J Extra Corpor Technol. 2017;49:182–191
The Journal of ExtraCorporeal Technology

Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review

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Abstract: Postoperative neurological complications (PNCs) following cardiac surgery with cardiopulmonary bypass (CPB) is a detrimental complication, contributing to increased mortality rates and health care costs. To prevent intraoperative cerebral desaturations associated with PNC, continuous brain monitoring using near-infrared spectroscopy has been advocated. However, clear evidence for a defined desaturation threshold requiring intervention during CPB is still lacking. Since cerebral oximetry readings are nonspecific, cerebral tissue oxygenation values need to be interpreted with caution and in the context of all available clinical information. Therefore, maintaining an intact autoregulatory activity during CPB rather than solely focusing on regional cerebral oxygen saturation measurements will collectively contribute to optimization of patient care during CPB. **Keywords:** cerebral autoregulation, cerebral oximetry, cardiopulmonary bypass, postoperative neurological complications. *J Extra Corpor Technol. 2017;49:182–191*

The advancement of extracorporeal circulation techniques in recent decades has played an essential role in minimizing complications following cardiac surgery with cardiopulmonary bypass (CPB) (1). The technical advancements have been, however, partially offset by changes in the patient population. These changes involve a more complex disease at advanced age and significant comorbidities (2–4), resulting in convoluted and lengthier procedures. Moreover, in older patients, the atherosclerotic disease process is farther advanced, which may nourish an increased risk for postoperative complications including perioperative stroke and neurocognitive impairment, including delirium (1,4,5). From these, stroke has been reported to be the most detrimental with rates varying from 1.5% to 11% (6–10). Furthermore, these postoperative neurological complications (PNCs) contribute to prolonged hospital stay, increased mortality rates and health care costs, constituting to an increased burden for health care providers (11,12).

Received for publication November 20, 2016; accepted March 22, 2017.
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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

The mechanism of cerebral injury following cardiac surgery with CPB is not yet clearly understood. Development of PNC possibly involves embolization or hypoperfusion causing cerebral ischemia (5,11,13,14). To prevent intraoperative cerebral desaturations associated with ischemic complications of the brain, continuous brain monitoring using near-infrared spectroscopy (NIRS) has been advocated (15,16). Although multiple studies proposed cerebral oximetry as a viable monitoring method to prevent these neurologic complications, clear threshold determinants for acute intervention are still lacking (14,17).

Furthermore, there seems to be a link between disturbed intraoperative cerebral autoregulation (CA) and PNC (18–21). The neuroprotective autoregulatory system prevents both hypo- and hyperperfusion by reactive vasodilation and constriction following changes in arterial blood pressure (ABP) and arterial partial pressure for carbon dioxide (p_aCO_2), also referred to as modifiable factors (13). These factors are mostly based on maintaining a mean ABP of 50–60 mmHg (22) and p_aCO_2 is only measured intermittently during CPB. Obviously, there is a lack of optimal control for CA functionality.

Clinical application of cerebral oximetry, its limitations and association with PNC as well as the role of modifiable factors influencing the neuroprotective autoregulatory system during CPB are subsequently reviewed.

CEREBRAL TISSUE OXIMETRY

Cerebral oximetry allows clinicians to monitor regional cerebral tissue oxygen saturation (rSO_2) real-time in a non-invasive manner. Cerebral rSO_2 is dependent on several physiological variables that affect oxygen supply and consumption of the brain, including cardiac output, inspired oxygen concentration, pulmonary function, cerebral metabolism, temperature, and hemoglobin concentration (23,24). Cerebral oximetry readings are proposed to reflect the balance between regional oxygen supply and demand and thereby local cerebral metabolism (11,25–27). More specifically, a decreasing cerebral rSO_2 due to regional or global ischemia can be explained as an oxygen supply insufficient to meet the metabolic demand caused by, e.g., a decreased cardiac output (26,28). Unlike mixed venous oxygen saturation that is measured continuously via a pulmonary artery catheter, cerebral oximetry has shown to reflect alterations in blood pressure real time (29). This suggests that cerebral oximetry enables prompt assessment of tissue oxygenation, serving as a potential early indicator of neurologic injury.

The technique applied in cerebral oximetry uses NIRS based on the Beer–Lambert law (14,30). The elementary particles of near-infrared light are photons that penetrate tissue before reaching the underlying capillary network. Near-infrared light of different wavelengths within the so-called biological spectroscopic window is emitted to penetrate the skin, skull, and dura matter to reach the frontal lobe of either the left or right cerebral hemisphere (11). The photons emitted through a NIRS sensor travel via a banana-shaped pathway before being measured by photodiode detectors positioned at a fixed distance from the light emitter when they resurface. Within tissue, the light is partly reflected, scattered, and absorbed. To minimize residual error, two measurements with different emitter-diode spacings are performed simultaneously, resulting in a shallow-deep detector difference. With the light intensity held constant, the quantity of light absorbed by chromophores varies with the ratio of oxygenated hemoglobin relative to the total concentration of hemoglobin, which is used to estimate local oxygen content (14,17). Most clinical devices use one near-infrared light emitter in combination with two near-infrared light detectors, whereas other devices use several detectors per emitter. The latter may contribute to the accuracy of cerebral rSO_2 estimation; however, the measurement principle remains the same. In addition, the algorithm for estimating the oxygen content in cerebral blood requires an assumption on the ratio venous to arterial blood volume, which differs between clinical oximeter devices. The Food and Drug Administration approved four monitoring devices for clinical use in the United States, which include the Fore-sight cerebral oximeter (Cas Medical Systems, Inc., Branford, CT), Equanox (Nonin Medical Inc., Plymounth, MN), INVOS 5100C (Medtronic, Minneapolis, MN), and the CerOx (Ornim Medical, Lod, Israel). Both Fore-sight and Equanox use the ratio of 70% venous blood to 30% arterial blood, whereas INVOS 5100C and CerOx use a ratio of 75% venous to 25% arterial blood (29,31). Additionally, cerebral oximeters may provide one or several types of measurement, estimating absolute rSO_2 values (Fore-sight and Equanox), or values intended for trend monitoring (INVOS 5100C and CerOx).

Corresponding to the cerebral oximetry measurement principle, rSO_2 values can only partially reflect oxygen saturation in the anterior circulation of the prefrontal cortex, thereby limiting its monitoring ability to an area of approximately 1 cm^3 (23,29,32). Also extracerebral tissues including skin, bone, and connective tissue may contaminate the estimation of rSO_2 (33). In addition, tissue oximetry derived values are nonspecific, meaning that a decreasing rSO_2 may be the result of hypoperfusion, relative hypoxemia, and/or an increased metabolic rate (14). Hence, when interpreting changes in cerebral rSO_2 it is necessary to consider all available clinical information (23).

The algorithm to estimate cerebral rSO_2 takes the predominant venous part of the cerebral blood volume into account that is reflected by a strong correlation between rSO_2 and jugular venous oxygen saturation, an early indicator of brain ischemia (34,35). Other studies, however, reported that rSO_2 is unable to reflect changes in jugular venous bulb oximetry in the case of head injury (36,37). Nevertheless, a recent observational study has shown that cerebral oximetry is sensitive enough to effectively identify changes in rSO_2 following iatrogenic events including anesthetic induction, aortic cross clamping, and onset and termination of bypass (38). In addition, cerebral oximetry has shown to effectively depict the concomitant decline in cerebral oxygen saturation during cannula malposition (39–41), a failing oxygen line to the oxygenator in the CPB circuit (42) and acute innominate artery dissection (43). These findings indicate that cerebral oximetry may aid in early detection of potential adverse neurologic events and contribute toward preventing PNC by enabling alteration of current patient management.

Although absolute (fixed value for rSO_2) and relative (percentage of baseline rSO_2) desaturation thresholds have been previously applied (44,45), to date no consensus has been reached on the use of either an absolute or personalized cutoff value requiring prompt intervention (17,46). Nonetheless, it is generally accepted that both the extent and duration of cerebral desaturation are important (14,46). Furthermore, this lack of standardization may be related to the different monitoring devices which use varying numbers and wavelengths of light emitted as well as sensor-emitter spacings, affecting both the measurement itself and the rSO_2

calculation (3,30). Differences in applied algorithm between the devices further challenge cerebral oximetry standardization. Moreover, the algorithm itself cannot accommodate for inter-individual differences including variations in cranial anatomy (e.g., asymmetrical brain circulation (23), different percentages of venous cerebral blood circulating in the frontal lobe (47) and the influence of non-modifiable patient characteristics on baseline rSO_2 readings (25)). The algorithm requires the assumption of a constant optical path length that is actually decreased during CPB due to hemodilution, altering the absorbance of near-infrared light by chromophores. This may introduce an error in the estimation of the local oxygen content (30). In summary, focusing on an rSO_2 threshold as suggested by Douds et al. (48) would be a provocative step towards the use of cerebral oximetry as a preemptive marker for perioperative morbidity to optimize postoperative recovery.

CEREBRAL TISSUE OXIMETRY AND PNCs

Since the widespread clinical application of tissue oximetry, several studies investigated the relationship between cerebral oximetry readings and PNC. The current evidence on the relationship between cerebral desaturations as identified by cerebral oximetry and PNC following cardiac surgery with CPB is systematically reviewed in this section.

To identify relevant publications, PubMed and MEDline databases were searched for articles originating from January 2006 to August 2016. Two researchers searched and screened articles on title, abstract, and full text independently. Additional studies were identified by screening the references in the retrieved papers to capture articles that might have been missed.

The articles included were studies that focused on the relationship between cerebral oximetry readings and cognitive decline following cardiac surgery with CPB in adults. The search was limited to publications in English. Studies that were not published as a full-length article or did not discuss PNC outcome in relation to cerebral oximetry readings were excluded. Free search terms were divided in two main groups, the first representing cerebral oximetry and the second representing cardiac surgery with CPB. The cerebral oximetry category included the search terms "near infrared spectroscopy", "infrared spectroscopy", "NIRS", "cerebral oximetry", and "cerebral oxygen saturation", whereas the cardiac surgery with CPB category included the search terms "cardiac surgery", "CPB", "coronary artery bypass grafting" (CABG), "CABG", and "coronary artery bypass graft". For each search, one of the aforementioned search terms from both groups was combined.

RESULTS

The initial search focusing on cerebral oximetry resulted in 507 publications using all combinations of free search terms. Review of the title and abstract led to inclusion of 21 out of 507 articles. A total of 13 observational and 7 interventional studies were identified as depicted in Table 1.

Several studies found a relationship between cerebral desaturations and neurological complications, including a study by Colak et al. who showed an increased occurrence of stroke in patients with cerebral desaturations, defined by both absolute (area under the curve of >50 minutes$\cdot$% under 50% absolute rSO_2) and relative (area under the curve >150 minutes$\cdot$% under 20% of baseline rSO_2) thresholds (45). Similarly, Slater et al. and de Tournay-Jetté et al. found a significant relationship with early postoperative neurocognitive decline when the absolute desaturation threshold of 50% rSO_2 was exceeded (50,63). In patients undergoing aortic arch surgery, Fischer et al. noted more conservative absolute desaturation thresholds of 65% and 60% to indicate an increased risk of adverse outcome (51). Contrastingly, Kok et al. in a pilot study failed to show a relationship between cerebral desaturation and PNC (64).

Moving forward to interventional-guided studies, Slater et al. through a prospective randomized interventional trial found a positive relation between cerebral desaturations and PNC using the mini-mental state examination (MMSE) (63). In another prospective randomized interventional trial, Murkin et al. studied cerebral desaturations and postoperative morbidity in cardiac surgical patients undergoing CPB (62). More patients in the control group ($n = 96$) (i.e., no intervention based on normalization of intraoperative rSO_2 within 75% of baseline) underwent prolonged cerebral desaturation episodes compared to the intervention group ($n = 98$). Stroke rate, however, did not significantly differ between groups. The authors attributed this finding to the fact that their study lacked adequate statistical power for assessment of stroke ($n = 4$ in the control group, vs. $n = 1$ in the intervention group), as the a priori power analysis was based on major organ morbidity and mortality. Nevertheless, they conclude that intraoperative monitoring and management using cerebral oximetry may have a clinical benefit for the cardiac surgical patient.

INTERPRETATION

Several studies suggest that cerebral oximetry is a valuable monitoring tool and implicate that early intervention based on cerebral oximetry monitoring can potentially prevent or decrease the occurrence of PNC. Murkin even proposed that cerebral oximetry can be applied as an index organ, indicating that maintaining adequate cerebral rSO_2 values is beneficial for all vital organs (15). Despite these

Table 1. Overview of the studies included in the systematic literature search.

Author	Year	Type of Study	Device Used	*n*	Relation rSO_2-PNC	rSO_2 Threshold	Outcome Measured	Measuring Complications
Negargar (49)	2007	PO	INVOS	72	No	Absolute decrease <40% and 50%, >20% absolute desturation from baseline	Neuropsychological state	MMSE
De Tournay-Jetté (50)	2011	PO	INVOS	61	Yes	Absolute decrease <50%, >30% decrease from baseline	Early (4–7 days) and late (1 month) POCD (drop of 1SD from baseline (the day before surgery) on ≥2 more neuropsychologic indices)	Trail Making Test part A and B, Verbal Fluency Test, Ray's Auditory Verbal Learning Test, Logical Memory Subtest (Rivermead battery), digit symbol, Stroop Test
Fischer (51)	2011	PO	Fore-sight	30	Yes	Absolute decrease <50%, <55%, <60%, <65%	Severe adverse outcome, including stroke	not specified
Schoen (52)	2011	PO	INVOS	231	Yes	Absolute decrease <50% absolute, >80% decrease baseline	Delirium	MMSE, CAM-ICU
Hong (53)	2008	PO	INVOS	100	No	Absolute decrease <40%, 50%, >20% decrease from baseline	POCD	MMSE, Trail-Making Test (Part A), Grooved Pegboard Test
Fudickar (54)	2011	PO	Niro	35	Yes	Absolute decrease <65%	Postoperative cognitive deficit	Trail Making Test, Verbal Learning Test, Ray's Auditorial Verbal Fluency Test, Digit Symbol Substitution Test, Digit Span Test
Olsson (55)	2006	RO	INVOS	46	Yes	None	Stroke	New neurologic deficit that did not resolve before discharge confirmed by CT and/or specialist neurologic assessment
Urbanski (56)	2013	PO	Niro	122	No	Absolute decrease ≤55%, <80% change from baseline	Adverse neurological outcome (permanent focal neurological deficit or temporary neurological dysfunction)	Permanent focal neurological deficit: confirmed by a neurologist and CT or MRI. Temporary neurological dysfunction: confusion, delirium, agitation or temporary focal deficits without evidence on CT or MRI.
Kakihana (57)	2012	PO	Hamamatsu	10	Yes	None	Stroke	MMSE
Hassan (58)	2010	POP	Fore-sight	1	Yes	Absolute decrease <55%	Neurocognitive deficit	not reported
Greenberg (59)	2013	PO	Fore-sight	53	No	Absolute decrease <60% ≥60 seconds in ≥1 hemisphere	Delirium	not reported
Senanayake (60)	2012	PO	INVOS	27	Yes	None	Permanent or temporary neurological deficit	Permanent neurological deficit: any new postoperative neurological deficit that included new focal stroke or global coma which did not resolve by discharge, and confirmed by a new cerebral infraction on CT. Temporary neurological deficit: any postoperative neurological deficit that included motor deficit, confusion, agitation, or transient delirium that resolved spontaneously before discharge with no new cerebral infarction on CT.

Table 1. *Continued.*

Author	Year	Type of Study	Device Used	*n*	Relation rSO_2-PNC	rSO_2 Threshold	Outcome Measured	Measuring Complications
Kamenskaya (61)	2015	PO	INVOS	61	Yes	Absolute decrease <40%	Neurological complications (encephalopathy, stroke)	MMSE, GCS
Murkin (62)	2007	PRI	INVOS	194	No	AUC <70% of baseline >150 minutes•%, desaturation AUC <40% asbolute	Stroke	Focal neurologic deficit persisting >24hrs and confirmed by CT
Colak (45)	2015	PI	INVOS	200	Yes	Absolute decrease <50%, AUC >150%•min <20% of baseline, AUC >50min•%	Cognitive decline	MMSE, Color Trail Test 1, Grooved-Pegboard Test
Slater (63)	2009	PRI	INVOS	240	Yes	Desaturation score >3000	Early POCD	Neurocognitive test battery
Kok (64)	2014	PIP	INVOS (but both INVOS and Fore-sight were measured)	60	No	AUC 40% >10 minutes•%	Postoperative cognitive decline (4 days (early) and 3 months (late))	CogState brief computerised cognitive test battery
Mohandas (65)	2013	PI	Equanox	100	Yes	>20% decrease from baseline	PNC	MMSE, ASEM
Colak (66)	2012	PI	INVOS	58	Yes	AUC>150 minutes•% for <20% of baseline or >50 minutes•% for <50% of absolute value	Stroke, coma, stupor	Coma: profound state of unconsciousness without response to verbal call, pain or any other stimulus. Stupor: state of unconsciousness from which patient can be aroused only by vigorous physical stimulation. Stroke: acute onset of a neurologic deficit that persists for at least 24 hours and reflects focal involvement of the central nervous system. Delirium/ encephalopathy: confusion, agitation, disorientation, decreased alertness, sleep disturbances, memory deficit or seizure without obvious focal neurological deficit.
Murkin (67)	2011	PI	INVOS	57	No	Decrease <75% of baseline >15 seconds.	New-onset stroke, major-organ morbidity and mortality	Unclear

ASEM, antisaccadic eye movement; AUC, area under curve; CAM-ICU, confusion assessment method on the intensive care unit; CT, computed tomography; GCS, Glasgow coma scale; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PI, prospective interventional; PIP, prospective interventional pilot; PNC, postoperative neurological complication; PO, prospective observational; POCD, postoperative cognitive dysfunction; POP, prospective observational pilot; PRI, prospective randomized interventional; RO, retrospective observational; rSO_2, regional cerebral tissue oxygen saturation.

findings it remains unclear if this is part of a causal relationship or just a reflection of overall morbidity (14).

In a recent systematic review, data on the specificity of rSO_2 monitoring to ensure cerebral perfusion could not be established, i.e., the absence of acute reductions in rSO_2 did not ensure adequate cerebral blood flow (CBF) (17). Furthermore, Kok et al. reported no relationship between cerebral desaturations and PNC, which can be explained by the fact that low rSO_2 occurred only sporadically in their patient population (64). This suggests that factors other than intraoperative hypoxic episodes contribute to the development of PNC. Moreover, the incidence of PNC following cardiovascular procedures is relatively low, which affects the ability of studies to demonstrate a significant association with cerebral desaturations (3,4,68). A plausible explanation for the low PNC occurrence can be found in the applied perfusion protocol, which includes maintaining the mean ABP within a certain range (70–90 mmHg),

maintaining normoxia (partial arterial oxygen pressure between 11.0–14.0 kPa or 83–105 mmHg) and normocapnia ($paCO_2$ 4.5–5.5 kPa or 34–41 mmHg), with a hematocrit level >28% throughout the intraoperative period (69). Further, it has been shown that avoiding large fluctuations in hemodynamic parameters during CPB decreases the risk of postoperative neurologic complications (70).

Besides perfusion protocols, additional factors that likely alter the risk of PNC occurrence include patient and surgery-related parameters. Previous studies identified the factors advanced age, a history of neurologic events, insulin-dependent diabetes mellitus, congestive heart failure, peripheral vascular disease, prolonged CPB time, and a more complex surgical procedure to be linked to PNC occurrence (6–9,17,20,45,68,71–74). In contrast, Fink et al. in a recent review state that the evidence linking cardiovascular procedures to cognitive outcome is scarce, and persistent postoperative cognitive impairment may solely reflect the presence of cognitive impairment prior to surgery (3).

Moreover, the lack of standardization in the diagnosis of PNCs make comparison between studies focusing on its determinants challenging. In the current literature, different cognitive assessment methods are applied to identify cognitive decline, of which the MMSE is most frequently used (12). These tests require measurements to be performed at different time points prior to and following surgical intervention. For diagnosis of stroke additional computed tomography scanning or magnetic resonance imaging is required (75). Furthermore, the MMSE does not account for frontal lobe abnormalities, which is the typical area for cerebral rSO_2 measurement (76), possibly causing a false-negative test result.

In summary, there is a lack of intervention-guided trials linking disturbances in cerebral oxygen saturation to occurrence of PNC. It is therefore doubtful whether regional rSO_2 can be used as a specific brain monitor.

CEREBRAL AUTOREGULATION

Besides intraoperative cerebral desaturations, disturbances in the neuroprotective cerebral autoregulatory system are known to result in adverse neurological outcome (18,77,78). The definition of CA is the intrinsic ability of the cerebral vasculature to provide a constant CBF despite changes in cerebral perfusion pressure (79). In case of an intact CA, the cerebral perfusion pressure is coupled with the cerebral metabolic demands, preventing both ischemia and hyperemia (77). The central homeostatic system of CA provides neuroprotection against hypo-, hyperperfusion, and ischemia through vasodilation and vasoconstriction of the cerebral vasculature. Proportionate alterations in CBF and subsequent maintenance of brain metabolism ensure adequate oxygen saturation and removal of carbon dioxide and other metabolites. The cerebral vasculature receives its postganglionic sympathetic innervation from the superior cervical ganglion containing neuropeptide Y and norepinephrine. This vascular response is dependent on vessel size and mostly initiated by the pial arteries extending from the circle of Willis (80). In case of a sudden increase in blood pressure, the cerebral autoregulatory response prevents cerebral hyperemia and disruption of the blood-brain barrier (81).This is reflected by the fact that when the CA fails, worsened clinical outcome can be expected, including an increased risk of PNC (82).

According to previous studies, cerebral oximetry reflects CA by close association with a determinant of autoregulation, i.e., the cross-correlation between middle cerebral artery blood flow velocity and mean ABP (83,84). Likewise, the positive association of a change in rSO_2 with a change in ABP is thought to reflect the absence of CA, also referred to as pressure passive cerebral perfusion (85,86). On the other hand, in the case of hyperperfusion (also referred to as luxury brain perfusion (87)), cerebral rSO_2 values can be close to baseline while the CA is severely disturbed. This can be explained by the fact that the cross-correlation between middle cerebral artery blood flow velocity and mean ABP is merely an intermediate indicator of CA, as the phase relationship in the autoregulatory response is not taken into account (88).

For assessing cerebral autoregulatory activity, either its efficiency or its efficiency combined with the time necessary for cerebrovascular resistance to adapt can be determined. These two methods are also referred to as steady-state CA or static CA and dynamic CA, respectively (89). In both static and dynamic assessment of CA, ABP as well as CBF velocity (CBFV) need to be taken into account. Mostly transcranial Doppler is used for quantification of CBFV, utilizing high-frequency sound waves to penetrate the acoustic temporal window of the cranium. One commonly used method validated for determining the current state of CA using transcranial Doppler is transfer function analysis that estimates phase shift, coherence, and gain. The phase shift is the time difference observed between ABP (input) signal and the CBFV (output) signal, whereas coherence reflects the strength of the linear relationship between ABP and CBFV. Gain represents the magnitude of the transfer function between CBFV and ABP (90). The result of the transfer function analysis is an autoregulation index ranging from 0 (absence of autoregulatory activity) to 9 (strongest autoregulatory activity) (91). In patients, fluctuations in ABP and thereby CBFV need to be initiated to provoke adaptation in cerebrovascular resistance. In awake subjects, this can be achieved through metronome-triggered

breathing while during CPB the indexed pump flow can be varied in a cyclic manner (69).

Although the association between cerebral desaturations and PNC remains inconclusive, the link between disturbances in the intrinsic autoregulatory system and PNC occurrence is well recognized (18,21,77,82,92–94). Despite this fact, disturbances in the CA are reported to occur relatively frequently, in 20% of patients undergoing CPB (18). The primary requisite to maintain an intact CA is targeting a mean ABP within a certain range, i.e., the lower and upper autoregulatory limits. A range of 60–150 mmHg has been recommended to attain intact CA, although these pressures can be affected by sympathetic nervous activity (95), which is the case in chronic hypertension (81). Also, the lower limit of CA has a wide inter-individual range, and thereby poses a challenge to predict an intact CA based on preoperative measurements (84). Within the autoregulatory range, CBF velocity appears unaffected by CPB pump flow (96). However, when ABP falls below the lower limit of CA, cerebral hypoperfusion and ischemia can result, as the cerebral vasculature cannot compensate any further for the reduction in perfusion pressure (97). Low CBF increases the risk of ischemic brain lesions leading to functional neuronal impairment or possibly even permanent neuronal injury (77). This has been confirmed by multiple studies reporting a positive relationship between a lowered mean ABP and the occurrence of adverse neurologic events (18,92,94). More specifically, a >15 mmHg reduction in ABP caused a 10% cerebral desaturation (98). In addition, a lowered perfusion pressure during bypass (60–70 mmHg) has been previously associated with an increased occurrence of postoperative delirium, while no differences in intraoperative cerebral oximetry values were found between a low and high systemic perfusion pressure group (99). On the other hand, an ABP above the upper limit leads to cerebral hyperperfusion and possibly even edema, swelling, and hemorrhages (77,78,100), predisposing the patient to an increased risk of postoperative delirium (94). Thus, maintenance of an adequate target ABP is important to enable autoregulatory vascular compensation (17) and thereby minimizing thrombotic and hypoxic events contributing to PNC (101,102). A recent study by Moerman et al. described several patterns of autoregulatory activity in response to a 20% change in blood pressure by administration of vasoactive drugs (29). One would expect that when CA is intact, CBF and rSO_2 remain constant despite changes in perfusion pressure. However, Moerman et al. observed a paradoxical response in some of the patients, i.e., a decrease in rSO_2 when the perfusion pressure was increased and an increase in rSO_2 when the perfusion pressure was decreased under normocapnic conditions. The authors contributed this phenomenon to an overcompensation of CA and considered it part of the normal physiologic response. Since multiple reaction patterns in cerebral autoregulatory activity were observed, they concluded that individualization of ABP targets might be the optimal approach to prevent hypo- and hyperperfusion. For example, in traumatic brain injury patients, CA may vary within a short time scale, underlining the importance of continuous CA monitoring (82).

Presumably this may prove beneficial in terms of PNC risk. Although carbon dioxide reactivity has shown to influence CBF and thus CA, all measurements in the study of Moerman et al. were performed at normocapnia, thereby precluding analysis of individual patterns of CA at different levels of $paCO_2$.

Apart from the influence of mean ABP, several studies showed elevated levels of $paCO_2$ to be accompanied by a decreased level of CA (69,87,103), affecting hemoglobin saturation and CBF (23). The report by Ševerdija et al. illustrated that hypercapnia is associated with a decreased autoregulatory activity (compared to normocapnia), whereas under hypocapnic conditions the level of CA is relatively close to baseline values (69). This effect has been elucidated through several studies and can be explained by the phenomena of hypocapnia causing an expansion of the autoregulatory plateau, resulting in improved CA functionality (104–106). In other words, both ABP and $paCO_2$ influence CBF and are still not tightly controlled within the autoregulatory limits during CPB (mean ABP between 60 and 150 mmHg and $paCO_2$ between 4.7 and 5.3 kPa or 35 and 40 mmHg) (69,107).

Additionally, the extent of hemodilution (hematocrit level ≤18% or <19%) showed to be related to PNC and possibly an increased risk of mortality (108,109). Mathew et al. even had to prematurely terminate their study due to the occurrence of adverse events attributed to profound hemodilution (108). Specifically, hemodilution has been associated with perioperative stroke in cardiac surgical patients (110). This relation can be partially explained by its adverse effects on CA (111). Ševerdija et al. showed that patients with a reduced hematocrit (<28%) during bypass have decreased levels of CA (69), whereas Karkouti et al. reported that a 12% decrease in hematocrit is associated with neurocognitive decline (110). Hemodilution combined with hypercapnia even resulted in the largest decrease in autoregulatory activity during CPB (69). These studies, therefore, emphasize the adverse effects of nadir hemodilution during CPB.

In conclusion, disturbances in CA are associated with cerebral malperfusion, contributing to adverse neurological outcome following cardiac surgery with CPB. Therefore, tight control of mean ABP within the autoregulatory range, avoiding hypercapnia and minimizing hemodilution and hemodynamic fluctuations during CPB will collectively contribute to preservation of CA and a further decrease in PNC occurrence. Although the literature linking cerebral

oximetry readings and PNC remains inconclusive, clinicians should prioritize maintaining an intact CA rather than solely focusing on maintaining rSO_2 values above a certain threshold. Future studies should aim at determining personalized values of mean ABP and $paCO_2$ to preserve an intact CA.

SUMMARY

PNCs following cardiac surgery with CPB are a detrimental complication, contributing to increased mortality rates and health-care costs. To prevent intraoperative cerebral desaturations associated with PNC, continuous brain monitoring using NIRS has been advocated. However, clear evidence for a defined desaturation threshold requiring intervention during CPB is still lacking. Since cerebral oximetry readings are nonspecific, cerebral tissue oxygenation values need to be interpreted with caution and in the context of all available clinical information. Therefore, maintaining an intact autoregulatory activity during CPB rather than solely focusing on regional cerebral oxygen saturation measurements will collectively contribute to optimization of patient care during CPB.

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