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.

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).

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 (pCO2), also referred to as modifiable factors (13). These factors are mostly based on maintaining a mean ABP of 50–60 mmHg (22) and pCO2 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., Plymouth, 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 rSO2 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 rSO2 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·% under 50% absolute rSO2) and relative (area under the curve >150 minutes·% under 20% of baseline rSO2) 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% rSO2 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 rSO2 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 rSO2 values is beneficial for all vital organs (15). Despite these
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th>Device Used</th>
<th>n</th>
<th>Relation rSO2-PNC</th>
<th>rSO2 Threshold</th>
<th>Outcome Measured</th>
<th>Measuring Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negargar (49)</td>
<td>2007</td>
<td>PO</td>
<td>INVOS</td>
<td>72</td>
<td>No</td>
<td>Absolute decrease &lt;40% and 50%, &gt;20% absolute desturation from baseline</td>
<td>Neuropsychological state</td>
<td></td>
</tr>
<tr>
<td>De Tournay-Jetté (50)</td>
<td>2011</td>
<td>PO</td>
<td>INVOS</td>
<td>61</td>
<td>Yes</td>
<td>Absolute decrease &lt;50%, &gt;30% decrease from baseline</td>
<td>Early (4–7 days) and late (1 month) POCD (drop of 1SD from baseline (the day before surgery) on ≥2 more neuropsychologic indices)</td>
<td>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</td>
</tr>
<tr>
<td>Fischer (51)</td>
<td>2011</td>
<td>PO</td>
<td>Fore-sight</td>
<td>30</td>
<td>Yes</td>
<td>Absolute decrease &lt;50%, &lt;55%, &lt;60%, &lt;65% absolute, &gt;80% decrease baseline</td>
<td>Severe adverse outcome, including stroke</td>
<td>not specified</td>
</tr>
<tr>
<td>Schoen (52)</td>
<td>2011</td>
<td>PO</td>
<td>INVOS</td>
<td>231</td>
<td>Yes</td>
<td>Absolute decrease &lt;50%, &lt;55%, &lt;60%, &lt;65% absolute, &gt;80% decrease baseline</td>
<td>Delirium</td>
<td>MMSE, CAM-ICU</td>
</tr>
<tr>
<td>Hong (53)</td>
<td>2008</td>
<td>PO</td>
<td>INVOS</td>
<td>100</td>
<td>No</td>
<td>Absolute decrease &lt;40%, &gt;50%, &gt;20% decrease from baseline</td>
<td>POCD</td>
<td>MMSE, Trail-Making Test (Part A), Grooved Pegboard Test</td>
</tr>
<tr>
<td>Fudickar (54)</td>
<td>2011</td>
<td>PO</td>
<td>Niro</td>
<td>35</td>
<td>Yes</td>
<td>Absolute decrease &lt;65% absolute</td>
<td>Postoperative cognitive deficit</td>
<td>Trail Making Test, Verbal Learning Test, Ray’s Auditory Verbal Fluency Test, Digit Symbol Substitution Test, Digit Span Test</td>
</tr>
<tr>
<td>Olsson (55)</td>
<td>2006</td>
<td>RO</td>
<td>INVOS</td>
<td>46</td>
<td>Yes</td>
<td>None</td>
<td>Stroke</td>
<td>New neurologic deficit that did not resolve before discharge confirmed by CT and/or specialist neurologic assessment</td>
</tr>
<tr>
<td>Urbanski (56)</td>
<td>2013</td>
<td>PO</td>
<td>Niro</td>
<td>122</td>
<td>No</td>
<td>Absolute decrease ≤55%, &lt;80% change from baseline</td>
<td>Adverse neurological outcome (permanent focal neurological deficit or temporary neurological dysfunction)</td>
<td>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.</td>
</tr>
<tr>
<td>Kakihana (57)</td>
<td>2012</td>
<td>PO</td>
<td>Hamamatsu</td>
<td>10</td>
<td>Yes</td>
<td>None</td>
<td>Stroke</td>
<td>MMSE</td>
</tr>
<tr>
<td>Hassan (58)</td>
<td>2010</td>
<td>POP</td>
<td>Fore-sight</td>
<td>1</td>
<td>Yes</td>
<td>Absolute decrease &lt;55% absolute</td>
<td>Neurocognitive deficit</td>
<td>not reported</td>
</tr>
<tr>
<td>Greenberg (59)</td>
<td>2013</td>
<td>PO</td>
<td>Fore-sight</td>
<td>53</td>
<td>No</td>
<td>Absolute decrease &lt;60% ≥60 seconds in ≥1 hemisphere</td>
<td>Delirium</td>
<td>not reported</td>
</tr>
<tr>
<td>Senanayake (60)</td>
<td>2012</td>
<td>PO</td>
<td>INVOS</td>
<td>27</td>
<td>Yes</td>
<td>None</td>
<td>Permanent or temporary neurological deficit</td>
<td>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 infarction on CT. Temporary neurological deficit: any new postoperative neurological deficit that included motor deficit, confusion, agitation, or transient delirium that resolved spontaneously before discharge with no new cerebral infarction on CT.</td>
</tr>
</tbody>
</table>
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 rSO2 monitoring to ensure cerebral perfusion could not be established, i.e., the absence of acute reductions in rSO2 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 rSO2 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).

### Table 1. Continued.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th>Device Used</th>
<th>n</th>
<th>Relation rSO2-PNC</th>
<th>rSO2 Threshold</th>
<th>Outcome Measured</th>
<th>Measuring Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamenskaya</td>
<td>2015</td>
<td>PO</td>
<td>INVOS</td>
<td>61</td>
<td>Yes</td>
<td>Absolute decrease &lt;40%</td>
<td>Neurological complications (encephalopathy, stroke)</td>
<td>MMSE, GCS</td>
</tr>
<tr>
<td>Murkin</td>
<td>2007</td>
<td>PRI</td>
<td>INVOS</td>
<td>194</td>
<td>No</td>
<td>AUC &lt;70% of baseline &gt;150 minutes*%, desaturation AUC &lt;40% absolute</td>
<td>Stroke</td>
<td>Focal neurologic deficit persisting &gt;24hrs and confirmed by CT</td>
</tr>
<tr>
<td>Colak</td>
<td>2015</td>
<td>PI</td>
<td>INVOS</td>
<td>200</td>
<td>Yes</td>
<td>Absolute decrease &lt;50%, AUC &gt;150%<em>min &lt;20% of baseline, AUC &gt;50min</em>%</td>
<td>Cognitive decline</td>
<td>MMSE, Color Trail Test 1, Grooved-Pegboard Test</td>
</tr>
<tr>
<td>Slater</td>
<td>2009</td>
<td>PRI</td>
<td>INVOS</td>
<td>240</td>
<td>Yes</td>
<td>Desaturation score &gt;3000 AUC 40% &gt;10 minutes*%</td>
<td>Early POCD</td>
<td>Neurocognitive test battery</td>
</tr>
<tr>
<td>Kok</td>
<td>2014</td>
<td>PIP</td>
<td>INVOS (but both INVOS and Fore-sight were measured)</td>
<td>60</td>
<td>No</td>
<td>Desaturation score &gt;3000 AUC 40% &gt;10 minutes*%</td>
<td>Early POCD, Postoperative cognitive decline (4 days (early) and 3 months (late))</td>
<td>CogState brief computerised cognitive test battery</td>
</tr>
<tr>
<td>Mohandas</td>
<td>2013</td>
<td>PI</td>
<td>Equanox</td>
<td>100</td>
<td>Yes</td>
<td>&gt;20% decrease from baseline AUC&gt;150 minutes*% for &lt;20% of baseline or &gt;50 minutes*% for &lt;50% of absolute value</td>
<td>PNC</td>
<td>MMSE, ASEM</td>
</tr>
<tr>
<td>Colak</td>
<td>2012</td>
<td>PI</td>
<td>INVOS</td>
<td>58</td>
<td>Yes</td>
<td>Decrease &lt;75% of baseline &gt;15 seconds.</td>
<td>Stroke, coma, stupor</td>
<td>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.</td>
</tr>
<tr>
<td>Murkin</td>
<td>2011</td>
<td>PI</td>
<td>INVOS</td>
<td>57</td>
<td>No</td>
<td>Decrease &lt;75% of baseline &gt;15 seconds.</td>
<td>New-onset stroke, major-organ morbidity and mortality</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

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; rSO2, regional cerebral tissue oxygen saturation.
hyperlperfusion, and ischemia through vasodilation and system of CA provides neuroprotection against hypo-, both ischemia and hyperemia (77). The central homeostatic coupled with the cerebral metabolic demands, preventing case of an intact CA, the cerebral perfusion pressure is CBF despite changes in cerebral perfusion pressure (79). In outcome (18,77,78). The de
bances in the neuroprotective cerebral autoregulatory system are known to result in adverse neurological occurrence (6–9,17,20,45,68,71–74). In contrast, Fink et al. in a recent review state that the evidence linking cardio-
vascular 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 rSO2 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 rSO2 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 rSO2 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 rSO2 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 hyperperfusion 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 vasactive drugs (29). One would expect that when CA is intact, CBF and rSO2 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 rSO2 when the perfusion pressure was increased and an increase in rSO2 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 paCO2.

Apart from the influence of mean ABP, several studies showed elevated levels of paCO2 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 paCO2 influence CBF and are still not tightly controlled within the autoregulatory limits during CPB (mean ABP between 60 and 150 mmHg and paCO2 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 neurologic 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 rSO2 values above a certain threshold. Future studies should aim at determining personalized values of mean ABP and PaCO2 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.

**REFERENCES**


