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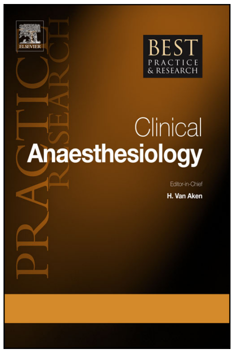

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NON INVASIVE NEUROMONITORING IN THE OPERATING ROOM AND ITS ROLE IN THE PREVENTION OF DELIRIUM

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Delirium is a frequent and serious complication after surgery. It has a variable incidence between twenty and forty percent with the highest incidence in elderly people undergoing major or cardiac surgery. The development of postoperative delirium is associated with increased hospital stay lengths, morbidity, the need for home care and mortality.

Studies have appeared in the last decade that evaluate the use of non-invasive monitoring to prevent its development.

The evaluation of the depth of anesthesia with processed EEG allows to avoid awareness and burst suppression events. The cessation of brain activity is associated with the development of delirium. Another non-invasive monitoring technique is NIRS for cerebral tissue hypoxia detection by measuring regional oxygen saturation. The reduction of this parameter does not seem to be associated with the development of postoperative delirium but with postoperative cognitive dysfunction.

There are few studies in the literature and with conflicting results on the use of the pupillometer and transcranial doppler in predicting the development of post-operative delirium.

Key words:

- Delirium
- Processed EEG
- Pupillometry
- Trans-cranial-color-doppler
- Near Infrared Spectroscopy
- Noninvasive neuromonitoring

As the age, frailty and comorbidities of the surgical population increase, physicians need to know, prevent, identify and potentially treat delirium in population most at risk. Delirium is a clinical feature and, as such a diagnostic and therapeutic challenge in the ICU, before any treatment is undertaken a possibly reversible cause should be investigated: drug intoxication or withdrawal syndrome, toxin, hypoxemia, infections/sepsis, disturbances of electrolytes [1]. In addition, according to the guidelines of Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anesthesia practice, delirium may be an early warning sign of post-operative complication [2]. Finally, the Clinical Practice Guidelines for the Prevention and Management of Pain, Agitations / Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU, underline the need to regularly verify the development of delirium using a valid tool such as Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) [3].
According to Diagnostic and Statistical Manual of Mental Disorders (DSM V) delirium is an acute or subacute disorder, usually developing within hours to days, which represents a change from the patients baseline cognitive functioning, characterized by disturbances in attention, awareness, and multiple aspects of cognitive functioning, not better explained by a preexisting or other neurocognitive disorders [4].
Disturbances of cognition may occur acutely, in the form of postoperative delirium (POD) (if symptomatology appears in hospital up to 1-week post procedure or until discharge), or after hospital discharge as postoperative cognitive dysfunction (POCD). POCD describes an objectively measurable decline in cognitive function after anesthesia and surgery, up to 3 months e 7.5 years after surgery [5]. There might be discrepancy between criteria used for POCD with the DSM-V and criteria for mild and major neurocognitive disorders (NCD). The DSM-V stresses that both cognitive concern by the individual or clinician and objective

evidence is essential to satisfy a diagnosis of NCD, and evidence of either maintained

activities of daily living (ADLs) (mild NCD) or impaired ADLs (major NCD). In an article appeared on the British Journal of Anesthesiology, Evered recommended the clinical nomenclature for impairment in cognition temporally associated with anesthesia and surgery to be changed from POCD to 'delayed neurocognitive recovery' and mild or major NCD (DSM-V), depending on timing and magnitude [5].

Incidence of POD is 20 to 45% among older surgery patients [6]. However, this incidence increases up to 80% in post-operatively intensive care patients [7]. The highest incidence occurs in elderly patients (age is an independent risk factor for delirium, with an increase of 3% in patients less than 65 years of age, 14% for patients between 65 and 74 years and 36% in patients older than 65 years [8]) and in major cardiac surgery and non-cardiac surgery [7]. POCD is experienced by 20 to 50% of older patients three months after cardiac surgery [9] and by 5 to 55% of those undergoing other major surgeries [10] [11]. A recent meta-analysis conducted on more than 90000 patients who underwent coronary bypass grafting underlined the high prevalence of delirium and the importance of using standardized instruments of diagnosis; cognitive impairment peaked at over 40% within the first four days following coronary artery bypass grafting (CABG), attenuated at around 1-year, and then rose again to 40% from 1 to 5 years. In the long-term, after 5-years following surgery, cognitive impairment was found in 16%, which is uncharacteristically low compared to other long term estimates and may be due to attrition and death of patients during follow-up [12].

The type of surgery is a risk factor as well: complexity and duration of the procedure, need for transfusions, intraoperative blood pressure, glycemic control, depth of anesthesia (burst suppression). Finally, the choice to use certain drugs (benzodiazepines, scopolamine, ketamine, morphine, zolpidem, histamine-receptor antagonists) is related to an increase in POD rate.

Three subtypes of delirium are recognized based on the pattern of symptoms: hyperactive (25%, agitated and combative, refusal to cooperate with medical care) hypoactive (65%, decreased alertness, lethargy, motor activity and anhedonia) and mixed forms (10%, psychomotor activity level rapidly fluctuates, attention and awareness are disturbed) [8]; among the elderly patients, the hypoactive-type delirium is the most common: this is a reason why health practitioners need to know how to prevent, identify, and treat delirium in high-risk populations when age, frailty and comorbidity burden increases in order to reduce the incidence of POD and its associated negative outcomes [7].

Although delirium is an acute syndrome, it is associated with long-term impairments in overall function, cognitive function and quality of life. Furthermore, the development of POD is the strongest predictor of the occurrence of cognitive impairment after surgery.

There are many causes for POD and POCD, and anesthesia is an important risk factor that cannot be ignored [13]. In 1982, Savageau and colleagues introduced neuropsychological testing to asses cognitive alterations after cardiac surgery using Trail Making Tests and the Visual Reproduction (VR) Test of the Wechsler Memory Scale (WMS): postoperative cognitive detriment were documented in 11% to 17% of the patients [14]. One of the first large multicenter trial was performed in 1998 by the International Study of PostOperative Cognitive Dysfunction (ISPOCD) group testing over 1000 patients undergoing major noncardiac surgery using battery of neuropsychological tests [15]. The study showed that cognitive dysfunction was present in nearly 10% of elderly individuals at 3 months after noncardiac surgery and found associations of POCD with increasing age and fewer years of education, two factors associated with cognitive decline in the wider community. The occurrence of POCD after noncardiac surgery suggested that cardiopulmonary bypass or cardiac surgery itself were not the only determinants at play [10]. Silbert et al. found no difference in POCD between postsurgical patients and nonsurgical controls at 12 month, suggesting that POCD may be a transitory phenomenon identifiable at 3 months which

becomes indistinguishable from the nonsurgical population at 12 months [16].

Although there is a temporal relationship between POCD, anesthesia and surgery, this does not in any way imply causation. Anesthetic drugs have been circumstantially implicated because the brain is the target organ of all anesthetic agents [17]. Despite extensive investigations, the pathophysiology, etiology and natural history of perioperative cognitive disorders is still limited and largely speculative and requires further investigations. Causal association remains unclear because of lack of well-defined baseline cognitive assessment. Besides, the reported incidence of delirium in the elderly after anesthesia and surgery is considerably dependent on how it is diagnosed and screened, including how clinical staff are trained to assess it.

Delirium in the recovery room and the day after surgery is a predictor of an increased LOS. This prolonged hospitalization has the direct consequence of healthcare cost increase. Delirium causes higher morbidity and mortality, delays in functional and social recovery i.e. difficulties with daily activities, early retirement, higher dependency following hospital discharge, higher rates of readmission, admission to nursing home [7].

Most of the studies have found a correlation between POD and mortality, this association is confirmed regardless of surgical interventions performed as an emergency or elective procedure [18]. Conversely, other studies (after statistical analysis performed with adjustments for preoperative cognitive conditions) did not find an association between postoperative delirium and mortality, and delirium does not independently predict mortality at 2-year, although delirium outcome is worsen when other risk factors are present [19][20]. There is evidence that POD is associated with deteriorating cognition in both the short term (months) and long term (over 1 years) [18].

The importance of the recognition of delirium is highlighted by the American Society for Enhanced Recovery and Perioperative of 2020, which recommends developing protocols to reduce the incidence and consequences of delirium through a multidisciplinary assessment of the high risk patients (Strong recommendation, grade D evidence) [7].

Taking into account the numerous and complex pathophysiological mechanisms associated with delirium, and the correlation with poor outcome, it become of paramount importance to monitor patients undergoing surgery mainly under general anesthesia, but also patients undergoing regional anesthesia with increased risk factors; especially considering the significant increase in the number of patients over 60yrs undergoing surgery and anesthesia and the projection of further increase. We focused on types of intraoperative neuromonitoring available, their strengths and weaknesses investigated so far (Table 1)

A. Processed EEG (BIS, ENTROPY)

General anesthesia is a reversible loss of consciousness (reversible coma) induced by drugs. A patient undergoing general anesthesia is characterized by unconsciousness, immobility and control of autonomic responses to nociceptive stimulation. Traditionally, drugs are administered based on the patient's body weight, leading to the loss of somatic and autonomic responses secondary to surgical stimulation.

Administration of drugs based on body weight is effective and safe in most patients. However, in some subjects, even if the dose of drug administered is correct, awareness events may occur during anesthesia (incidence of 1 to 2 cases/1000 in North America and Europe [21]). The correct drug dosage can’t be determined on autonomic responses because heart rate and blood pressure are misleading. Modifications of these parameters are secondary to spinal and cortical reflexes that indicate an antinociceptive state rather than a

state of consciousness of the patient [22].

To prevent this serious intraoperative complication, systems have been developed to verify the correct depth of anesthesia, minimizing the incidence of awareness. However, in recent years this systems have also found applications as useful exam to diagnose and prevent brain insults that may lead to poor outcomes such as POD and cognitive dysfunction. Particular attention has been paid to patients who are specifically susceptible to anesthetic drugs: the administration of higher doses entails side effects on various organs: cardiovascular, respiratory and neurological. The use of high doses of anesthetic drugs (if not necessary) must be avoided to reduce possible damage to neurons [23]. Since anesthetic drugs target consciousness, the interpretation of the EEG is fundamental. The European Society of Anesthesiology recommends in the recent Guidelines on postoperative delirium (2017) to monitoring depth of anesthesia with the aim of reducing the adverse effects of anesthetics and the incidence of POD (Level A) [18].

To simplify the interpretation of the raw EEG traces, systems have been created that can process the traces by providing a-dimensionless number that represents the depth of sedation and anesthesia (Figure 1). The numerical value is indicative of hypnosis-anesthesia. It begins to decrease in relation to the changes shown by the trace starting from a value equal to 100 (awake patient) (Figure 2) up to a value suitable for anesthesia (Figure 3, 4). In the absence of brain activity (isoelectric) the numerical value will drop to zero (Figure 5). Bispectral index (BIS) is one of the indicator monitoring the depth of anesthesia through the use of processed EEG (pEEG), allowing for anesthetic dose reduction that allegedly reduces the rate of delirium and cognitive impairment after surgery.

Periods of intraoperative burst suppression (Figure 6) have been associated with increased incidence of POD [24] but changing the anesthesiologic practice through the use of pEEG to avoid high burst suppression rate and over sedation did not lead to a reduction in delirium in

the ENGAGES trial. However, the protocol of this trial does not meaningfully modify anesthetic exposure (as opposed to the prior Cognitive Dysfunction) [25]. The connection between burst suppression and delirium has not been established [26]. It is unclear whether EEG suppression is a modifiable factor or simply a marker of patients' pre-existing vulnerability (sensitive brain hypothesis).

The CODA Trial confronted BIS-guided and routine care general anesthesia and assessed for comorbidity, surgical history and level of education, monitored delirium daily using Confusion Assessment Method (CAM) criteria until discharge, SF-36 for functional health status and cognitive function before operation and at 3 months after surgery and found a significant reduction in POCD at three months [27].

The Cochrane Database of Systematic Reviews conducted in 2016 included 2 studies (2,057 patients). This study found that BIS-guided anesthesia reduces the incidence of delirium when compared with BIS-blinded anesthetic or clinical judgment (RR 0.71, 95% CI = 0.60 to 0.85) with moderate quality [28]. Following this study Lu et al. have conducted in 2018 a meta-analysis on 4 eligible and highly reliable RCTs, and drew the conclusion that there is no significant correlation between depth of anesthesia, monitored through processed EEG, and risk of POCD (RR 0.84 [95% CI, 0.21, to 3.45]), $p > 0.05$). Although only one study evaluated the POD, the light anesthesia induces less POD when compared depth anesthesia (RR 2.09 [95% CI, 1.13 to 2.88], $p = 0.019$). However, further investigations with larger sample size needs to be done in order to evaluate the correlation between the use of pEEG and delirium in high risk population [29].

Even though conclusive proof has not yet been brought forward and lack of consensus, participants in the American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention conference expressed that there is sufficient evidence to support the (weak) recommendation for the

use of EEG monitoring in elderly and patients at increased risk of developing POD with the aim of reducing this complication. This statement derives from the fact that there are 3 randomized studies that demonstrate the reduction of POD through the monitoring of the depth of anesthesia guided by the EEG [7].

The use of pEEG help in identifying patients at greater risk of developing delirium and it also provides indications on POD. Alpha activity in awake patients is reduced in subjects with cognitive impairment (Alzheimer's disease) as well as those with mild cognitive impairment. The alteration of alpha activity has been observed in the parietal and occipital regions in patients with POD. Furthermore, the reduction in intraoperative activity of the frontal alpha band is related to a reduction in cognitive function in patients over the age of 65 [30].

B. Near Infrared Spectroscopy

Cerebral oximetry using Near Infrared Spectroscopy (NIRS) can detect tissue hypoxia by measuring regional oxygen saturation (rSO_2) and involves the placement of self-adhesive pads on the forehead that contain a light source and sensing optodes (Figure 7). NIRS monitoring algorithms assume a fixed distribution between venous and arterial blood (70%-75% venous to 25%-30% arterial). Intra-individual and inter-individual variability in the venous arterial blood distribution potentially can influence the accuracy of rSO_2 measurements [31]. This monitoring allows for assessing the adequacy of cerebral oxygen delivery in response to cerebral oxygen metabolic demand.

NIRS has been extensively used especially in cardiac surgery and many studies have been produced on the prevention of neurological adverse outcomes through the use of this device.

Holmgaard and colleagues have conducted in 2019 a secondary analysis on a RCT physician-

blinded NIRS monitoring on 148 patients and neurocognitive assessment at discharge from hospital and at 3 months after surgery. Mini Mental State Examination (MMSE) has been used to detect patients with score <24 and exclude them from the trial. The patients enrolled have been tested with the International Study of PostOperative Cognitive Dysfunction (ISPOCD) test battery. No significant difference were found in the cumulative duration of time ≥10% below the rSO_2 preoperative value in patients with and without POCD at discharge or between the patients with and without POCD at discharge when analysing preoperative rSO_2, mean rSO_2 during cardiopulmonary bypass or during surgery, minimum rSO_2, time spent below preoperative rSO_2 or 20% below preoperative rSO_2, or the accumulated cerebral desaturation load [32].

Ortega-Loubon and his group recently undertook a pairwise and network meta-analyses involving both major cardiac and non-cardiac procedures including a total of 12 eligible RCTs with NIRS monitoring involving over 1600 surgical patients [33]. This meta-analysis suggests there is evidence that brain NIRS-based algorithms are useful in preventing POCD and POD in cardiac surgery, but not in major non-cardiac surgery and maintaining the rSO_2 > 80% of the baseline is the target that seems to result in the maximum benefit in terms of prevention of POCD and POD in cardiac surgery. Thus, the analysis contributes to the debate regarding the use of NIRS monitoring, at least in cardiac surgery.

Slater et al. in 2009 found a correlation between rSO_2 time below 50% and cognitive decline defined as decrease of one standard deviation or more in performance on at least one neurocognitive test [34]. The review from Zheng et al. found a low level of evidence of correlation between rSO_2 during cardiological surgery and postoperative neurological complications [35].

In 2018, the Cochrane Database of Systematic Reviews found no utility of NIRS monitoring on

POD (RR 0.63, [95% CI 0.27 to 1.45]; 1 study, 190 participants; low-quality evidence). On the contrary, such monitoring can reduce the incidence of mild POCD one week after surgery (RR 0.53, [95% CI 0.30 to 0.95], 126 participants low-quality evidence) [36].

Several studies have shown the possibility of using rSO_2 as a surrogate for cerebrovascular self-regulation [37][38]. Starting from this concept, the variable cerebral oximetry index was created cerebral oximetry index (COx) which provides a dimensionless correlation number between cerebral perfusion pressure and rSO_2. Concept similar to Mx which evaluates cerebral self-regulation with the aid of the TCD. When the CBF is beyond the COx self-regulation values it approaches 1, while if the self-regulation is confirmed the value approaches 0 or becomes negative. In a study of 491 patients, cerebral self-regulation and the development of delirium were evaluated. The product of the magnitude and duration that MAP was above the ULA was associated with a 1.09 odds ratio [95% CI, 1.28 to 1.15, p = 0.001] for predicting delirium when adjusted for age, mechanical ventilation hours, prior stroke, congestive heart failure, and preoperative antidepressant usage [39].

C. Automated pupillometry

Examination of the pupillary light reflex (PLR) has long been a standard element in ICU, but in the last years modern pupillometers are gaining popularity for prognostic evaluation, assessment of intraoperative and postoperative pain (Figure 8): pupillometry provide accurate and reliable evaluation of various aspects of the PLR at precision levels and it changed the accuracy and reliability of the PLR assessment. Pupillometry is a non-invasive quantitative measurement of dynamic changes in pupil size in reaction to light (Figure 9). Pupillary reactivity provides insight into the balance between the sympathetic and parasympathetic nervous system and help to assess patients during acute neurologic disease; reduced functioning of the cholinergic antiinflammatory reflex is implicated in the

pathophysiology of secondary critical illness-related brain dysfunction [40]. Thus, since the pupillary light reflex is regulated by the cholinergic system, automated infrared pupillometry represents an attractive diagnostic and non-invasive tool for evaluating parasympathetic activity in the clinical setting [41].

In 2017 Yang et al. firstly conducted a prospective observational study and proposed the use of infrared pupillometry to screen and predict delirium on 47 patients undergoing general anesthesia for surgical interventions, the PLR has been measured before, during and after induction of anesthesia , after post anesthesia care unit (PACU) and upon discharge; delirium was assessed using CAM-ICU test. Receiver operating curve (ROC) and the area under the curve (AUC) were estimated and best threshold for marker was computed using Youden's index. The study presented that the processed parameters, especially percentage constriction and the dilation velocity, assessed after 15 min from PACU admission had excellent performance in predicting delirium at 60 min and were superior to other, non-pupillary predictors (age, length of surgery, benzodiazepines use) [42].

In 2020 the latest study on pupillometry and delirium in ICU setting appeared on Critical Care by Oddo's group; a prospective observational cohort study on 100 patients, both medical and surgical critically ill patients requiring sedation and mechanical ventilation for at least 48 h, at high risk (about 50%) of ICU delirium. This study found a reduction in PLR and pupil constriction velocity (CV) values at all time points tested starting at day 3 from mechanical ventilation, and up to day 5. The patients with ICU delirium have lower values of PLR (20 [IQR, 15 to 28] vs. 25 [IQR, 19 to 31] % $p=0.012$) and CV (1.7 [IQR, 1.4 to 2.4] vs. 2.5 [IQR, 1.7 to 2.8] mm/s $p=0.017$) at day 3, results confirmed up to day 5 ($p<0.05$). Even the administration of opioid and sedative drugs did not reduce the association between delirium and PLR. Low PLR values are associated with an increased risk of delirium of OR 1.057 [95% CI, 1.007 to 1.113] at day 3; p = 0.03) [43].

D. Transcranial Color Doppler

Since 1982, when Rune Aaslid introduced Transcranial Doppler (TCD) as a bedside tool in monitoring neurocritical patients, this technique has recorded an increasing role in the routine monitoring and although not extensively used for assessing delirium, a few studies have been published in the last years about its role in predicting delirium (Figure 10).

The Korean group led by Soh [44] conducted a prospective observational trial on 113 patients scheduled for valvular heart surgery, their eligibility was assessed before surgery with CAM-ICU and MMSE to evaluate baseline cognitive function and depressive mood; before anesthetic induction, all patients received a TCD evaluation (measuring bilaterally middle cerebral artery (MCA) mean blood flow velocity (MFV)) and underwent continuous bi-hemispheric NIRS observation until ICU transfer. Postoperative delirium was observed in 16 patients: intraoperative hemodynamic parameters and arterial blood gas analysis data were comparable between the groups, number of ICU days and number of hospital days were increased in the delirium group but a significant relationship between the preoperative MCA MFV value and postoperative delirium could not be detected (lower MCA MFV (cm/s) 37±13 vs 39±11, p=0.548) (lower MCA MFV < 30 cm/s (%) 4 (25) vs 21 (22), p=0.751).

In 2012 Benvenuti et al. [45] performed a neurosonologic evaluation on a relatively small group of right-handed patients admitted for cardiac surgery measuring bilateral MCA blood flow velocity at rest and neuropsychological evaluation before surgery (Trail-Making Test A and B, approximately 15 days before) and the day before hospital (approximately 7 days after surgery) 45% showed a clinically significant cognitive decline after surgery. In this study POCD was predicted by education, EuroSCORE (which includes sex, age, and cardiac- and operation-related factors e.g., unstable angina, pulmonary hypertension, emergency

operation, ventricular septal rupture), and the left CBF velocity (OR = 0.90, [95% CI, 0.82 to 0.98], $p < 0.02$) but not the right CBF velocity (OR = 1.07, [95% CI, 0.99 to 1.16], $p = 0.39$).

Transcranial Doppler has been used other than in surgical settings to assess delirium. Caplan and his group in 2014 [46] used this non-invasive technique to evaluate delirium superimposed on dementia suggesting that a switch to anaerobic glycolysis in the CNS during delirium compared to Alzheimer's dementia might be related to a greater hypoperfusion. Fourty-four patients were eligible for inclusion in this cohort study and recruited in four groups: acute illness and delirium but no history of dementia, the Delirium superimposed on dementia (DSD) group, acute illness without delirium or dementia and no acute illness or delirium, known Alzheimer's dementia.

TCD was able to distinguish DSD from all other groups with a mean middle cerebral artery blood FV cut-off of 32.25 cm/s able to accurately diagnose delirium superimposed on dementia with a sensitivity of 0.875 and specificity of 0.788.

David Pfister et al. [47] studied sepsis-associated delirium and the possible correlation with cerebral perfusion using TCD and ICM+ software®(Intensive Care Monitoring developed by the Clinical Neuroscience Department in Cambridge (Department of Neurosurgery, Addenbrooke's Hospital Cambridge, University of Cambridge) in order to analyze cerebral autoregulation. Time Correlation Method (Mx index) is a correlation between cerebral perfusion pressure (CPP) and flow velocity (FV). Values of Mx of greater than 0.3 have been shown to be associated with disturbed autoregulation [48]. Cerebral perfusion assessed with TCD and NIRS showed no difference between patients with and without sepsis-associated delirium, but the state of autoregulation differed between the two groups ($p=0.015$) and this may be due to harmful effect of inflammation impeding cerebrovascular endothelial function

A. Summary

Patients undergoing surgery have a variable incidence between 20 and 45% of developing delirium in the following hours and days. POD is associated with increased morbidity, mortality and length of hospital stay. It represents a direct risk factor for developing cognitive impairment after surgery. The anesthetist can reduce the incidence of POD by using non-invasive neuromonitoring in the operating room with the aim of reducing the risks associated with the anesthesia itself. The depth of anesthesia guided by pEEG represents a risk factor for the development of POD. This tool is able to reduce the warnings and burst suppression phases. Although not all studies agree, the use of pEEG would seem to reduce the incidence of POD. The use of other non-invasive intraoperative monitoring (NIRS, TCCD, automated pupillometry) in preventing POD represent a high variability of results, therefore the design of clinical studies capable of asking a definitive answer to this question becomes fundamental.

- Delirium is a sign of possible postoperative complication.
- It is essential to identify patients at risk of developing POD. Anesthesiologist must reduce as much as possible the risk factors related to the anesthesia itself.
- The use of pEEG allows monitoring of the depth of anesthesia, reducing awareness and burst suppression episodes.
- There is evidence (weak) to support the recommendation for the use of EEG monitoring in elderly and high risk patients with the aim of reducing POD.
- Use of NIRS, TCCD and automated pupillometry have questionable utility in preventing POD.

Research agenda

- Future research will have to evaluate the use of the pupillometer and TCCD in identifying patients at risk of developing POD and whether the identification can improve the outcome.
- A study with larger sample size is needed to definitively answers the usefulness of pEEG in preventing burst suppression and development of POD and POCD.
- The research should evaluate whether the use of more non-invasive neuromonitoring in the operating room is able to reduce the incidence of POD more than the single instrument.

Conflict of Interest: None

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Monitoring	**Study**	**Design**	**Patients**	**Main findings with delirium**
pEEG	Fritz *et al.*, 2016. [23]	Observational cohort study. Surgery: cardiac and non-cardiac.	727	Patients with more suppression were more likely to experience delirium (p<0.0001). Duration of BIS<20 predicted postoperative delirium with a moderate c-statistic of 0.57 [95% CI, 0.52 to 0.62]. EEG suppression may have been associated with reduced functional independence (Spearman partial correlation coefficient -0.15, p=0.02).
	Wildes *et al.*, 2019. [24]	Randomized clinical trial. Receive EEG-guided anesthetic administration or usual anesthetic care. Major surgery.	1232	Postoperative delirium occurring in 157 of 604 (26.0%) in the guided group and 140 of 609 (23.0%) in the usual care group (difference, 3.0% [95% CI, -2.0% to 8.0%]; p=0.22). EEG suppression was significantly less in the guided group (7 vs 13 minutes; difference, −6.0 [95% CI, −9.9 to −2.1]).
	Chan *et al.*, 2013.	Randomized clinical	1657	There were fewer patients with delirium in the BIS-guided

	[25]	trial double blended: receive either BIS guided anesthesia or routine care. General surgery.		group compared with routine care (15.6% vs. 24.1%, OR 0.58 [95% CI, 0.41 to 0.80] p=0.01). Patients in the BIS group had a lower rate of POCD at 3 months compared with routine care (10.2% vs 14.7%; adjusted odd ratio 0.67 [95% CI, 0.32 to 0.98, p=0.025]).
	Siddiqui *et al.*, 2016. [26]	Cochrane Database Systematic Reviews.	2057	BIS-guided anesthesia reduces the incidence of delirium when compared with BIS -blinded anesthetic or clinical judgment (RR 0.71, [95% CI, 0.60 to 0.85]). BIS-guided anesthesia reduces cognition at 3 months (RR 0.71, [95% CI, 0.53 to 0.97].
	Lu *et al.*, 2018. [27]	Metaanalysis	-	POCD showed no significant difference between low and high BIS groups (RR 0.84 [CI 95%, 0.21 to 3.45], P>0.05) POD showed significant difference between low and high BIS group (RR 2.09 [CI 95%, 1.13 to 3.88], P=0.019)
NIRS	Holmgaard *et al.*, 2019. [28].	This is a secondary analysis of the PPCI	153	The median time with rScO2 >10% below preoperative values did not differ for patients with and without POCD at discharge (difference1⁄40.0 min; Hodges-Lehmann [CI

		trial. The association between intraoperative rSO_2 values and POCD at discharge from hospital and at 3 months after surgery was investigated. Cardiac surgery.		95%, - 3.11 to 1.47, P=0.88).
	Zheng *et al.,* 2013. [29]	Systemic review: 13 case reports, 27 observational studies, and 2 prospectively randomized intervention trials. Cardiac surgery.	-	They found that preoperative rSO_2 was lower in patients who developed postoperative delirium than in those who did not (mean ± SD, 58.1% ± 7.7% vs 63.1% ± 7.2%, P≤0.001). The area under the curve for an rSO_2 cutoff of 50% was larger (41.6 ± 114.9 vs 19.5 ± 94.9, P ≤ 0.001) and the minimal rSco2 lower (48.6% ± 9.3% vs 55.1% ± 8.6%, P≤0.001) for patients who developed delirium than for

				those who did not. rSO_2 for predicting delirium (0.73; [95% CI, 0.66–0.80, P=0.0001]) showed that an rSO_2 cutoff of 51% best predicted delirium (sensitivity, 60.0%; specificity, 75.6%).
	Yu *et al.,* 2018. [30]	Cochrane Library	-	We are uncertain whether active cerebral NIRS monitoring has an important effect on postoperative delirium because of the wide confidence interval (RR 0.63, [95% CI, 0.27 to 1.45]; 1 study, 190 participants; low-quality evidence). Two studies with 126 participants showed that active cerebral NIRS monitoring may reduce the incidence mild (POCD) (RR 0.53, [95% CI, 0.30 to 0.95).
	Ortega-Loubon *et al.,* 2019. [31]	Meta-Analyses. Surgery: cardiac and non-cardiac.	1626	NIRS-based algorithms are useful in preventing POCD/POD in cardiac surgery (OR 0.34 [95% CI 0.14 to 0.85], but not in major noncardiac surgery (OR 0.33 [95% CI 0.10 to 1.14]. Maintaining brain-oxygen saturation (bSo_2) > 80% of the baseline appeared to have the most pronounced impact.

	Slater *et al.,* 2009. [32]	Prospectively randomized trial to a blinded control group or an unblinded intervention group. Cardiac surgery.	240	Patients with rSO_2 desaturation score greater than 3,000%-second had a significantly higher risk of early postoperative cognitive decline [p<0.024]. Patients with rSO_2 desaturation score greater than 3,000%-second also had a near threefold increased risk of prolonged hospital stay (>6 days) [p < 0.007].
	Hori *et al.,* 2014. [33]	Prospective observational study. Cardiac surgery.	491	Duration of MAP above an ULA (mm Hg h; OR, 1.09; 95% CI, 1.03-1.15) and age (per year of age; OR, 1.01; [95% CI, 1.01 – 1.07]) were independently associated with postoperative delirium.
Automated pupillometry	Yang *et al.*, 2018. [34]	Prospective observational. Ambulatory surgery.	47	Percent constriction (AUC=0.93, optimal threshold=18.5%) and dilation velocity (AUC=0.93, optimal threshold=0.35 mm/s) predicted delirium.
	Favre *et al,* 2020. [21]	Observational cohort study. Critically ill patients in ICU.	100	ICU delirium had lower values of q-PLR (20 [IQR:15-28] vs. 25 [IQR:19-31] %) and CV (1.7 [IQR:1.4-2.4] vs. 2.5 [IQR:1.7–2.8] mm/s) at day 3, and at all additional time-

				points tested ($p<0.05$). Lower q-PLR was associated with an increased risk of ICU delirium (OR 1.057 [95% CI, 1.007 to 1.113] at day 3; p = 0.03).
TCCD	Soh *et al.,* 2019. [35]	Prospective observational trial. Cardiac surgery. Predictive value of MCA MFV and rSO_2, before induction of anesthesia for delirium.	113	MCA MVF values could not predict the development of delirium. Low preoperative rSO_2 (<60%) showed association with delirium. Low preoperative rSO_2 (<60%) (OR 6.748, [95% CI 1.647 to 27.652], P=0.008) independent predictor of delirium.
	Benvenuti *et al.,* 2012. [36]	Prospective observational study. Cardiac surgery. Relationship between	31	Cerebral hypoperfusion in the left MCA selectively predicted the incidence of POCD (OR = 0.90 [95% CI, 0.82 to 0.98] p <0.02), whereas CBF velocity in the right MCA was unrelated to POCD (OR = 1.07, [95% CI, 0.99

		MCA blood flow velocity at rest and neuropsychological evaluation before surgery and the day before hospital (7 day after surgery).		to 1.16] p = 0.39).
	Caplan *et al.,* 2014. [37]	Prospective cohort study. Delirium superimposed on dementia (DSD) is associated with greater reductions in CBF by noninvasive, safe transcranial Doppler (TCD).	44	TCD was able to distinguish DSD from all other groups with a mean middle cerebral artery blood FV cut-off of 32.25 cm/s able to accurately diagnose delirium superimposed on dementia with a sensitivity of 0.875 and specificity of 0.788 (AUC 0.884 p=0.001).

	Pfister *et al.*, 2008. [38]	Prospective observational study. Sepsis- associated delirium in the ICU.	16	No significant difference in MAP or cerebral perfusion assessed with TCD and NIRS in the two groups of patients (delirium and no delirium). Significant association between sepsis-associated delirium and disturbed autoregulation (*P* = 0.015).

Table 1: Non-invasive monitoring and delirium. Abbreviations: bSo_2 brain-oxygen saturation. DSD: Delirium superimposed on dementia. ICU: Intensive Care Unit. IQR: Interquartile range. MAP: Mean arterial pressure. MCA: Middle cerebral artery. MFV: Mean blood flow velocity. OR: odds ratio. pEEG: processed EEG. POCD. Postoperative cognitive dysfunction. POD: postoperative delirium. rSO_2: cerebral oximetry. TCD: transcranial doppler. ULA: upper limit autoregulation. ±: standard deviation

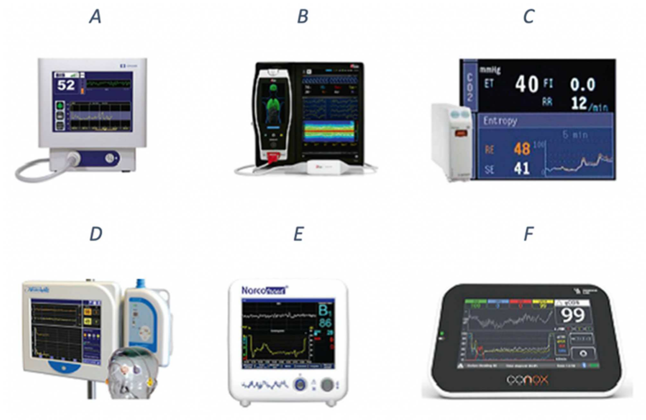

Figure 1: Examples of the processed EEG (A: BIS (Medtronic, Boulder, CO); B: SEDLine (Masimo Corp, Irvine, CA); C: E-Entropy (GE Healthcare, Helsinki, Finland); D: NeuroSENSE (NeuroWave Systems, Inc., Cleveland Heights, OH); E: Narcotrend (Narcotrend Gruppe, Hannover, Germany); F: CONOX (Fresenius Kabi, Hong Kong).

Figure 2: Patient during induction of general anesthesia (Arrow: frontal raw EEG) (Data delivered by processed EEG devices: BIS, Medtronic, Boulder, CO.).

Figure 3: Patient under general anesthesia (Arrow: frontal raw EEG) (Data delivered by processed EEG devices: BIS, Medtronic, Boulder, CO.).

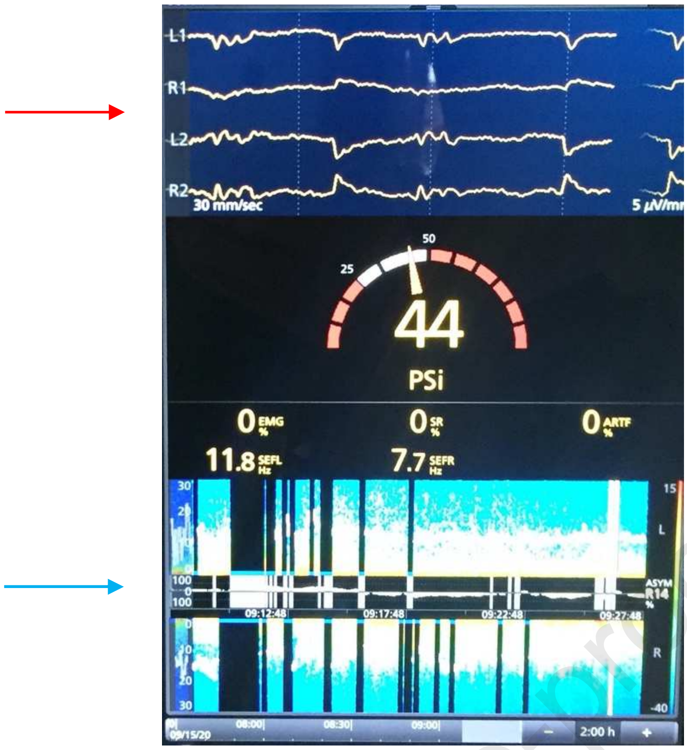

Figure 4: Patient under general anesthesia (Red arrow: bi-frontal raw EEG; blue arrow: Density Spectral Array; PSi: Patient State Index) (Data delivered by processed EEG devices: SEDLine, Masimo Corp, Irvine, CA).

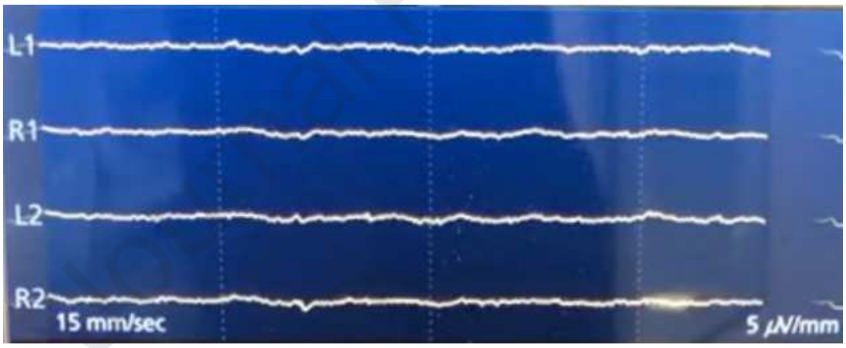

Figure 5: Absence of brain activity (isoelectric) (Data delivered by processed EEG devices: SEDLine, Masimo Corp, Irvine, CA).

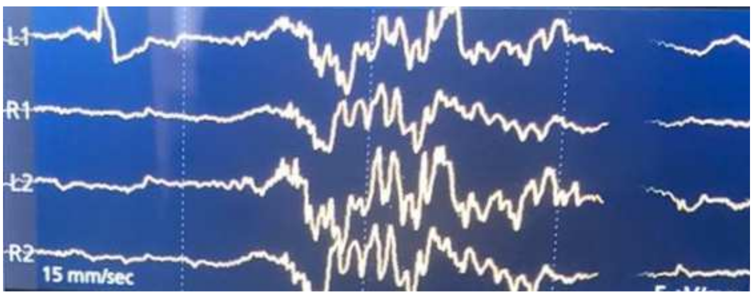

Figure 6: Burst suppression (Data delivered by processed EEG devices: SEDLine, Masimo Corp, Irvine, CA).

Figure 7: Cerebral oximetry using Near Infrared Spectroscopy (NIRS) (Arrow: rSO_2: regional oxygen saturation left and right) (Data delivered by INVOS™ 5100C Cerebral/Somatic Oximeter, Medtronic, Boulder, CO).

Figure 8: Examples of the automated pupillometry (A: Neurolight-Algiscan, IDMED, Marseille, FR; B: NeurOptics NPi-200, NeurOptics, Laguna Hills, CA).

	Destra	Sinistra	Diff
NPi	4.8	4.4	D > S 0.4
Dia	2.01 mm	1.90 mm	D > S 0.11
MIN	1.49 mm	1.65 mm	S > D 0.16
CH	26%	13%	
CV	1.21 mm/s	0.92 mm/s	
MCV	1.83 mm/s	1.19 mm/s	
LAT	0.23 sec	0.27 sec	
DV	0.50 mm/s	0.16 mm/s	

Figure 9: Example of the automated infrared pupillometry devices available on the market (NPi: Neurological Pupillary index; Dia: Diameter (mm); MIN: Minimum pupil size (mm); CH: Change in the pupil in %; CV: Constriction velocity (mm/s); MCV: Maximum constriction velocity(mm/s); LAT: Latency (sec); DV: Maximum dilation velocity(mm/s))(Data delivered by NeurOptics NPi-200, NeurOptics, Laguna Hills, CA).

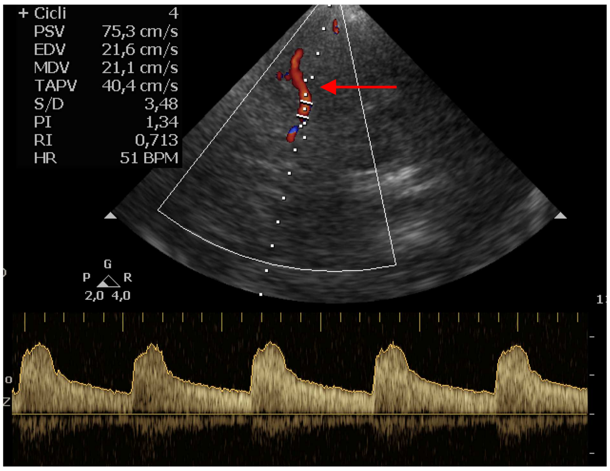

Figure 10: Transcranial Color Doppler (Arrow: middle cerebral artery).

Conflicts of Interest Statement

Manuscript title:

NON INVASIVE NEUROMONITORING IN THE OPERATING ROOM AND ITS ROLE IN THE PREVENTION OF DELIRIUM

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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This statement is signed by all the authors to indicate agreement that the above information is true and correct

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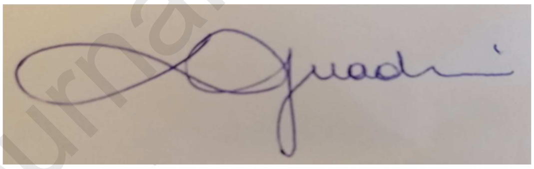
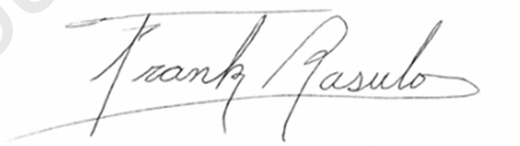
Lucrezia Guadrini		28/08/2020
Frank Rasulo		28/08/2020