BIS EEG within the first 12 hours did not regain consciousness which corresponded to a PPV of 100% (95% CI: 56 – 100%) and NPV of 59% (95% CI: 44 – 72%) (Table 4). Nine patients had a burst suppression rhythm of whom four (45%) and five (55%) had a good and poor neurological outcome, respectively (p=1.000; Table 3). Twenty-one patients experienced cerebral inactivity within the first 12 hours of whom 9 (43%) died (p=0.418; Table 3). Twenty-three patients had a slow diffuse rhythm within the initial 12 hours following admission of whom 17 (74%) had a good and 6 (26%) a poor neurological outcome (p=0.009; Table 3). As such, an initial slow diffuse rhythm predicted good neurological outcome with a PPV of 74% (95% CI: 51 – 89%) and NPV of 62% (95% CI: 45 – 77%) (Table 4).

BIS EEG AT THE END OF THE HYPOTHERMIC PHASE (18 – 24 HOURS)

Between 18 and 24 hours following CCU admission, ten patients showed epileptic activity on the BIS EEG of whom nine (90%) died, corresponding to a PPV of 90% (95% CI: 54 – 100%) and NPV of 57% (95% CI: 42 – 71%) (Table 3-4). BIS EEG showed a burst suppression pattern in 7 and cerebral inactivity in 15 patients, and both patterns were not discriminative for neurological outcome (p=1.000 and p=0.230, respectively; Table 3). Around the end of the hypothermic phase of TTM at 33°C, a slow diffuse rhythm was observed on BIS EEG in 25 patients of whom 19 (76%) had a good neurological outcome at 180 days post-CA (p<0.001; Table 3).

BIS EEG AT NORMOTHERMIA (36 – 48 HOURS)

At normothermia, 13 out of the 14 (93%) patients showing epileptic activity on the BIS EEG died. Hence, the presence of epileptic activity within the normothermic phase predicted poor neurological outcome with a PPV of 93% (95% CI: 64 – 100%) and NPV of 64% (95% CI: 48 – 78%) (Table 3-4). A burst suppression rhythm was apparent in 5 patients was not predictive for poor neurological outcome (p=1.000; Table 3). In contrast to the initial 24 hours, all seven patients experiencing cerebral inactivity between 36 and 48 hours after admission died (p<0.001), corresponding to a PPV of 100% (95% CI: 56 – 100%; Table 3-4). Finally, 30 patients had a slow diffuse rhythm on the BIS EEG of whom 24 (75%) survived with a good neurological outcome (p<0.001; Table 3). Therefore, a slow diffuse rhythm observed at normothermia predicted good neurological outcome with a PPV of 80% (95% CI: 61 – 92%) and NPV of 85% (95% CI: 64 – 95%) (Table 4).

Table 3. Incidence of EEG rhythms over three time frames based on simplified BIS EEG.

EEG rhythm	At 6 – 12 hours			At 18 – 24 hours			At 36 – 48 hours		
	CPC1-2	CPC3-5	P	CPC1-2	CPC3-5	P	CPC1-2	CPC3-5	P
Epileptic activity (%)	0 (0)	7 (100)	**0.004**	1 (10)	9 (90)	**0.012**	1 (7)	13 (93)	**<0.001**
Burst suppression (%)	5 (55)	4 (45)	1.000	3 (43)	4 (57)	1.000	3 (60)	2 (40)	1.000
Cerebral inactivity (%)	9 (43)	12 (57)	0.418	5 (33)	10 (67)	0.230	0 (0)	7 (100)	**0.010**
Slow diffuse (%)	17 (74)	6 (26)	**0.009**	19 (76)	6 (24)	**<0.001**	24 (80)	6 (20)	**<0.001**
Missing (%)	1 (33)	2 (67)		4 (67)	2 (33)		4 (57)	3 (43)	

Data are shown as n (%). Percentages are calculated with respect to the total number of patients with a certain EEG rhythm within one of the time frames (e.g. 7 out of 7 (100%) patients with epileptic activity between 6 and 12 hours had a poor neurological outcome. CPC1-2 = Good neurological outcome and CPC3-5 = poor neurological outcome.

Table 4. Prognostic predictive value of EEG rhythm over time.

EEG rhythm	Sensitivity	Specificity	PPV	NPV	FPR	Accuracy	RR
Epileptic activity							
6-12 hours	23 (10–41)	100 (89–100)	100 (56–100)	59 (44–72)	0 (0–44)	62 (49–74)	2.41 (1.75–3.32)
18-24 hours	29 (14–48)	97 (84–100)	90 (54–100)	57 (42–71)	10 (5–46)	63 (50–75)	2.12 (1.43–3.13)
36-48 hours	42 (25–61)	97 (84–100)	93 (64–100)	64 (48–78)	7 (4–36)	70 (57–81)	2.60 (1.69–4.00)
Burst suppression							
6-12 hours	13 (4–30)	84 (67–95)	44 (15–77)	51 (37–65)	56 (23–85)	49 (36–62)	0.91 (0.42–1.98)
18-24 hours	13 (4–30)	91 (75–98)	57 (25–85)	50 (36–64)	43 (12–80)	52 (39–65)	1.14 (0.57–2.30)
36-48 hours	6 (1–21)	91 (75–98)	40 (7–83)	49 (35–63)	60 (17–93)	49 (37–62)	0.79 (0.26–2.37)
Cerebral inactivity							
6-12 hours	39 (22–58)	72 (53–86)	57 (34–77)	56 (40–72)	43 (23–66)	56 (42–68)	1.31 (0.78–2.19)
18-24 hours	32 (17–51)	84 (67–95)	67 (39–87)	50 (36–64)	33 (13–61)	59 (46–71)	1.47 (0.90–2.40)
36-48 hours	23 (10–41)	100 (89–100)	100 (56–100)	57 (42–71)	0 (0–44)	62 (49–74)	2.33 (1.69–3.22)
Slow diffuse							
6-12 hours	53 (35–71)	81 (63–93)	74 (51–89)	62 (45–77)	26 (11–49)	67 (54–78)	1.95 (1.21–3.15)
18-24 hours	59 (41–76)	81 (63–93)	76 (55–90)	77 (57–89)	24 (10–46)	70 (57–81)	2.70 (1.49–4.90)
36-48 hours	75 (57–89)	81 (63–93)	80 (61–92)	85 (64–95)	20 (8–39)	78 (65–87)	5.20 (2.07–13.0)

Diagnostic parameters are shown as percentages (95% confidence interval). Epileptic activity, burst suppression and cerebral inactivity were used for the prediction of a poor neurological outcome and slow diffuse rhythm for good neurological outcome.

FPR = false positive ratio; NPV = negative predictive value; PPV = positive predictive value; RR = relative risk ratio.

EVOLUTION OF BIS EEG PATTERNS

The evolution of the four BIS EEG patterns starting from the initial (hypothermic) phase towards the normothermic phase of TTM at 33°C is depicted in figure 3. Four patients with a slow diffuse rhythm and three patients with cerebral inactivity between 6 and 12 hours had no corresponding BIS EEG sample at 36 - 48 hours. All seven patients in whom epileptic activity remained present from the initial up to the normothermic phase deceased. Two out of the three patients with a persisting burst suppression rhythm between 36 and 48 hours regained consciousness. Interestingly, all patients evolving from an initial pattern of cerebral inactivity towards a pattern with epileptic activity at normothermia died. Likewise, all patients in whom cerebral inactivity remained unchanged at normothermia did not regain consciousness. In contrast, seven out of the eight patients in whom cerebral inactivity evolved towards a slow diffuse pattern survived with a good neurological outcome. Finally, among the 19 patients with a slow diffuse rhythm within the initial 12 hours, 18 patients still had a slow diffuse rhythm at normothermia of whom 14 regained consciousness, whereas one patient developed epileptic activity and died.

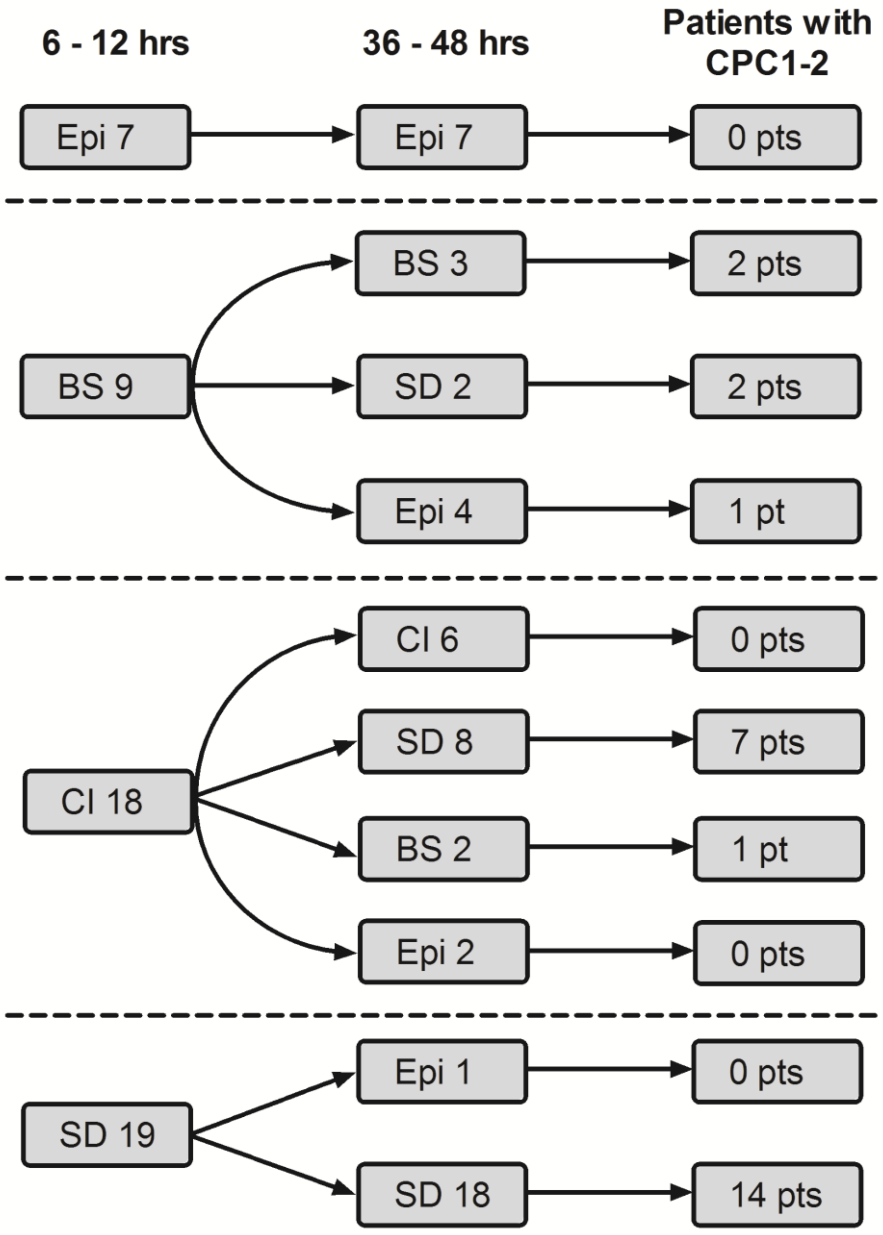


Figure 3. Evolution of BIS EEG patterns. This figure illustrates the evolution of the four BIS EEG patterns starting from the initial (hypothermic) phase (6-12 hours) towards the normothermic phase of TTM at 33°C (36- 48 hours). Abbreviations: Epi = epileptic activity; BS = burst suppression; CI = cerebral inactivity and SD = slow diffuse rhythm.

DISCUSSION

Simplified EEG traces obtained from a BIS device might be able to assist with outcome prognostication in successfully resuscitated OHCA patients. The main study results, based on BIS EEG samples, can be summarized as follows: (1) development of epileptic activity accurately predicted a poor neurological outcome from the earliest time point, (2) burst suppression rhythms were not predictive for neurological outcome at any time point, (3) cerebral inactivity was only indicative for a poor prognosis when it appeared after the return to normothermia, but not earlier and, (4) the presence or the evolution towards a slow diffuse rhythm was strongly associated with a good neurological outcome.

Tools intended to support outcome prediction in OHCA patients should ideally be based on multiple assessments of the post-ischemic status of the brain. Others have previously illustrated that the development of specific EEG patterns provides valuable prognostic information in OHCA patients (47). Additionally, the temporal evolution of these patterns has been suggested to play a more prominent role in terms of outcome prognostication than single EEG measurements. Based on this solid evidence, international guidelines implemented a statement to monitor EEG frequently in all post-CA patients, and when possible in a continuous manner (20, 21, 48). Unfortunately, cEEG is expensive and most often not available in a general ICU setting, and more importantly, it warrants the continuous presence of experienced personnel to evaluate these serial EEG recordings. These limitations have hampered the widespread applicability of cEEG in current clinical practice and hence, simplified EEG devices are now being considered as attractive alternatives. In this context, the prognostic value of amplitude-integrated EEG (aEEG) in post-CA patients has been successfully investigated by others, even though aEEG was not validated against full EEG (49-52). In contrast to others, we decided to validate the accuracy of simplified BIS EEG traces before an attempt was made to assess its prognostic role in OHCA patients and showed a high concordance between both systems ($r=0.810$) (169).

Epileptic activity is commonly observed in post-CA patients and our results confirm that its presence bares a poor prognosis at any time point (146, 150, 151). To date, it remains under debate whether treatment of epileptic activity improves outcome or whether epileptic activity simply represents an epiphenomenon of the post-ischemic brain injury (154). Others previously suggested that the type of epileptic activity originating from an EEG showing continuous activity reflect a less injured and therefore salvageable brain.

Epileptic activity evolving from a burst suppression pattern, on the other hand, have been argued to be therapy-refractory (50, 52). Nonetheless, in this study, one patient developed epileptic activity evolving from a burst suppression rhythm and still attained a good neurological outcome. Exceptional cases like these might illustrate the importance of detecting epileptic activity in an early stage in which BIS EEG could perfectly serve as early warning signal. Until the ongoing TELLSTAR trial provides no conclusive answer, it remains plausible that patients might benefit from a specific anti-convulsive treatment, at least in case of early detection (154). In our validation study, we previously showed that even investigators without any experience in the interpretation of EEG were able to indicate the presence of epileptic activity (169). As such, the use of simplified BIS EEG, especially when cEEG is not available, could be a valid alternative to achieve this goal. Still, a full EEG will always be mandatory to confirm the diagnosis based on simplified BIS EEG. Furthermore, it needs to be stressed that a simplified EEG tool should never intend to replace routine (intermittent) EEG assessments in clinical practice. Like many other simplified EEG montages, BIS EEG only covers the frontotemporal area through which focal or more specific EEG patterns occurring outside this area probably remain unnoticed. In a recent study by Elmer et al., two specific EEG patterns of post-anoxic multifocal myoclonus were identified on standard EEG. Development of myoclonus with continuous EEG background and vertex spike-wave discharges was indicative for a favourable neurological recovery, whereas a suppression-burst background with high-amplitude polyspikes was invariably associated with a poor prognosis (170). Specific EEG patterns like these bare a prognostic value, yet will likely be missed on simplified BIS EEG.

Inconsistent with other studies, a burst suppression rhythm on BIS EEG was not predictive for poor neurological outcome at any time point (44, 45). Nonetheless, not all studies reported a remarkable prognostic accuracy for the presence of a burst-suppression pattern (150, 171). This inconsistency might be explained by the variability in definitions used across studies. On the other hand, the potential influence of sedatives administered during TTM at 33°C might be a more plausible explanation since propofol is able to induce burst-suppression patterns pharmacologically, independent of the severity of brain injury (150, 171). In fact, only burst suppression patterns with identical bursts are invariably associated with a poor outcome after CA (44, 45).

Our results confirm that cerebral inactivity within the period of TTM at 33°C is not uncommon in OHCA patients. In fact, an acute failure in synaptic transmission occurs

immediately after circulatory arrest perfectly clarifying the manifestation of cerebral inactivity (137, 138). It is for this reason that solely the presence of a flat (BIS) EEG is of no prognostic value when observed in the initial 24 hours following resuscitation (44-46, 143). Likewise, it has been shown that BIS values equal to zero are not unlikely to occur within this time frame, but do not preclude full recovery of consciousness (159). On the other hand, all study patients, who failed to recover from a BIS EEG pattern with cerebral inactivity after the return to normothermia, attained a poor neurological outcome. In analogy with previous studies, this study shows that a persisting suppression of cerebral inactivity is strongly associated with a poor prognosis, and that a timely improvement towards a continuous EEG is vital to attain a good neurological outcome (49, 50, 139-141).

The timing of outcome prognostication in OHCA patients should preferably be postponed beyond the earliest time point at which cerebral structures are known to recover their function (172). Nowadays, guidelines advise to delay outcome prognostication until at least 72 hours following OHCA (20, 21). Therefore, the underlying motivation of early neuroprognostication, especially within the period of TTM at 33°C, should perhaps be on the prediction of good rather than poor neurological outcome (173). In this context, our study findings are similar to prior studies indicating the presence of a slow diffuse rhythm within the initial 24 hours as an accurate predictor of good neurological outcome. Moreover, our data support previous observations that an improvement of EEG towards a slow diffuse rhythm is highly predictive for a favourable prognosis (44, 45, 47, 50, 52).

Several study limitations need to be addressed. First, this was a retrospective data analysis which is known to be intrinsically vulnerable for limitations such as selection bias and missing data. Secondly, the study was performed in a single centre and the sample size was rather small to make firm conclusions about the prognostic validness of BIS EEG in an OHCA population. Therefore, well-powered prospective, observational studies are warranted to confirm our preliminary results before it can be implemented in clinical practice. Third, treating personnel was not kept blinded for the BIS EEG traces in order to assure adequate signal quality at all times. Nonetheless, EEG traces displayed on the BIS monitor were never taken into account to initiate anti-epileptic therapy or for the decision to withdraw life-sustaining treatment efforts. In fact, treating physicians were all cardiologists, who are completely unfamiliar with the use and interpretation of BIS (EEG). Besides, BIS EEG samples were retrospectively interpreted by neurologists, limiting the

risk of a self-fulfilling prophecy. However, we certainly cannot rule out a self-fulfilling prophecy when standard EEG is being considered since the main reason to withdraw therapy was the presence of therapy-refractory epileptic activity. Especially since we previously showed a high correlation between standard and BIS EEG when looking at epileptic activity, we have to admit that an indirect self-fulfilling prophecy for epileptic activity cannot be fully ruled out. Next, our study design did not allow us to compare the prognostic performance of BIS EEG against a reference standard such as full EEG, as the latter was not consistently available at the standardized time frames used in our analysis. This obviously limited us from reporting our results fully according to STARD guidelines. Besides, BIS (EEG) monitoring was most often not in place any more at the time a standard EEG was requested. As such, our study findings should be considered as hypothesis-generating definitely raising some interesting thoughts. Future (multicentre) studies with a larger sample size are now paramount to assess whether the prognostic performance of BIS EEG is at least equal to highly prognostic tools such as standard EEG or even clinical examination. Concomitantly with BIS EEG monitoring, the study design of these trials should include (continuous) standard EEG or a clinical examination at standardized time points (and preferably already within the hypothermic phase after OHCA). Fifth, our simplified EEG terminology was not fully in line with standard EEG terminology as was used by Westhall et al. (47). Nonetheless, all EEG patterns were defined in advance and our simplified EEG terminology might facilitate others to use BIS EEG similarly. Finally, as compared to full EEG, BIS sensors only cover the frontotemporal area, which is not different from other simplified EEG devices that have been previously investigated (52, 167). Still, frontal sensors might provide sufficient prognostic information, especially since a CA generally induces global ischemic cerebral injury (174).

CONCLUSION

Simplified EEG traces obtained by a BIS monitor might contribute to the prediction of good and poor neurological outcome in OHCA patients. Moreover, the dynamics of brain activity, based on serial (BIS) EEG recordings, provided additional prognostic information. Although multicentre studies are now essential to verify our study findings, our data indicate that BIS EEG might once become a valid alternative when cEEG is unavailable. Future studies are also warranted to address the added value of BIS EEG in terms of therapeutic implications and its effect on neurological outcome.

CHAPTER 6

A prediction model for good neurological outcome in successfully resuscitated out-of-hospital cardiac arrest patients

Eertmans W, Tran TMP, Genbrugge C, Peene L, Mesotten D, Dens J, Jans F, De Deyne C

Submitted

ABSTRACT

Background: In the initial hours after an out-of-hospital cardiac arrest (OHCA), it remains difficult to estimate whether the degree of post-ischemic brain damage will be compatible with good long-term neurological outcome. Using variables that are bedside available, we aimed to construct prognostic models able to predict a good neurological outcome of OHCA patients within 48 hours after CCU admission.

Methods: Based on prospectively gathered data, a retrospective data analysis was performed on 107 successfully resuscitated OHCA patients with a presumed cardiac cause of arrest. Targeted temperature management at 33°C was initiated at CCU admission. Prediction models for good neurological outcome (CPC1-2) at 180 days post-CA were constructed at hour 1, 12, 24 and 48 after CCU admission. Following multiple imputation, variables were selected using the elastic-net method. Each imputed dataset was divided into training and validation sets (80% and 20% of patients, respectively). Logistic regression was fitted on training sets and prediction performance was evaluated on validation sets using misclassification rates.

Results: The prediction model at hour 24 predicted good neurological outcome with the lowest misclassification rate (21.5%), using a cut-off probability of 0.55 (sensitivity=75%; specificity=82%). This model contained sex, age, diabetes status, initial rhythm, percutaneous coronary intervention, presence of a BIS 0 value, mean BIS value and lactate as predictive variables for good neurological outcome.

Conclusion: This study shows that good neurological outcome after OHCA can be reasonably predicted as early as 24 hours following ICU admission using parameters that are available bedside. These prediction models could identify patients who would benefit the most from intensive care.

BACKGROUND

Despite improvements in advanced life-support and efforts to improve the quality of post-resuscitation care, in-hospital survival after out-of-hospital cardiac arrest (OHCA) remains poor. Within the current post-cardiac arrest (CA) period, outstanding though expensive treatment strategies exist for all comatose patients successfully resuscitated after OHCA (16, 19, 20, 175). Especially within this time period, the uncertain prognosis of OHCA patients fuels the continuous drive of physicians to identify those patients who will benefit the most from aggressive intensive care. Therefore, any argument in favour of a good outcome could support the critical decision to use all ICU resources on those patients. Moreover, healthcare workers continuously encounter the optimistic expectations of relatives, and so providing any early information about the likelihood of a good outcome could facilitate communication with patients' next of kin.

Before the era of targeted temperature management (TTM), a careful interpretation of the clinical neurological examination was considered as the gold standard to determine the prognosis in comatose OHCA survivors (136). With the implementation of TTM and its concomitant use of sedatives, specific clinical signs have become unreliable for outcome prediction within the initial 24 hours (20, 21). Multiple prognostic markers (i.e. electroencephalography (EEG), somatosensory-evoked potentials (SSEPs), biochemical markers and brain imaging) have been introduced to aid with poor outcome prognostication after OHCA, but on their own, they do not possess enough discriminatory power to predict outcome. Moreover, they are not always continuously or sometimes only locally available, they are expensive, laborious and above all, require expertise for reliable interpretation (10, 20-22). Early outcome prognostication should therefore perhaps focus on good rather than poor outcome prediction, especially since guidelines state that the decision to withdraw life-sustaining therapy should be postponed to at least 72 hours after CA. Models for the prediction of neurological outcome have been described previously, but use often variables that are rather ambiguous or unavailable at the bedside (176-181). A prediction model capable of estimating the probability of a good outcome in the early hours based on parameters that are available bedside, could be of major interest for physicians to identify those patients with a reasonable chance of recovery. Additionally, these prediction models might also provide assistance for patient stratification in future randomized controlled trials or epidemiological studies. Therefore, this retrospective study aimed to develop prognostic models – using a training and (internal) validation set – to

predict good neurological outcome as soon as possible in OHCA patients using variables that are available bedside after ICU admission.

METHODS

STUDY POPULATION

All consecutive adult comatose survivors who were successfully resuscitated from OHCA and admitted to the Coronary Care Unit (CCU) of our tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium) were prospectively enrolled between March 2011 and May 2015. Exclusion criteria were an obvious non-cardiac cause of arrest, in-hospital cardiac arrest and inadequately performed TTM at 33°C. A head computed tomography (CT) scan was performed if no obvious cause of arrest was found. In this patient cohort, we previously investigated the prognostic value of Near-Infrared Spectroscopy (NIRS) and BIS monitoring, which are neuromonitoring tools known for their non-invasiveness, ease of use and bedside availability (126, 168). Based on these prospectively gathered data, this retrospective study aimed to construct multivariate prediction models for good neurological outcome using these non-invasive cerebral parameters in conjunction with other variables that are readily available following CCU admission. The study protocol was approved by the local Committee for Medical Ethics (11/066). Written informed consent was obtained from the patients' next of kin and was reconfirmed if the patient regained consciousness.

POST-RESUSCITATION PROTOCOL

Our institutional post-resuscitation protocol has been described elsewhere (38, 126). All patients were intubated, mechanically ventilated and sedated by intravenous administration of remifentanil and propofol or midazolam. Unless an obvious non-cardiac cause of arrest could be identified, urgent coronary angiography was performed by interventional cardiologists, followed by a percutaneous coronary intervention. Immediately after admission to the emergency department, TTM at 33°C was initiated by administering cold saline intravenously (4°C – 15-30ml/kg). Once admitted to the CCU, TTM was further mechanically induced and maintained at 33°C for 24 hours using endovascular (Icy-Catheter, Coolgard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGel™ pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems. Hereafter, patients were rewarmed over the next 12 hours (0.3°C/hour). All systems were equipped with a feedback loop system to control target temperature using an oesophageal temperature probe. Only in case of muscle shivering was cisatracurium

administered. Within the TTM period, sedation was titrated to obtain values between -3 and -5 on the Richmond Agitation-Sedation scale. Cannulation of the radial artery ensured a continuous registration of blood pressure. Placement of a pulmonary artery catheter was left at the discretion of the treating physician and provided information about mixed venous blood oxygen saturation. According to the guidelines, mean arterial pressure was maintained strictly above 65mmHg using norepinephrine (96). Additionally, an hourly blood gas analysis was performed including the determination of lactate. From February 2012 onwards, neuron-specific enolase (NSE) was determined at hour 24 and 48 following CCU admission. Patients were extubated when their neurological, respiratory and hemodynamic status had been sufficiently recovered.

NEUROMONITORING

Cerebral tissue oxygen saturation ($SctO_2$) was continuously measured using FORE-SIGHT™ technology (CAS Medical systems, Branford, CT, USA) for 72 hours following CCU admission. Furthermore, Bispectral Index (BIS) monitoring using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA) was started as soon as possible and continued up to 72 hours. Both NIRS and BIS sensors were bilaterally placed on the forehead before the start of TTM and covered to prevent ambient light interference. According to manufacturer's instructions, the BIS sensor was placed above the eyebrows and NIRS sensors were positioned above the BIS sensor. In patients with a limited amount of space on the forehead to place both NIRS and BIS sensors, priority was given to NIRS, ignorant which of both parameters contained the highest prognostic power. Obviously, this clarifies the high degree of missingness of BIS data in our entire study cohort. Together with hemodynamic data, $SctO_2$ was collected with a 2 second time interval and BIS data was stored every second. Although treating physicians were not blinded to the recorded NIRS and BIS values, therapeutic interventions were performed according to the guidelines and at the discretion of the treating physician. As such, the collected NIRS and BIS data were solely being collected for research purposes and were not being used to guide therapeutic interventions or to assist with the process of neuroprognostication.

OUTCOME ASSESSMENT

At 180-days post-CA, surviving patients were interviewed at follow-up by attending cardiologists. These medical reports were retrospectively assessed by a single assessor (W.E.) who defined patients' outcome using the Cerebral Performance Category (CPC)

scale. No outcome data was missing. According to the scale classification, CPC 1 indicates good cerebral performance; CPC 2 signifies a moderate disability but sufficient cerebral functioning for independent daily-life activity; CPC 3 implies severe disability with dependency on others; CPC 4 indicates coma or vegetative state and CPC 5 stands for death (99). A CPC1-2 and CPC3-5 was considered as a good and a poor neurological outcome, respectively.

STATISTICAL ANALYSIS

Prediction models for good neurological outcome at 180 days post-CA (CPC1-2) were constructed at hour 1, 12, 24 and 48 after CCU admission (Fig. 1). Variables considered to be included at all time points were: sex, age, diabetes status, witnessed arrest, initial rhythm (with asystole as reference category), percutaneous coronary intervention, initial lactate, initial haemoglobin, initial creatinine, mean arterial pressure, BIS value of 0, mean BIS, mean cerebral oxygen saturation. Along with these variables, the following parameters were considered to be included: lactate, haemoglobin, creatinine and mixed venous oxygen saturation levels at the respective time points. Furthermore, NSE was considered at hour 24 and 48.

To account for missing variables, multiple data imputation was performed. Predictive mean matching imputation was used for continuous variables and logistic regression with bootstrap was performed to impute binary variables. For categorical variables with more than two levels, polytomous logistic regression was used to impute (182). The number of imputations was equal to the percentage of missingness at each data set for four different time points (183). The elastic-net method was then used to perform variable selection for all imputed datasets (184). Variables repeatedly retained in more than 50% of the imputed datasets were chosen for model fitting. To select the optimal values of the elastic-net penalty α and the tuning parameter λ, ten-fold cross-validation was used. The logistic regression model can be specified as:

$$log\left[\frac{P(Y_i = 1)}{1 - P(Y_i = 1)}\right] = \beta_0 + \sum_{j=1}^{p} \beta_1 X_{ij}$$

Where j (1, p) is the j predictor included in the model and $i = 1$, n is the number of observations in each imputed data set and $P(Y_i = 1)$ is the probability of survival for patient i.

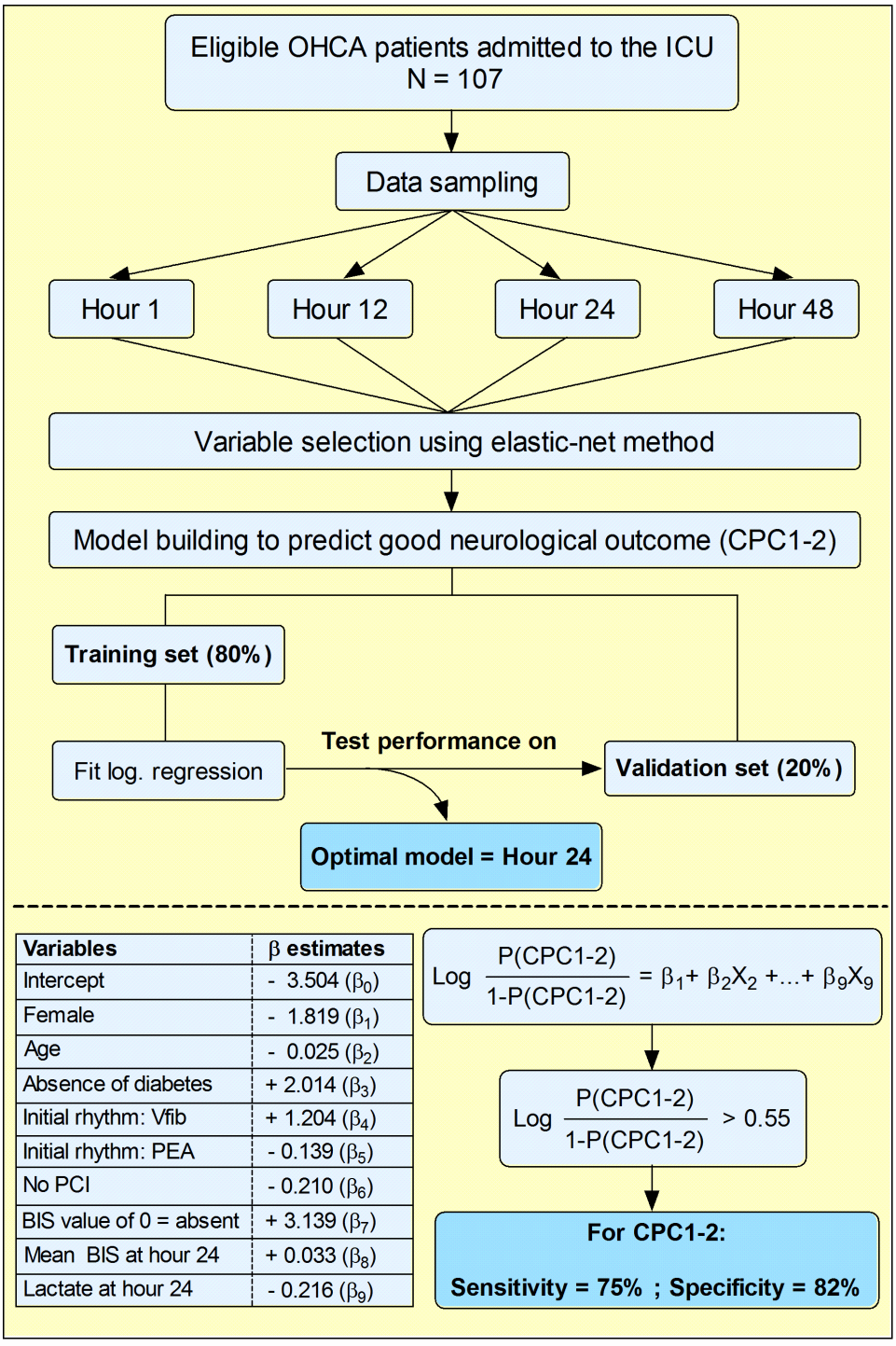
Once the variables were selected, the performance of the final multivariate logistic regression was assessed for each imputed dataset and results were pooled to make a final inference for data at each time point. Each imputed dataset was randomly divided into a training set (80% of patients) and a validation set (20% of patients). Logistic regression was fitted on the training sets and the prediction performance of the resulting model was evaluated on the validation sets by means of misclassification rates (i.e. percentage of cases misclassified; Fig. 1). For this purpose, diverse cut-off points were prespecified. Logistic regression was fitted on all imputed datasets per time point with cut-off points ranging from 0.10 to 0.90 by an increment of 0.05. When the calculated probability from logistic regression was larger than the chosen cut-off point, the patient was categorized as survival (CPC1-2). The corresponding sensitivities and specificities were calculated. Cut-off points that produced both a sensitivity and specificity larger than 70% were chosen. After the cut-off points were determined, the performance of the final (multivariate) logistic regression models constructed at the four time points was assessed by means of the misclassification rate. The optimal cut-off point for each time point was the one with the smallest misclassification rates. Additionally, the area under the receiver operating characteristics curve (AUROC) was calculated for each imputed data set and pooled per time point. We used R 3.2.1 statistical software (R Foundation for Statistical Computing, Vienna, Austria) for multiple imputation and model selection, and SAS Software version 13.2 (SAS, Cary, NC, USA) for pooling the results over the different imputed data sets using logistic regression.

RESULTS

Between March 2011 and May 2015, 147 successfully resuscitated comatose OHCA patients, admitted to the emergency department and transferred to the Coronary Care Unit, were screened for eligibility. The data of 25 patients were excluded due to the following ineligibility reasons: cooling with mattress (n=8), in-hospital cardiac arrest (n=10), drowning/hanging (n=3), no TTM at 33°C (n=4). Furthermore, 15 out of 122 eligible patients were not retained for final data analysis due to the following reasons: coronary-artery bypass graft surgery at day 2 (n=1) and not included due to no storage of (continuous) hemodynamic, $SctO_2$ and BIS data (n=14). In total, 107 successfully resuscitated comatose OHCA patients with a cardiac cause of arrest were included for data analysis, 50 (47%) of whom had a good (CPC1-2) and 57 (53%) a poor neurological outcome (CPC3-5) at 180 days post-CA. Demographic data of all included patients are provided in table 1. Prediction models for good neurological outcome at 180 days post-CA

were constructed at hour 1, 12, 24 and 48 after CCU admission. As two patients died before hour 12, 105 patients were retained for the models at hour 12 and hour 24. Ten patients died between hour 24 and hour 48, resulting in 95 patients who were retained for the model at hour 48.

In total, 13, 17, 18 and 18 variables were considered in the prediction models at hour 1, 12, 24 and 48, respectively (Table 2). Based on the elastic-net method, 5, 9, 8 and 7 variables were retained in the models at hour 1, 12, 24 and 48, respectively. Variables retained in all prediction models were diabetes, initial rhythm, percutaneous coronary intervention, mean BIS value at the respective time point and the presence of a BIS 0 value within the respective time frames. Lactate and sex were present at hour 12, 24 and 48, while age was only retained at hour 12 and 24 following CCU admission. In addition, creatinine was predictive for good neurological outcome at hour 12 after CCU admission. NSE was determined at hour 24 and 48, but was only retained in the model at hour 48. Mean $SctO_2$ values were not present at a single time point (Table 2).



Variables	β estimates
Intercept	- 3.504 (β_0)
Female	- 1.819 (β_1)
Age	- 0.025 (β_2)
Absence of diabetes	+ 2.014 (β_3)
Initial rhythm: Vfib	+ 1.204 (β_4)
Initial rhythm: PEA	- 0.139 (β_5)
No PCI	- 0.210 (β_6)
BIS value of 0 = absent	+ 3.139 (β_7)
Mean BIS at hour 24	+ 0.033 (β_8)
Lactate at hour 24	- 0.216 (β_9)

Figure 1 (page on the left). Development of prediction models and calculation used to predict good neurological outcome at hour 24. This flowchart demonstrates the developmental process of the constructed prediction models at selected time points following CCU admission. Twenty-four hours after CCU admission, good neurological outcome was predicted with the lowest misclassification rate (i.e. the optimal model; *top of figure*). The probability for good neurological outcome can be calculated using the correlation coefficients from all variables *(bottom of figure)*. For example, an 84-year old female patient without diabetes, successfully resuscitated from an OHCA with ventricular fibrillation as initial rhythm, was admitted to the emergency department and was transferred to the catherization lab where she received a percutaneous coronary intervention. Twenty-four hours after CCU admission, she did not experienced a BIS value of 0, mean BIS over 24 hours was 46 and lactate was 1.2mmol/l. Based on the formula, the calculated probability of good neurological outcome in this patient would be 0.68 which is higher than the proposed cut-off probability of 0.55. In this specific patient, good neurological outcome can be predicted with a sensitivity of 75% and specificity of 82%.

Table 1. Demographics.

Parameter	Survivors (CPC1-2)	Non-survivors (CPC3-5)	P-value
Patients, n (%)	50 (53)	57 (47)	/
Age, mean (±SD)	61±13	65±13	0.058
Male, n (%)	39 (78)	36 (63)	0.094
Surface cooling, n (%)	25 (50)	36 (63)	0.178
Endovascular cooling, n (%)	25 (50)	21 (37)	0.178
Initial rhythm			
Ventricular fibrillation, n (%)	42 (84)	26 (46)	<0.001
Pulseless electrical activity, n (%)	4 (8)	7 (12)	0.527
Asystole, n (%)	4 (8)	20 (35)	<0.001
Witnessed arrest, n (%)	45 (90)	46 (81)	0.246
Coronary angiography, n (%)	46 (92)	41 (72)	0.012
Percutaneous coronary intervention, n (%)	36 (72)	22 (39)	0.001

Multivariate logistic regression was performed and the results were pooled for each time point (Table 2). The pooled χ^2 of the Hosmer and Lemeshow test for the prediction model at hour 1, 12, 24 and 48 was 0.95, 0.90, 0.96 and 0.99, respectively, indicating a good fit for all models. Subsequently, the performance of all prediction models was assessed by means of the misclassification rate, where the most optimal model is considered as the one generating the lowest misclassification rates. All models predicted good neurological outcome with a sensitivity and specificity above 70% (Table 3). However, the prediction model at hour 24 predicted good neurological outcome with the lowest misclassification rate (21.5%; 95% CI: 19.5 – 23.5) using a cut-off probability of 0.55 (Mean AUROC = 0.918; Fig. 1).

The probability (P) of survival at hour 24 following CCU admission can be calculated using the following equation:

Log [P̂ (Survival)/(1 – P̂ (Survival))] =
- **3.504** (intercept)
- **1.244** (if patient is female)
- **0.025** x age of patient
+ **2.014** (if diabetes is absent)
+ **1.204** (if initial rhythm is ventricular fibrillation)*
- **0.139** (if initial rhythm is pulseless electrical activity)*

**asystole as initial rhythm was set as reference category*

- **0.210** (if no percutaneous coronary intervention was performed)
+ **3.139** (if a BIS value of 0 was absent within the first 24 hours)
+ **0.033** x mean BIS value at hour 24
- **0.216** x lactate value at hour 24

Using this cut-off point of 0.55, the prediction model at hour 24 predicted good neurological outcome with a sensitivity of 75.3% (95% CI: 72.1 – 78.2) and specificity of 82.2% (95% CI: 79.3 – 85.1) (Fig. 1).

Table 2. Prediction models with retained variables at the four time points following ICU admission.

Variables	Hour 1 (χ^2 = 0.95)		Hour 12 (χ^2 = 0.90)		Hour 24 (χ^2 = 0.96)		Hour 48 (χ^2 = 0.99)	
	Estimate (SE)	***P***	***Estimate (SE)***	***P***	***Estimate (SE)***	***P***	***Estimate (SE)***	***P***
Intercept	-4.462 (1.258)	<0.001	-1.213 (2.297)	0.598	-3504 (2.242)	0.118	-1.124 (1.544)	0.467
Female	/	/	-1.819 (0.843)	0.031	-1.244 (0.763)	0.103	-1.622 (0.939)	0.085
Age	/	/	-0.032 (0.028)	0.245	-0.025 (0.025)	0.332	/	/
Absence of diabetes	1.196 (0.725)	0.099	1.673 (0.982)	0.089	2.014 (0.977)	0.039	1.880 (1.176)	0.110
Initial rhythm								
Ventricular fibrillation	2.213 (0.734)	0.003	0.653 (0.915)	0.475	1.204 (0.872)	0.168	0.717 (0.960)	0.455
Pulseless electrical activity	0.861 (0.972)	0.376	-1.456 (1.234)	0.238	-0.139 (1.228)	0.910	-0.504 (1.387)	0.716
No PCI	-0.776 (0.553)	0.160	-0.630 (0.752)	0.402	-0.210 (0.662)	0.751	-0.315 (0.734)	0.668
Absence of BIS value of 0	1.966 (0.751)	0.009	3.717 (0.942)	<0.001	3.139 (0.898)	0.001	2.878 (0.942)	0.002
Mean BIS at respective hour	0.017 (0.014)	0.231	0.027 (0.016)	0.085	0.033 (0.019)	0.092	/	/
Lactate at respective hour	/	/	-0.219 (0.187)	0.242	-0.216 (0.235)	0.358	-0.136 (0.533)	0.799
Creatinine at respective hour	/	/	-0.331 (0.310)	0.287	/	/	/	/
Neuron-specific enolase					/	/	-0.023 (0.016)	0.153

BIS = Bispectral Index; PCI = Percutaneous coronary intervention; SE = Standard error; χ^2 = chi-square statistic indicating the goodness-of-fit

These are the final multivariate logistic regression models with retained variables based on the elastic-net method.

- Variables considered to be included at all time points: sex, age, diabetes status, witnessed arrest, initial rhythm (with asystole as reference category), PCI, initial lactate, initial haemoglobin, initial creatinine, mean arterial pressure, BIS value of 0, mean BIS, mean cerebral oxygen saturation
- Variables considered to be included at hour 12, 24 and 48: lactate, haemoglobin, creatinine and mixed venous oxygen saturation at respective time points
- Variable considered to be included at hour 24 and 48: NSE at respective time points

Table 3. Prediction performance of the four prediction models.

Cut-off probability	Misclassification rate				Sensitivity				Specificity			
	H1	*H12*	*H24*	*H48*	*H1*	*H12*	*H24*	*H48*	*H1*	*H12*	*H24*	*H48*
0.45	26.2 (9.1)	22.9 (8.0)	21.8 (8.2)	-	75.2 (12.5)	78.4 (12.2)	79.8 (12.4)	-	70.8 (14.9)	76.2 (11.8)	77.4 (13.2)	-
0.50	25.3 (9.2)	22.5 (8.2)	21.5 (8.2)	-	72.9 (12.8)	76.5 (12.8)	77.6 (12.9)	-	77.4 (13.7)	78.9 (11.6)	79.9 (12.6)	-
0.55	24.8 (9.2)	22.3 (8.3)	21.5 (8.4)	23.7 (9.6)	70.5 (13.1)	74.1 (13.5)	75.3 (13.6)	78.6 (14.2)	74.3 (14.4)	81.5 (11.3)	82.2 (12.3)	74.6 (15.6)
0.60	-	-	-	23.4 (9.5)	-	-	-	76.8 (14.4)	-	-	-	77.2 (15.0)
0.65	-	-	-	23.3 (9.4)	-	-	-	74.6 (14.6)	-	-	-	77.4 (13.2)

Misclassification rate is the percentage of cases misclassified. The optimal cut-off probability yielding the smallest misclassification rate is indicated in bold for each time point. Misclassification rate, sensitivity and specificity are presented in percentage (standard deviation).

At hour 24, missingness was present in 12 variables, namely initial haemoglobin (0.9%), diabetes (1.9%), witnessed arrest (2.8%), initial Rhythm (3.7%), initial lactate (8.4%), initial creatinine (8.4%), mean MAP at hour 24 (9.5%), mean SvO_2 at hour 24 (21%), NSE (26.7%), BIS 0 value (27.6%) and mean BIS value at hour 24 (38.1%). Missingness at the other time points is shown in figure 2.

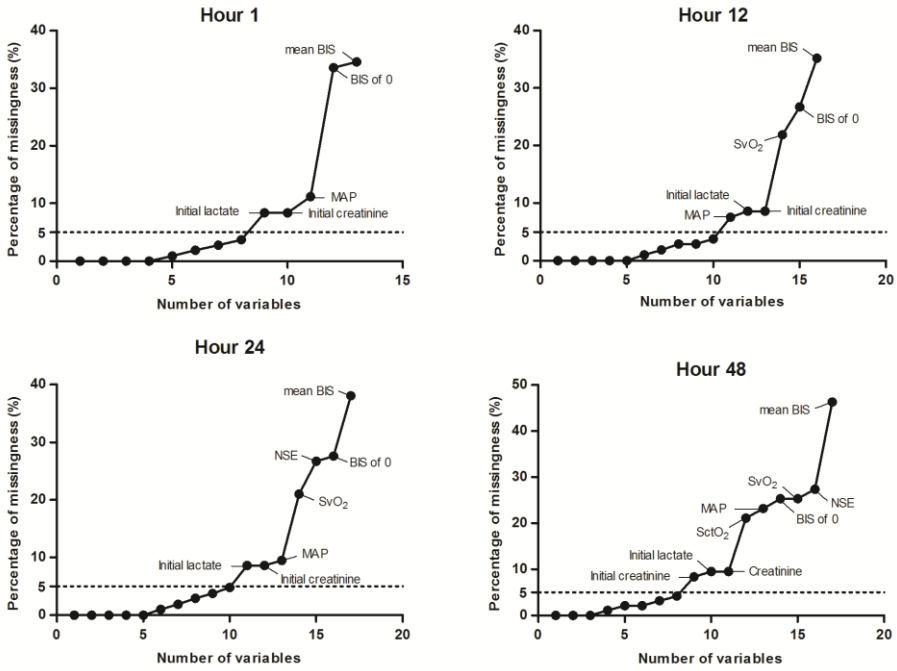


Figure 2. Missingness across all selected time points. This figure shows the variables considered to be included at all selected time points that have more than 5% missingness across the study cohort.

DISCUSSION

Our data show that good neurological outcome at 180 days post-CA can be predicted in successfully resuscitated comatose OHCA patients treated with TTM at 33°C using prediction models containing variables that are early and available bedside after CCU admission. In order to predict good neurological outcome as early as possible, multilevel prediction models were constructed at hour 1, 12, 24 and 48 after CCU admission which all reached a sensitivity and specificity above 70%. Using a cut-off point of 0.55, the

prediction model at hour 24 predicted good neurological outcome with the smallest misclassification rate, corresponding to a sensitivity of 75% and specificity of 82%.

Identifying post-CA patients who would maximally benefit from full supportive therapy without unnecessary suffering remains hard to achieve once admitted to the ICU. Nowadays, specific clinical signs in the initial 24 hours have become inaccurate due to the implementation of TTM (20, 21). Electro-encephalography, SSEPs, biomarkers and brain imaging are prognostic tools recommended by current guidelines to assist with outcome prognostication, but are often not always available in daily clinical practice, are time-consuming, expensive and require clinical expertise (20, 185-188). In an attempt to account for these hurdles and facilitate bedside prognostication, we previously investigated the role of NIRS and BIS monitoring in terms of outcome prediction (126, 159, 168). In order to predict good neurological outcome after OHCA, this retrospective analysis now aimed to construct multivariate regression models including these cerebral parameters combined with variables, readily available at ICU admission,. Unlike scoring systems developed by others, we decided to ignore ambiguous variables such as 'low-flow' and 'no-flow' times as these are often unknown or incorrectly reported (176-181). In this study, the constructed prediction models at hour 1, 12, 24 and 48 after admission succeeded in predicting good neurological outcome at 180 days post-CA, all with a sensitivity and specificity above 70%. The model which classified OHCA patients with the lowest misclassification errors was the one at hour 24 and contained sex, age, diabetes status, initial rhythm, percutaneous coronary intervention, the absence of a BIS 0 value within the first 24 hours, mean BIS value at hour 24 and lactate as predictive variables for good neurological outcome. This model was able to predict good neurological outcome with a sensitivity of 75% and specificity of 82% when 0.55 was used as the cut-off point. It has to be stated that the obtained predictive performance of our model should be considered as rather modest. Hence, we certainly do not advise the use of our prediction models to assist with the clinical prognostication process at the moment. On the contrary, external validation in a large patient cohort without missing data will be a prerequisite before clinical implementation will be possible. Additionally, further research attempts should now investigate whether the performance of our constructed prediction models could be improved by adding other prognostic parameters. Therefore, our research findings might be considered as one of the first steps in the development of an easy tool, that is able to identify OHCA patients who might benefit the most from aggressive treatment, and for whom finite healthcare sources should be optimized. For now, our models might be of

potential interest as guidance for designing risk stratification models in clinical research with variable resource allocation or could be used to enhance future research initiatives focusing on new therapies. Additionally, the results of this study could be helpful for the design of future epidemiological studies as it is often difficult to select which data should be assembled and when these should optimally be collected after CCU admission (189).

As shown by others, initial rhythm, percutaneous coronary intervention and diabetes status prior to CA were variables retained at all selected time points in this study (190-192). Likewise, both mean BIS values and the absence of a BIS 0 value appear to be predictors for good neurological outcome across all time points, thereby confirming the prognostic validity of BIS monitoring in the post-CA setting once again (58, 59, 61, 159, 168). In line with previous studies, gender, age as well as lactate and creatinine levels were predictive for good neurological outcome, albeit not immediately following ICU admission (193-196). Finally, NSE was only retained in the model at hour 48 which is in accordance with previous studies (187, 197).

In recent years, the prognostic value of $SctO_2$ has been examined thoroughly in the post-CA setting. Several studies have demonstrated that high $SctO_2$ values during TTM at 33°C were associated with a higher likelihood of favourable neurological outcome (38, 40). Storm and co-authors even suggested an $SctO_2$ value of 50% as therapeutic target (39). In the largest post-resuscitation cohort so far, we previously showed that the overall course of $SctO_2$ was different between OHCA patients with a good and poor neurological outcome. Nonetheless, the observed $SctO_2$ margin seemed to be too narrow to likely represent outcome differentiation. As such, it was concluded that $SctO_2$ lacked prognostic power on its own to serve in outcome prognostication (126). The role of $SctO_2$ as a prognostic marker included in a multivariate prediction model on the other hand, has not been investigated until now. Based on our analysis, we are the first to show that $SctO_2$ was not retained in any multivariate regression model at a single time point upon CCU admission. Therefore, this study illustrates once more the limited prognostic value of $SctO_2$ by itself in the early hours following ICU admission.

This study has several limitations. First, this was a single-centre study with a limited number of patients included. Secondly, multiple imputation was used to account for missingness in certain variables. Nevertheless, imputed values were deemed persuasive, based on the generated density plots of the observed and imputed data *(not shown)*. On the other hand, a possible selection bias could not have been excluded if only the cases

were included with all available parameters. Third, BIS monitoring might not be routinely applied in other centres which might complicate the usefulness of our prediction models. Nonetheless, BIS monitoring is cost-effective, non-invasive and can be made available at the bedside rather easily. On the other hand, BIS data were not kept blinded for treating physicians through which we cannot fully exclude the possibility that the prognostic value of BIS was being artificially inflated during the study period. Nonetheless, treating physicians were cardiologists who are not familiar with the use and interpretation of BIS values. Finally, our prediction models were only validated internally. Even though it has been shown that n-fold cross validation generates stable estimates with low bias, external validation on an independent data set is mandatory before these models can be used in routine clinical practice (198).

CONCLUSION

Prognostic models for the prediction of survival in OHCA patients were constructed at hour 1, 12, 24 and 48 following CCU admission. The prediction model which classified OHCA patients with the lowest misclassification errors was the one at hour 24, yielding a sensitivity of 75% and specificity of 82%. In this model, sex, age, diabetes status, initial rhythm, percutaneous coronary intervention, the presence of a BIS 0 value, mean BIS value and lactate were the variables identified as predictive for good neurological outcome. At the moment, external validation in a larger patient cohort is mandatory before this model can be translated into clinical practice.

PART II

The role of cerebral tissue oxygen saturation monitoring in the cardiac surgery patient

CHAPTER 7

Influence of continuously evolving transcatheter aortic valve implantation technology on cerebral oxygenation

Eertmans W, Genbrugge C, Fret T, Beran M, Engelen K, Gutermann H, Vander Laenen M, Boer W, Ferdinande B, Jans F, Dens J, De Deyne C

J Clin Monit Comput (2017) 31:1133-1141.

ABSTRACT

Objective: This study assessed the influence of the evolution in Transcatheter Aortic Valve Implantation technology on cerebral oxygenation.

Methods: Cerebral oxygenation was measured continuously with Near-Infrared Spectroscopy and compared retrospectively between balloon-expandable, self-expandable and differential deployment valves which were implanted in 12 (34%), 17 (49%) and 6 patients (17%), respectively. Left and right $SctO_2$ values were averaged at four time points and used for analysis (i.e. at baseline, balloon-aortic valvuloplasty, valve deployment, and at the end of the procedure).

Results: During balloon-aortic valvuloplasty and valve deployment, cerebral oxygenation decreased in patients treated with balloon or self-expandable valves (balloon-expandable: $p=0.003$ and $p=0.002$; self-expandable: $p<0.001$ and $p=0.003$, respectively). The incidence of cerebral desaturations below 80% of baseline was significantly larger in patients treated with balloon-expandable valves ($p=0.001$). In contrast, patients who received differential deployment valves never experienced a cerebral desaturation below 80% of baseline. Furthermore, both the incidence and duration below a cerebral oxygenation of 55% was significantly different between balloon and self-expandable valves ($p=0.038$ and $p=0.018$, respectively).

Conclusions: This study demonstrated that Transcatheter Aortic Valve Implantation procedures are associated with significant cerebral desaturations, especially during balloon-aortic valvuloplasty and valve deployment. Moreover, our results showed that latest innovations in Transcatheter Aortic Valve Implantation technology beneficially influenced the adequacy of cerebral perfusion.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is considered as the treatment of choice for inoperable patients with severe aortic stenosis and has become an acceptable alternative treatment option to surgical aortic valve replacement (SAVR) for patients considered to be at high surgical risk (199-201). It was the first successful in-human TAVI in 2002 that fuelled the drive to establish optimal devices, which led to an exponential improvement in technology (202). Consequently, novel valves were introduced in clinical practice over the years with the scope to minimize complications such as paravalvular regurgitation, stroke and the need for pacemaker implantation (203, 204). Nevertheless, (silent) cerebrovascular complications remain a major issue in patients undergoing TAVI. These complications can be partly attributed to repetitive wire and catheter manipulations, provoking the release of atherosclerotic or gaseous microemboli (205, 206). Besides, neurological impairment may also be related to rapid ventricular pacing (RVP), which is necessary during balloon aortic valvuloplasty (BAV) and deployment of balloon-expandable valve types. When a transient cardiac standstill is induced by RVP, the subsequent loss in cardiac output has been shown to have a profound effect on the microvascular cerebral tissue perfusion (207, 208).

In recent years, Near-Infrared Spectroscopy (NIRS) has emerged as a valuable non-invasive neuromonitoring tool to assess cerebral oxygenation ($SctO_2$) at microvascular level (30). There is a paucity of $SctO_2$ data available during TAVI, although critically low $SctO_2$ values were already correlated with a worsening in neurological outcome during cardiac surgery in general (82, 83). Some authors previously reported cerebral desaturations during TAVI, and particularly during RVP (209-211). As the necessity to use RVP during TAVI procedures diminished considerably with the introduction of the newest valve types, it might be that the procedure itself has become less harmful on a cerebral level. Therefore, this study aimed to describe the influence of the evolution in TAVI technology on the adequacy of cerebral perfusion during TAVI procedures, as assessed by NIRS.

MATERIALS AND METHODS

Patients suffering from severe aortic stenosis, deemed as ineligible or considered to be at too high risk for conventional SAVR, were evaluated by a multidisciplinary team and scheduled for TAVI between May 2010 and March 2016 in Ziekenhuis Oost-Limburg (Genk, Belgium). Risk assessment was based on preoperative comorbidities and calculated by the logistic Euroscore II.

Depending on the patient's vascular status, TAVI was carried out either through a transfemoral (TF) retrograde or transapical (TA) antegrade approach using the Edwards Sapien™ (Edwards Lifesciences Inc, Irvine, CA), Medtronic CoreValve™, Engager™ or Evolut R (Medtronic, Inc, Minneapolis) or Lotus™ Valve System (Boston Scientific Corporation, Marlborough, Massachusetts). The first TAVI procedures were performed using first-generation Edwards Sapien™ valves. Thereafter, first- and second-generation Medtronic valves were used and our final procedures were executed using the Lotus™ Valve System. To describe the impact of the evolution in valve technology on $SctO_2$, Edwards Sapien™, Medtronic and Lotus™ Valve systems will be indicated as balloon-expandable, self-expandable and differential deployment valves, respectively. The use of RVP during TAVI is dependent on the selected valve (Table 1).

Table 1. The use of Rapid Ventricular Pacing for different valves.

Valve	BAV	Valve Deployment
Balloon-expandable	+	+
Self-expandable	+	-
Differential deployment	NA	-

Use of Rapid Ventricular Pacing; + : Yes or - : No.
BAV: Balloon aortic valvuloplasty; NA: Not applicable

All procedures were performed under general anaesthesia according to a standard protocol. Before induction of anaesthesia, invasive arterial pressure monitoring was applied. Anaesthesia was induced using weight-adapted doses of remifentanil, propofol and cisatracurium and maintenance was ensured with remifentanil and sevoflurane in an O_2-air-mixture. A temporary ventricular pacemaker catheter was inserted in the right internal jugular vein.

Cerebral oxygenation was measured continuously with NIRS using FORE-SIGHT™ technology (CAS Medical systems, Branford, CT, USA). NIRS sensors were applied bilaterally on the forehead before induction of anaesthesia. Cerebral saturation data were collected with a sampling rate of two seconds.

With approval of the local Committee for Medical Ethics (16/046U), $SctO_2$ data were compared retrospectively between three valve types. As there was no bilateral difference in $SctO_2$, left and right $SctO_2$ was averaged at four time points and used for analysis (i.e. at baseline, BAV, valve deployment, and at the end of the procedure). Baseline $SctO_2$ values were defined during a five minute period before induction of anaesthesia while breathing room air. The absolute and relative $SctO_2$ decrease during BAV and valve deployment was calculated and compared between all valve types. The absolute $SctO_2$ decrease was computed by subtracting the minimum absolute $SctO_2$ recorded during TAVI from the baseline $SctO_2$. The relative $SctO_2$ decrease was derived by dividing the absolute $SctO_2$ decrease by the baseline $SctO_2$. Finally, the time under absolute threshold limits of 50%, 55% and 60% during the entire intra-operative period was calculated.

Statistical analysis was performed using SPSS Version 22.0 (SPSS Inc, Chicago, USA). Figures are made using GraphPad Prism 5.01 (GraphPad Software, CA, USA). Discrete data were compared using Chi-square or Fisher's exact tests. Equal distribution was tested with a Kolmogorov-Smirnov test. Student T tests were used to compare normally distributed continuous variables between two groups. A One-way ANOVA or Kruskal-Wallis test was used to compare normally and not normally distributed continuous data between multiple groups. Post-hoc analyses were performed using Bonferroni or Dunn-Bonferonni post-hoc tests. A within group analysis was performed using the Friedman test for repeated measures. Post-hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied for multiple testing. A p-value <0.05 was considered as significant.

RESULTS

STUDY POPULATION

Fifty-six severe aortic stenosis patients underwent TAVI. Nineteen patients were excluded from retrospective data analysis due to the use of intra-operative nasal cooling (n=7) and absent $SctO_2$ data (n=12). Additionally, two patients were excluded as they experienced a cardiac arrest during implantation of a balloon-expandable valve after which in one patient

extra-corporal membrane oxygenation (ECMO) was initiated (Fig. 1). Nevertheless, no patient died during the TAVI procedure itself. Thirty-five patients were retained for further analysis.

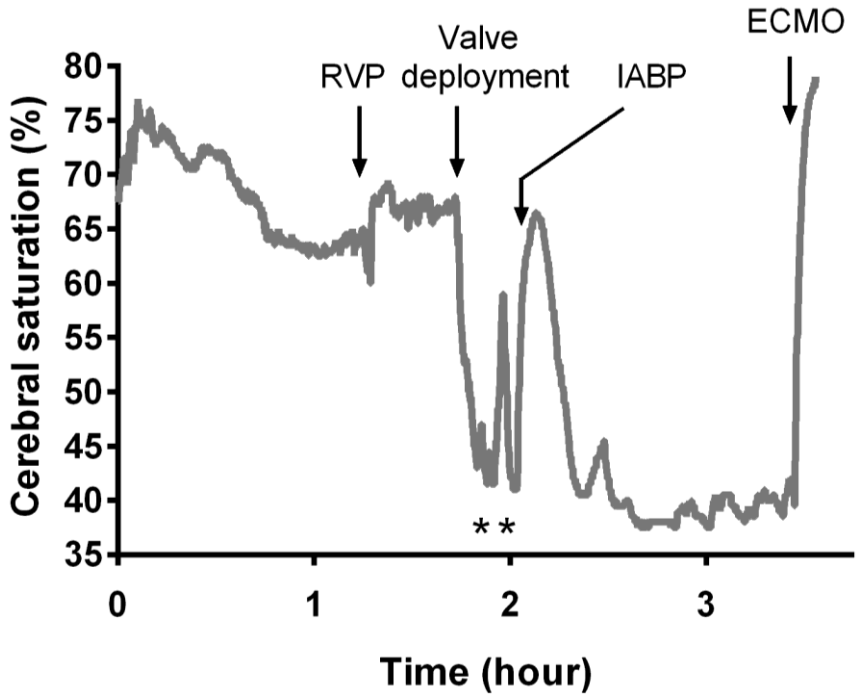


Figure 1. Patient with persistent left ventricular failure after valve deployment. Asystole followed by ventricular fibrillation (*) occurred after valve deployment under rapid ventricular pacing (120 beats/min) with a reduction in SctO2 towards 41%. External CPR and defibrillation improved SctO2 to 59%. Ventricular fibrillation (*) reoccurred followed by a decrease to 41%. As left ventricular failure was considered as the probable cause of ventricular fibrillation, an IABP was inserted, resulting in a temporary increase in SctO2. Despite continuous maximal CPR efforts (with mean arterial pressure values above 40-50 mmHg during CPR), SctO2 dropped to 38% and only returned to normal after ECMO was initiated. (RVP = Rapid Ventricular Pacing; IABP = Intra-aortic balloon pump; ECMO = Extra-corporal membrane oxygenation)

Baseline characteristics of all patients are summarized in Table 2. Balloon-expandable, self-expandable and differential deployment valves were implanted in 12 (34%), 17 (49%) and 6 patients (17%), respectively. Due to the retrospective nature of this study and the lack of continuous hemodynamic data, the exact moment of deployment was

missing in 6 patients treated with a self-expandable valve. TAVI procedures were performed using a TF or TA approach in 22 (67%) and 11 (33%) patients, respectively. Before valve implantation, BAV was performed under RVP in all patients treated with a balloon-expandable device and in 16 (94%) patients receiving a self-expandable valve.

Table 2. Baseline characteristics.

	Balloon-expandable (n=12)	Self-expandable (n=17)	Differential deployment (n=6)	P
Male/Female, n (%)	3 (25) / 9 (75)	8 (47) / 9 (53)	1 (25) / 5 (75)	0.321
Age, mean ± SD	84±4	81±9	86±2	0.416
NYHA class III or IV, n (%)	4 (30)	7 (41)	2 (33)	0.900
Heart failure, n (%)	9 (75)	7 (41)	5 (83)	0.124
Myocardial infarct, n (%)	1 (8)	1 (6)	2 (33)	0.208
Diabetes, n (%)	4 (30)	5 (29)	3 (50)	0.725
Arterial hypertension, n (%)	10 (83)	8 (47)	4 (67)	0.135
Dyslipidaemia, n (%)	4 (30)	5 (29)	3 (50)	0.725
Cerebrovascular Accident, n (%)	0 (0)	4 (24)	1 (17)	0.169
Coronary Artery Bypass Graft, n (%)	4 (30)	6 (35)	1 (17)	0.792
PCI, n (%)	6 (50)	5 (29)	1 (17)	0.401
Peripheral vessel disease, n (%)	3 (25)	5 (29)	2 (33)	1.000
CKI, n (%)	5 (42)	6 (35)	1 (17)	0.651
COPD, n (%)	2 (17)	3 (18)	2 (33)	0.726
Atrial fibrillation, n (%)	5 (42)	7 (41)	4 (67)	0.603
Euroscore II, mean ± SD	14.64±15.12	9.28±7.43	5.11±3.35	0.459

CKI = Chronic Kidney Insufficiency (Glomerular Filtration Rate<60ml/min/1.73m²); COPD = Chronic Obstructive Pulmonary Disease; PCI = Percutaneous Coronary Intervention.

THE OVERALL COURSE OF CEREBRAL OXYGENATION FOR THREE TAVI VALVE TYPES

Figure 2 shows the $SctO_2$ course of three patients undergoing TAVI, all treated with different valve systems. Generally, the overall course of $SctO_2$ during TAVI is strongly dependent on the used valve type. Therefore, the represented evolution in $SctO_2$ of each patient could be generalized for each valve type (Fig. 3). During TAVI procedures using balloon-expandable and self-expandable valves, BAV under RVP was accompanied by a significant cerebral desaturation with an immediate return towards baseline values once RVP was stopped ($p=0.003$ and $p<0.001$, respectively). In contrast, BAV was never performed in patients undergoing TAVI with a differential deployment valve (Table 1).

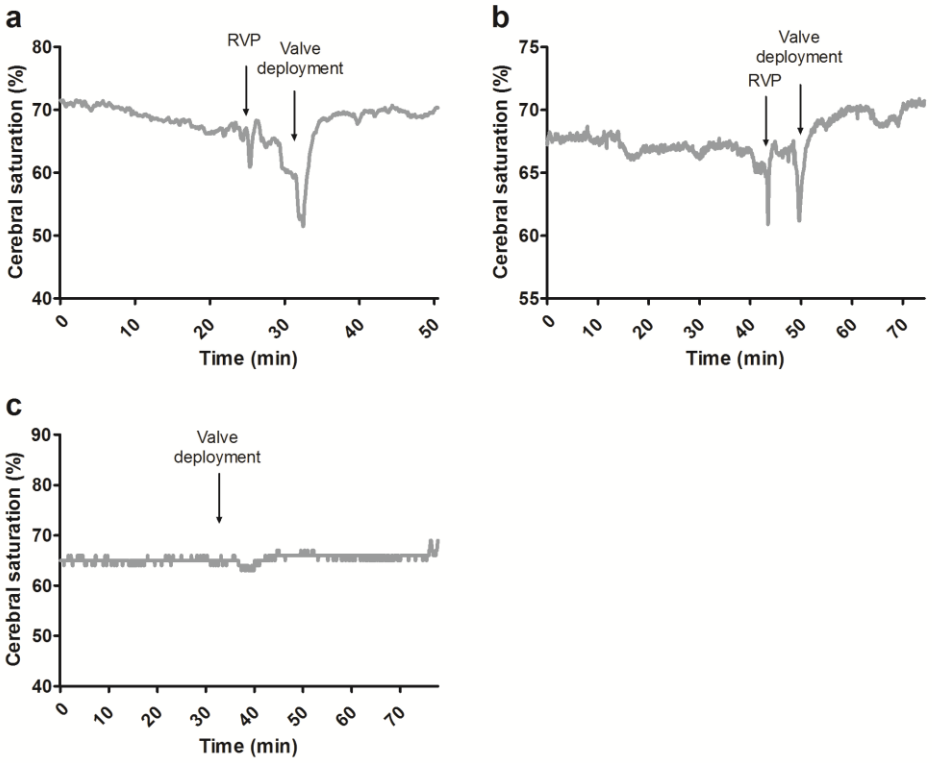


Figure 2. Cerebral oxygenation pattern for three patients undergoing TAVI with a different valve type. This figure shows the $SctO_2$ course of patients receiving a balloon-expandable **(A)** self-expandable **(B)** or differential deployment valve **(C)** (BAV = balloon aortic valvuloplasty; $SctO_2$ = cerebral oxygenation; TAVI = Transcatheter Aortic Valve Implantation).

The deployment itself of both balloon and self-expandable valves, on the other hand, was associated with a cerebral desaturation, variable in depth and duration depending on the chosen valve type. As valve placement of balloon-expandable valves is performed using BAV under RVP, the magnitude of cerebral desaturation was more pronounced as compared to valve implantation of other valves ($p<0.001$). While $SctO_2$ returned almost immediately towards baseline values after deployment of a self-expandable valve, the recovery of $SctO_2$ after implantation of the balloon-expandable valve was typically subjected to a certain delay (Fig. 2). Nevertheless, $SctO_2$ significantly decreased during deployment of both balloon and self-expandable valves ($p=0.002$ and $p=0.003$, respectively). In contrast, no significant change in $SctO_2$ was observed during implantation

of the differential deployment valve after correcting for multiple testing (p>0.017; Figure 3).

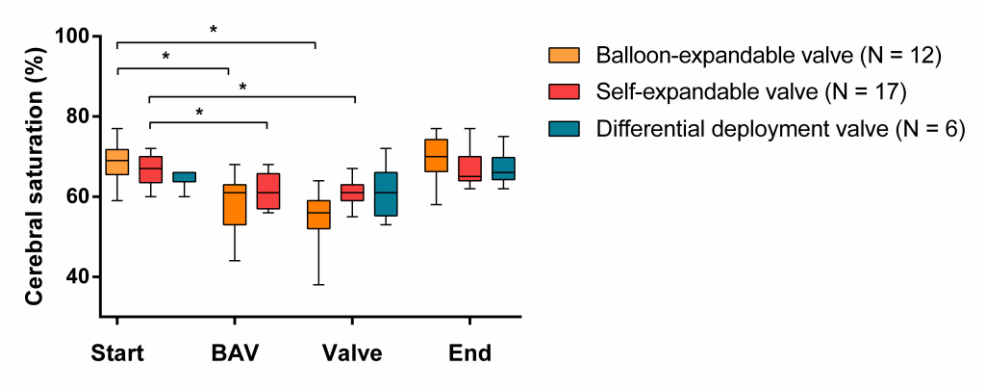


Figure 3. Overall intra-operative evolution of cerebral oxygenation. Compared to baseline values, $SctO_2$ significantly decreased during BAV and valve deployment in patients who received a balloon or self-expandable valve (BAV = balloon aortic valvuloplasty; $SctO_2$ = cerebral oxygenation).

CEREBRAL OXYGEN DESATURATION PERIODS DURING TAVI

Cerebral oxygenation values at distinct time points during TAVI were summarized in Table 3. Baseline $SctO_2$ values were comparable between all groups (p=0.187). Both absolute and relative $SctO_2$ decrease during BAV were significantly different between patients receiving balloon and self-expandable valves (Table 3). During valve deployment, the lowest observed $SctO_2$ was significantly different between patients receiving balloon-expandable devices and patients treated with self-expandable or differential deployment valves. In addition, the absolute and relative $SctO_2$ decrease during valve deployment was significantly larger in patients receiving balloon-expandable valves (Table 3). No significant differences in $SctO_2$ were observed during valve placement of self-expandable and differential deployment valves. Final $SctO_2$ values recovered towards baseline values in all patients with no significant difference between all valves (p=0.312).

Cerebral desaturation below 80% of baseline was observed in 9 patients of which 8 (67%) and 1 (6%) were treated with balloon and self-expandable valves, respectively (p=0.001). In contrast, $SctO_2$ remained above 80% of baseline in all patients receiving differential deployment valves. A reduction in $SctO_2$ below an absolute value of 50% was recorded in 3 (25%) patients treated with balloon-expandable valves. Furthermore, an incidence of

absolute $SctO_2$ values below 55% was observed in 6 (50%) and 2 (12%) patients who received balloon and self-expandable valves, respectively (p=0.038). Likewise, one patient (17%) treated with a differential deployment valve experienced a cerebral desaturation below 55% for 43 seconds. A reduction in $SctO_2$ below 60% was recorded in 12 (86%), 9 (53%) and 4 (67%) patients treated with balloon, self-expandable and differential deployment valves, respectively. The duration under an absolute $SctO_2$ threshold of 55% was significantly different between balloon and self-expandable valves (143±320 vs. 3±10 seconds; p=0.018).

OUTCOME

Within 30 days after TAVI, one patient treated with a balloon-expandable valve suffered from a cardiac arrest and died. All other patients were still alive six months after TAVI. One patient treated with a balloon-expandable and one patient treated with a self-expandable valve experienced a stroke within six months after TAVI. In general, no significant differences in stroke rate and mortality were observed between the different valve types.

Table 3. Intraoperative characteristics.

	Balloon-expandable (n=12)	Self-expandable (n=17)	Differential deployment (n=6)	P
TAVI				
Transfemoral / Transapical, n (%)	5 (42) / 7 (58)	13 (76) / 4 (24)	6 (100) / 0 (0)	**0.035**
Duration of procedure, mean ± SD (min)	161±56	182±23	215±55	**0.004**[a]
Baseline $SctO_2$ (%)	69±5	67±4	65±2	0.187
$SctO_2$ during BAV				
Lowest $SctO_2$ during BAV (%)	58±7	61±4	/	0.206
Abs. $SctO_2$ decrease during BAV (%)	10±4	6±4	/	**0.006**
Rel. $SctO_2$ decrease during BAV (%)	15±6	9±6	/	**0.007**
$SctO_2$ during valve placement				
Lowest $SctO_2$ during valve placement (%)	55±7	61±3	61±7	**0.027**[b]
Abs. $SctO_2$ decrease during valve placement (%)	14±6	6±4	4±6	**<0.001**[a]
Rel. $SctO_2$ decrease during valve placement (%)	20±9	8±5	5±9	**0.001**[a]
Time below $SctO_2$ thresholds				
Time below $SctO_2$ of 60%, mean ± SD (sec)	379±522	166±332	325±308	0.311
Time below $SctO_2$ of 55%, mean ± SD (sec)	143±320	3±10	7±18	**0.019**[b]
Time below $SctO_2$ of 50%, mean ± SD (sec)	68±192	0±0	0±0	**0.047**[b]

a. Post-hoc analysis showing significance between balloon and self-expandable valves as well as balloon-expandable and differential deployment valves.

b. Post-hoc analysis showing significance between balloon and self-expandable valves.

DISCUSSION

This study demonstrated that TAVI procedures are associated with significant fluctuations in $SctO_2$, especially during BAV and valve deployment. More importantly, our results have put forward that latest innovations in TAVI technology beneficially influenced the adequacy of cerebral perfusion during TAVI.

In line with previous studies, a transient imbalance between oxygen demand and supply was present in most patients undergoing TAVI (209-211). More specifically, cerebral oxygen supply was most compromised during periods of RVP and during valve deployment itself, as reflected by significant cerebral desaturations. However, to our knowledge, this is the first study evaluating the adequacy in cerebral perfusion in patients undergoing TAVI treated with either balloon-expandable, self-expandable or differential deployment valves. As compared to the differential deployment valves and to a minor extent in self-expandable valves as well, the absolute and relative decrease in $SctO_2$ during BAV and valve deployment was larger in balloon-expandable valves. Although not statistically significant, a larger drop in $SctO_2$ during both BAV and valve placement was observed in self-expandable valves with respect to differential valve deployment valves. Therefore, based on our results, we could demonstrate that the severity and duration of cerebral desaturation during TAVI has diminished considerably with the introduction of new-generation differential deployment valves. This phenomenon may be explained by the fact that the leaflets of this valve function immediately once valve deployment is initiated, omitting the requirement of RVP on the one hand and ensuring hemodynamic stability throughout the procedure on the other (212). This is in contrast to balloon and self-expandable valves who both require short-term use of RVP during BAV, and an additional and longer RVP period during valve deployment for balloon-expandable valves only (204).

Although it has been reported that performing TAVI without RVP is feasible, it is still preferred in most institutions as it minimizes cardiac motion and pulsatile transaortic flow, which beneficially influences valve positioning (213). Nevertheless, the rapid increment in heart rate combined with a transient left ventricular dysfunction induces a decrease in cardiac output during RVP. Within the setting of cardiac arrest as within TAVI, $SctO_2$ has been proven to be correlated with mixed venous cerebral saturation which, in turn, is assumed to be a surrogate measure for cardiac output (117, 214). As such, RVP will as expected result in a transient cerebral hypoperfusion period. Therefore, a difference in

cerebral perfusion indicated by NIRS monitoring due to different RVP procedures and/or valve types was to be expected. Nevertheless, the severity and duration of this hypoperfusion might be of great importance as Nuis et al. showed that not all neurological complications after TAVI are caused by cerebrovascular embolic incidents (205). Based on brain CT, they reported that 26% of the post-TAVI strokes revealed lacunar infarcts, which is commonly regarded as caused by procedural cerebral hypoperfusion. Therefore, they concluded that adequate brain perfusion should be maintained during TAVI at all costs, which could be partially guided by non-invasive cerebral oximetry (205). Even though all efforts were made to keep RVP periods as short as possible, RVP in both balloon and self-expandable valves was indeed associated with a significant and therefore, potentially harmful cerebral desaturation. In contrast, patients treated with a differential valve deployment valve never experienced a RVP period during the TAVI procedure, which may partially explain the overall unaltered $SctO_2$ pattern associated with this valve. Aside from the expected cerebral desaturation during RVP and valve deployment, the return towards baseline might be even more clinically relevant. In nearly all patients, $SctO_2$ returned almost immediately towards baseline values, except in two excluded patients of whom one experienced a cardiac arrest and the other patient had a prolonged low output failure. In one of these patients, cerebral saturation remained below 55% despite ongoing CPR efforts and only returned to baseline after initiation of ECMO (Fig. 1). Although the patient's hemodynamic status stabilized hereafter, the patient was declared brain dead 48 hours post-TAVI. Therefore, any delay in the return towards baseline $SctO_2$ values should urge immediate intervention with aggressive treatment.

Unfortunately, detailed neurocognitive follow-up with a standardized test battery was not carried out in our patient population. As such, we are not able to comment on the possible correlation between neurocognitive impairment and these (subclinical) cerebral desaturations during BAV and valve deployment. Still, several clinical studies clearly demonstrated the relationship between intra-operative cerebral oxygen desaturations and the manifestation of neurophysiological dysfunction after cardiac surgery (83, 84). Moreover, two randomized controlled trials were able to show that neurological and overall outcome improved significantly by implementing cerebral oximetry during cardiac surgery combined with a protocol-based interventional strategy (79, 82). Interestingly, as no clear difference in the incidence of cerebral desaturations was shown between patients receiving SAVR and TAVI, it is plausible to advise the use of a similar protocol during TAVI procedures (215). In addition, Fischer et al. showed, in a setting of aortic arch surgery,

that both the incidence and duration below certain $SctO_2$ thresholds were negatively associated with neurological outcome (102). In comparison with patients who received self-expandable or differential deployment valves, patients treated with balloon-expandable valves spent more time below absolute $SctO_2$ thresholds of 50 and 55%. To some extent, this may be explained by the fact that TAVI procedures using balloon-expandable valves contain two RVP periods, in which the one during valve deployment is considerably longer, inducing deeper cerebral desaturations. Furthermore, this patient cohort was already at high surgical risk as reflected by higher Euroscores, rendering them even more vulnerable to any reduction in cardiac output. This may explain the significant difference in absolute and relative decrease during BAV between patients treated with balloon-expandable and self-expandable valves.

Over the years, TAVI has become widely accepted as an alternative treatment strategy for both inoperable and high-risk patients with severe aortic stenosis, irrespective of the chosen valve (199-201, 216). Unfortunately, one of the most frequent (cerebrovascular) complications reported in the perioperative period remains stroke. However, recent results of the PARTNER II trial showed a lower rate of disabling stroke in the TF TAVI cohort which may be attributed to an increased operator experience and beneficial evolution in valve technology (217). To date, only one meta-analysis investigated whether the overall stroke rate differed between balloon and self-expandable devices, demonstrating similar risk rates for both valve types. Interestingly, they concluded that the overall risk for stroke declined considerably over the years due to better patient selection, improvements in technology and a continuous growth in knowledge and expertise (218). In line with this conclusion, we showed that the severity and duration of cerebral desaturations decreased significantly using new-generation (differential deployment) valve types as compared to the first-generation balloon and self-expandable valves. This cannot only be ascribed to differences in valve characteristics and the specific deployment mechanism, but may be caused by a significant learning effect and advancements in valve technology. As such, an honest comparison between all used devices is not entirely possible. Based on our observations, we can only state that the continuous drive to optimize valve technology confirms the current trend that TAVI procedures have become safer, at least at the cerebral level.

This study has several limitations. First, this was a single-centre, retrospective study with a small number of patients studied. Second, general cerebral hypoperfusion cannot be

detected by NIRS-technology as $SctO_2$ is only measured in the frontal cortex. As such, it would have been interesting if other cerebral hemodynamic parameters were gained similarly using Transcranial Doppler (TCD) (219). Furthermore, diffusion-weighted Magnetic Resonance Imaging (DWI-MRI) studies already pointed out that TAVI is associated with an extremely high incidence of silent embolic cerebrovascular incidents (206, 220, 221). Unfortunately, we were not able to assess whether the observed cerebral desaturations influenced the incidence of (silent) embolic cerebrovascular incidents and the neurocognitive outcome, and if so, to compare it between different valves. Fourth, we need to acknowledge that the observed differences might be biased by a learning curve. Finally, patients treated with balloon-expandable valves had higher Euroscores which made them more vulnerable to any reduction in cardiac output, leading to deeper cerebral desaturations.

CONCLUSION

This is the first study comparing frontal cerebral oxygenation using NIRS-technology between first-generation balloon and self-expandable valves and new-generation differential deployment valves. We demonstrated that TAVI in general is accompanied by transient cerebral desaturations, particularly during BAV and valve deployment. More importantly, $SctO_2$ recovered hereafter towards baseline values in nearly all patients although two cases illustrated that any delay in the return towards baseline $SctO_2$ values should urge immediate intervention. In addition, the overall $SctO_2$ pattern was significantly different between all valve systems, in which frontal cerebral perfusion was less disturbed in differential deployment valves. Nevertheless, we strongly believe that it was the continuous evolution in valve technology which beneficial influenced the adequacy of cerebral perfusion, irrespective of the chosen valve. Still, this study was underpowered to assess the effect of (short) cerebral desaturations on neurological outcome. As such, this preliminary study should be considered as a hypothesis-generating one which raised some interesting thoughts. Hence, future and larger studies should focus on the consequence of these transient cerebral desaturations on the overall neurological outcome using advanced neuromonitoring and neurocognitive follow-up. These studies might then elucidate whether NIRS technology could play a role as guidance tool to restore or optimize $SctO_2$ during periods where cerebral perfusion is expected to become compromised.

CHAPTER 8

Postoperative cerebral oxygen desaturation increases the risk of postoperative delirium in elderly patients undergoing cardiac surgery

Eertmans W, De Deyne C, Genbrugge G, Marcus B, Bouneb S, Beran M, Fret T, Gutermann H, Boer W, Vander Laenen H, Heylen R, Mesotten D, Vanelderen P, Jans F

Submitted

ABSTRACT

Objective: Near-infrared spectroscopy (NIRS) non-invasively measures regional cerebral oxygen saturation ($SctO_2$) at the microvascular level. Intraoperative cerebral desaturations have previously been associated with a worsened neurological outcome. We specifically investigated whether postoperative cerebral desaturations are associated with the development of postoperative delirium (POD) in elderly patients undergoing cardiac surgery.

Design: Prospective observational study.

Setting: Operating theatre and ICU of a tertiary care centre.

Patients: Patients (age≥70yrs) scheduled for on-pump cardiac surgery were included between 2015 and 2017.

Interventions: NIRS monitoring using FORE-SIGHT ELITE™ technology.

Measurements and main results: Baseline $SctO_2$ was measured one day before surgery. Throughout surgery and following ICU admission, $SctO_2$ was monitored continuously up to 72hrs postoperatively. Presence of POD was assessed using the CAM-ICU. Ninety-six out of 103 included patients were used for data analysis and 29 (30%) developed POD. Intraoperative $SctO_2$ measurements were not predictive for POD. Lowest postoperative $SctO_2$ was 55±6% and 58±4% in patients with and without POD, respectively (p=0.001). Absolute and relative $SctO_2$ decrease were lower in patients with POD (13±6% and 19±9%, respectively), as compared to patients without POD (9±4% and 14±5%; p=0.002 and p=0.001, respectively). Binary logistic regression identified older age, higher Euroscore II, lower preoperative Mini-Mental Status Examination and higher absolute postoperative $SctO_2$ decrease as independent predictors for POD.

Conclusions: This study shows that a higher absolute decrease in postoperative $SctO_2$ is associated with a higher likelihood for developing POD in elderly patients undergoing cardiac surgery, independent of age, Euroscore II, and preoperative cognitive function.

INTRODUCTION

Elderly patients undergoing cardiac surgery are at risk of developing postoperative delirium (POD) (222). Delirium has been associated with a prolonged intensive care and hospital stay, long-term neurocognitive deterioration and increased mortality. Identifying predictors for the development of POD is therefore important in the prevention and early treatment of this condition (71-75). Intraoperative cerebral hypoperfusion and hypoxia have frequently been suggested as one of the main factors contributing to the development of POD after cardiac surgery (5, 223-225). Near-infrared spectroscopy (NIRS) non-invasively measures the regional cerebral oxygen saturation ($SctO_2$) at the microvascular level in the frontal lobe, thereby enabling the detection of a subtle mismatch between oxygen delivery and consumption (30). In recent years, studies reported an association between a prolonged intraoperative cerebral oxygen desaturation as measured by NIRS and neurological complications (80-83, 226). However, the incidence of these postoperative neurological complications remained unchanged when a protocol-based interventional strategy was used to restore intraoperative cerebral desaturations (85, 86). Other studies previously indicated that cerebral desaturations continue to occur in the ICU (93, 227). As such, we specifically hypothesized that there is an association between postoperative cerebral desaturation and the development of POD. Therefore, we conducted a prospective, observational study to determine the association between postoperative cerebral desaturations on the ICU and the presence of delirium after cardiac surgery.

MATERIALS AND METHODS

The study was conducted in a tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium). Patients were prospectively enrolled between June 2015 and July 2017. The study protocol was approved by the institutional Committee for Medical Ethics (15/037U) and was registered on clinicaltrials.gov (NCT02532530). Adult patients (age≥70 years) undergoing elective, on-pump aortic valve replacement, coronary artery bypass surgery or a combination of both were eligible for inclusion after informed consent. Exclusion criteria were insufficient knowledge of the Dutch language, alcohol consumption of more than two units alcohol/day, Mini-Mental State Examination (MMSE) ≤ 20 and preoperative use of antipsychotics. Patients in whom the duration of postoperative mechanical ventilation exceeded 36 hours were excluded from post-hoc data analysis. One day before surgery, the preoperative cognitive status was assessed with the MMSE (W.E.) and surgical risk assessment was based on the logistic Euroscore II.

General anaesthesia was induced using propofol (0.5mg/kg) or diazepam (0.05 – 0.1mg/kg) and sufentanil (0.5 - 1µg/kg). Tracheal intubation was facilitated by a bolus of cisatracurium (0.2mg/kg). General anaesthesia was maintained at the discretion of treating anaesthesiologist with either target-controlled infusion of propofol or sevoflurane in an O_2-air mixture accompanied with a sufentanil infusion (0.025µg/kg/h) and continuous administration of cisatracurium.

Cardiopulmonary bypass (CPB) circuit was primed with 1.0l Plasmalyte A (Baxter S.A., Lessines, Belgium) and 500ml Volulyte 6%. (Fresenius Kabi, Schelle, Belgium). Before CPB initiation, an initial dose of heparin (300U/kg) was administered followed by continuous infusion (100U/kg) during CPB to attain an activated clotting time above 480sec. Subsequently, the ascending aorta and right atrium were cannulated. Myocardial protection was provided by either anterograde or retrograde blood cardioplegia, and was repeated every 15-30 minutes. Management of CPB comprised pH-stat management with strict normocapnia, mean arterial pressure targeted at 50-80mmHg and maintenance of CPB flow between 2.4 and 2.8 L/min/m². Hemodynamic monitoring was applied according to institutional guidelines.

After sternal closure, patients were transferred to the Intensive Care Unit (ICU) where they received a continuous propofol infusion (0.3 – 4.0mg/kg/h) until extubation criteria were fulfilled (i.e. adequate oxygenation (pO_2 > 60mmHg with FiO_2 ≤ 40%); adequate ventilation (VT>5ml/kg, spontaneous respiratory rate > 8/min, end tidal pCO_2 <

50mmHg); hemodynamically stable and neurologically intact (follows verbal commands)). Postoperative analgesic management consisted of a loading dose morphine (75mg/50ml) with additional boluses on demand combined with paracetamol.

In the ICU, the presence of delirium was assessed by a trained investigator three times per day using the confusion assessment method for ICU (CAM-ICU) during the first 72 hours following ICU admission (i.e. at the end of each 8-hour lasting nurse shift), with the first one starting four hours following extubation (228). First, the sedation status was determined using the Richmond Agitation Sedation Scale (RASS), where an RASS score of at least 3 is necessary before the CAM-ICU can be performed. The CAM-ICU consists out of four features: acute change or fluctuating course of the mental condition [1], inattention [2], altered consciousness level [3] and disorganized reasoning [4]. The CAM-ICU is considered positive when the first two features are present together with either feature [3] or [4]. The RASS score was used for the differentiation between hyperactive and hypoactive delirium. Delirium was defined as either a positive CAM-ICU or the need for administration of antipsychotic medications to treat delirium (as determined by the treating ICU physicians) at any time point. Following ICU discharge, a second MMSE was performed to reassess the patients' cognitive function.

On the day before cardiac surgery, bilateral $SctO_2$ sensors (FORE-SIGHT ELITE™, CAS Medical systems, Branford, CT, USA) were placed on the patients' forehead and preoperative $SctO_2$ was determined without supplemental oxygen during 5 minutes. In the operating room, $SctO_2$ sensors were placed bilaterally (before pre-oxygenation and induction) and remained in place up to maximally 72 hours postoperatively. NIRS monitoring was stopped before 72 hours in case of earlier discharge from ICU. Throughout surgery and during the entire ICU stay, $SctO_2$ values were blinded for physicians and nursing staff. As such, clinical decisions were never based on $SctO_2$ values. All $SctO_2$ values were captured with a 2sec time-interval. Left and right $SctO_2$ values were averaged and mean $SctO_2$ values were used for further data analysis. Subsequently, lowest $SctO_2$, absolute and relative decrease in $SctO_2$ and the incidence of desaturations below absolute $SctO_2$ values of 60% and 55% as well as the incidence of desaturations below 80% of baseline were calculated for both the intraoperative and postoperative period. Intraoperative baseline $SctO_2$ was defined during a 2min period before induction of anaesthesia while breathing room air. The preoperative $SctO_2$, on the other hand, was considered as baseline $SctO_2$ for the postoperative period so that $SctO_2$ levels expected in

more or less similar conditions were represented in the best possible manner. In addition, the area under the curve (AUC) of $SctO_2$ values below 60% and 55% was calculated.

Statistical analysis was performed with SPSS version 24 (IBM Corp., Armonk, NY, USA). Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Categorical variables are shown in numbers with percentages. Continuous data are expressed as mean±SD when normally distributed, or as median with first and third quartile when non-normally distributed. Depending on normality, categorical data were compared between patients with and without delirium with a Chi-square test or Fishers' exact test and continuous data were compared using an unpaired Student T-test or a Mann-Whitney U test. Finally, significant univariate parameters ($p<0.1$) entered a forward multiple logistic regression analysis. All included variables were checked for multicollinearity in advance and variables with a variance inflation factor > 3 were excluded. The Hosmer-Lemeshow test was used for the evaluation of the goodness-of-fit of the final multivariate logistic regression model. The predictive ability of this final model was assessed by a receiver operating characteristics (ROC) curve and the area under the curve (AUC) was calculated to assess performance in predicting POD. Statistical significance was set at $p < 0.05$.

RESULTS

From June 2015 until July 2017, 103 patients scheduled for cardiac surgery with CPB were included in this prospective, observational study. Seven patients were excluded for data analysis. In two patients, the procedure was performed without CPB after patient enrolment, and in five patients, the duration of postoperative mechanical ventilation exceeded 36 hours. Ninety-six were included in the data analysis. Coronary artery bypass artery surgery, aortic valve replacement and a combined procedure were performed in 27 (28%), 32 (33%) and 37 (39%) patients, respectively. Twenty-nine patients (30%) developed POD, of whom 13 (45%) experienced the hyperactive, 12 (41%) the hypoactive and 4 (14%) the mixed form of delirium. Demographic data of both patient cohorts are presented in Table 1. Patients with POD were older, had a worse preoperative cognitive status based on MMSE and had a higher Euroscore II as compared to patients without POD. While the duration of the surgical procedure was similar in both groups ($p=0.080$), the duration of postoperative mechanical ventilation and length of ICU stay were longer in patients who developed POD (both with $p<0.001$; Table 1).

Table 1. Patient characteristics.

Parameter	Delirium (N = 29)	No delirium (N = 67)	P-value
Baseline demographics			
Male sex	19 (66)	45 (67)	1.000
Age	79 (75 – 83)	75 (73 – 79)	**0.001**
Body mass index in kg/m²	27 ± 5	28 ± 3	0.146
Cognitive status			
Preoperative MMSE	28 (24 – 29)	29 (28 – 29)	**0.012**
Postoperative MMSE	24 (23 – 29)	29 (27 – 30)	**<0.001**
Surgical procedure			0.072
Aortic valve replacement	7 (24)	20 (30)	
CABG	6 (21)	26 (39)	
Combined procedure	16 (55)	21 (31)	
Preoperative morbidity			
Previous myocardial infarct	3 (10)	9 (13)	0.752
Previous PCI	5 (17)	16 (24)	0.595
Previous cardiac surgery	1 (3)	0 (0)	0.302
Arterial hypertension	21 (72)	52 (78)	0.609
Hypercholesterolemia	19 (66)	47 (70)	0.811
COPD	6 (21)	5 (8)	0.083
Chronic Kidney Insufficiency	5 (17)	19 (28)	0.311
Atrial Fibrillation	4 (14)	12 (18)	0.770
Diabetes	9 (31)	13 (19)	0.290
Euroscore II	2.61 (1.75 – 4.68)	1.86 (1.02 – 3.37)	**0.019**
Surgery variables			
Duration of surgical procedure (minutes)	372 ± 93	342 ± 69	0.080
Duration of CPB (minutes)	149 (114 – 186)	132 (103 – 159)	0.263
Duration of aortic cross clamp (minutes)	114 ± 44	105 ± 37	0.314
Duration of reperfusion (minutes)	23 (18 – 36)	20 (13 – 25)	**0.037**
ICU variables			
Duration of mechanical ventilation (minutes)	614 (508 – 1118)	449 (377 – 627)	**<0.001**
Duration of ICU stay (hours)	74 (47 – 118)	46 (42 – 59)	**<0.001**

MMSE = Mini-Mental Status Examination; CABG = Coronary Artery Bypass Graft surgery; PCI = Percutaneous Coronary Intervention; COPD = Chronic Obstructive Pulmonary Disease; CPB = Cardio-pulmonary Bypass; ICU = Intensive Care Unit.

Intraoperative and postoperative baseline $SctO_2$ were similar (both 68±3%; p=0.824). Univariate comparison of perioperative $SctO_2$ parameters between patients with and without POD is shown in Table 2. The preoperative $SctO_2$ was not different between patients with and without POD (p=0.785). Likewise, intraoperative baseline $SctO_2$ did not differ between both groups (p=0.679). In general, none of the investigated intraoperative $SctO_2$ variables were predictive for POD (Table 2). In contrast to $SctO_2$ measured intraoperatively, lowest postoperative $SctO_2$ was lower in the group with POD (p=0.001). The absolute and relative decrease in postoperative $SctO_2$ were higher in the POD group (p=0.002 and p=0.001, respectively). Furthermore, the incidence below a postoperative absolute $SctO_2$ threshold of 55% and below 80% of postoperative baseline $SctO_2$ were higher in patients with POD (p=0.014 and p=0.023, respectively). The AUC of postoperative $SctO_2$ values below 60% and 55% were higher in patients with POD (p=0.021 and p=0.021, respectively). Hemodynamic variables monitored at ICU are displayed in Table 3. Patients with POD experienced lower SpO_2, SaO_2, PaO_2, $PaCO_2$ values throughout their ICU stay. Additionally, blood loss, transfusion of packed cells and thrombocytes and total fluid administration were all higher in the group with POD (p=0.040; p=0.001; p=0.023 and p=0.006, respectively). While postoperative mean arterial pressures were similar in both groups (p=0.186), patients with POD received more noradrenaline postoperatively (p=0.016).

Table 4 demonstrates univariate and multivariate predictors for the development of POD. Older age, a worse preoperative cognitive status based on MMSE, a higher Euroscore II and a more prominent postoperative decrease in absolute $SctO_2$ were independently associated with a higher likelihood to develop POD after cardiac surgery (AUC=0.800; p<0.001). In fact, this model predicted POD more precisely than the model without the absolute decrease in $SctO_2$ (AUC=0.762; p<0.001; Fig. 1).

Table 2. Perioperative cerebral tissue oxygenation in patients with and without postoperative delirium.

$SctO_2$ variables	Delirium (N = 29)	No delirium (N = 67)	P-value
Preoperative $SctO_2$	68 ± 3	68 ± 3	0.785
Intraoperative $SctO_2$ variables			
Baseline $SctO_2$ (%)	68 (65 – 69)	68 (66 – 70)	0.372
Lowest $SctO_2$ (%)	60 (55 – 62)	59 (55 – 62)	0.533
Absolute $SctO_2$ decrease (%)	10 (7 – 12)	9 (5 – 13)	0.533
Relative $SctO_2$ decrease (%)	13 (7 – 19)	14 (10 – 18)	0.462
AUC 60% (%.min)	0 (0 – 4)	0.23 (0 – 23)	0.350
AUC 55% (%.min)	0 (0 – 0)	0 (0 – 0)	0.639
Desaturation < 60%, n (%)	14 (48)	36 (54)	0.661
Desaturation < 55%, n (%)	8 (28)	22 (33)	0.642
Desaturation < 80% of baseline, n (%)	7 (24)	16 (24)	1.000
Postoperative $SctO_2$ variables			
Lowest $SctO_2$ (%)	56 (53 – 59)	58 (56 – 61)	**0.003**
Absolute $SctO_2$ decrease (%)	13 ± 6	9 ± 4	**0.002**
Relative $SctO_2$ decrease (%)	19 ± 9	14 ± 5	**0.001**
AUC 60 (%.min)	36 (1 – 170)	1 (0 – 80)	**0.021**
AUC 55 (%.min)	0 (0 – 2)	0 (0 – 0)	**0.045**
Desaturation < 60%, n (%)	24 (83)	38 (57)	**0.019**
Desaturation < 55%, n (%)	17 (59)	21 (31)	**0.014**
Desaturation < 80% of baseline, n (%)	16 (55)	20 (30)	**0.023**

AUC = Area under the curve; $SctO_2$ = regional cerebral tissue oxygen saturation.

Table 3. Hemodynamic variables at the Intensive Care Unit.

Variables	Delirium (N = 29)	No delirium (N = 67)	P-value
SpO_2			
Lowest, in %	73 (67–78)	80 (76–84)	**0.001**
Mean, in %	98 (97–98)	98 (97–99)	0.821
Heart rate			
Lowest, in bpm	57 (53–67)	59 (53–66)	0.817
Mean, in bpm	80 ± 9	78 ± 8	0.424
Mean arterial pressure			
Lowest, in mmHg	43 ± 6	45 ± 8	0.186
Mean, in mmHg	73 (70–79)	74 (71–78)	0.767
Cardiac output			
Lowest, in L/min	3.0 (2.5–3.5)	3.4 (3.0–3.9)	0.064
Mean, in L/min	4.4 (3.7–4.9)	4.5 (4.1–5.2)	0.340
Cardiac index			
Lowest, in L/min/m²	1.6 (1.5–1.9)	1.8 (1.6–1.9)	0.077
Mean, in L/min/m²	2.4 ± 0.4	2.4 ± 0.3	0.890
Blood variables			
Lowest haemoglobin, in g/dl	8.0 (7.1–9.2)	8.9 (7.9–10.1)	**0.002**
Lowest haematocrit, in %	25.1 (22.4–28.4)	27.4 (24.2–30.9)	**0.003**
Lowest SaO_2, in %	93.1 (77.8–94.3)	94.7 (93.6–96.3)	**<0.001**
Lowest PaO_2, in mmHg	62.1 (52.3–68.0)	70.5 (64.0–75.9)	**0.001**
Lowest $PaCO_2$, in mmHg	32.1 ± 3.7	34.3 ± 3.4	**0.004**
Highest lactate, in mmol/L	2.9 (2.2–3.5)	2.4 (2.0–3.2)	0.162
Postoperative fluid management			
Total blood transfusion, in ml	690 (400–1222)	551 (475–761)	0.409
Cell Saver, in ml	460 (0–596)	500 (409–551)	0.254
Packed cells, in ml	0 (0–353)	0 (0–0)	**0.001**
Thrombocytes, in ml	0 (0–164)	0 (0–0)	**0.023**
Plasma, in ml	0 (0–360)	0 (0–0)	0.114
Albumin, in ml	0 (0–0)	0 (0–0)	0.800
Total fluid administration, in ml	9250 (7475–11078)	7650 (6733–8939)	**0.006**
Blood loss, in ml	770 (685–1475)	720 (470–1180)	**0.040**
Total fluid balance, in ml	4407 (3358–5565)	3893 (2842–4853)	0.069
Postoperative vasopressor support			
Noradrenaline, in µg/kg	98 (38–255)	29 (8–124)	**0.016**

DISCUSSION

In elderly patients undergoing cardiac surgery, the absolute decrease in postoperative $SctO_2$ is associated with a higher likelihood to develop POD, independent of the patients' age, the Euroscore II and their preoperative cognitive function. In this way, this study adds novel insights into the potential benefit of using cerebral oximetry in the postoperative setting to improve the alertness for POD development in elderly patients undergoing cardiac surgery.

As the brain is known to consume around 20% of the total amount of oxygen supplied to the body, the cerebral function is extremely vulnerable to hypoxemia. Especially in the setting of high-risk cardiac surgery, the importance of avoiding cerebral oxygen deficiency has paved the way for cerebral oximetry as a non-invasive tool to assess the adequacy of cerebral oxygen delivery (79, 82, 92, 102). In recent years, observational studies already delivered solid evidence that a compromised cerebral oxygenation during cardio-thoracic surgery was associated with a worsened neurological outcome, thereby concluding that a persisting cerebral desaturation should be reversed at all costs (81, 83, 84). However, the clinical benefit of NIRS technology during cardiac surgery has been questioned recently as protocol-based interventions to restore acute cerebral desaturation events were not effective in reducing the incidence of postoperative neurological complications (85-87). In line with these trials, none of the investigated intraoperative $SctO_2$ variables in our study differentiated patients with POD from patients without. Correspondingly, $SctO_2$ measured on the day before surgery was not predictive for POD unlike what others have shown previously (226, 229, 230). Therefore, our data indicate that low pre- nor low intra-operative $SctO_2$ by itself is associated with a higher risk to develop POD in elderly patients undergoing cardiac surgery.

This study demonstrates that patients with POD had lower $SctO_2$ values after ICU admission. In specific, patients with POD experienced more frequently a (longer) cerebral desaturation below 55%, 60% and 80% of preoperative baseline, possibly indicating that long-lasting desaturation periods below these thresholds should be avoided. Moreover, independent of the patients' age, their surgical risk as assessed by the Euroscore II and their preoperative cognitive status based on MMSE, a higher absolute decrease in postoperative $SctO_2$ was associated with a higher likelihood for developing POD. This was the first study showing that elderly cardiac surgery patients, who developed POD, were more likely to experience potentially harmful cerebral desaturation events in the

postoperative period. In this way, this study adds novel information about the potential use of NIRS technology on the ICU to prevent POD after cardiac surgery or at least improve the alertness for this syndrome. More large-scale (multi-centre) studies are now needed to confirm our study findings. Additionally, these studies should probably incorporate a multimodal neuro- and hemodynamic monitoring strategy – together with more frequent CAM-ICU measurements – in order to explore whether the observed postoperative desaturations can provide any explanatory information for the underlying pathophysiological mechanism of POD. Due to the observational nature of this study, we can only state that low postoperative $SctO_2$ is associated with an increased risk of developing POD. Nonetheless, to determine the presence of a causal relationship between POD development and postoperative cerebral desaturation, interventional studies are indispensable.

Table 4. Univariate and multivariate logistic regression analysis for prediction of POD development after cardiac surgery.

Variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Baseline characteristics						
Age	1.17	1.05 – 1.30	0.003	1.13	1.00 – 1.27	0.049
COPD	3.24	0.90 – 11.63	0.072	-	-	-
MMSE preoperative	0.73	0.61 – 0.89	0.001	0.79	0.65 – 0.97	0.025
Euroscore II	1.23	1.02 – 1.48	0.028	1.21	1.01 – 1.45	0.044
Postoperative $SctO_2$						
Absolute $SctO_2$ decrease	1.17	1.04 – 1.31	0.006	1.17	1.02 – 1.34	0.028
Lowest $SctO_2$	0.84	0.75 – 0.94	0.003	-	-	-
Desaturation < 55%	3.10	1.26 – 7.64	0.014	-	-	-
Desaturation < 80% baseline	2.89	1.18 – 7.11	0.021	-	-	-

MMSE = Mini-Mental State Examination; COPD = Chronic Obstructive Pulmonary Disease; $SctO_2$ = regional cerebral tissue oxygen saturation.

This study is subjected to several limitations. First, this was a single-centre study with a small number of patients included. Larger multicentre studies are needed to confirm the association between postoperative cerebral desaturation and POD after cardiac surgery. Secondly, FORE-SIGHT technology, known for its absolute rather than relative accuracy, was used to measure $SctO_2$. Unfortunately, each manufacturer's device responds

differently to hemodynamic fluctuations (231, 232). Hence, study results obtained with one NIRS device might not be applicable when another NIRS device is being used which possibly explains why results from published studies are conflicting. Finally, NIRS only provides information on the frontal cortex, leaving us unaware of the adequacy of cerebral perfusion in other parts of a delirious brain. As compared to NIRS alone, occasional Transcranial Doppler sessions combined with neuroimaging techniques performed before, during and after delirium resolution would offer a better understanding of the underlying pathophysiology of delirium (223-225, 233). Moreover, the information gained with those techniques could provide us with the missing piece of the puzzle linking cerebral hypoperfusion, the subsequent cerebral ischemia and the onset of POD.

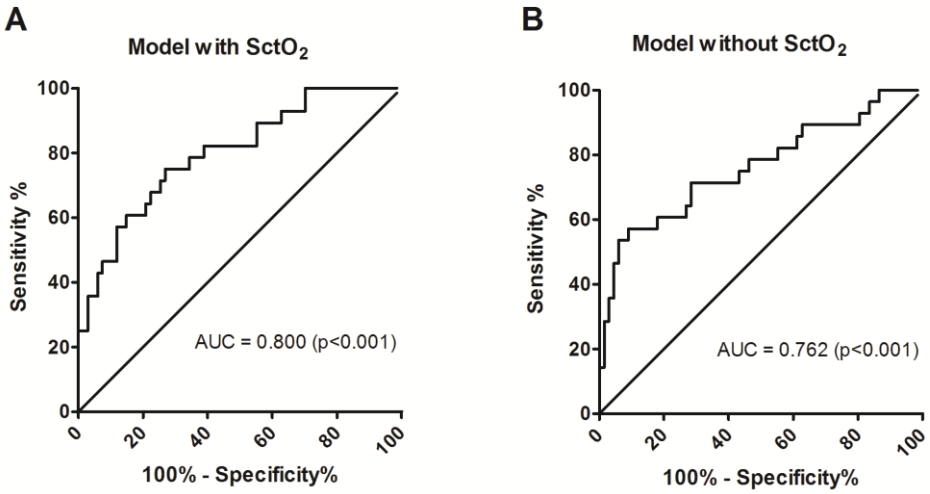


Figure 1. Prediction performance of multivariate logistic regression models with and without SctO2. The multivariate model (A) containing age, preoperative MMSE, Euroscore II and the postoperative decrease in absolute SctO2 predicted the occurrence of POD with a higher accuracy as compared to the similar model (B) without the absolute decrease in SctO2 (AUC=800 and AUC=0.762, respectively; both with p<0.001).

CONCLUSION

This study shows that a higher absolute decrease in postoperative $SctO_2$ increases the likelihood for developing POD in elderly patients undergoing cardiac surgery, independent of other identified risk factors such as age, Euroscore II and the preoperative cognitive status.

GENERAL DISCUSSION
AND
SUMMARY

GENERAL DISCUSSION

PART I: THE PROGNOSTIC ROLE OF NIRS AND BIS MONITORING IN SUCCESSFULLY RESUSCITATED OUT-OF-HOSPITAL CARDIAC ARREST PATIENTS

With the implementation of TTM and its concomitant use of sedatives, early neuroprognostication has become challenging after OHCA. To avoid any premature decision, guidelines nowadays recommend to postpone the decision to withdraw life-sustaining therapy until at least 72 hours after the return to normothermia. Most importantly, this decision should not rely on a single parameter, but should rather be based on a multimodal neuroprognostication approach. Parameters embedded in this multimodal algorithm fall under four main modalities which – whenever possible – should be used in conjunction with each other, i.e. clinical neurological examination, electrophysiology, biomarkers and brain imaging (20, 21). These parameters all have proven their prognostic value, yet, are often expensive, not continuously available or require the presence of trained physicians (9, 10, 22). Especially within the initial hours following ICU admission, bedside-available tools with the ability to continuously assess the post-anoxic status of the brain can be of substantial value when other prognostic tools are not at hand (e.g. overnight, in the weekends or in ICU environments with fewer facilities). NIRS and BIS monitoring perfectly suit in this context and have been used by others in the field of CA research. This thesis aimed to assess the prognostic performance of both monitoring systems in an OHCA patient population.

As NIRS and BIS each assess another pathophysiological process occurring after CA, with the first evaluating cerebral tissue oxygenation, and the second measuring cortical activity, we will discuss their potential use in the post-CA setting separately.

CEREBRAL OXYGEN SATURATION MONITORING IN THE POST-CA PATIENT (CHAPTER 1 AND 6)

In recent years, others previously assessed the potential of NIRS monitoring to predict neurological outcome after CA. These studies, rather small in sample size, reported higher $SctO_2$ values in patients with a good neurological outcome (38-40). In a prospective observational study, $SctO_2$ was measured continuously within the initial 48 hours following CCU admission *(Chapter 1; (126))*. As compared to previous studies, our study represented the largest and most homogeneous post-resuscitation cohort so far, which consisted exclusively out of OHCA patients. In contrast to previous studies who only

performed a mean-by-mean analysis, we additionally used a linear mixed model analysis to assess whether $SctO_2$ evolved differently over time in both outcome groups. This analysis indeed revealed that the overall course of $SctO_2$ within the investigated time frame was significantly different between patients with and without a favourable neurological outcome. More specifically, survivors followed a logarithmic $SctO_2$ curve over time while non-survivors followed a linear one. These study findings suggest that the imbalance between oxygen demand and supply seems to recover in an outcome-dependent manner. Nonetheless, one should be aware that this kind of (post-hoc) information was based on mathematical calculations (linear mixed models) that are obviously unavailable at the bedside. Moreover, the margin of this observed $SctO_2$ difference seemed to be too narrow to likely represent any clinically relevant outcome differentiation. Only during the rewarming phase, higher mean $SctO_2$ values were observed in patients with a good neurological outcome, possibly implying that the influence of rewarming on cerebral hemodynamics is different in both outcome groups. Multiple studies previously suggested that rapid rewarming eliminated any possible benefit of the neuroprotection rendered by hypothermia (120-123). As such, our results might be supportive for future studies targeting an optimal rewarming rate following treatment with TTM at 33°C. Still, based on our observational data, we were forced to conclude that $SctO_2$ by itself lacked prognostic power in the first 48 hours after OHCA. In an attempt to evaluate the contribution of $SctO_2$ in a multivariate prediction model, $SctO_2$ remained of limited value to serve in outcome prognostication *(Chapter 6)*.

Instead of using cerebral oximetry for outcome prediction, it might be clinically more valuable to use $SctO_2$ for targeting a patient-tailored mean arterial pressure (MAP). Adapted from sepsis guidelines, a MAP of 65mmHg is still being recommended for all post-CA patients (96, 234-236). Nonetheless, cerebral autoregulation is known to be absent or right-shifted in approximately one-third of all post-CA patients, thereby questioning whether the recommended MAP target is sufficiently high to avoid cerebral hypoperfusion (107, 115). Our research group previously suggested that MAPs should rather be in the range between 85 and 100mmHg to guarantee an optimal cerebral perfusion (115, 117). Interventional studies are now investigating whether neurological outcome will improve substantially when MAP levels are being targeted within these autoregulatory limits (237). Independent of the outcome of these studies, future (interventional) studies, assessing whether a patient-tailored hemodynamic optimization using an index of autoregulation (COx) would improve neurological outcome after OHCA, are of remaining interest.

BIS MONITORING IN THE POST-CA PATIENT (CHAPTER 2-3 AND 6)

Over the past decade, multiple studies – with slightly methodological differences – assessed the prognostic performance of BIS monitoring in post-CA patients (57-63, 124). Our observational data confirmed that OHCA patients experiencing low BIS and high SR values within the initial 24 hours post-CA are more prone to attain a poor neurological outcome *(Chapter 2; (168))*. However, the true novelty of our study consisted in the fact that our patient population was fully treated according to ICU guidelines (69). Unlike previous studies, NMBs were only administered in case of shivering. This treatment policy allowed us to assess whether BIS monitoring was still able to predict poor neurological outcome after OHCA even though EMG activity interference was not minimized in all study patients. In our study cohort, mean BIS ≤ 25 and mean SR ≥ 3 at respectively hour 12 and 23 predicted poor neurological outcome with a reasonable accuracy *(Chapter 2; (168))*. Interestingly, Stammet and colleagues suggested mean BIS values of 23, calculated over 12.5 hours, as optimal prognostic target for poor outcome (61). In this context, we were the first study confirming the results published by Stammet et al., even though EMG activity was not continuously supressed in our post-CA patients. Therefore, our study results do provide valuable – yet only confirmatory – information, which is not unimportant as one considers that it remains hard to validate study findings of others in clinical research (238). Another remarkable observation was the absence of any correlation between EMG and BIS ≤ 25, implying that EMG activity interference is most likely negligible below this cut-off value. In this way, BIS values ≤ 25 appear to be reliable to assist with poor outcome prognostication in OHCA patients, even without the concomitant use of (continuous) NMBs. Still, our suggested BIS and SR thresholds should be interpreted with caution since no FPR of 0% was reached. As such, we certainly do not advise to use BIS and SR as single outcome predictors. For now, our results only underline the potential of BIS monitoring to assist with early neuroprognostication. Large-scale (multicentre) studies are now paramount to investigate whether a poor neurological outcome can be predicted, even earlier than 12 hours post-CA and with a FPR of 0%, by combining BIS and SR with other highly prognostic parameters (e.g. EEG, SSEPs, NSE and MRI).

Based on the earliest publications examining the role of BIS in the field of CA research, one was convinced that BIS values equal to zero (BIS 0) at any time point were univocally associated with a poor neurological outcome (59, 62). A subsequent study showed that isolated BIS 0 values still remained early indicators of poor outcome, yet without a

specificity of 100% (58). Consistent with those results, six OHCA patients in our study cohort experienced a BIS 0 value and still attained a good neurological outcome, yielding a specificity of 84% *(Chapter 3; (159))*. Even within the first minute following circulatory arrest, cerebral ischemia is known to induce an acute failure of synaptic transmission, eventually resulting in a flat EEG (137, 138). Therefore, BIS values as low as zero are not exceptional within the initial hours following CA, but do not preclude full neurological recovery. In fact, others previously demonstrated that solely the presence of an initial flat EEG was of no prognostic value (49, 50, 139). In contrast, the persisting suppression of cortical activity 24 hours after resuscitation, but not earlier, has been shown to be a strong indicator of poor neurological outcome (44-46, 143). In our study, a prolonged duration with BIS 0 values served as a better outcome predictor as compared to a single observation. All OHCA patients experiencing BIS 0 values exceeding half an hour within the first 12 hours after admission achieved a poor neurological outcome. Likewise, Stammet et al. showed that a mean BIS below 2.4, calculated over the first 6.5 hours, was a certain predictor for poor outcome (61). Generally, our results suggest that the BIS monitor might target post-CA patients with a potentially salvageable brain already in the initial hours following ICU admission. In this way, maximal treatment efforts could be allocated in an early stage to those patients with a higher likelihood of regaining consciousness. Without contradicting resuscitation guidelines, one could perhaps decide to apply standard intensive care (and withhold therapeutic upgrades) in those patients with persistently low BIS values, until one is allowed to carry out prognostication within the time frame suggested by guidelines. Given its ease-of-use, the continuous availability and prognostic power in the initial hours following admission, a BIS device could once serve as a triage parameter in successfully resuscitated OHCA patients. Furthermore, mean BIS values and the presence of BIS 0 values were also retained in the multivariate prediction models at all time points, thereby confirming the prognostic validity of BIS monitoring once again *(Chapter 6)*.

SIMPLIFIED BIS EEG MONITORING IN THE POST-CA PATIENT (CHAPTER 4-5)

According to current resuscitation authorities, EEG should be monitored frequently in all post-CA patients, and should preferably be initiated within the initial 24 hours following CA. Whenever possible, guidelines even recommend to monitor EEG in a continuous manner (20, 21, 48). Nonetheless, hardly any (tertiary care) hospital has experience with cEEG. Besides, the continuous necessity of trained personnel – together with its financial implications – hampers its widespread use in clinical practice. It has to be stressed that

(future) research should never intend to replace standard/continuous EEG. Instead, one should better investigate whether (already available) simplified EEG tools could serve as adjunct to intermittent EEG in ICU environments where cEEG is unavailable. Over the years, some centres investigated the use of amplitude-integrated EEG (aEEG) systems in the post-CA setting to overcome some of the limitations inherent to cEEG. Although aEEG was not adequately validated against standard EEG, these centres suggested that it could serve as prognostication tool in an OHCA population. (49-52). Interestingly, the BIS monitor is currently the most widespread used simplified EEG system in the operating theatre. BIS devices process raw frontotemporal EEG traces and apply a proprietary algorithm to convert these traces into a real-time BIS value. Currently, only one commercially available BIS device, i.e. the BIS VISTA™, actually displays these raw frontotemporal EEG traces online. Before any efforts were made to assess the prognostic performance of these BIS EEG traces in post-CA patients, we – unlike previous studies – decided to validate them first against standard EEG *(Chapter 4;(169))*. In a validation study, we demonstrated a high concordance between raw BIS EEG tracings and standard EEG when we used a simple classification system with five EEG patterns (i.e. slow diffuse rhythm, burst suppression pattern, cerebral inactivity, periodic epileptic discharges (PEDs) and status epilepticus). Only 9% of all BIS EEG samples were interpreted incorrectly, all from patients with PEDs. In fact, the low sensitivity to detect these PEDs was to be expected as these focal EEG patterns probably occur outside the frontotemporal area of the BIS sensors (165). In contrast to these rather focal EEG patterns, we were the first to demonstrate the ability of the BIS VISTA™ to detect more prominent EEG patterns after CA, such as cerebral inactivity or a status epilepticus, in a reliable manner.

Unlike previous studies, we considered our efforts to validate BIS EEG as rather fundamental before further assessments concerning its usefulness in clinical practice were feasible. In fact, the use of (any) simplified EEG system can only become clinically valuable if it enables physicians to use it for prognostic or therapeutic purposes. Hence, we (retrospectively) investigated whether a prognostic value exists behind simplified BIS EEG *(Chapter 5; (239))*. Although our sample size was rather small, simplified BIS EEG traces seemed to have potential to assist with neuroprognostication. Our BIS EEG results revealed that cerebral inactivity is indicative for poor outcome, but only after the return to normothermia. This observation was comparable with our previous findings that a prolonged duration with BIS 0 values is indicative for a poor neurological outcome. In line with prior studies, the presence or at least a timely improvement towards a slow diffuse

rhythm on BIS EEG was strongly indicative for a good neurological outcome (44-46, 49, 50, 139, 140, 143, 240). Inconsistent with previous studies, we showed that a burst suppression pattern on BIS EEG was of no prognostic value at any time point (44, 45). While the variability in definitions across studies might explain this inconsistency, the influence of sedatives during TTM at 33°C provides a more plausible explanation. Regardless of the severity of cerebral injury, propofol is known to induce burst-suppression rhythms pharmacologically (171). Only burst suppression patterns, where bursts consecutively appear to be identical, have been invariably associated with poor outcome after OHCA (44, 45).

As previously alluded by others, our BIS EEG results confirmed that seizures, at any time point after CA, are associated with mortality (150, 155, 241, 242). During TTM at 33°C, the clinical motor signs of seizures are often masked by sedatives and NMBs. Consequently, about 20% of seizures in OHCA patients treated with TTM remain undiscovered without EEG monitoring (146, 148, 151). To date, whether treatment of epileptic activity with anticonvulsants improves outcome or not, remains a matter of debate. The ongoing TELLSTAR trial will likely answer this burning question in part (154). Still, the time between EEG-based diagnosis of seizures and treatment is often too wide in most ICU environments to likely have an impact on neurological outcome (153, 243). As such, it remains plausible to assume a clinical benefit of anticonvulsive treatment, at least in case of an early detection. Our validation study showed that investigators without any experience in the interpretation of EEG were also able to indicate the presence of epileptic activity *(Chapter 4;(169))*. In this way, our simplified BIS EEG system, especially when cEEG is unavailable, could serve as a screening tool for seizures in an early stage. In this way, any suspicion of epileptic activity on BIS EEG should trigger physicians to request a full EEG for confirmation. Based on our study findings, future (randomized-controlled) trials are now paramount to evaluate whether the early detection of epileptic activity using the BIS VISTA™, followed by immediate anticonvulsive therapy, will improve long-term neurological outcome after OHCA.

GENERAL LIMITATIONS AND FUTURE DIRECTIONS (PART I)

The results described in Part I of this thesis were derived from a prospective, observational study performed in a single centre *(Chapter 1-2)*. In total, 107 and 77 OHCA patients were considered as eligible to assess the prognostic value of NIRS and BIS monitoring, respectively. Although the sample size was rather small, our study cohort was

homogeneous as it exclusively consisted out of OHCA patients who were all treated with a similar post-CA protocol in a single centre setting. Secondly, all patients were treated with TTM at 33°C which does not allow us to generalize our results to patient cohorts treated with TTM at 36°C. Nonetheless, the effect of temperature by itself was considered to be limited since both survivors and non-survivors received a similar temperature regimen and moreover, time to target temperature was not different in both outcome groups.

Concerning the use of $SctO_2$ in the post-CA setting, we believe that studies with a larger sample size will most likely not gain additional information in the underlying pathophysiology responsible for the observed $SctO_2$ curves (*Chapter 1)*. Instead of using $SctO_2$ for prognostic implications, we strongly believe that future research on the use of cerebral oximetry after OHCA should focus on targeting a patient-tailored MAP based on a cerebral autoregulation index. The prognostic value of BIS monitoring, on the other hand, deserves further investigation in a multicentre trial, but then in combination with other prognostic markers recommended by current guidelines *(Chapter 2-3)*.

The remaining chapters and conclusions of Part I were based on retrospective analyses of prospectively gathered data, which are by definition vulnerable to a selection bias and missing data *(Chapter 3-6)*. Altogether, these results should be considered as hypothesis-generating and need to be (externally) validated in prospectively designed trials with a larger sample size. These trials should simultaneously assess whether our prognostic parameters (i.e. mean BIS and SR values, duration and presence of BIS 0 and BIS EEG) could once become part of the multimodal prognostication algorithm as suggested by current guidelines. In addition, the added value of using simplified BIS EEG for the early detection and treatment of epileptic activity should be investigated in future trials.

The fact that all results and the ensuing conclusions were deducted from the same study population can be considered as a methodological flaw. Especially with regard to the BIS related results, it was to be expected that BIS values bare an equivalent prognostic value as BIS EEG when they are being analysed in a similar study population. Therefore, the results presented as a whole in this thesis might be perceived as a vicious circle. An external validation cohort, either from our own or from another centre, could have offered better insights in the true prognostic value of both BIS related parameters, and should certainly be considered for future research perspectives.

Another limitation concerning our BIS related studies was the absence of blinding *(Chapter 2-5)*. This is more or less inherent to all BIS studies since values should remain unblinded to ensure an optimal signal quality. Nonetheless, BIS monitoring was never used in the decision to withdraw life-sustaining therapy. Moreover, treating physicians were always cardiologists, who are completely unfamiliar with the use and interpretation of BIS monitoring. Finally, both NIRS and BIS sensors only cover the frontal part of the cortex, thereby not providing information about other parts of the brain. Still, the area covered might provide sufficient information given that CA generally induces global brain ischemia and the frontal part is known to be most susceptible to hypoxemia.

PART II: IS THERE ANY BENEFICIAL ROLE OF NIRS TECHNOLOGY IN HIGH-RISK CARDIAC SURGERY PATIENTS? (CHAPTER 7-8)

High-risk patients undergoing cardiac surgery frequently develop cerebral ischemic events. Especially since brain hypoxia has been suggested to increase the risk for postoperative (neurological) complications, a compromised oxygen supply should be avoided at all costs (80-83, 226). Within the field of cardiac surgery, others already demonstrated that maintaining cerebral perfusion within normal ranges could be partially guided by non-invasive cerebral oximetry (79). Nowadays, there is a general consensus to use cerebral oximetry in high-risk cardiac interventions to maintain adequate cerebral oxygenation. Over the years, cerebral oximetry has been shown to be a quick responder to hemodynamic changes which might ensue into cerebral hypoperfusion (210, 211, 214, 232). Interestingly, our retrospective analysis in a Transcatheter Aortic Valve Implantation (TAVI) patient cohort confirmed the high sensitivity of $SctO_2$ to systemic fluctuations induced by rapid ventricular pacing or by valve deployment *(Chapter 7; (244))*. Although our study design was not able to link these transient cerebral desaturations with a worsening in neurological outcome, our study did reveal a beneficial influence of the continuously evolving TAVI technology on cerebral oxygenation. In this regard, cerebral oximetry might be used to determine whether technological improvements within the field of cardiac surgery, or even within other high-risk patient populations, also reduce cerebral ischemic events.

Over the years, multiple studies, both in a cardiac and non-cardiac surgery setting, have reported a positive association between perioperative cerebral oxygen desaturations and an increased neurological complication rate (80-84, 102, 226, 227, 230, 245-248). Two randomized-controlled trials recently demonstrated that 95-97% of all cerebral

desaturations, recorded during cardiac surgery, could be restored successfully using a predefined treatment strategy (249, 250). Moreover, a majority of studies even demonstrated that interventional strategies like these can be effective in improving (neurological) outcome (79, 90-92, 245, 251). Nonetheless, two large-scale studies – recently supported by two systematic reviews – failed to show any beneficial impact on neurological outcome by restoring acute cerebral desaturations during cardiac surgery (85, 86, 88, 252). Certainly from the perspective of non-users, these rather negative conclusions might have been considered as a deadly blow (253). Still, before classifying the intra-operative use of cerebral oximetry for improving clinical outcomes definitively as a 'case closed', it needs to stressed that both trials had several methodological issues (85, 86, 253, 254). First, cardiac surgery patients included in both trials had already a high risk-profile for the development of postoperative neurological complications. About 10% of the patients studied by Lei et al. underwent cardiac surgery with hypothermic circulatory arrest and 11% already had preoperative $SctO_2$ values below 50%. Moreover, Lei et al. included also patients with a known alcohol abuse or a depression. In the study by Rogers et al., on the other hand, more patients with a history of cerebral vascular disease were randomized to the intervention arm (11% vs 5% in the control group). By refusing to exclude patients with significant predisposing risk factors for postoperative neurological complications, it is probably too optimistic to assume that by optimising only one intraoperative parameter their manifestation can be prevented. Secondly, both trials reported a rather high lack of compliance to the treatment algorithm, with 9% and 18% for Lei and Rogers et al., respectively. Third, as anaesthesiologists treated patients in both the intervention and control arm, a learning effect could have biased the results. Considering these issues, we believe that future randomized-controlled trials might still provide evidence that neurological outcome can be improved by optimizing the intraoperative $SctO_2$, but only if they succeed in addressing these limitations. Besides, cerebral oximetry is an evolving technology (255). Others have used NIRS monitoring to quantify a cerebral autoregulation index (COx), representing the moving correlation coefficient between $SctO_2$ and continuous mean arterial blood pressures (256, 257). Interestingly, cerebral autoregulation is impaired in about 35% of cardiac surgery patients and the lower limit of autoregulation has been shown to vary among patients (40-90mmHg) (258, 259). As such, empirically chosen MAPs will inevitably cause patients to experience MAPs below the lower or above the upper limit of autoregulation. Based on post-hoc calculations, multiple studies showed that a persisting MAP outside the

autoregulatory limits increased the risk of acute kidney injury, stroke, and POD and even mortality (78, 260, 261). Future randomized-controlled trials are now paramount to examine whether a patient-tailored blood pressure management based on real-time cerebral autoregulation (COx) monitoring is able to improve neurological outcome following cardiac surgery.

Several reports revealed that cerebral desaturations continue to occur on the ICU (93, 227). Therefore, we specifically hypothesized that elderly patients experiencing cerebral desaturations in the postoperative period would more likely develop POD *(Chapter 8)*. To our knowledge, we are the first to demonstrate that a more pronounced absolute decrease in postoperative $SctO_2$ increases the risk to develop POD, independent of the patients' age, their surgical risk as assessed by the Euroscore II and their preoperative cognitive status based on a MMSE. In fact, our results might shed a differential light on the use of cerebral oximetry in the perioperative period in (elderly) patients undergoing cardiac surgery. Future large-scale studies are now paramount to confirm our study findings. In addition, these trials should attempt to incorporate a multimodal neuro- and hemodynamic monitoring strategy in order to investigate whether the observed postoperative cerebral desaturations can provide any explanatory information for the underlying pathophysiological mechanism of POD. On the other hand, our data also suggest that cerebral oximetry in the postoperative setting might be used to target those patients that are most vulnerable for the development of POD and for whom preventive strategies might be initiated. For now, it stands to reason that the observational nature of our study only allows us to suggest the presence of an association between lower postoperative $SctO_2$ values and the manifestation of POD.

GENERAL LIMITATIONS AND FUTURE DIRECTIONS (PART II)

The results described in part II of this thesis were derived from (1) a retrospective analysis (based on prospectively gathered $SctO_2$ data) in a TAVI patient cohort, and (2) a prospective, observational study in elderly patients undergoing on-pump cardiac surgery. Unfortunately, both studies were rather small in sample size. The reason for a small-sized TAVI cohort could be that these surgical procedures were not being reimbursed in Belgium at that time *(Chapter 7)*. A post-hoc power analysis of our observational study *(Chapter 8)* on the other hand, revealed that the power to detect a mean difference in an absolute $SctO_2$ decrease of 4% between patients with and without POD was 90% with $\alpha = 0.05$ (effect size = 0.73). Therefore, the sample size of our patient cohort undergoing on-pump

cardiac surgery was considered to be sufficient to observe relevant results. Still, large-scale trials are mandatory to confirm our results, but should simultaneously investigate whether POD can be prevented by maintaining $SctO_2$ above critical desaturation thresholds.

In contrast to previous (observational) studies, we found no association between low intraoperative $SctO_2$ values and POD *(Chapter 8)*. This might be partially explained by the fact that each commercially available NIRS device responds differently to hemodynamic fluctuations (231, 232). Most (observational) trials, showing an intraoperative benefit of cerebral oximetry, indeed used another NIRS device, i.e. the INVOS system. Hence, results can be conflicting across studies when NIRS devices are being used interchangeably (262). It stands to reason that NIRS users should always interpret published results with caution, and before implementing these in clinical practice, they should first take into account the limitations inherent to each NIRS device. On the other hand, relatively few study patients experienced long-lasting intraoperative desaturations which might have been another explanation for the fact that intraoperative $SctO_2$ was not predictive for the development of POD.

Finally, the adequacy of cerebral perfusion was solely based on $SctO_2$ measurements in both studies *(Chapter 7-8)*. Nonetheless, focal cerebral ischemic events might occur outside the frontal area covered by NIRS sensors, which therefore may remain unnoticed. Aside from using NIRS by itself, occasional Transcranial Doppler sessions combined with other neuroimaging options (e.g. functional MRI and PET scanning) could have offered additional information regarding the underlying pathophysiology of POD following cardiac surgery (219, 221, 223, 225, 263). As such, future research should ideally combine these techniques to investigate the adequacy of cerebral perfusion (but also neuronal functioning) before, during and after delirium resolution. In fact, an in-depth understanding of how and when cerebral hypoperfusion – as reflected by $SctO_2$ fluctuations – might induce POD will be essential to take full advantage of NIRS in the perioperative period following cardiac surgery.

SUMMARY

About 50% of the patients successfully resuscitated form out-of-hospital cardiac arrest (OHCA) will succumb to neurological sequelae of the post-ischemic brain injury. Guidelines strongly recommended to postpone any decisive evaluation concerning prognosis beyond 72 hours following OHCA. However, any earlier indication of neurological outcome would allow clinicians to maximize therapy in patients with a likely favourable outcome. Likewise, this would avoid futile and expensive treatment efforts in those with no reasonable chances of recovery. Unfortunately, most prognostic tools are not continuously available, rather labour-intensive and above all, they require trained personnel for a correct interpretation. Especially within the initial 24 hours following admission, tools providing a glimpse of the post-anoxic status of the brain can be of substantial value when other tools fail to do so. Given their ease of use, bedside availability and continuous and non-invasive character, Near-Infrared Spectroscopy (NIRS) and Bispectral Index (BIS) monitoring perfectly suit in this context. NIRS non-invasively quantifies the regional cerebral oxygen saturation ($SctO_2$) at the microvascular level in the frontal lobe, and BIS devices convert raw sampled frontal EEG signals into a simple and real-time BIS index ranging from 0 (iso-electric EEG) to 100 (normal electrical activity in awake subjects).

In part I of this thesis, the prognostic performance of both monitoring systems was assessed in an OHCA patient population. Although the overall course of SctO2 within the initial 48 hours after the initiation of TTM was different between patients with and without a favourable neurological outcome, we concluded that $SctO_2$ by itself lacked prognostic power (Chapter 1 and 6). In contrast to $SctO_2$ monitoring, our results demonstrated an interesting potential of the BIS monitor to assist with neuroprognostication after OHCA (Chapter 2-3 and 6). Based on our observational data, BIS values ≤ 25 at hour 12 and SR values ≥ 3 at hour 23 predicted poor neurological outcome with a high accuracy. However, the true novelty of our study consisted in the fact that our patients were fully treated according to guidelines. Unlike previous studies, neuromuscular blockers (NMBs) were only administered in case of shivering. Interestingly, the absence of any correlation between electromyographic (EMG) activity and BIS ≤ 25 was indicative for a negligible interference of EMG activity below this cut-off value. Therefore, even without the concomitant use of NMBs, BIS values ≤ 25 are still reliable to assist with poor outcome prognostication. Based on available BIS literature, one was convinced that BIS values equal to zero (BIS 0) were univocally associated with a poor neurological outcome.

Nonetheless, six OHCA patients in our study cohort experienced a BIS 0 value and still survived. In contrast, all OHCA patients experiencing BIS 0 values exceeding half an hour within 12hrs after admission attained a poor outcome. In this way, a prolonged duration with BIS 0 values served as a better outcome predictor than a single observation (Chapter 3). Altogether, our results contribute to the concept that BIS monitoring might once serve as early triage tool to target patients with a potentially salvageable brain. Aside from the numeric BIS and SR values, raw EEG traces are being displayed on some BIS devices. Based on a retrospective data analysis, we successfully validated these simplified BIS EEG traces against standard EEG, and even showed that unexperienced investigators are able to indicate the presence of seizures on BIS EEG (Chapter 4). In this way, the use of our simplified BIS EEG system, especially when continuous EEG is unavailable, could serve as a screening tool for the detection of seizures in an early stage. In chapter 5, we also investigated the prognostic potential of these raw BIS EEG traces. Based on BIS EEG, seizure development at any time point as well as a persisting cerebral inactivity were strong indicators for a poor neurological outcome. On the other hand, the presence or the evolution towards a slow diffuse rhythm was strongly associated with a good neurological outcome. Therefore, our results suggest a potential benefit of using simplified BIS EEG for outcome prognostication after OHCA, especially when continuous EEG is unavailable.

In part II of this thesis, the clinical value of NIRS monitoring was investigated in an elderly population undergoing cardiac surgery. First, we revealed a beneficial influence of the continuously evolving Transcatheter Aortic Valve Implantation (TAVI) technology on cerebral oxygenation (Chapter 7). In this regard, cerebral oximetry might be used to determine whether technological developments within the field of cardiac surgery, or even in other areas of research, preserve cerebral integrity by reducing cerebral ischemic events. Secondly, we investigated whether elderly cardiac surgery patients experiencing cerebral desaturations in the postoperative period were more likely to develop postoperative delirium (POD). Our results demonstrated that a more severe decrease in postoperative absolute $SctO_2$ increases the risk to develop POD, independent of the patients' age, their surgical risk as assessed by the Euroscore II and their preoperative cognitive status (Chapter 8). In this way, this study adds novel insights into the potential benefit of using cerebral oximetry in the postoperative setting to prevent or reduce the incidence of POD in elderly patients undergoing cardiac surgery.

SAMENVATTING

Ongeveer de helft van alle patiënten die succesvol gereanimeerd worden na een hartstilstand buiten het ziekenhuis (OHCA) zal uiteindelijk sterven aan de gevolgen van neurologische (post-ischemische) hersenschade. Momenteel raden huidige richtlijnen aan om elke vorm van prognose uit te stellen tot ten vroegste 72 uur na het optreden van een hartstilstand. Desondanks zou elke vroegere indicatie met betrekking tot de prognose van de patiënt clinici in staat stellen om de therapie te maximaliseren bij patiënten met een hoge overlevingskans. Tegelijkertijd zou men nutteloze en dure behandelingsinspanningen kunnen vermijden wanneer de kans op functioneel herstel onbestaande is. Helaas zijn de meeste prognostische parameters niet continue beschikbaar, tamelijk arbeidsintensief en bovendien hebben ze ervaren personeel nodig voor een correcte interpretatie. Parameters die in staat zijn om de post-ischemische toestand van het brein in te schatten binnen de eerste 24u na opname kunnen van toegevoegde waarde zijn, voornamelijk wanneer andere prognostische parameters hierin falen. Gezien de gebruikersvriendelijkheid, het niet-invasieve karakter en de continue inzetbaarheid, komen zowel "Near-Infrared Spectroscopie (NIRS)" als "Bispectrale index (BIS)" monitoring hiervoor in aanmerking. NIRS technologie maakt gebruik van bijna-infrarode golflengtes om de regionale cerebrale zuurstofsaturatie ($SctO_2$) te meten in de microcirculatie van de frontale cortex. BIS toestellen converteren ruwe, frontale EEG signalen naar een simpel BIS getal, gaande van 0 (iso-elektrisch EEG) tot 100 (normale EEG activiteit bij een wakkere persoon).

In het eerste deel van dit proefschrift werd de prognostische waarde van beide monitoringsystemen onderzocht in OHCA patiënten. Overheen de eerste 48u na de start van therapeutische hypothermie bleek de evolutie van $SctO_2$ te verschillen tussen patiënten met een goede en slechte neurologische uitkomst. Desondanks bleek $SctO_2$ op zichzelf van geen meerwaarde te zijn voor prognostische doeleinden (Hoofdstuk 1 en 6). In tegenstelling tot $SctO_2$ monitoring bleek BIS monitoring wel van toegevoegde waarde te zijn voor de voorspelling van neurologische uitkomst na OHCA (Hoofdstuk 2, 3 en 6). Onze observationele data toonden namelijk aan dat BIS waardes ≤ 25 op uur 12 en SR waardes ≥ 3 op uur 23 adequate voorspellers zijn voor een slechte prognose na OHCA. Het innovatieve aspect van onze studie was echter dat alle studiepatiënten behandeld werden volgens de huidige richtlijnen, dit in tegenstelling tot voorgaande BIS-studies. Onze studiepatiënten kregen namelijk enkel neuromusculaire blokkers toegediend in geval van rillingen waardoor de mogelijke interferentie van electromyografische (EMG) activiteit

op het BIS getal niet steevast onderdrukt werd. Desondanks bleek er geen correlatie bestaande te zijn tussen EMG en BIS waarden ≤ 25, hetgeen impliceerde dat de interferentie van EMG quasi verwaarloosbaar is bij BIS waarden onder deze cutoff waarde. Continue suppressie van EMG met behulp van NMB's is dus niet essentieel voor een slechte neurologische uitkomst te voorspellen met behulp van BIS monitoring. BIS waarden ≤ 25 blijken namelijk betrouwbaar te zijn en kunnen dus helpen met het voorspellen van een slechte prognose na een hartstilstand. Uitgaande van voorgaande literatuur was men er ook van overtuigd dat de aanwezigheid van een BIS waarde gelijk aan 0 (BIS 0) volstond om met zekerheid een slechte prognose te voorspellen na een hartstilstand. In ons studiecohort waren er echter zes patiënten waarbij een BIS 0 waarde opgemerkt werd, waarna deze alsnog overleefden. Alle patiënten daarentegen waarbij de duur van een BIS 0 waarde meer dan een half uur bedroeg binnen de eerste 12u na opname stierven. Een langere duur met een BIS 0 waarde blijkt dus een betere voorspellende waarde te hebben dan enkel en alleen de aanwezigheid ervan (Hoofdstuk 3). De resultaten hierboven beschreven suggereren dat in de nabije toekomst de BIS dienst zou kunnen doen als triage parameter om zo patiënten met een hoge overlevingskans te onderscheiden van patiënten met een hoogst waarschijnlijke slechte prognose. Naast de numerieke BIS en SR waarden zelf zijn de ruwe EEG tracings - die nota bene gebruikt worden om voorgenoemde waarden te berekenen - ook zichtbaar op bepaalde BIS toestellen (i.e. BIS EEG). Gebruikmakende van een retrospectieve data analyse slaagden we erin om dit BIS EEG met succes te valideren ten opzichte van standaard EEG. Daarnaast konden we zelfs aantonen dat onervaren onderzoekers ook in staat zijn om epileptische activiteit herkennen op het BIS EEG (Hoofdstuk 4). Zeker wanneer (continue) EEG niet toegankelijk is, zou gesimplificeerd BIS EEG dus kunnen fungeren als screeningsinstrument voor epileptische activiteit te detecteren in een vroeg stadium. In hoofdstuk 5 werd er onderzocht of deze BIS EEG tracings de neurologische prognose na een hartstilstand kon inschatten. Zowel de aanwezigheid van epileptische activiteit op eender welk tijdstip na hartstilstand alsook een aanhoudende cerebrale inactiviteit bleken sterke voorspellers te zijn voor een slechte neurologische uitkomst. De aanwezigheid van of de evolutie naar een traag diffuus EEG ritme was een goede indicatie voor een goede neurologische prognose (Hoofdstuk 5). Dergelijke resultaten geven duidelijk het potentieel aan van een gesimplificeerd BIS EEG instrument ter ondersteuning van het voorspellen van de neurologische prognose na een hartstilstand.

In het tweede deel van deze thesis werd de klinische relevantie van het gebruik van NIRS monitoring onderzocht in oudere patiënten die een hartoperatie ondergaan. In een eerste (retrospectieve) studie konden we aantonen dat de technologische ontwikkelingen voor de niet-invasieve implantatie van een aortaklep (TAVI) de cerebrale oxygenatie gunstig beïnvloedden. In dit opzicht zou men met behulp van cerebrale oximetrie kunnen nagaan of toekomstige ontwikkelingen binnen de cardiochirurgie, of zelfs andere onderzoeksgebieden, de cerebrale integriteit vrijwaren door ischemische events te beperken. Ten slotte gingen we in deze thesis na of oudere patiënten die een hartoperatie ondergingen, en na opname op Intensieve Zorgen frequenter cerebrale desaturaties ervoeren, een hoger risico hadden op het ontwikkelen van postoperatieve verwardheid (POD). In deze observationele studie konden we aantonen dat lagere postoperatieve $SctO_2$ waarden het risico verhogen op POD, onafhankelijk van de leeftijd, het cardiologisch risicoprofiel én de preoperatieve cognitieve toestand van de patiënt (Hoofdstuk 8). Aldus, het uitbreiden van het gebruik van cerebrale oximetrie naar Intensieve Zorgen blijkt mogelijks in staat om de incidentie van POD te reduceren bij oudere patiënten die een hartoperatie ondergaan.

REFERENCES

1. Moerman A, De Hert S. Cerebral oximetry: the standard monitor of the future? Curr Opin Anaesthesiol. 2015;28:703-9.
2. Scheeren TWL, Kuizenga MH, Maurer H, Struys M, Heringlake M. Electroencephalography and Brain Oxygenation Monitoring in the Perioperative Period. Anesth Analg. 2018.
3. Sinha N, Parnia S. Monitoring the Brain After Cardiac Arrest: a New Era. Curr Neurol Neurosci Rep. 2017;17:62.
4. Reis C, Akyol O, Araujo C, Huang L, Enkhjargal B, Malaguit J, et al. Pathophysiology and the Monitoring Methods for Cardiac Arrest Associated Brain Injury. Int J Mol Sci. 2017;18:129.
5. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. Eur J Cardiothorac Surg. 2011;40:200-7.
6. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013;39:1972-80.
7. De Deyne C, Eertmans W, Dens J. Neurological assessment of the acute cardiac care patient. In: Tubaro M, Vranckx P, Price S, C. V, editors. The ESC Textbook of Intensive and Acute Cardiovascular Care (2 ed): Oxford University Press; 2018.
8. Stocchetti N, Le Roux P, Vespa P, Oddo M, Citerio G, Andrews PJ, et al. Clinical review: neuromonitoring - an update. Crit Care. 2013;17:201.
9. Taccone F, Cronberg T, Friberg H, Greer D, Horn J, Oddo M, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care. 2014;18:202.
10. Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol. 2016;15:597-609.
11. Brady K, Hogue CW. Intraoperative hypotension and patient outcome: does "one size fit all?". Anesthesiology. 2013;119:495-7.
12. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation. 2005;67:75-80.
13. Rea TD, Eisenberg MS, Sinibaldi G, White RD. Incidence of EMS-treated out-of-hospital cardiac arrest in the United States. Resuscitation. 2004;63:17-24.
14. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010;81:1479-87.
15. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188-95.

16. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369:2197-206.
17. Stiell IG, Nichol G, Leroux BG, Rea TD, Ornato JP, Powell J, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. N Engl J Med. 2011;365:787-97.
18. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger 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;118:2452-83.
19. Dragancea I, Rundgren M, Englund E, Friberg H, Cronberg T. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. Resuscitation. 2013;84:337-42.
20. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015;95:202-22.
21. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85:1779-89.
22. Oddo M, Friberg H. Neuroprognostication after cardiac arrest in the light of targeted temperature management. Curr Opin Crit Care. 2017;23:244-50.
23. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science. 1977;198:1264-7.
24. Owen-Reece H, Smith M, Elwell CE, Goldstone JC. Near infrared spectroscopy. Br J Anaesth. 1999;82:418-26.
25. Pellicer A, Bravo Mdel C. Near-infrared spectroscopy: a methodology-focused review. Semin Fetal Neonatal Med. 2011;16:42-9.
26. Scheeren TW, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. J Clin Monit Comput. 2012;26:279-87.
27. Germon TJ, Evans PD, Barnett NJ, Wall P, Manara AR, Nelson RJ. Cerebral near infrared spectroscopy: emitter-detector separation must be increased. Br J Anaesth. 1999;82:831-7.

28. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. Anesthesiology. 2012;116:834-40.
29. Green DW, Kunst G. Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia. 2017;72 Suppl 1:48-57.
30. Ikeda K, MacLeod DB, Grocott HP, Moretti EW, 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;119:1381-92.
31. Benni PB, MacLeod D, Ikeda K, Lin HM. A validation method for near-infrared spectroscopy based tissue oximeters for cerebral and somatic tissue oxygen saturation measurements. J Clin Monit Comput. 2018;32:269-84.
32. Parnia S, Yang J, Nguyen R, Ahn A, Zhu J, Inigo-Santiago L, et al. Cerebral Oximetry During Cardiac Arrest: A Multicenter Study of Neurologic Outcomes and Survival. Crit Care Med. 2016;44:1663-74.
33. 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*. Crit Care Med. 2014;42:930-3.
34. Meex I, De Deyne C, Dens J, Scheyltjens S, Lathouwers K, Boer W, et al. Feasibility of absolute cerebral tissue oxygen saturation during cardiopulmonary resuscitation. Crit Care. 2013;17:R36.
35. Genbrugge C, Meex I, Boer W, Jans F, Heylen R, Ferdinande B, et al. Increase in cerebral oxygenation during advanced life support in out-of-hospital patients is associated with return of spontaneous circulation. Crit Care. 2015;19:112.
36. Nishiyama K, Ito N, Orita T, Hayashida K, Arimoto H, Beppu S, et al. Regional cerebral oxygen saturation monitoring for predicting interventional outcomes in patients following out-of-hospital cardiac arrest of presumed cardiac cause: A prospective, observational, multicentre study. Resuscitation. 2015;96:135-41.
37. Genbrugge C, De Deyne C, Eertmans W, Kurt A, Dirk V, Ilse M, et al. Cerebral saturation in cardiac arrest patients measured with near-infrared technology during pre-hospital advanced life support. Results from Copernicus I cohort study. Resuscitation. 2018;129:107-13.
38. 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;84:788-93.
39. Storm C, Leithner C, Krannich A, Wutzler A, Ploner CJ, Trenkmann L, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients--a prospective outcome study. Resuscitation. 2014;85:1037-41.
40. 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;85:522-6.

41. 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. N Engl J Med. 2002;346:557-63.
42. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549-56.
43. Friberg H, Cronberg T, Dunser MW, Duranteau J, Horn J, Oddo M. Survey on current practices for neurological prognostication after cardiac arrest. Resuscitation. 2015;90:158-62.
44. Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology. 2015;85:137-43.
45. Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JJ, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med. 2015;41:1264-72.
46. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJ. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med. 2012;40:2867-75.
47. Westhall E, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, Horn J, Ullen S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86:1482-90.
48. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013;39:1337-51.
49. Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med. 2006;32:836-42.
50. Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38:1838-44.
51. Oh SH, Park KN, Kim YM, Kim HJ, Youn CS, Kim SH, et al. The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation. 2013;84:200-5.
52. Oh SH, Park KN, Shon YM, Kim YM, Kim HJ, Youn CS, et al. Continuous Amplitude-Integrated Electroencephalographic Monitoring Is a Useful Prognostic Tool for Hypothermia-Treated Cardiac Arrest Patients. Circulation. 2015;132:1094-103.
53. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology. 1998;89:980-1002.

54. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev. 2014:CD003843.
55. Johansen JW. Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol. 2006;20:81-99.
56. Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. J Clin Monit Comput. 2000;16:593-6.
57. Shibata S, Imota T, Shigeomi S, Sato W, Enzan K. Use of the bispectral index during the early postresuscitative phase after out-of-hospital cardiac arrest. J Anesth. 2005;19:243-6.
58. Stammet P, Wagner DR, Gilson G, Devaux Y. Modeling serum level of s100beta and bispectral index to predict outcome after cardiac arrest. J Am Coll Cardiol. 2013;62:851-8.
59. 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 Med. 2010;36:281-8.
60. Selig C, Riegger C, Dirks B, Pawlik M, Seyfried T, Klingler W. Bispectral index (BIS) and suppression ratio (SR) as an early predictor of unfavourable neurological outcome after cardiac arrest. Resuscitation. 2014;85:221-6.
61. Stammet P, Collignon O, Werer C, Sertznig C, Devaux Y. Bispectral index to predict neurological outcome early after cardiac arrest. Resuscitation. 2014;85:1674-80.
62. 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;80:437-42.
63. 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;81:1133-7.
64. Hoedemaekers CW, Abdo WF. Bispectral index for prognostication after cardiac arrest: the holy grail at last? Crit Care Med. 2014;42:1312-3.
65. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology. 2003;99:9-17.
66. Salciccioli JD, Cocchi MN, Rittenberger JC, Peberdy MA, Ornato JP, Abella BS, et al. Continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients. Resuscitation. 2013;84:1728-33.
67. Price D, Kenyon NJ, Stollenwerk N. A fresh look at paralytics in the critically ill: real promise and real concern. Ann Intensive Care. 2012;2:43.
68. Lascarrou JB, Le Gouge A, Dimet J, Lacherade JC, Martin-Lefevre L, Fiancette M, et al. Neuromuscular blockade during therapeutic hypothermia after cardiac arrest: observational study of neurological and infectious outcomes. Resuscitation. 2014;85:1257-62.

69. Murray MJ, DeBlock H, Erstad B, Gray A, Jacobi J, Jordan C, et al. Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Crit Care Med. 2016;44:2079-103.
70. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367:30-9.
71. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27:1892-900.
72. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med. 2004;32:955-62.
73. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306-16.
74. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement. 2016;12:766-75.
75. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr., et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291:1753-62.
76. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013;21:1190-222.
77. Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. Crit Care Clin. 2017;33:461-519.
78. Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, et al. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. Br J Anaesth. 2014;113:1009-17.
79. 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. Anesth Analg. 2007;104:51-8.
80. 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. Heart Surg Forum. 2004;7:E376-81.
81. de Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2011;25:95-104.
82. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM, 3rd, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg. 2009;87:36-44.

83. Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 2004;18:552-8.
84. 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;108:623-9.
85. Lei L, Katznelson R, Fedorko L, Carroll J, Poonawala H, Machina M, et al. Cerebral oximetry and postoperative delirium after cardiac surgery: a randomised, controlled trial. Anaesthesia. 2017;72:1456-66.
86. Rogers CA, Stoica S, Ellis L, Stokes EA, Wordsworth S, Dabner L, et al. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. Br J Anaesth. 2017;119:384-93.
87. Kok WF, van Harten AE, Koene BM, Mariani MA, Koerts J, Tucha O, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass*. Anaesthesia. 2014;69:613-22.
88. Serraino GF, Murphy GJ. Effects of cerebral near-infrared spectroscopy on the outcome of patients undergoing cardiac surgery: a systematic review of randomised trials. BMJ Open. 2017;7:e016613.
89. Zorrilla-Vaca A, Healy R, Grant MC, Joshi B, Rivera-Lara L, Brown C, et al. Intraoperative cerebral oximetry-based management for optimizing perioperative outcomes: a meta-analysis of randomized controlled trials. Can J Anaesth. 2018;65:529-42.
90. Colak Z, Borojevic M, Bogovic A, Ivancan V, Biocina B, Majeric-Kogler V. Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: a randomized, prospective study. Eur J Cardiothorac Surg. 2015;47:447-54.
91. Mohandas BS, Jagadeesh AM, Vikram SB. Impact of monitoring cerebral oxygen saturation on the outcome of patients undergoing open heart surgery. Ann Card Anaesth. 2013;16:102-6.
92. Palmbergen WA, van Sonderen A, Keyhan-Falsafi AM, Keunen RW, Wolterbeek R. Improved perioperative neurological monitoring of coronary artery bypass graft patients reduces the incidence of postoperative delirium: the Haga Brain Care Strategy. Interact Cardiovasc Thorac Surg. 2012;15:671-7.
93. Greenberg SB, Murphy G, Alexander J, Fasanella R, Garcia A, Vender J. Cerebral desaturation events in the intensive care unit following cardiac surgery. J Crit Care. 2013;28:270-6.
94. Chan MJ, Chung T, Glassford NJ, Bellomo R. Near-Infrared Spectroscopy in Adult Cardiac Surgery Patients: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth. 2017;31:1155-65.

95. Deakin CD, Nolan JP, Soar J, Sunde K, Koster RW, Smith GB, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. Resuscitation. 2010;81:1305-52.
96. 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):S768-86.
97. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1:480-4.
98. Brain Resuscitation Clinical Trial ISG. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med. 1986;314:397-403.
99. Grenvik A, Safar P. Brain failure and resuscitation. New York: Churchill Livingstone; 1981. x, 268 p. p.
100. Verbeke G MG. Linear mixed models for longitudinal data. 1st ed. ed2000.
101. Lemiale V, Huet O, Vigue B, Mathonnet A, Spaulding C, Mira JP, et al. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. Resuscitation. 2008;76:17-24.
102. Fischer GW, Lin HM, Krol M, Galati MF, Di Luozzo G, Griepp RB, et al. Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. J Thorac Cardiovasc Surg. 2011;141:815-21.
103. Bickler PE, Feiner JR, Rollins MD. Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. Anesth Analg. 2013;117:813-23.
104. Gur RE, Gur RC. Gender differences in regional cerebral blood flow. Schizophr Bull. 1990;16:247-54.
105. Esposito G, Van Horn JD, Weinberger DR, Berman KF. Gender differences in cerebral blood flow as a function of cognitive state with PET. J Nucl Med. 1996;37:559-64.
106. Semenas E, Nozari A, Sharma HS, Basu S, Rubertsson S, Wiklund L. Sex differences in cerebral injury after severe haemorrhage and ventricular fibrillation in pigs. Acta Anaesthesiol Scand. 2010;54:343-53.
107. 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;32:128-32.
108. Bisschops LL, van der Hoeven JG, Hoedemaekers CW. Effects of prolonged mild hypothermia on cerebral blood flow after cardiac arrest. Crit Care Med. 2012;40:2362-7.
109. Ames A, 3rd, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia. II. The no-reflow phenomenon. Am J Pathol. 1968;52:437-53.
110. Chiang J, Kowada M, Ames A, 3rd, Wright RL, Majno G. Cerebral ischemia. III. Vascular changes. Am J Pathol. 1968;52:455-76.
111. Fischer M, Hossmann KA. No-reflow after cardiac arrest. Intensive Care Med. 1995;21:132-41.

112. Bisschops LL, Pop GA, Teerenstra S, Struijk PC, van der Hoeven JG, Hoedemaekers CW. Effects of viscosity on cerebral blood flow after cardiac arrest. Crit Care Med. 2014;42:632-7.
113. Davis DH, Sundt TM, Jr. Relationship of cerebral blood flow to cardiac output, mean arterial pressure, blood volume, and alpha and beta blockade in cats. J Neurosurg. 1980;52:745-54.
114. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke. 1997;28:1569-73.
115. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets? Resuscitation. 2015;90:121-6.
116. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol. 2002;40:2110-6.
117. Ameloot K, Meex I, Genbrugge C, Jans F, Boer W, Verhaert D, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study. Resuscitation. 2015;91:56-62.
118. Ameloot K, Meex I, Genbrugge C, Jans F, Malbrain M, Mullens W, et al. Accuracy of continuous thermodilution cardiac output monitoring by pulmonary artery catheter during therapeutic hypothermia in post-cardiac arrest patients. Resuscitation. 2014;85:1263-8.
119. Bisschops LL, Hoedemaekers CW, Simons KS, van der Hoeven JG. Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest. Crit Care Med. 2010;38:1542-7.
120. Maxwell WL, Watson A, Queen R, Conway B, Russell D, Neilson M, et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. J Neurotrauma. 2005;22:873-84.
121. Alam HB, Rhee P, Honma K, Chen H, Ayuste EC, Lin T, et al. Does the rate of rewarming from profound hypothermic arrest influence the outcome in a swine model of lethal hemorrhage? J Trauma. 2006;60:134-46.
122. Kawahara F, Kadoi Y, Saito S, Goto F, Fujita N. Slow rewarming improves jugular venous oxygen saturation during rewarming. Acta Anaesthesiol Scand. 2003;47:419-24.
123. Lavinio A, Timofeev I, Nortje J, Outtrim J, Smielewski P, Gupta A, et al. Cerebrovascular reactivity during hypothermia and rewarming. Br J Anaesth. 2007;99:237-44.
124. Seder DB, Dziodzio J, Smith KA, Hickey P, Bolduc B, Stone P, et al. Feasibility of bispectral index monitoring to guide early post-resuscitation cardiac arrest triage. Resuscitation. 2014;85:1030-6.

125. 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. Crit Care Med. 2014;42:1204-12.
126. Genbrugge C, Eertmans W, Meex I, Van Kerrebroeck M, Daems N, Creemers A, et al. What is the value of regional cerebral saturation in post-cardiac arrest patients? A prospective observational study. Crit Care. 2016;20:327.
127. Riker RR, Stone PC, Jr., May T, McCrum B, Fraser GL, Seder D. Initial bispectral index may identify patients who will awaken during therapeutic hypothermia after cardiac arrest: a retrospective pilot study. Resuscitation. 2013;84:794-7.
128. Perman SM, Kirkpatrick JN, Reitsma AM, Gaieski DF, Lau B, Smith TM, et al. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia*. Crit Care Med. 2012;40:719-24.
129. Cronberg T, Horn J, Kuiper MA, Friberg H, Nielsen N. A structured approach to neurologic prognostication in clinical cardiac arrest trials. Scand J Trauma Resusc Emerg Med. 2013;21:45.
130. Kamps MJ, Horn J, Oddo M, Fugate JE, Storm C, Cronberg T, et al. Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature. Intensive Care Med. 2013;39:1671-82.
131. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67:301-7.
132. Mathew JP, Weatherwax KJ, East CJ, White WD, Reves JG. Bispectral analysis during cardiopulmonary bypass: the effect of hypothermia on the hypnotic state. J Clin Anesth. 2001;13:301-5.
133. Honan D, Doherty D, Frizelle H. A comparison of the effects on bispectral index of mild vs. moderate hypothermia during cardiopulmonary bypass. Eur J Anaesthesiol. 2006;23:385-90.
134. Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, Toornvliet AC, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. Ann Neurol. 2012;71:206-12.
135. Hirsch KG, Mlynash M, Jansen S, Persoon S, Eyngorn I, Krasnokutsky MV, et al. Prognostic value of a qualitative brain MRI scoring system after cardiac arrest. J Neuroimaging. 2015;25:430-7.
136. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S, Quality Standards Subcommittee of the American Academy of N. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67:203-10.
137. Hofmeijer J, van Putten MJ. Ischemic cerebral damage: an appraisal of synaptic failure. Stroke. 2012;43:607-15.

138. van Dijk JG, Thijs RD, van Zwet E, Tannemaat MR, van Niekerk J, Benditt DG, et al. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. Brain. 2014;137:576-85.
139. Jorgensen EO, Holm S. The natural course of neurological recovery following cardiopulmonary resuscitation. Resuscitation. 1998;36:111-22.
140. Crepeau AZ, Rabinstein AA, Fugate JE, Mandrekar J, Wijdicks EF, White RD, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: prognostic and clinical value. Neurology. 2013;80:339-44.
141. Tjepkema-Cloostermans MC, Hofmeijer J, Beishuizen A, Hom HW, Blans MJ, Bosch FH, et al. Cerebral Recovery Index: Reliable Help for Prediction of Neurologic Outcome After Cardiac Arrest. Crit Care Med. 2017;45:e789-e97.
142. Hofmeijer J, van Putten MJ. EEG in postanoxic coma: Prognostic and diagnostic value. Clin Neurophysiol. 2016;127:2047-55.
143. Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ. Electroencephalogram predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia. Crit Care Med. 2015;43:159-67.
144. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62:1743-8.
145. Knight WA, Hart KW, Adeoye OM, Bonomo JB, Keegan SP, Ficker DM, et al. The incidence of seizures in patients undergoing therapeutic hypothermia after resuscitation from cardiac arrest. Epilepsy Res. 2013;106:396-402.
146. Legriel S, Hilly-Ginoux J, Resche-Rigon M, Merceron S, Pinoteau J, Henry-Lagarrigue M, et al. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. Resuscitation. 2013;84:343-50.
147. Lybeck A, Friberg H, Aneman A, Hassager C, Horn J, Kjaergaard J, et al. Prognostic significance of clinical seizures after cardiac arrest and target temperature management. Resuscitation. 2017;114:146-51.
148. Legriel S, Bruneel F, Sediri H, Hilly J, Abbosh N, Lagarrigue MH, et al. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care. 2009;11:338-44.
149. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia. 1994;35:27-34.
150. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. Neurocrit Care. 2012;16:114-22.
151. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation. 2012;83:840-7.

152. Hirsch LJ, Claassen J. The current state of treatment of status epilepticus. Curr Neurol Neurosci Rep. 2002;2:345-56.
153. Fujikawa DG. Prolonged seizures and cellular injury: understanding the connection. Epilepsy Behav. 2005;7 Suppl 3:S3-11.
154. Ruijter BJ, van Putten MJ, Horn J, Blans MJ, Beishuizen A, van Rootselaar AF, et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials. 2014;15:433.
155. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology. 2009;72:744-9.
156. Friberg H, Westhall E, Rosen I, Rundgren M, Nielsen N, Cronberg T. Clinical review: Continuous and simplified electroencephalography to monitor brain recovery after cardiac arrest. Crit Care. 2013;17:233.
157. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. Anesth Analg. 2009;109:506-23.
158. Crepeau AZ, Fugate JE, Mandrekar J, White RD, Wijdicks EF, Rabinstein AA, et al. Value analysis of continuous EEG in patients during therapeutic hypothermia after cardiac arrest. Resuscitation. 2014;85:785-9.
159. Eertmans W, Genbrugge C, Haesevoets G, Dens J, Boer W, Jans F, et al. Recorded time periods of bispectral index values equal to zero predict neurological outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21:221.
160. Fernandez-Torre JL, Hernandez-Hernandez MA. Utility of bilateral Bispectral index (BIS) monitoring in a comatose patient with focal nonconvulsive status epilepticus. Seizure. 2012;21:61-4.
161. Dahaba AA, Liu DW, Metzler H. Bispectral index (BIS) monitoring of acute encephalitis with refractory, repetitive partial seizures (AERRPS). Minerva Anestesiol. 2010;76:298-301.
162. Chamorro C, Romera MA, Balandin B, Valdivia M. Nonconvulsive status and bispectral index. Crit Care Med. 2008;36:2218-9.
163. Ochiai K, Shiraishi A, Otomo Y, Koido Y, Kanemura T, Honma M. Increasing or fluctuating bispectral index values during post-resuscitation targeted temperature management can predict clinical seizures after rewarming. Resuscitation. 2017;114:106-12.
164. Karakis I, Montouris GD, Otis JA, Douglass LM, Jonas R, Velez-Ruiz N, et al. A quick and reliable EEG montage for the detection of seizures in the critical care setting. J Clin Neurophysiol. 2010;27:100-5.
165. Kolls BJ, Husain AM. Assessment of hairline EEG as a screening tool for nonconvulsive status epilepticus. Epilepsia. 2007;48:959-65.
166. Young GB, Sharpe MD, Savard M, Al Thenayan E, Norton L, Davies-Schinkel C. Seizure detection with a commercially available bedside EEG monitor and the subhairline montage. Neurocrit Care. 2009;11:411-6.

167. You KM, Suh GJ, Kwon WY, Kim KS, Ko SB, Park MJ, et al. Epileptiform discharge detection with the 4-channel frontal electroencephalography during post-resuscitation care. Resuscitation. 2017;117:8-13.
168. Eertmans W, Genbrugge C, Vander Laenen M, Boer W, Mesotten D, Dens J, et al. The prognostic value of bispectral index and suppression ratio monitoring after out-of-hospital cardiac arrest: a prospective observational study. Ann Intensive Care. 2018;8:34.
169. Haesen J, Eertmans W, Genbrugge C, Meex I, Demeestere J, Vander Laenen M, et al. The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients. Resuscitation. 2018;126:179-84.
170. Elmer J, Rittenberger JC, Faro J, Molyneaux BJ, Popescu A, Callaway CW, et al. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. Ann Neurol. 2016;80:175-84.
171. Amorim E, Rittenberger JC, Zheng JJ, Westover MB, Baldwin ME, Callaway CW, et al. Continuous EEG monitoring enhances multimodal outcome prediction in hypoxic-ischemic brain injury. Resuscitation. 2016;109:121-6.
172. Geocadin RG, Peberdy MA, Lazar RM. Poor survival after cardiac arrest resuscitation: a self-fulfilling prophecy or biologic destiny?*. Crit Care Med. 2012;40:979-80.
173. Oddo M. Prognostication of coma after cardiac arrest: think positive. Resuscitation. 2013;84:855-6.
174. Choi SP, Park KN, Park HK, Kim JY, Youn CS, Ahn KJ, et al. Diffusion-weighted magnetic resonance imaging for predicting the clinical outcome of comatose survivors after cardiac arrest: a cohort study. Crit Care. 2010;14:R17.
175. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004;30:2126-8.
176. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J. 2006;27:2840-5.
177. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation. 1997;96:3308-13.
178. Hayakawa K, Tasaki O, Hamasaki T, Sakai T, Shiozaki T, Nakagawa Y, et al. Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: the Utstein Osaka Project. Resuscitation. 2011;82:874-80.
179. Okada K, Ohde S, Otani N, Sera T, Mochizuki T, Aoki M, et al. Prediction protocol for neurological outcome for survivors of out-of-hospital cardiac arrest treated with targeted temperature management. Resuscitation. 2012;83:734-9.

180. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, et al. A novel scoring system for predicting the neurologic prognosis prior to the initiation of induced hypothermia in cases of post-cardiac arrest syndrome: the CAST score. Scand J Trauma Resusc Emerg Med. 2017;25:49.
181. Maupain C, Bougouin W, Lamhaut L, Deye N, Diehl JL, Geri G, et al. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J. 2016;37:3222-8.
182. van Buuren S G-OK. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45.
183. Graham JO, AE. ; Gilreath, TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8:206-13.
184. Zou HH, T. Regularization and variable selection via the elastic net. JR Statist Soc B 2005;67:301-20.
185. Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care. 2010;14:R173.
186. Dragancea I, Horn J, Kuiper M, Friberg H, Ullen S, Wetterslev J, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33 degrees C versus 36 degrees C: Results from a randomised controlled clinical trial. Resuscitation. 2015;93:164-70.
187. Stammet P, Collignon O, Hassager C, Wise MP, Hovdenes J, Aneman A, et al. Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33 degrees C and 36 degrees C. J Am Coll Cardiol. 2015;65:2104-14.
188. Hirsch KG, Mlynash M, Eyngorn I, Pirsaheli R, Okada A, Komshian S, et al. Multi-Center Study of Diffusion-Weighted Imaging in Coma After Cardiac Arrest. Neurocrit Care. 2016;24:82-9.
189. Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital 'sudden' cardiac arrest. Resuscitation. 2002;52:235-45.
190. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010;3:200-7.
191. Kroupa J, Knot J, Ulman J, Bednar F, Dohnalova A, Motovska Z. Characteristics and Survival Determinants in Patients After Out-of-Hospital Cardiac Arrest in The Era of 24/7 Coronary Intervention Facilities. Heart Lung Circ. 2017;26:799-807.
192. Parry M, Danielson K, Brennenstuhl S, Drennan IR, Morrison LJ. The association between diabetes status and survival following an out-of-hospital cardiac arrest: A retrospective cohort study. Resuscitation. 2017;113:21-6.
193. Mahapatra S, Bunch TJ, White RD, Hodge DO, Packer DL. Sex differences in outcome after ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation. 2005;65:197-202.

194. Rea TD, Eisenberg MS, Becker LJ, Murray JA, Hearne T. Temporal trends in sudden cardiac arrest: a 25-year emergency medical services perspective. Circulation. 2003;107:2780-5.
195. Lee TR, Kang MJ, Cha WC, Shin TG, Sim MS, Jo IJ, et al. Better lactate clearance associated with good neurologic outcome in survivors who treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Crit Care. 2013;17:R260.
196. Hasper D, von Haehling S, Storm C, Jorres A, Schefold JC. Changes in serum creatinine in the first 24 hours after cardiac arrest indicate prognosis: an observational cohort study. Crit Care. 2009;13:R168.
197. Wiberg S, Hassager C, Stammet P, Winther-Jensen M, Thomsen JH, Erlinge D, et al. Single versus Serial Measurements of Neuron-Specific Enolase and Prediction of Poor Neurological Outcome in Persistently Unconscious Patients after Out-Of-Hospital Cardiac Arrest - A TTM-Trial Substudy. PLoS One. 2017;12:e0168894.
198. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774-81.
199. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-607.
200. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
201. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370:1790-8.
202. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106:3006-8.
203. Rodes-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol. 2012;9:15-29.
204. Fanning JP, Platts DG, Walters DL, Fraser JF. Transcatheter aortic valve implantation (TAVI): valve design and evolution. Int J Cardiol. 2013;168:1822-31.
205. Nuis RJ, Van Mieghem NM, Schultz CJ, Moelker A, van der Boon RM, van Geuns RJ, et al. Frequency and causes of stroke during or after transcatheter aortic valve implantation. Am J Cardiol. 2012;109:1637-43.
206. Rodes-Cabau J, Dumont E, Boone RH, Larose E, Bagur R, Gurvitch R, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol. 2011;57:18-28.
207. Sack S, Kahlert P, Khandanpour S, Naber C, Philipp S, Mohlenkamp S, et al. Revival of an old method with new techniques: balloon aortic valvuloplasty of the calcified aortic stenosis in the elderly. Clin Res Cardiol. 2008;97:288-97.

208. Selle A, Figulla HR, Ferrari M, Rademacher W, Goebel B, Hamadanchi A, et al. Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol. 2014;103:902-11.
209. De Deyne C, Meex I, Jans F, Engelen K, Gutermann H, Dens J. Non-invasive monitoring of cerebral perfusion during transcatheter aortic valve implantation procedure. Am J Cardiol. 2013;111:302.
210. Argiriadou H, Anastasiadis K, Karapanagiotidis G, Papakonstantinou C. Subclinical decline in cerebral oxymetry saturation during rapid pacing in transfemoral aortic valve replacement. Ann Thorac Surg. 2010;90:1023.
211. Brodt J, Vladinov G, Castillo-Pedraza C, Cooper L, Maratea E. Changes in cerebral oxygen saturation during transcatheter aortic valve replacement. J Clin Monit Comput. 2016;30:649-53.
212. Meredith IT, Hood KL, Haratani N, Allocco DJ, Dawkins KD. Boston Scientific Lotus valve. EuroIntervention. 2012;8 Suppl Q:Q70-4.
213. Grube E, Naber C, Abizaid A, Sousa E, Mendiz O, Lemos P, et al. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. JACC Cardiovasc Interv. 2011;4:751-7.
214. Paarmann H, Heringlake M, Heinze H, Hanke T, Sier H, Karsten J, et al. Non-invasive cerebral oxygenation reflects mixed venous oxygen saturation during the varying haemodynamic conditions in patients undergoing transapical transcatheter aortic valve implantation. Interact Cardiovasc Thorac Surg. 2012;14:268-72.
215. Alassar A, Soppa G, Edsell M, Rich P, Roy D, Chis Ster I, et al. Incidence and mechanisms of cerebral ischemia after transcatheter aortic valve implantation compared with surgical aortic valve replacement. Ann Thorac Surg. 2015;99:802-8.
216. Meredith IT, Walters DL, Dumonteil N, Worthley SG, Tchetche D, Manoharan G, et al. 1-Year Outcomes With the Fully Repositionable and Retrievable Lotus Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results of the REPRISE II Study. JACC Cardiovasc Interv. 2016;9:376-84.
217. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374:1609-20.
218. Athappan G, Gajulapalli RD, Sengodan P, Bhardwaj A, Ellis SG, Svensson L, et al. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. J Am Coll Cardiol. 2014;63:2101-10.
219. Erdoes G, Basciani R, Huber C, Stortecky S, Wenaweser P, Windecker S, et al. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. Eur J Cardiothorac Surg. 2012;41:778-83.

220. Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol. 2010;55:1427-32.
221. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation. 2010;121:870-8.
222. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, et al. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial. Anesthesiology. 2016;124:362-8.
223. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. Psychiatry Clin Neurosci. 2003;57:337-9.
224. Fong TG, Bogardus ST, Jr., Daftary A, Auerbach E, Blumenfeld H, Modur S, et al. Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT. J Gerontol A Biol Sci Med Sci. 2006;61:1294-9.
225. Caplan GA, Lan Z, Newton L, Kvelde T, McVeigh C, Hill MA. Transcranial Doppler to measure cerebral blood flow in delirium superimposed on dementia. A cohort study. J Am Med Dir Assoc. 2014;15:355-60.
226. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. Crit Care. 2011;15:R218.
227. Cerebral O, Neurological Outcomes Following Critical Illness Research G, Canadian Critical Care Trials G, Wood MD, Maslove DM, Muscedere JG, et al. Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: A prospective observational study. J Crit Care. 2017;41:289-95.
228. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703-10.
229. Morimoto Y, Yoshimura M, Utada K, Setoyama K, Matsumoto M, Sakabe T. Prediction of postoperative delirium after abdominal surgery in the elderly. J Anesth. 2009;23:51-6.
230. Heringlake M, Garbers C, Kabler JH, Anderson I, Heinze H, Schon J, et al. Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. Anesthesiology. 2011;114:58-69.
231. Tomlin KL, Neitenbach AM, Borg U. Detection of critical cerebral desaturation thresholds by three regional oximeters during hypoxia: a pilot study in healthy volunteers. BMC Anesthesiol. 2017;17:6.

232. Moerman A, Vandenplas G, Bove T, Wouters PF, De Hert SG. Relation between mixed venous oxygen saturation and cerebral oxygen saturation measured by absolute and relative near-infrared spectroscopy during off-pump coronary artery bypass grafting. Br J Anaesth. 2013;110:258-65.
233. Omiya H, Yoshitani K, Yamada N, Kubota Y, Takahashi K, Kobayashi J, et al. Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. Can J Anaesth. 2015;62:595-602.
234. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S465-82.
235. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43:304-77.
236. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45:486-552.
237. Ameloot K, De Deyne C, Ferdinande B, Dupont M, Palmers PJ, Petit T, et al. Mean arterial pressure of 65 mm Hg versus 85-100 mm Hg in comatose survivors after cardiac arrest: Rationale and study design of the Neuroprotect post-cardiac arrest trial. Am Heart J. 2017;191:91-8.
238. Niven DJ, McCormick TJ, Straus SE, Hemmelgarn BR, Jeffs L, Barnes TRM, et al. Reproducibility of clinical research in critical care: a scoping review. BMC Med. 2018;16:26.
239. Eertmans W, Genbrugge C, Haesen J, Drieskens C, Demeestere J, Vander Laenen M, et al. The Prognostic Value of Simplified EEG in Out-of-Hospital Cardiac Arrest Patients. Neurocrit Care. 2018.
240. Tjepkema-Cloostermans MC, Hofmeijer J, Beishuizen A, Hom HW, Blans MJ, Bosch FH, et al. Cerebral Recovery Index: Reliable Help for Prediction of Neurologic Outcome After Cardiac Arrest. Crit Care Med. 2017;45:e789-e97.
241. Hofmeijer J, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, van Putten MJ. Unstandardized treatment of electroencephalographic status epilepticus does not improve outcome of comatose patients after cardiac arrest. Front Neurol. 2014;5:39.
242. Rossetti AO, Logroscino G, Liaudet L, Ruffieux C, Ribordy V, Schaller MD, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology. 2007;69:255-60.
243. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. J Neurosci. 2005;25:7724-33.

244. Eertmans W, Genbrugge C, Fret T, Beran M, Engelen K, Gutermann H, et al. Influence of continuously evolving transcatheter aortic valve implantation technology on cerebral oxygenation. J Clin Monit Comput. 2017;31:1133-41.
245. 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. Anesth Analg. 2005;101:740-7.
246. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S, et al. Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. Eur J Anaesthesiol. 2007;24:59-65.
247. Lin R, Zhang F, Xue Q, Yu B. Accuracy of regional cerebral oxygen saturation in predicting postoperative cognitive dysfunction after total hip arthroplasty: regional cerebral oxygen saturation predicts POCD. J Arthroplasty. 2013;28:494-7.
248. Kim J, Shim JK, Song JW, Kim EK, Kwak YL. Postoperative Cognitive Dysfunction and the Change of Regional Cerebral Oxygen Saturation in Elderly Patients Undergoing Spinal Surgery. Anesth Analg. 2016;123:436-44.
249. Subramanian B, Nyman C, Fritock M, Klinger RY, Sniecinski R, Roman P, et al. A Multicenter Pilot Study Assessing Regional Cerebral Oxygen Desaturation Frequency During Cardiopulmonary Bypass and Responsiveness to an Intervention Algorithm. Anesth Analg. 2016;122:1786-93.
250. Deschamps A, Hall R, Grocott H, Mazer CD, Choi PT, Turgeon AF, et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery: A Randomized Controlled Feasibility Trial. Anesthesiology. 2016;124:826-36.
251. Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, et al. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. PLoS One. 2012;7:e37410.
252. Yu Y, Zhang K, Zhang L, Zong H, Meng L, Han R. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. Cochrane Database Syst Rev. 2018;1:CD010947.
253. Kunst G, Milan Z. Cerebral oximetry: another blow to non-invasive monitoring? Anaesthesia. 2017;72:1435-8.
254. Lewis C, Hogue CW. Lack of benefit of near-infrared spectroscopy monitoring for improving patient outcomes. Case closed? Br J Anaesth. 2017;119:347-9.
255. Moerman A, De Hert S. Recent advances in cerebral oximetry. Assessment of cerebral autoregulation with near-infrared spectroscopy: myth or reality? F1000Res. 2017;6:1615.
256. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, et al. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. Stroke. 2007;38:2818-25.

257. 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;41:1951-6.
258. Moerman AT, Vanbiervliet VM, Van Wesemael A, Bouchez SM, Wouters PF, De Hert SG. Assessment of Cerebral Autoregulation Patterns with Near-infrared Spectroscopy during Pharmacological-induced Pressure Changes. Anesthesiology. 2015;123:327-35.
259. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg. 2012;114:503-10.
260. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. Crit Care Med. 2013;41:464-71.
261. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg. 2014;147:483-9.
262. Schmidt C, Heringlake M, Kellner P, Berggreen AE, Maurer H, Brandt S, et al. The effects of systemic oxygenation on cerebral oxygen saturation and its relationship to mixed venous oxygen saturation: A prospective observational study comparison of the INVOS and ForeSight Elite cerebral oximeters. Can J Anaesth. 2018;65:766-75.
263. Haggstrom L, Welschinger R, Caplan GA. Functional neuroimaging offers insights into delirium pathophysiology: A systematic review. Australas J Ageing. 2017;36:186-92.

CURRICULUM VITAE

EERTMANS Ward

Date of birth: 6 February 1991 (Genk, Belgium)
Nationality: Belgian
Address: Heuvelstraat 76/13
3620 Lanaken
E-mail: eertmansward@hotmail.com

EDUCATION

2013-2014 Proficiency in Laboratory Animal Science
FELASA C
Antwerp University

2012 – 2014 Master in Biomedical Sciences (MSc) *Magna cum laude*
Major in Neurosciences
Minor in Preclinical and Clinical Research
Antwerp University

2009 – 2012 Bachelor in Biomedical Sciences (BSc)
Hasselt University

PROFESSIONAL EXPERIENCE

2014 – 2018 PhD research, Hasselt University, Ziekenhuis Oost-Limburg
Department of Anaesthesiology, Intensive Care and Emergency Medicine and Pain Therapy

SCIENTIFIC TRAINING

2015	Basic Parametric Statistics and Linear Regression Flames Summer School – VUB (Belgium)
2016	Brain Physics Department of Clinical Neurosciences, Addenbrookes Hospital, Cambridge University, UK Tutor: Prof. dr. Marek Czosnyka
2016	Academic English Hasselt University, Belgium
2017	Good Clinical Practice for Investigator Site Teams & Ethics Commitees FormaliS, Luxemburg
2017	Introduction to R Hasselt University, Belgium
2017	Effective Image Editing Hasselt University, Belgium
2017	Public Speaking Hasselt University, Belgium
2018	Project management Hasselt University, Belgium

SCIENTIFIC ACHIEVEMENTS

PAPERS PUBLISHED IN INTERNATIONAL PEER-REVIEWED JOURNALS

1. Genbrugge C., Dens J, Meex I, Boer W, **Eertmans W**, Sabbe M, Jans F, De Deyne C. Regional Cerebral Oximetry during Cardiopulmonary Resuscitation: Useful or useless? Journal of Emergency Medicine. 2016;50(1):198-207.

2. Genbrugge C, Viaene E, Meex I, De Vadder K, **Eertmans W**, Boer W, Jans F, De Deyne C, Dens J, Ferdinande B. Impact of time of admission on outcome in out-of-hospital cardiac arrest patients. Eur J Emerg Med. 2017;24(4):249-54.

3. Ameloot K, Genbrugge C, Meex I, **Eertmans W**, Jans F, De Deyne C, Dens J, Mullens W, Ferdinande B, Dupont M. Is venous congestion associated with reduced cerebral oxygenation and worse neurological outcome after cardiac arrest? Crit Care. 2016; 20(1):146.

4. Genbrugge C*, **Eertmans W***, Meex I, Van Kerrebroeck M, Daems N, Creemers A, Jans F, Boer W, Dens J, De Deyne C. What is the value of regional cerebral saturation in post-cardiac arrest patients? A prospective observational study. Crit Care. 2016;20(1):327. * *shared first authorship*

5. **Eertmans W**, Genbrugge C, Fret T, Beran M, Engelen K, Gutermann H, Vanderlaenen M, Willem B, Dens J, De Deyne C. Influence of continuously evolving transcatheter aortic valve implantation technology on cerebral oxygenation. J Clin Monit Comput. 2017;31(6):1133-41.

6. Genbrugge C, **Eertmans W**, Jans F, Boer W, Dens J, De Deyne C. Regional cerebral saturation monitoring during withdrawal of life support until death. Resuscitation. 2017;121:147-50.

7. **Eertmans W**, Genbrugge C, Haesevoets G, Boer W, Dens J, Jans F, De Deyne C. Recorded time periods of bispectral index values equal to zero predict neurological outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21(1):221.

8. Ameloot K, De Deyne C, Ferdinande B, Dupont M, Palmers PJ, Petit T, **Eertmans W**, Moonen C, Belmans A, Lemmens R, Dens, Janssens S. Mean arterial pressure of 65 mm Hg versus 85-100 mmHg in comatose survivors after cardiac arrest: Rationale and study design of the Neuroprotect post-cardiac arrest trial. Am Heart J. 2017;191:91-8.

9. Moonen C, Lemmens R, Van Paesschen W, Wilmer A, **Eertmans W**, Ferdinande B, Dupont M, De Deyne C, Dens J, Janssen S, Ameloot K. The impact of global hemodynamics, oxygen and carbon dioxide on epileptiform EEG activity in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2018;123:92-7.

10. Haesen J*, **Eertmans W***, Genbrugge C, Meex I, Demeestere J, Vander Laenen M, Boer W, Mesotten D, Dens J, Jans F, Ernon L, De Deyne C. The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients. Resuscitation. 2018;126:179-84. * *shared first authorship*

11. **Eertmans W**, Genbrugge C, Vander Laenen M, Boer W, Mesotten D, Dens J, Jans F, De Deyne C. The prognostic value of bispectral index and suppression ratio monitoring after out-of-hospital cardiac arrest. A prospective observational study. Ann Intensive Care. 2018;8(1):34.

12. Genbrugge C, De Deyne C, **Eertmans W**, Anseeuw K, Voet D, Mertens I, Sabbe M, Stroobants J, Bruckers L, Mesotten D, Jans F, Boer W, Dens J. Cerebral saturation in cardiac arrest patients measured with near-infrared technology during pre-hospital advanced life support. Results from Copernicus I cohort study. Resuscitation. 2018.

13. **Eertmans W**, Genbrugge C. Near infrared light at the end of the postcardiac arrest tunnel. Resuscitation. 2018.

14. **Eertmans W**, Genbrugge G, Haesen J, Drieskens C, Demeestere J, Vander Laenen M, Boer W, Mesotten D, Dens J, Ernon L, Jans F, De Deyne C. The prognostic value of simplified EEG in out-of-hospital cardiac arrest patients. Neurocrit Care 2018.

PAPERS IN REVIEW IN INTERNATIONAL PEER-REVIEWED JOURNALS

15. **Eertmans W**, Tran TMP, Genbrugge C, Peene L, Mesotten D, Dens J, Jans F, De Deyne C. A prediction model for good neurological outcome in successfully resuscitated out-of-hospital cardiac arrest patients

16. **Eertmans W,** De Deyne C, Genbrugge C, Marcus B, Beran M, Fret T, Gutermann H, Boer W, Vander Laenen M, Heylen R, Vanelderen P, Mesotten D, Jans F. Postoperative cerebral oxygen desaturation increases the risk of postoperative delirium after cardiac surgery.

BOOK CHAPTER

17. De Deyne C, **Eertmans W**, Dens J. Chapter 16: Neurological assessment of the acute cardiac care patient. Chapter in ESC Textbook of Acute Cardiovascular Care. 2017.

ABSTRACTS AT (INTER)NATIONAL CONFERENCES

18. **Eertmans W**, Genbrugge C, Meex I, Dens J, Jans F, De Deyne C. The evolution of cerebral oxygen saturation in post-cardiac arrest patients treated with therapeutic hypothermia. (Poster, 36th International Symposium on Intensive Care And Emergency Medicine 2016, Brussels, Belgium).

19. **Eertmans W**, Genbrugge C, Meex I, Dens J, Jans F, De Deyne C. Continuous cerebral saturation monitoring during therapeutic hypothermia in out-of-hospital cardiac arrest patients (Poster, Euroneuro 2016, Barcelona, Spain).

20. **Eertmans W**, Ameloot K, Genbrugge C, Jans F, Dens J, De Deyne C. Disturbed cerebral autoregulation, assessed by Near Infrared Spectroscopy, can guide patient-tailored hemodynamic approach in post-cardiac arrest patients. (Poster, Euroneuro 2016, Barcelona, Spain).

21. **Eertmans W**, Haesen J, Genbrugge C, Jans F, Dens J, De Deyne C. Monitoring of brain oxygenation in post-cardiac arrest patients during EEG-confirmed status epilepticus. (Poster, Euroneuro 2016, Barcelona, Spain).

22. **Eertmans W**, Genbrugge C, Meex I, Dens J, Jans F, De Deyne C. Outcome prediction in out-of-hospital cardiac arrest patients using Near-Infrared Spectroscopy. (Poster, Euroanesthesia 2016, London, UK).

23. **Eertmans W**, Genbrugge C, Boer W, Dens J, De Deyne C, Jans F. The use of bispectral index and suppression ratio to predict poor neurological outcome in post-cardiac arrest patients treated with targeted temperature management at 33°C. (Poster, 37th International Symposium on Intensive Care And Emergency Medicine 2017, Brussels, Belgium).

24. Buyse K, Vander Laenen M, Mesotten D, **Eertmans W**. Lung protective ventilation in a non-ARDS setting: A tertiary centre survey and audit (Poster, Euroanesthesia 2017, Geneva, Switzerland).

25. Auwerx M, Mesotten D, Vanelderen P, Dens J, De Deyne C, **Eertmans W**. The prediction of good neurological outcome after cardiac arrest in the first hou rafter ICU admission: a novel prognostic model. (Poster, Besedim 2018, Brussels, Belgium).

26. Castermans T, Vanelderen P, Dens J, Mesotten D, De Deyne C, **Eertmans W**. A novel prognostic model for the prediction of good neurological outcome after cardiac arrest. (Poster, 38th International Symposium on Intensive Care And Emergency Medicine 2018, Brussels, Belgium).

27. **Eertmans W**, Heylen R, Vander Laenen M, Mesotten D, De Deyne C, Jans F.. Postoperative cerebral tissue oxygen desaturation is associated with the development of postoperative delirium after cardiac surgery. (Poster, Euroanesthesia 2018, Kopenhagen, Denmark).

DANKWOORD

De belangrijkste mijlpalen in iemands leven worden zelden bereikt zonder de hulp en steun van anderen, en dit geldt uiteraard ook voor het uitvoeren en schrijven van dit proefschrift. Ik ben ervan overtuigd dat deze thesis het ultieme bewijs vormt dat ik omringd ben geweest door vele helpende handen. In het begin van mijn doctoraat werd er mij verteld dat doctoreren 'volwassen worden' is, en achteraf bekeken is dit inderdaad het geval. Niet enkel als wetenschapper, maar misschien belangrijker ben ik ook als persoon enorm gegroeid. Via deze weg wil ik daarom iedereen bedanken die mij in de afgelopen jaren van raad heeft voorzien om dit doctoraat tot een goed einde te brengen. Een aantal personen zou ik echter graag in het bijzonder noemen.

Ik wil graag Prof. De Schepper, rector van Universiteit Hasselt, bedanken alsook Prof. Stinissen, decaan van de faculteit Geneeskunde en Levenswetenschappen, voor de opportuniteit, omkadering en financiering van mijn doctoraatsonderzoek aan de Universiteit Hasselt.

I would like to express my gratitude towards the members of the jury for taking their time to review my PhD thesis and making the trip to Hasselt: Prof. Dr. Cariou, Dr. Hoedemaekers, Prof. Dr. Moermans, Dr. Stammet, Prof. Dr. Taccone. Your insightful comments have substantially improved my manuscript. I would also like to thank Prof. Dr. Hendrix for being the chair of my public PhD defence.

Uiteraard gaat mijn grootste dank uit naar mijn promotor, Prof. Dr. Cathy De Deyne. Eerst en vooral wil ik u bedanken om mij als biomedicus, met een destijds beperkte klinische kennis, de kans te geven een klinisch doctoraat te doen. Bedankt om mij de nodige tijd te gunnen om te groeien als (klinisch) wetenschapper en als persoon. Het behalen van mijn doctoraat was enkel mogelijk dankzij uw vertrouwen in mij, en natuurlijk ook de klinische en wetenschappelijke kennis waar ik de afgelopen vier jaar nuttig gebruik van heb mogen maken. Verder wil ik benadrukken dat ik enorm veel geleerd heb van uw goede raad en uw kritische doch nuttige commentaar op de artikels. U wist me steeds te motiveren waardoor dit proefschrift uiteindelijk is uitgegroeid tot een mooi resultaat. Bedankt!

Prof. Dr. Frank Jans, ik wil u enorm bedanken voor uw nuchtere visie, uw tijd en energie voor het nalezen van de artikels én de daaropvolgende waardevolle en constructieve feedback. Door het delen van uw kennis en ervaring heeft u van mij een betere wetenschapper gemaakt, waarvoor dank!

Prof. Dr. Pascal Vanelderen en Prof. Dr. Bert Brône, ik wil jullie beiden graag bedanken om deel uit te maken van mijn doctoraatscommissie, me doorheen deze vier jaar te begeleiden en raad te geven waar nodig. Jullie inzichten en suggesties tijdens de bijeenkomsten van de doctoraatscommissie hebben ertoe geleid dat dit doctoraat een mooi geheel vormt. Ook het aandeel van Dr. Willem Boer mag hierin zeker niet vergeten worden. Bedankt!

Prof. Dr. Dieter Mesotten, of Dieter, want u staat er namelijk op dat ik u bij voornaam noem. Uw enthousiasme, gedrevenheid, eerlijkheid en nederigheid zijn eigenschappen waar ik veel bewondering voor vertoon, en werken zeer motiverend. Uw wetenschappelijke kennis kent geen grenzen. Dit alles maakt dat ik het een voorrecht vond om van u te mogen leren. Ik wil u graag persoonlijk bedanken omdat u rust bracht wanneer ik dit het hardst nodig had. Bedankt!

Dr. René Heylen, als diensthoofd van de dienst Anesthesie in Ziekenhuis Oost-Limburg, ben ik u uitermate dankbaar voor de kansen die u me gegeven heeft mijn onderzoek uit te voeren binnen uw dienst. Met zowel uw steun als deze van de gehele maatschap ben ik blij dat ik vier jaar deel mocht uitmaken van uw dienst, waarvoor mijn allergrootste dank.

Prof. Dr. Jo Dens, ik wil u ook bedanken voor uw scherp analytisch inzicht en uw kalmte. Ondanks uw druk werkschema, voorzag u mijn manuscripten steeds van een razendsnelle en adequate commentaar, waaruit ik ontzettend veel geleerd heb. Uw efficiënte en doordachte werkstrategie zijn bewonderenswaardig. Bedankt voor uw steun alsook het vertrouwen in mij!

Verder zou ik me graag willen richten tot alle stafleden van de dienst Anesthesie en Cardiologie om mij te steunen én jullie mij toch het gevoel gaven te appreciëren als 'niet-clinicus'. Daarnaast wil ik zeker ook alle assistenten en residenten anesthesie, urgentiegeneeskunde en cardiologie bedanken, alsook de verpleegkundigen van Intensieve Zorgen en de CCU, en natuurlijk ook de perfusionisten (Maarten, Sonia, Bert en Dieter). Dit proefschrift zou nooit tot stand zijn gekomen zonder jullie enthousiasme en inzet.

Ik wil ook graag Veronique Pousset bedanken, want zonder haar inspanningen (zelfs gedurende haar verlof) zouden de laatste weken nog zwaarder zijn geweest.

Hartelijk dank aan alle collega's (doctoraatstudenten): Lieselotte, Rob, Elien, Cornelia, Pieter, Joren, Petra, Philippe, Sébastien, Jeroen, Frederik, Kristof, Sharona, Özgur, Dana, Hélène, Dorien, Thijs, Melanie, Annelies, Amber, Anneleen, Ingrid, Inge, Lars, Yves, Julie, Pauline en Elisa. Het is jullie verdienste dat ik iedere keer met plezier mij naar de bureau begaf. Jullie zijn stuk voor stuk topcollega's en toponderzoekers die steeds klaar stonden voor een toffe babbel en hulp boden waar nodig.

Cornelia, wanneer ik terugdenk aan de eerste twee jaren van mijn doctoraat, denk ik aan jou. Dit doctoraat is ook jouw verdienste en ik ben er zeker van dat ik mijn dankwoord nu niet aan het schrijven was als jij er niet was geweest. Jij hebt me op pragmatisch vlak doorheen alle stappen van het klinisch onderzoek geleid. Als biomedicus was ik (zeker in het begin) nogal onwetend over de praktische aspecten van klinisch onderzoek, hetgeen met tijd en stond tot lachwekkende situaties heeft geleid (*denk maar aan mijn steriliteitsfout bij mijn eerste TAVI-patiënt).* Jij gaf me de nodige inzichten zodat ik snel mijn weg kende in het ziekenhuis en op mijn eigen benen kon staan. Verder vond ik dat wij een zeer sterk team waren dat elkaar telkens wist aan te vullen waar nodig. Ik kan je vertellen dat ik jou het afgelopen jaar enorm gemist heb, ondanks dat we toch regelmatig contact hadden. Ik hoop dat we dit contact weten te onderhouden in de komende jaren. Bedankt voor alles!

Ingrid, ook jou wil ik graag in dit dankwoord vernoemen. Wij hebben nooit als daadwerkelijke collega's samengewerkt, maar het is ook dankzij jouw harde werk op de CCU dat ik dit doctoraat succesvol heb kunnen afronden. Jij hebt namelijk het overgrote merendeel van de hartstilstandpatiënten weten includeren, waarvoor ik met alle plezier mijn petje afdoe. Bedankt!!

Joren, jij hebt jouw doctoraat al succesvol weten af te ronden, maar toch wil ik jou graag persoonlijk bedanken. In de afgelopen jaren heb ik meermaals mogen ondervinden wat voor een fantastische collega (lees: vriend) jij was met een steeds luisterend oor. Ik kon altijd bij jou aankloppen en jou was niets te veel. In de tussentijd brengt onze passie voor motors/auto's ons nog steeds bij elkaar en ik hoop uit de grond van mijn hart dat we ons gaan blijven, ook al ben je verhuisd van Lanaken naar Opglabbeek.

Natuurlijk wil ik alle inwoners van 't (warmste) Kotje afzonderlijk bedanken waarmee ik de afgelopen jaren lief en leed heb gedeeld. Jullie steun naar mij toe kende werkelijk geen grenzen. Jullie zijn na al die jaren meer dan collega's geworden, jullie zijn vrienden!

Lieselotte, ik heb zo hard genoten van jouw aanwezigheid in ons kotje. Ik vermoed dat het tussen ons zo goed klikt omdat ik zoveel van mij in jou herken, zodat je misschien wel de vrouwelijke versie van mij zou kunnen zijn. Jij bent een fantastische onderzoeker en gaat nog hoge toppen scheren in het onderzoek na jouw doctoraat – dat nota bene een schot in de roos zal zijn! Ik ga zoveel aan jou missen, als collega weliswaar, want ik weet dat we ons niet uit het oog zullen verliezen. Om maar enkele dingen op te noemen: ik ga je missen om jou (samen met Rob) op vrijdag te plagen, jou dingen wijs te maken, jouw oreoballs, onze serieuze babbels, maar natuurlijk de momenten waarop je mij kon kalmeren wanneer dit nodig was (dat laatste was vaak ook wederzijds ☺). Verder waren jouw gedrevenheid, passie en doorzettingsvermogen een drijfveer voor mij om nooit op te geven. Cornelia, nogmaals bedankt voor alles, zéker voor de foute minuutjes die de sfeer in ons kotje zeker ten goede kwamen, alsook voor ons up-to-date te houden met nagenoeg alles wat op HLN verscheen. Rob, (mediageile) kameraad, het was een waar plezier om dagdagelijks achter jou te zitten. Jij bent veruit één van de meest efficiënte en correcte mensen die ik ken. Daarenboven heb je een nuchtere en objectieve kijk op heel veel zaken (zowel werk als privé-gerelateerd), waar ik vaak van heb kunnen profiteren. Verder straal jij een bepaalde rust en wijsheid uit waardoor ik vaak in stressvolle situaties moest denken: "Hoe zou Rob dit aanpakken?". Jij bent een prachtige mens, een prachtige vader voor Louis en Georges en een zorgzame man voor Ruth. Ik genoot ervan om het te hebben over jouw gezinsleven en om de foto's en filmpjes te bekijken van jouw twee opgroeiende zonen. Jouw gevoel voor humor, en onze wederzijdse steekpartijen, hebben ervoor gezorgd dat ik vaak plat lag van het lachen. Ik weet zeker dat we ons gaan blijven zien na mijn doctoraat! Ten slotte, Elien, wat een top-collega ben jij! Jij bent er als laatste bij gekomen, maar dat maakt jou niet minder speciaal. Ik denk dat we nagenoeg meteen een klik hadden én dat we op deze korte tijd (naar mijn mening) vrienden zijn geworden. Alleen al wat betreft jouw muzieksmaak was ik blij dat je ons kotje kwam vervoegen, want het niveau voorheen was gene vette ☺ (Bedankt om me Lili Grace te leren kennen en me te steunen als Rob meermaals Kendrik Lamar of andere zogenaamd goede rapmuziek met ons wilde delen). Jij bent een superharde werker waar je binnen een drietal jaren de vruchten van zult plukken. Ik twijfel er namelijk niet aan dat jouw thesis van hoge kwaliteit zal zijn. Ik ga jou om ontzettend veel redenen missen, maar voornamelijk omdat ik enorm goed met jou kon babbelen. Jouw persoonlijkheid is werkelijk charmerend: jij bent Elien en je zal je nooit voordoen als iemand anders. Dat is mijn inziens de mooiste eigenschap die iemand kan hebben. Verder ben jij veruit de

eerlijkste persoon die ik ken, en je cijfert jezelf moeiteloos weg om anderen (en vaak ook mij) te helpen. Bedankt!!

Aan mijn vrienden hoor ik uiteraard ook een welgemeende dankjewel te zeggen. Het risico op jullie allemaal bij naam te noemen en vervolgens iemand te vergeten is te groot, maar besef dat jullie allemaal enorm belangrijk zijn voor mij. Het zijn juist jullie die mij in de vrije tijd die me restte hebben doen ontspannen.

Papa, mama, Marlies en Jos, bedankt dat jullie me de kans gaven om te studeren. Jullie hebben me geleerd om zelfstandig te zijn en nooit op te geven, hetgeen twee eigenschappen zijn die een doctorandus steevast nodig heeft om succesvol te zijn. Bedankt! Gert en Lien, bedankt om gewoon mijn broer en zus te zijn en er altijd voor mij te zijn. Soms zijn er niet veel woorden nodig om dankbaarheid te tonen. Mijn schoonouders (Jos en Marielle), schoonzusje Kathleen, Poat en Moe hebben ook een speciale plek in mijn hart. Jos, tijdens de weekends bracht ik met veel plezier, en ondertussen passie, door in jouw kelder om te sleutelen aan de kever en te werken aan andere projecten. Daarnaast bracht het bezoeken van oldtimer-beurzen vaak de nodige ontspanning. Aangezien ik zeker niet de handigste ben, moest ik me met mijn volle verstand focussen op hetgeen ik ondernam in de kelder. Wat in jouw ogen vaak kinderspel leek, was voor mij verre van evident. Dit is en blijft pure ontspanning voor mij, aangezien dit vaak de enige momenten zijn dat mijn brein mij niet toelaat om aan het werk te denken (*anders bega ik weer een of andere onhandige stommiteit hè ;)*). Bedankt voor jouw oneindige geduld en vriendschap! Marielle, jouw zorgzaamheid heeft me altijd geraakt. Jij gaf en geeft me het gevoel er altijd voor mij te zijn alsof ik jouw eigen zoon zou kunnen zijn. Jij cijfert je weg voor jouw gezin én stelt alles in staat om iedereen gelukkig te maken. Hier slaag je met verve in. Jij bent de beste schoonmoeder die ik me kon wensen, waarvoor dank.

En dan ten slotte… Michèle! Hoe kan ik ooit in woorden beschrijven hoe veel jij voor mij hebt betekent de afgelopen jaren. Wij zijn op het eerste zicht zodanig verschillend, maar vormen in mijn ogen juist daarom het sterkste team, dat elkaar aanvult op alle aspecten. Jij bent diegene die me nooit te lang laat stilstaan bij problemen en mij al zeker niet de kans geeft om hierover klagen. Door jou zal ik nooit mijn doelen uit het oog verliezen. Ik voel aan alles wat jij voor mij doet, dat je dit met heel veel liefde en plezier doet. Je laat me voelen dat je supertrots op me bent dat ik nu mijn doctoraat kan afleggen, maar ik

ben eigenlijk diegene die nog trotser is u sinds kort mijn vrouw te mogen noemen. Aan wie anders dan u, draag ik mijn thesis op. Ik hou van u!!