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REVIEW

Cerebral oxygenation monitoring in patients during and after cardiac arrest -- a narrative review of current methods and evidence

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Abstract

Hypoxic-ischemic brain injury (HIBI) is a leading cause of mortality in post-cardiac arrest (post-CA) patients who successfully survive the initial cardiopulmonary resuscitation (CPR) but later die in the Intensive Care Unit (ICU). Therefore, a key priority of post-resuscitation ICU care is to prevent and limit the impact of HIBI by optimizing the balance between cerebral oxygen delivery and demand. Traditionally, an optimal systemic oxygen balance is considered to ensure the brain's oxygen balance. However, the validity of this assumption is uncertain, as the brain constitutes only 2% of the body mass while accounting for approximately 20% of basal oxygen consumption at rest. Hence, there is a real need to monitor cerebral oxygenation realistically. Several imaging and bedside monitoring methods are available for cerebral oxygenation monitoring in post-CA patients. Unfortunately, each of them has its limitations. Imaging methods require transporting a critically ill unstable patient to the scanner. Moreover, they provide an assessment of the oxygenation state only at a particular moment, while brain oxygenation is dynamic. Bedside methods, specifically near-infrared spectroscopy (NIRS), brain tissue oxygen tension (PbtO2), and jugular venous oxygen saturation monitoring (SjvO2), have not often been used in studies involving post-CA patients. Hence there is ambiguity regarding clear recommendations for using these bedside monitors. Presently, the most promising option seems to be using the NIRS as an indicator of effective CPR. We present a narrative review focusing on bedside methods and discuss the evidence for their use in adult patients after cardiac arrest.

Keywords

Cerebral oxygenation monitoring; Near-infrared spectroscopy; Brain tissue oxygen tension monitoring; Jugular venous oxygen saturation monitoring

1. Background

Cardiac arrest (CA) is a condition with significant mortality and morbidity broadly affecting individuals across gender, age, and ethnicity. In-hospital cardiac arrest (IHCA) affects 1–2 patients per 1,000 admissions in the United Kingdom and Australia [1, 2], and only 20% of them survive to hospital discharge. In out-of-hospital cardiac arrests (OHCA) situations, the percentage of survivors is even worse. Annually, OHCA is experienced by 1 in 1000 European Union's citizens [3], return of spontaneous circulation (ROSC) is achieved in 35%, rate of survival to hospital admission is 25% and only 10% survive to hospital discharge [4].

The whole-body ischemia-reperfusion response that develops during CA and subsequent resumption of systemic circulation results in complex of pathophysiological processes known as post-CA syndrome [5]. One of the core components of post-CA syndrome is post-CA hypoxic-ischemic brain injury. It accounts for more than 50% of deaths in patients who initially achieve ROSC but subsequently die in the ICU [6, 7]. Therefore, the logical aim of the ICU post-resuscitation care must be to prevent or at least minimize extent of this hypoxic-ischemic neurological injury. For this reason, there is a need to monitor cerebral oxygenation more objectively and in real time.

A few modern cerebral imaging techniques (e.g., positron emission tomography-computed tomography: PET-CT, functional magnetic resonance imaging: fMRI) provide specific information regarding cerebral oxygenation [8, 9]. These modalities image the structure and the function of the nervous system using the fact that the brain is almost entirely dependent on oxidative metabolism. The techniques that quantitatively measure parameters of brain activity are cerebral metabolic rate for oxygen (CMRO2) or oxygen extraction fraction (OEF). These measurements mainly diagnose brain diseases, e.g., tumors, stroke, Alzheimer's disease, that cause significant brain

TABLE 1. Bedside monitoring of cerebral oxygenation.

	Advantages	Disadvantages	Comments
NIRS	• Real-time • Continuous • Non-invasive • Regional monitoring in the area of interest • Simultaneous monitoring of other areas	• The extracerebral circulation "contaminates" the sample in the area of interest	• Measures normal oxygenation values in patients with brain death, including those with confirmed intracranial flow arrest
PbtO2	• Real-time • Continuous • Monitoring of regional oxygenation within the area of interest • Option of simultaneous intracranial pressure and temperature monitoring through the same burr hole	• Invasive • Risk of hematoma, infection, bone fragmentation, catheter dislocation • Monitors a small area within the immediate vicinity of the microcatheter - not sensitive to ischemia in other parts of the brain	• Requires presence of an experienced intensivist or neurosurgeon to insert the microcatheter into the brain tissue • Coagulopathy is a contraindication
SjvO2	• Real-time • Continuous or intermittent • Global oxygenation status	• Invasive • Risk of venous thrombosis or hematoma secondary to carotid artery puncture • Not sensitive to regional brain hypoxia	• It is technically as demanding as central vein cannulation - may be introduced by any intensivist

metabolism changes. Unfortunately, most imaging modalities have fundamental limitations in post-CA patients, such as the need to transport the unstable patient to the scanner. Moreover, the imaging techniques provide an assessment of the oxygenation state only for a particular moment, while brain oxygenation is dynamic. For these reasons, imaging methods are not emphasized in this article.

This article focuses on the bedside methods which are suitable in everyday clinical practice and discuss the evidence for their use in adult patients. The techniques, which can be used in real-time and able to monitor and reveal hypoxia of brain tissue continuously are (1) near-infrared spectroscopy (NIRS), (2) brain tissue oxygen tension monitoring (PbtO2), and (3) jugular venous oxygen saturation monitoring (SjvO2). The advantages and disadvantages of the three bedside techniques are summarized in Table 1 and discussed in the following sections.

An initial search of PubMed (Medline) consisted of the following combinations of search terms: (A) cardiac arrest and cerebral oxygenation and near-infrared spectroscopy, (B) cardiac arrest and cerebral oxygenation and brain tissue oxygen tension, and (C) cardiac arrest and cerebral oxygenation and jugular bulb oxygen saturation. There were 173 articles retrieved under (A), 26 articles under (B), and 25 articles under (C) published in English since 1990. After excluding identical studies (7), case reports (4), experimental studies (47), paediatric studies (34), reviews (9), and studies with an irrelevant focus (37), there were only 86 studies that became the base source of information for this narrative review.

2. Near-Infrared Spectroscopy (NIRS)

NIRS is currently the only non-invasive method that monitors regional cerebral oxygenation. The concept was introduced as early as 1977 [10], and the first commercially available device was introduced in the early 90s for clinical use. Since then, efforts have been made to use the method in post-resuscitation care and CPR. NIRS involves a near-infrared light source (wavelength 700–950 nm) and a detector placed on the area of interest, commonly above the frontal lobes (Fig. 1). The emitted light is then reflected, redirected, scattered, and absorbed but still penetrates the skin and bones of the skull easily. The incident light changes its spectrum on contact with the hemoglobin molecule in the brain tissue, depending on its oxygenation status. The light detector then senses and analyses the emergent light. NIRS examines arterial, venous, and capillary blood in the probe field, and the obtained value represents the saturation of these three components. Since most of the blood is venous (70%), a regional cerebral oxygen saturation (rSO2) of 60–80% is considered normal [11]. Apart from its non-invasiveness, NIRS has other benefits: though similar to pulse oximetry, rSO2 can be detected in no or low blood-flow states during CPR. Again, unlike electroencephalogram (EEG), it is resistant to movement artifacts generated during CPR.

2.1 NIRS during CPR

The quality of CPR is linked to the survival of patients after cardiac arrest. When carried out per the guidelines, CPR provides only 30% to 40% of normal blood flow to the brain [12]. Therefore, there is a need to optimize CPR quality to maximize survival from cardiac arrest. In this scenario, NIRS may reflect the CPR efficiency.

A review of 26 observational studies demonstrated a clear correlation between higher rSO2 values measured during CPR and successful return of spontaneous circulation (the averaged mean rSO2 for patients achieving ROSC was 41 $\pm$ 12% vs. 30 $\pm$ 12% for non-ROSC (p = 0.009). In terms of outcome, a mean of 47 $\pm$ 11% was associated with a favorable and 38 $\pm$ 12% with an unfavorable neurological outcome. However,

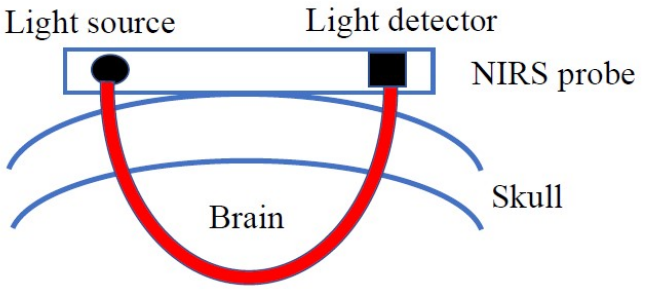

FIGURE 1. Near-Infrared Spectroscopy. A light source emits near-infrared light (NIRL) with a wavelength of 700–950 nm. NIRL penetrates the skull and reaches the brain tissue. NIRL changes spectrum as it comes in contact with the hemoglobin molecule, depending on its oxygenation status. After that, the reflected light is detected and quantified by the light detector.

there was a significant overlap in rSO2 values between the two groups [13]. Similar results were found in another systematic reviews by Liu Y, *et al.* [14] and Takegawa R, *et al.* [15]

Cournoyer A, *et al.* [16], found in their systematic review, that only two of the 75 patients who achieved ROSC had a mean NIRS saturation under 30%. It has been proposed to include prolonged failure to obtain a NIRS saturation higher than 30% in a multimodal approach to the decision of terminating resuscitation efforts [16].

Genbrugge C, *et al.* [17], in their study, showed that a better predictor of successful ROSC is the trend rather than the absolute rSO2 values. The rSO2 values increased during advanced life support in both the ROSC and non-ROSC groups; however, in the ROSC group, the rSO2 increased twice as much, and the best predictor for ROSC was an increase in rSO2 value greater than 15% [17].

2.2 NIRS in post-resuscitation care

Cerebral autoregulation is the inherent ability of the cerebral vasculature to maintain relatively constant cerebral blood flow (CBF) within a wide range of mean arterial pressure (MAP). Compensatory vasoconstriction (in hypertension) and vasodilation (in hypotension) occurs to ensure a constant flow despite fluctuating MAP within the autoregulatory range MAP. Historically, a total loss of autoregulation after cardiac arrest has been assumed [18], but in reality, a zone of autoregulation is often preserved, although narrowed and varying from patient to patient [19, 20]. When autoregulation is compromised, rSO2 values are positively correlated with MAP. Conversely, when autoregulation is intact, rSO2 values remain constant despite fluctuations in MAP. These values are referred to as patient-specific optimal mean arterial pressure (MAPOPT). Some investigators have attempted to determine the intact zone of autoregulation by NIRS as follows. Ameloot *et al.* [20] proved that a negative neurological outcome correlates with the duration of time during which the MAP remains lower than its optimal value. However, the findings of Griesdale *et al.* [21] do not support this notion.

Studies on monitoring brain oxygenation by NIRS during the post-resuscitation period in the ICU yielded immensely variable results. Storm C *et al.* [22] demonstrated significantly higher median rSO2 values in patients with favorable outcomes but with significant overlaps between the outcome groups. Ahn A *et al.* [23] detected significantly higher median rSO2 values in the first 24-hour period only in patients with the favorable outcome; however, in the following 24 hours, the values were not significantly higher. Jakkula P *et al.* [24] did not identify any correlation between rSO2 values and the neurological outcome or serum concentration of neuron-specific enolase, an indicator of neurological injury.

2.3 NIRS summary

Even though NIRS has been used to monitor brain oxygenation for 30 years and has been considered a promising method, it has its limitations, as discussed above. The expectations placed in it by the scientific community have not been fulfilled. Several studies have tested NIRS in brain-dead patients and recorded normal cerebral oxygenation values despite both brain death and absence of CBF were confirmed. This concludes that there can be undesired contamination of rSO2 with the extracerebral circulation [25–27]. Based on current evidence, NIRS may not be recommended as a precise clinical tool for routine cerebral oxygenation monitoring during post-resuscitation ICU care [28, 29]. However, there is still ample room for improvement of evidence. On the contrary, NIRS values measured during CPR might reflect the whole-body perfusion rather than inconsistencies in actual brain perfusion. Nevertheless, considering the correlation between higher rSO2 values during CPR and successful ROSC or favorable neurological outcomes, NIRS can still be regarded as an acceptable brain-monitoring technique – absolute or delta rSO2 values trend can be used as a physiological target and an indicator of a well-performed CPR.

3. Brain tissue oxygen tension monitoring (PbtO2)

Oxygen, during its transport from the pulmonary alveolus to the brain cells, transits the cerebral circulation. According to the concentration gradient, oxygen diffuses from the capillary into the brain tissue, where we intend to evaluate the amount of oxygen by the brain tissue oxygen tension (PbtO2) method [30]. PbtO2 monitors regional values of oxygen's partial pressure using a microcatheter inserted directly into the brain parenchyma. The measurement is limited to the immediate vicinity of the microcatheter. In patients with traumatic brain injury, insertion of the microcatheter in "at-risk" perilesional tissue is suggested. Precise placement of the microcatheter can be technically challenging. Therefore, the standard practice is to insert it in normal-appearing frontal subcortical white matter, especially in patients with diffuse brain injury [31]. It seems logical to place a probe in patients' frontal subcortical white matter after cardiac arrest, preferably on the non-dominant side (Fig. 2).

3.1 The PbtO2 monitoring technology

Present devices use two technologies to monitor PbtO2: polarographic or luminescence technique. The former uses the

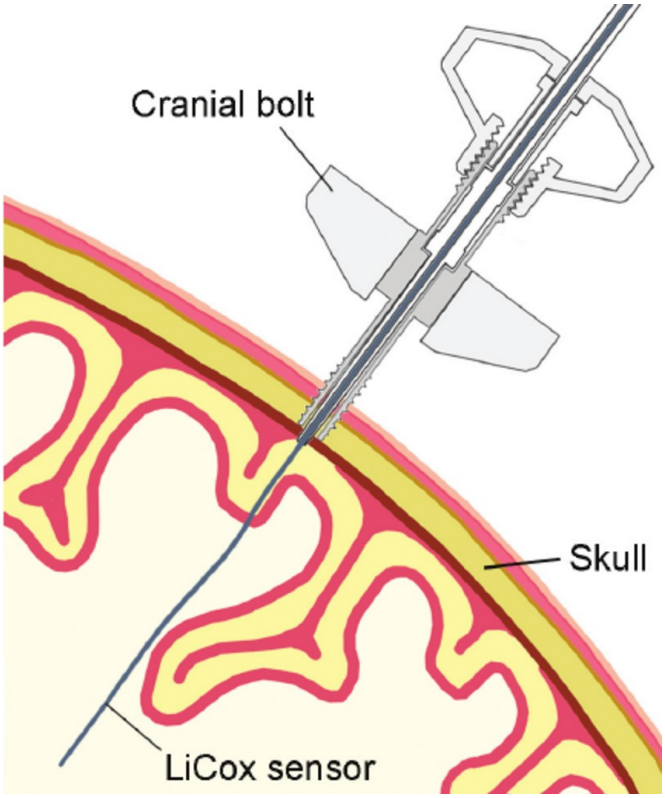

FIGURE 2. The brain tissue oxygen catheter. Monitoring brain tissue oxygen tension is possible by introducing a small catheter directly into the brain parenchyma in the area of interest. It is reproduced from www.integralife.com by permission of Integra LifeSciences Services.

polarographic Clark's electrode, consisting of two metallic electrodes (a silver anode and a gold cathode) immersed in an electrolyte solution and surrounded by a membrane. The greater the oxygen partial pressure in the tissue, the more oxygen diffuses through the membrane and the greater the electric current generated due to electrochemical reduction at the cathode [32]. This method was initially developed to monitor oxygen tension in muscle tissue and has been used since 1993 in the Licox monitoring system (Integra Neuroscience, Plainsboro, New Jersey, USA) to monitor oxygen tension in brain tissue [33].

The luminescence technique relies on the principle that a luminescent dye absorbs energy from a light source and re-emits the light's energy at a different wavelength, detectable by a light detector. Because oxygen can quench the process efficiently, the quenching of the re-emitted light is directly proportional to the partial pressure of oxygen in the vicinity of the dye [34].

The previously used Neurotrend device (Codman; Raynham, Massachusetts, USA) was based on the luminescence technique. However, *in vitro* and *in vivo* comparative studies demonstrated that the Neurotrend device was less accurate than the Licox, and catheter malfunction was frequently reported [35, 36]. Therefore, Neurotrend's production was terminated, and the Licox system has become the standard. Neurovent (Neurovent-PTO, Raumedic; Helmbrechts, Germany) is a newer device based on the luminescence technique and is comparable to the Licox device, as demonstrated by in vitro studies. Although both devices measure oxygen tension with high accuracy [37, 38], most published clinical studies have used the Licox monitoring system.

3.2 PbtO2 validation

Apart from the technicalities, the clinical benefit of PbtO2 needs to be verified. Several preclinical studies demonstrated that only a slight swelling occurred in the area of the microcatheter inserted into the brain parenchyma, causing only minimal damage to the tissue itself [39]. Human studies, mainly in traumatic brain injury (TBI) patients, were focused on the so-called ischemic threshold. This threshold is based on consensus opinion and is in the range of PbtO2 15–20 mm Hg. Although PbtO2 has confirmed the association between poor neurological outcome and hypoxia [40], the clinical benefits of therapeutic interventions based on PbtO2 have not yet been established. The second phase of the BOOST-II study comparing the treatment of TBI patients managed according to intracranial pressure (ICP) and PbtO2, or ICP-only strategies, suggested better outcomes and lower mortality in the ICP and PbtO2 management group. Unfortunately, the study was not adequately powered to detect clinical efficacy unequivocally [41]. A third phase of the BOOST3 [42] study is in progress and expected to provide results in 2023.

3.3 PbtO2 monitoring after CA

In contrast to extensive literature describing the application of PbtO2 in TBI patients, there is a dearth of similar studies in post-CA patients. A systemic search of the terms "cardiac arrest" and "brain tissue oxygenation" and "cerebral oxygenation" in the MEDLINE e-database yielded only two studies in the period between 1990 and 2020, with a sample size of at least ten adult patients. Moreover, both studies were by the same group of investigators, further restricting the chances of a proper evaluation of the PbtO2 method in post-CA patients. However, both the studies detected interesting findings of the differences in brain oxygenation when monitored concurrently by PbtO2 and by jugular venous oximetry. One study demonstrated that despite PbtO2 detected brain hypoxia (defined as PbtO2 $<$20 mm Hg) was present in 38% of the monitored time, there was no concurrently occurred SjvO2 detected brain hypoxia (defined as SjvO2 $<$50%) [43]. The other study showed that the increased partial pressure of oxygen in jugular bulb blood (PjvO2) in patients with cerebral hypoxia (PbtO2 $<$20 mm Hg) compared to patients with normoxia (PbtO2 $>$ 20 mm Hg), which resulted in a significant difference in PjvO2 - PbtO2 gradient between normoxia and hypoxia group (16 mm Hg [SD, 6] versus 39 mm Hg [SD, 11]; $p <$ 0.001). The authors attributed such results to vasogenic edema, increasing the diffusion barrier distance and limiting oxygen diffusion from the capillary bed to brain tissue (low PbtO2). Therefore, oxygen remained in the bloodstream and resulted in arterialized jugular bulb blood (high PjvO2) [44].

3.4 PbtO2 summary

The invasive nature of monitoring remains the major limitation to the widespread use of PbtO2 technology in post-CA patients. PbtO2 is primarily used in TBI patients as there is a possibility to simultaneously monitoring ICP invasively. However, a BOOTS3 study's positive result might lead to more frequent use of PbtO2 technology also in post-CA patients.

4. Jugular venous oxygen saturation monitoring

SjvO2 monitors the hemoglobin saturation from jugular bulb blood. It is based on the fact that venous blood flows from the brain via the cerebral veins into venous sinuses and then leaves the cranial cavity through the jugular bulb down into the internal jugular vein.

4.1 SjvO2 equations

Applying Fick's principle, the amount of oxygen in jugular venous blood (CBF $\times$ CjvO2) corresponds to the difference between the amount of oxygen contained in the blood that flows into the brain (CBF $\times$ CaO2) and its metabolic consumption in the brain (CMRO2) [45]. Equations of SjvO2 calculation are as follows:

$$\mathrm{CBF} \times \mathrm{CjvO2} = \mathrm{CBF} \times \mathrm{CaO2} - \mathrm{CMRO2} \quad (1)$$

where CBF = cerebral blood flow; CjvO2 = jugular venous oxygen content; CaO2 = arterial oxygen content; CMRO2 = cerebral metabolic rate for oxygen.

The oxygen content in the arterial (CaO2) and venous (CjvO2) blood is the sum of the oxygen bound to hemoglobin and the oxygen dissolved in plasma. The amount of dissolved oxygen is, under normal conditions, minimal (about 3% of the total) and can be safely omitted [46]. Therefore, the values of CaO2 and CjvO2 can be replaced in the equation by SaO2 and SjvO2 values, respectively, and the equation becomes:

$$\mathrm{CBF} \times \mathrm{SjvO2} = \mathrm{CBF} \times \mathrm{SaO2} - \mathrm{CMRO2} \quad (2)$$

where SaO2 = arterial oxygen saturation and SjvO2 = jugular vein oxygen saturation.

Then, by simplifying Eqn. 2 we derive the equation for calculating the jugular vein oxygen saturation:

$$\mathrm{SjVO2} = \mathrm{SaO2} - (\mathrm{CMRO2}/\mathrm{CBF}) \quad (3)$$

Since the SjvO2 values are derived from the jugular bulb, they reflect the state of global brain oxygenation and can potentially be used to make clinical decisions about patient management in the ICU. Jugular oximetry can be monitored intermittently or continuously using a catheter introduced retrogradely into the dominant internal jugular vein with the tip positioned in the jugular bulb (Fig. 3). The correct placement of the catheter tip needs to be confirmed by a lateral cervical spine X-ray, and the catheter tip must be above the lower border of the C1 vertebra. The dominant side can be determined by various means. The simplest method is to compare the diameter of the internal jugular vein using ultrasound [47].

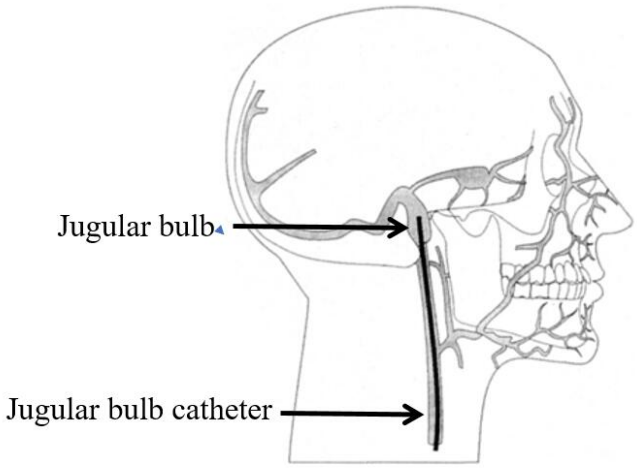

FIGURE 3. Jugular Venous Oximetry. The figure shows the catheter inserted by retrograde cannulation of the internal jugular vein and advanced into the jugular bulb.

4.2 SjvO2 monitoring in post-CA patients

Because of the lack of data about SjvO2 values in post-CA patients, determining the ischaemic threshold and what values should be considered standard are difficult. Therefore, such values need to be extrapolated from studies conducted on TBI patients. SjvO2 values of 55–75% can be considered as a normal range [46], and SjvO2 <50 % can be recommended as the ischaemic threshold [48]. Similar to TBI patients, it is generally accepted that SjvO2 <50% signals brain hypoxia requiring therapeutic interventions and results in an unfavorable outcome. On the other hand, high SjvO2 values (more than 75%) may evoke the idea that the brain is sufficiently oxygenized and reassuring. However, the earlier studies which compared the SjvO2 values to systemic mixed venous oxygenation values in post-CA patients, identified that higher SjvO2 leads to poor outcome [49, 50]. Such finding is confirmed by subsequent studies which compared SjvO2 values in post-CA survivors and non-survivors. Though the initial SjvO2 values showed no differences between both groups, there was a significant increase in SjvO2 values approximately 24 hours after cardiac arrest in the non-survivor group [51–53]. Studies by Lemiale V *et al*. [54] and Hoedemaekers CW *et al*. [55] demonstrated that the cause of high SjvO2 values in non-survivors was the decreased cerebral oxygen consumption. Several mechanisms, which could result in decreased oxygen consumption, have been suggested, such as irreversible post-anoxic neuronal damage [52, 54, 55], mitochondrial dysfunction [56] or potentially reversible mechanism: development of brain edema formation, increasing the diffusion barriers for oxygen and limiting its diffusion from capillary bed to neurons [57, 58]. It has not been clarified yet, which particular mechanism and its extent of contribution towards high SjvO2 values. Exploring the causes of high SjvO2 values could possibly suggest new therapeutic targets in post-resuscitation care.

4.3 SjvO2 summary

SjvO2 is the oldest bedside method to monitor cerebral oxygenation. Despite being widely used for decades, the benefit of SjvO2-directed therapy in clinical outcomes has yet to be confirmed. Therefore, it has been gradually replaced by other methods. SjvO2 monitoring tool has come to the forefront again after being recommended by the Brain Trauma Foundation guidelines 2016; however, the question remains whether this traditional method could offer anything new and conclusive.

5. Summary

HIBI is a significant contributory factor influencing the outcome of post-CA patients who achieve successful ROSC. Using appropriate monitoring methods to detect early cerebral hypoxia and subsequently monitor the effects of therapeutic intervention may be an objective solution to this problem. Unfortunately, monitoring modalities currently used have common pitfalls. They have been mostly used in studies on patients with brain injury caused by reasons other than cardiac arrest. It is not certain if the data obtained from such patients could be extrapolated for patients of post-CA brain injury. The paucity of studies in patients after cardiac arrest have resulted in the fact that European Resuscitation Council's (ERC) guidelines 2021 [59] do not recommend any bedside method for clinical application in post-resuscitation care. Moreover, apart from the use of NIRS during CPR, cerebral oxygenation-guided therapy has not demonstrated better clinical outcome yet. In conclusion, there is a real need for further studies in post-CA patients, to improve existing monitoring modalities or to develop newer technologies, that might ideally continuously, non-invasively, at bedside, reliably and in real time to monitor cerebral oxygenation and detect possible brain hypoxia.

AUTHOR CONTRIBUTIONS

JR, designed the study, wrote original draft, reviewed and edited; JM, wrote original draft, reviewed and edited; NC, reviewed, edited and corrected English; PS, designed the study, reviewed and edited; AES, reviewed and edited; RZ, supervised and reviewed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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