Intraoperative cerebral hypoperfusion and electroencephalogram suppression resulting in neurological complications after cardiac surgery: the need for an in depth investigation

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Abstract: Reports on the demographic profile of older populations estimate that, in 2050, 19 countries will have at least 10% of their population aged 80 years or more. Many high risk elderly patients undergo cardiac surgery. In addition, advanced age has been shown to be a strong predictor of adverse neurological outcome. Despite significant improvements achieved in the perioperative care of cardiac surgical patients, neurological complications remain a global health issue. Recent findings have pointed out that cerebral hypoperfusion and too deep levels of anesthesia are major sources of adverse neurological outcomes. Cerebral near-infrared spectroscopy provides information about cerebral perfusion non-invasively, and is increasingly used. Depth of anesthesia is evaluated using monitors that are based on processed electroencephalogram. This non-systematic review focuses on the results of studies performed with each monitor separately, and the need for a combined evaluation of their utility and eventual impact on neurological outcomes. The use of a combined cerebral monitoring strategy based on the two aforementioned monitors is proposed in order to optimize cerebral outcomes.

Key words: Postoperative cognitive dysfunction; postoperative delirium; stroke; cardiac surgery; cerebral monitoring; cerebral near-infrared spectroscopy; processed electroencephalogram monitor; burst suppression.

INTRODUCTION

In 2050, 19 countries, mostly in Europe, are projected to have at least 10% of their population aged 80 years or more (1). Many elderly, high risk patients undergo cardiac surgery, and this number increases every year, considering the growing number of innovative transcatheter heart valve therapies in these elderly patients where open heart surgery is too risky. Advanced age has been shown to be a strong predictor of adverse neurological outcome.

Despite continuing advances in cardiac surgery, neurological complications in this surgical population remain a burden to healthcare providers. The etiology of neurological complications after cardiovascular surgery is multifactorial, and may be specific to the surgery. However, these neurological complications can usually be classified into three major classes: cerebrovascular accident (CVA), postoperative cognitive dysfunction (POCD), and postoperative delirium (PD).

Recent literature shows that cerebral hypoperfusion states and overdose of general anesthetic agents are the major sources of cerebral complications. Several invasive and non-invasive cerebral monitors are available for detecting cerebral hypoperfusion. Cerebral near-infrared spectroscopy (NIRS) is one of them. This monitor is increasingly used. It allows obtaining information on cerebral blood flow through the measurement of surrogate parameters. Depth of anesthesia can be assessed using several processed electroencephalogram (pEEG)-based non-invasive monitors.

Given the extensive literature devoted to several types of cerebral monitoring devices, and the multifactorial etiology of neurological complications after cardiovascular surgery, this review will focus on cerebral NIRS and pEEG as currently the most widely used cerebral monitors in that indication.

Our review addresses shortly the three major classes of neurological complications, and discusses the usefulness of cerebral NIRS and pEEG for improving neurological outcome in cardiac surgery patients when used separately. The limits of each technology will be pointed out separately. Finally,
the need for a combined cerebral monitoring strategy to optimize cerebral outcome after cardiac surgery will be discussed.

NEUROLOGICAL complications

Cerebrovascular accident

Although cerebrovascular accidents (CVA) may occur intra-operatively, it has been shown that more than a half of strokes occur during the postoperative period (2, 3). Increased risk of stroke still exists during the ensuing 2 years after cardiac surgery (4). Stroke seems to occur in 1.4% to 3.8% of patients undergoing coronary artery bypass grafting (CABG) and up to 9.7% of patients undergoing double- or triple-valve surgery (5). Risk factors for early and late stroke may vary, according to the underlying pathophysiological mechanisms, but older age, previous stroke, and preoperative atrial fibrillation are among risk factors associated with both early and late stroke (2, 6).

Postoperative cognitive dysfunction

Another issue after cardiac surgery is the occurrence of postoperative cognitive dysfunction (POCD). POCD is defined as a new cognitive deficit arising immediately after surgery. It manifests in the form of memory loss and impaired performance on intellectual tasks up to 6 months postoperatively (7). Preoperative risk factors of POCD after cardiac surgery are multiple and include advanced age, low level of education, low baseline cognitive performance, and genetic factors (8-10). POCD is frequently the consequence of cerebral micro-emboli, global hypoperfusion, and inflammation (8). The incidence of POCD varies a lot among studies, and depends on the neurologic tests used to detect it. The testing method to be used and the magnitude of change corresponding to a clinically relevant modification are still not clear (11). The timing of testing is another matter of debate. When a battery of neurologic tests is used, POCD can be detected in up to 50% of patients during the early postoperative period (12, 13).

Postoperative delirium

Postoperative delirium (PD) is another frequent complication of cardiac surgery. PD is defined as an acute fluctuating state of consciousness, with disturbances of perception and emotional instability, associated with inappropriate behavior (11). It mostly occurs between postoperative day 1 and 3, and even after an initial lucid emergence from anesthesia. Its incidence has been reported to be around 30% following CABG (14), and is higher in patients undergoing CABG combined with valve surgery (15). There are many predisposing risk factors and various precipitating factors that increase the risk of developing PD after cardiac surgery: older age, cognitive impairment, postoperative pain, dehydration, infection, anemia, and perioperative transfusion (16).

Patients suffering from neurological problems after cardiac surgery are at an increased risk of morbidity and/or mortality (2, 6, 11). Whilst the incidence and the perioperative management of these three neurological complications may vary, they share some common risk factors for their occurrence: advanced age, cardiovascular morbidity including peripheral vascular disease, diabetes, previous stroke, preoperative cognitive impairment and dementia (6, 9, 16).

As most of these factors are not modifiable at the time of surgery, conditions that can be controlled during the perioperative period should deserve more focus to prevent the occurrence of neurological problems. Therefore, it is crucial to understand the main mechanisms of neurological complications, in order to focus on their detection and their treatment.

MECHANISMS OF NEUROLOGICAL COMPLICATIONS AND THEIR DETECTION

Many patients undergoing cardiac surgery show various types of extra- and/or intracranial atheromatosis. Moreover, they may present with mild to moderate narrowing of these vessels. Therefore, in addition to increased risk of micro- or macroemboli, they are at high risk of hypoperfusion.

Intraoperative cerebral hypoperfusion

Intraoperative cerebral hypoperfusion is generally accepted as a worsening factor of neurological complications (17-19). Recently, cerebral NIRS has been used as a real-time cerebral auto-regulation monitoring to detect the mean arterial pressure being at the lower limit of cerebral auto-regulation (20). Intact cerebral auto-regulation results in a cerebral blood flow that does not change in response to modifications of the arterial blood pressure. Several authors have demonstrated that approximately
20% of cardiac surgery patients have impaired cerebral auto-regulation during non-pulsatile cardiopulmonary bypass (CPB), as evaluated using cerebral NIRS (21, 22). In these studies, patients with impaired cerebral auto-regulation had a higher incidence of stroke (21) and major organ morbidity (22). Border zone or watershed infarcts are ischemic lesions that occur in specific locations, at the junction of two different drainage locations. Studies have shown that embolization and cerebral hypoperfusion are the main processes that explain border zone infarcts. Cerebral hypoperfusion seems to play a major role in aggravating the clinical course of infarcts, insofar as it impairs the washout of cerebral emboli (23).

**Cerebral Near-Infrared Spectroscopy**

The use of cerebral oximetry has significantly increased over the last years in adult as well as in congenital cardiac surgery. Numerous studies show that monitoring of cerebral oxygen saturation (ScO₂) allows the detection and treatment of episodes of cerebral hypoperfusion, resulting in improved outcome after cardiac surgery (24-28).

Cerebral NIRS is an easy and non-invasive method for estimating cerebral perfusion. It has, however, several limitations. Besides the high cost of this technology, the extent of extracranial contamination of ScO₂ readings is non-negligible (29, 30). Moreover, several important aspects should be kept in mind when interpreting results of neurological outcomes in studies using ScO₂ monitoring. At this time, there is no clear consensus on abnormal ScO₂ value range, and hence on indications for treatment. Authors have used different definitions of cerebral oxygen desaturation (24-28, 31-36). Considering that the brain undergoes physiological changes with aging (37), and that preoperative ScO₂ values may be low in specific patients (38), a clear definition of cerebral oxygen desaturation is needed for conducting future studies. On the other hand, very few studies have carried on cerebral oximetry monitoring in the intensive care unit after surgery (27, 36). Postoperative hemodynamic instability is not uncommon in cardiac surgical patients, and therefore, patients are still at risk of cerebral hypoperfusion beyond the intraoperative period. The other issue is that the three published trials having randomized patients into a control group and a treatment group based on ScO₂ readings were performed in patients undergoing CABG only (24, 25, 28) and few studies have included patients undergoing surgery without CPB (31). This is an important drawback in face of a growing number of high-risk patients undergoing surgery without CPB, e.g. transcatheter aortic valve implantation (39) and the results of meta-analyses that do not demonstrate a better cognitive outcome in patients undergoing surgery without CPB (40, 41). Except for very few (42), many of the aforementioned trials have included a rather small number of patients, based on their specific primary endpoint. Hence, to date, large trials looking at the three major complications simultaneously are still lacking.

**Supratherapeutic levels of general anesthetic agents**

Besides hypoperfusion states, an overdose of general anesthetic agents is among intraoperative factors that have been evoked to influence postoperative neurological complications. Too deep levels of anesthesia may result in PD and/or POCD as observed in cardiac (43-45) and non-cardiac surgery patients (46-48). Very deep levels of anesthesia manifest on the electroencephalogram (EEG) in the so called «burst suppression» pattern – characterized by periods of high-voltage electrical activity alternating with periods of electrical silence –, or even complete cerebral inactivity. Noteworthy, burst suppression may occur despite adequate levels of anesthesia. This phenomenon may be an illustration of the unusual sensitivity of the brain to general anesthetic agents, and its mechanism has to be elucidated in future research. Burst suppression despite adequate levels of anesthesia may also be due to cerebral ischemia.

**Monitoring depth of anesthesia based on processed electroencephalogram**

Many cardiac centers routinely use a depth-of-anesthesia monitor based on processed EEG (pEEG). Several depth-of-anesthesia monitoring technologies are available (49). A discussion of each technology is beyond the scope of this review article. The Bispectral Index (BIS®) is however the most widely used pEEG monitor for daily anesthesia practice, as well as in clinical research. BIS values between 40 and 60 are considered to reflect an adequate level of anesthesia. However, an important drawback of BIS use in studies associating neurological complications with deep levels of anesthesia must be underlined. BIS decrease becomes linear when suppression ratios increase over 40% and beyond. When BIS values are lower than 30, burst suppression ratio (BSR) is inversely correlated with BIS. However, when BSR is lower than
40%, this relation is no more linear (50-52). In other words, BIS does not reflect adequately an increased anesthetic drug effect as long as the BSR does not exceed 40%. As a consequence, BIS levels can vary between 30 and 40 despite increased drug pharmacodynamics as long as BSR < 40% (51). This is a major issue as the latter influences the obtained results. Recently, a new pEEG monitor, NeuroSENSE®, has been available where the relationship between the depth-of-anesthesia index and the suppression ratio is monotonous (53-55).

Surprisingly, in the 3 randomized trials (46-48) where the use of BIS monitor showed to decrease the incidence of PD, the authors used the amount of time or the percentage of BIS values < 20, < 40 or < 50 and not the suppression ratio. On the other hand, in the BAG-RECALL trial, patients who were delirious did not have an increased proportion of intraoperative time with BIS < 20 (45). This makes the results of studies based only on BIS questionable. Indeed, in all these studies, no information is available regarding BSR. In the study conducted by Radtke et al. (48) the average suppression ratio has been reported to be significantly lower in the BIS unblinded group, but the authors have not evaluated its impact on their obtained results. The study by Soehle et al. (43) is the only prospective trial in cardiac surgery where the BSR and the time spent in a state of burst suppression were evaluated. They observed a significantly higher BSR in patients who developed PD. However their study included only a small number of patients. Very recently, another study has shown that intraoperative EEG suppression predicts postoperative delirium. In this observational large study, adult patients who received general anesthesia with planned intensive care unit were included. Similar to the study by Soehle et al. (43) they evaluated the duration of burst suppression and not only the BIS values. However, their study was not exclusive to cardiac surgery patients (56).

One important aspect to consider is that results of cardiac surgery studies can be biased by the use of hypothermic CPB. Mild to moderate hypothermia induces various degrees of EEG suppression, and the latter can affect the information obtained from pEEG monitors (57, 58). Moreover, similar to cerebral oximetry monitors that give an idea of the magnitude of cerebral oxygen desaturation in the form of an area under the curve, information about the magnitude of burst suppression is mandatory before drawing any conclusions with respect to depth of anesthesia and neurological outcome of cardiac surgery patients.

Considering that electrocardiographic, electromyographic, and electrocautery artifacts can be major confounding factors for the interpretation of pEEG-derived indexes, results obtained through studies that are purely based on an anesthetic index may be biased. The percentage of burst suppression reflects the intraoperative state of the brain, independently from the anesthetic agent choice, and can result from high anesthetic concentrations but also from hypoperfusion states during cardiac surgery. As a matter of fact, sustained episodes of burst suppression may occur in high-risk vulnerable patients when hemodynamic instability occurs, and despite stable depth of anesthesia (59). In this way, pEEG monitoring during cardiac surgery helps in detecting intraoperative hypoperfusion states, in addition to its ability to monitor the depth of anesthesia. There has recently been considerable interest in the anesthesiology literature regarding anesthesiologists education in interpreting clinical EEG (60) and in using pEEG monitors. This is particularly important during cardiac surgery (61).
Many trials have focused only on one type of complication. The ability of each monitor to detect anomalies can definitely influence the obtained results, and should therefore be properly defined before starting the study, taking account of the technical aspects of these monitors. Lastly, it has been postulated that the type of general anesthetic agent can affect cognitive performance after cardiac surgery (36). Therefore, future trials need to consider this information.

We are currently conducting a large prospective study and use concomitantly the INVOS 5100® as a cerebral oximetry monitor, and the NeuroSENSE® as a pEEG monitor. Our study will evaluate the impact of cerebral oxygen desaturation and the magnitude of burst suppression, as separate entities and as a combined variable, on neurological outcome of patients undergoing various types of cardiac surgery (NCT02006212).

Obviously, cerebral NIRS and pEEG monitors give information about a limited area of the brain and have their limitations, similarly to many other monitors. However, their simultaneous use provides synergistic information, helping to shed light on a complex organ such as the brain (65).

Neurological complications after cardiac surgery are not uncommon and have a considerable impact on the short- and long-term outcome of patients undergoing cardiac surgery. Currently, several non-invasive brain monitors are available. This review illustrates that, despite the lack of firm evidence-based data, numerous studies are in favor of an integrated cerebral monitoring approach, with the aim of reducing the incidence of neurological complications.

References


