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CRITICAL CARE (S MAYER, SECTION EDITOR)

Monitoring the Brain After Cardiac Arrest: a New Era

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Abstract
Purpose of Review Of the approximately 350,000 out-of-hospital, and 750,000 after in-hospital cardiac arrest (CA) events in the US annually approximately 5-9% and 20% respectively may achieve return of spontaneous circulation (ROSC) after attempted cardiopulmonary resuscitation (CPR). Up to 2/3 of these initial survivors may go on die in the subsequent 24-72 hours after ROSC due to a combination of (1) on-going cerebral injury, (2) myocardial dysfunction and (3) massive systemic inflammatory response. In order to successfully manage patients more effectively, monitoring methods are needed to aid clinicians in the detection and quantification of intra-cardiac arrest and post-resuscitation pathophysiological cerebral injury processes in the intensive care unit.
Recent Findings Over the last few years many modalities have been used for cerebral monitoring during and after CA, these include quantitative pupillometry, transcranial doppler sonography, optic nerve sheath diameter measurements, microdialysis, tissue oxygenation monitoring, intra-cranial pressure monitoring, and electroencephalography. Current studies indicate that these modalities may be used for the purpose of neurological monitoring during cardiac arrest resuscitation as well as in the post-resuscitation period.
Summary Multiple overlapping processes, including alterations in cerebral blood flow (CBF), raised intracerebralpressure, disorders of metabolism, imbalanced oxygen delivery and reperfusion injury contribute to cell death during the post-resuscitation period has led to the birth of post-resuscitation management strategies in the 21st century. This review provides a succinct overview of currently available bedside invasive and non-invasive neuro-monitoring methods after CA.

Keywords Cardiac arrest · Post-resuscitation · Cerebral oximetry · Cerebral perfusion · Near-infrared spectroscopy (NIRS) · Cerebral blood flow

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Introduction

Annually, there are approximately 350,000 resuscitation attempts after out-of-hospital and 750,000 after in-hospital cardiac arrest (CA) events in the USA, with approximate survival rates of 5–9 and 20%, respectively [1, 2]. Due to the effects of ischemia/reperfusion injury and the resultant neurological and neuropsychological deficits, only 3–7% is estimated to recover to their pre-CA functional status [3–5]. These outcomes reflect the finale to a two-step brain injury process; (a) ischemia during CA, which typically leads to death in approximately 50–60% due to the inability to achieve return of spontaneous circulation (ROSC), followed by (b) a cascade of secondary injury processes in the 24–72 h, leading to death in 2/3 of those who initially survive beyond ROSC [6].

The realization that multiple overlapping processes, including alterations in cerebral blood flow (CBF), raised intracerebral pressure, disorders of metabolism, imbalanced oxygen delivery, and reperfusion injury contribute to cell death during the post-

resuscitation period has led to the birth of post-resuscitation management strategies in the twenty-first century [7–9].

In order to successfully manage patients more effectively, monitoring methods are needed to aid clinicians in the detection and quantification of intracardiac arrest and post-resuscitation pathophysiological cerebral injury processes in the intensive care unit. This review provides a succinct overview of currently available invasive and non-invasive monitoring methods that may be used for the purpose of neurological monitoring during cardiac arrest resuscitation as well as in the post-resuscitation period.

Methods to Monitor Cerebral Function and Perfusion

Non-invasive Methods

Quantitative Infrared Pupillometry

Quantitative pupillometers rely on near-infrared light to measure pupil size as well as changes in pupillary amplitude and velocity [10•]. While the pupillary light response (PLR) leads to pupillary constriction, noxious stimuli may elicit pupillary reflex dilatation (PRD) [11]. Variables such as latency of onset, maximum amplitude, duration of the reflex, and constriction and dilation velocities are amenable to analysis. After covering the non-measured eye, the pupillometer records an image every 30 ms in the opposite eye and the pupil size is averaged to provide a baseline. Measurements are then taken after 3–4 s [10•]. The PLR is diminished by reduction in CBF [12]. Therefore, this technique may potentially be used to monitor changes in CBF during CPR, as well as in the post-resuscitation period. While circulating vasoactive drugs may impact pupillary size, pupil reactivity remains, as PLR relies on blood flow through the posterior circulation and the actions of the Edinger-Westphal nucleus in the mid-brain. Variations in pupil size and response may also occur due to other factors such as age (estimated 0.4 mm decrease in size per decade of life), opioid, cathecholamine, and muscarinic agents [13].

Quantitative Infrared Pupillometry During Cardiac Arrest

In a study of 30 CA cases, PLR was measured during CPR by Behrends et al. who found that PLR was detectable in 25 cases (83%) at some point during resuscitative efforts [12]. The presence of PLR during CPR at any point was associated with early survival from CA ($p = 0.0002$). The absence of PLR for >5 min using quantitative infrared pupillometry (QIP) during CPR was associated with death or poor neurological outcomes (Cerebral Performance Category (CPC) scale 4–5) in 100% of cases (nine cases) at day 3 of the post-resuscitation period. The authors concluded that QIP could be used as an indirect marker of brain stem blood flow and may be useful in guiding CPR efforts. Additionally, they found that the use of epinephrine, atropine, and neuromuscular blockade did not impact the ability of QIP to detect PLR; however, conventional clinical pupillometry failed to detect the same, suggesting that QIP may be more sensitive than clinical pupil testing.

Quantitative Infrared Pupillometry During the Post-resuscitation Period

In a study of 50 post-resuscitation subjects, Suys et al. found that in 50 consecutive survivors of CA treated with hypothermia (33 °C) in patients with CPC 1–2 ($n = 23$, 46%) had a higher quantitative PLR (qPLR) than those with CPC 3–5 ($n = 27$, 54%) on days 1 and 2 after CA [14]. qPLR was expressed as the percent of pupillary response to a calibrated light stimulus. The best cutoff for outcome prediction was a qPLR of <13% measured 48 h into the post-resuscitation period under normothermic conditions and without sedation or analgesia. This could predict 90-day adverse neurological outcomes with an area under the receiver-operating curve (ROC) of 0.81. The prognostic accuracy of qPLR was found to be comparable with that of electroencephalography (EEG) and somatosensory-evoked potential (SSEP; 0.81 vs. 0.80 and 0.73, respectively). In this study, qPLR was part of a multimodal approach towards the decision to withdraw life support (WLS). All patients with poor outcomes had WLS thus limiting the applicability of qPLR to all situations. In another study of 82 post-resuscitation patients, Heimburger et al. identified a significant difference in median pupillary reactivity in patients with favorable neurological outcomes compared with those who died or suffered severe neurological injury (day 1, 13 vs. 8% ($p < 0.001$) and day 2, 17 vs. 8% ($p < 0.001$)) [15]. Additionally, a <7% change in PLR amplitude on day 2 provided 100% specificity for death or adverse neurological outcomes. Although further studies are needed, these data suggest that pupillometry may provide a simple method for the purpose of brainstem CBF monitoring during CA and in the post-resuscitation period. It is not known whether methods to augment CBF (leading to greater PLR) may help enhance survival and neurological outcomes.

Transcranial Doppler

Transcranial Doppler (TCD) utilizes ultrasound (US) to measure cerebral blood flow velocity (CBF-V) in the major intracranial arteries non-invasively [16]. TCD relies on low-frequency (≤2 MHz) US waves to insonate the basal cerebral arteries. Pulsed waves (PW) are reflected back from intravascular red blood cells (RBC), and the change in frequency of the reflected waves is used to calculate the velocity of RBC flow [17••]. Depending on the vessel being examined, CBF-V varies from 38 to 55 cm s^{-1} [18]. TCD can be used to measure the systolic, diastolic, and mean velocities, cerebral perfusion

pressure (CPP), and the cerebral vascular resistance (CVR) as well as resistance index (RI) and pulsatility index (PI) [19, 20] using the following equations [19–21]:

$$\mathrm{CPP}\ (mmHg) = \frac{\mathrm{MCA}\ velocity_{mean}}{\mathrm{MCA}\ velocity_{mean} - \mathrm{MCA}\ velocity_{diastolic}} \times (\mathrm{BP}_{mean} - \mathrm{BP}_{diastolic})$$

$$\mathrm{CVR} = \frac{\mathrm{CPP}}{mCBF}.$$

Mean cerebral blood flow (mCBF) is estimated by averaging flow rates in the arteries going to the brain over a 10-s period) [22].

The PI is calculated using peak systolic velocity (PSV), end diastolic velocity (EDV), and mean velocity (MV) using the following equation [23]:

$$\mathrm{PI} = \frac{\mathrm{PSV} - \mathrm{EDV}}{\mathrm{MV}}.$$

PI normally lies in the range 0.5 to 1.19 and is increased with increasing CVR with PI values >1.6 being considered abnormal [17••, 24]. PI may be lowered in the presence of carotid stenosis (if an area corresponding to post-stenotic dilation is measured) and arteriovenous malformations [25]. The Pourcelot resistivity index (RI) is a surrogate for downstream resistance and is affected by the similar variables that impact PI [17••].

$$\mathrm{RI} = \frac{\mathrm{PSV} - \mathrm{EDV}}{\mathrm{PSV}}$$

Values of RI >0.8 indicate increased downstream resistance [26].

While TCD allows dynamic monitoring, is inexpensive, and portable, it is operator dependent [27, 28]. Furthermore, 10–20% of patients may have inadequate transtemporal acoustic windows [24].

Transcranial Doppler During Cardiac Arrest

The use of TCD during CA is largely limited to case reports and case series [29, 30]. In one case report, the TCD waveform during CPR initially showed absent diastolic flow; however, after adjusting the depth of compressions, the diastolic flow was augmented [29]. While much of the information related to ineffective CPR in this case was obtained from hemodynamic measurements, the TCD profile provided additional information that demonstrated improved CBF after more effective CPR was instituted. In a study involving 14 patients with OHCA, CBF-V was on average 80% of normal during the initial period of CPR and declined to 15% of normal with increasing duration of CPR, possibly due to the rising CVR with time [31]. The administration of epinephrine and sodium bicarbonate augmented flow rates in 31 and 45% patients, respectively, for about 30 s. Administration of epinephrine decreased the diastolic no flow possibly due to its peripheral vasoconstrictive actions [31].

Transcranial Doppler During the Post-resuscitation Period

Wessels et al. studied flow velocities at five separate points during the initial 24 h and then at 72 h post-resuscitation in 39 patients and found significantly higher flow velocities at 4 h after ROSC (82 cm s^{-1} (systolic) and 31 cm s^{-1} (diastolic)) in 17 patients who survived to hospital discharge without persistent vegetative state (modified Ranklin scale 0–4) compared with 22 subjects who subsequently died (67 cm s^{-1} (systolic) and 24 cm s^{-1} (diastolic); $p < 0.05$) [32]. The average MCA systolic velocity was also significantly higher in survivors (101 vs. 80 cm s^{-1}; $p = 0.03$) at 72 h after CPR. Lemiale et al. studied TCD estimates of CBF through the middle cerebral artery (MCA) every 12 h in the initial 72 h after ROSC between 6 survivors and 12 non-survivors with OHCA treated with mild hypothermia (33 °F) and a targeted mean arterial pressure (MAP) of 75–85 mmHg under normocapnic conditions [33]. At admission, MV values were low (27.3 cm s^{-1} (21.5–33.6)) and the PI values were high (1.6 (1.3–1.9)), suggesting an increase in CVR in the initial resuscitative phase. Normal MV values were seen after 72 h (50.5 cm s^{-1} (36.7–58.1)), the MV and PI did not differ between survivors and non-survivors, and the EDV was higher in survivors at 72 h (39.6 vs. 29.3 cm s^{-1}; $p = 0.013$) again suggesting a lower CVR in survivors.

In a study of 17 post-resuscitation children after CA, in whom TCD was performed in three phases: pre-hypothermia phase, hypothermia phase (12–24 h after the body temperature had reached 33 °C), and rewarming phase (12–48 h after the body temperature had reached 36 °C), reversal of diastolic flow or undetectable flow patterns in any of the phases was associated with death or severe neurological deficits [34]. Normal mean flow velocity adjusted for age in the rewarming phase was associated with survival with favorable prognosis. This was seen in five of eight children with a pediatric CPC score of 1–2 at 3 months while none of the nine children with a pediatric CPC score of 3–6 had this finding ($p = 0.009$) [34]. The PI level in the pre-hypothermia phase did not influence the outcomes. A normal PI value (taken as 0.6–1.1 in this study) was associated with a significantly better outcome than higher PI levels during both the hypothermia and rewarming phases ($p = 0.002$ and 0.003, respectively). However, in another observational study of 53 patients, Doepp et al. calculated the CBF (through the sum of the flow through the four carotid and vertebral vessels supplying the brain). While CBF varied from 210 to 1100 ml min^{-1}, a correlation was not identified between CBF and survival outcomes [35]. The major limitation of this study was that measurements were

carried out at different times between different patients up to 48 h after ROSC. Yet, CBF is known to vary greatly depending on when it is measured after ROSC. In another observational study, Heimburger et al. studied 82 patients using both QIP and TCD on days 1 and 2 after ROSC [15]. TCD could be carried out in only 51 patients. Therapeutic hypothermia was used for 24 h and normoxia, normocarbia, and MAP at >75 mmHg were maintained. There were no differences in mFV and PI between survivors and non-survivors at 24 and 48 h; however, flow velocities were significantly higher at 48 h compared with 24 h for all subjects (mFV 45 cm s^{-1} (38–67) vs. 37 cm/s ($p = 0.001$), suggesting that CVR is elevated in the first 24 h after ROSC and subsequently decreases and leads to higher flow rates [15]. Bisschops et al. studied ten patients in whom mFV and PI in the middle cerebral artery was measured twice daily for 4.5 days. There were no differences in mean flow velocity in the middle cerebral artery, PI, and jugular bulb oxygenation between survivors and non-survivors [36].

Therefore, based on current data, the role of TCD in prognostication of post-resuscitation patients remains unclear, although it may have a role in individualization of hemodynamic and ventilation goals to ensure adequate cerebral perfusion and blood flow [16, 37].

Intracranial Pressure Monitoring

Invasive ICP Monitoring During the Post-resuscitation Period

Normal intracranial pressure (ICP) is 5–15 mmHg in healthy supine adults and an elevation of >20 mmHg especially for >30 min is associated with brain damage [38].

In a post-resuscitation study in which invasive ICP monitoring was carried in 20 children, 50% of those with an ICP of <20 mmHg survived without neurological deficits ($n = 3/6$) [39]. However, all children with an ICP of >20 mmHg either died ($n = 10/14$) or suffered a persistent vegetative state ($n = 4/14$). Similarly, in a retrospective study of 84 adult post-resuscitation patients in whom ICP monitoring had taken place, Gueugniaud et al. found that all patients with a peak ICP of >25 mmHg either died or survived with severe neurological injuries [40]. In a case series with six post-resuscitation subjects, ICP remained <20 mmHg in the first 24 h. However, three patients developed raised ICP with a peak pressure between 40 and 120 mmHg. This was thought to be related to post-ischemic hyperemia. Of these, two died and one developed a persistent vegetative state [41]. As hypothermia attenuates the rise in ICP, Naito et al. studied the time course of ICP and CPP changes in nine patients treated with mild therapeutic hypothermia (TH) [42, 43•]. ICP increased during both the hypothermia and rewarming phases. At the beginning of hypothermia treatment, ICP was 6.0 mmHg (4.0–9.0) but subsequently increased to 14.0 mmHg (10.0–15.0) at the initiation of the rewarming phase at 24 h and was 16.0 mmHg (12.0–26.0) at the end of the rewarming phase at 36 h ($p = 0.008$). However, cerebral perfusion pressure did not change significantly during this period and ranged from 74.3 mmHg (52.0–87.3) to 83.3 mmHg (80.1–91.0) ($p = 0.31$). All subjects with either an ICP of >25 mmHg or a CPP of <40 mmHg died.

Non-invasive ICP Monitoring During the Post-resuscitation Period

Optic Nerve Sheath Diameter by Ultrasound

As the optic nerve is surrounded by dura mater, raised ICP leads to changes in the optic nerve sheath diameter (ONSD) [44]. This is measured 3 mm behind the globe at an axis perpendicular to the optic nerve, using a 7.5-MHz linear probe lightly placed on the upper eyelid. Measurements are made in the sagittal and transverse planes and averaged [45]. Normal values were determined from 120 healthy volunteers (55 males and 65 females) [46]. ONSD did not vary with age, weight, or height but did vary with sex. Mean ONSD measurements for men were 3.78 mm (95% confidence interval (CI), 3.23–4.48) compared with 3.60 mm (95% CI, 2.83–4.11) for women. In a study of 50 brain-injured patients and 26 normal controls, OSND was measured along with an intraparenchymal measurement of ICP. A cutoff threshold for ONSD corresponding with an elevated ICP of >20 mmHg was 5.7 mm (sensitivity = 74.1% and specificity = 100%) [47]. ONSD was found to have good diagnostic accuracy compared with invasive monitoring in a systematic review of six studies and 231 patients by Dubourg et al. [48]. The included studies exhibited low heterogeneity with respect to the calculated values for sensitivity, specificity, positive, and negative likelihood ratios as well as diagnostic odds ratios ($P_{het} = 0.09$). For the detection of raised ICP, the overall pooled sensitivity was 0.90 (95% CI, 0.80–0.95), pooled specificity was 0.85 (95% CI, 0.73–0.93, $P_{het} = 0.13$), and the pooled diagnostic odds ratio was 51 (95% CI, 22–121). The area under the summary ROC curve was 0.94 (95% CI, 0.91–0.96). They concluded that ultrasonographic ONSD shows a good level of diagnostic accuracy for detecting an ICP of >20 mmHg [48].

In a study of 17 post-resuscitation patients, an ONSD of ≤5.4 mm was an indicator of survival with favorable neurological outcome (Glasgow outcome scale 4 or higher), with a sensitivity of 83%, specificity of 73%, positive likelihood ratio of 3.1, and negative likelihood ratio of 0.23 [49]. In a study of OSND measured serially on days 1, 2, and 3 after non-traumatic, non-neurological cause of CA arrests, it was

found that OSND was significantly higher in the post-resuscitation period in non-survivors than survivors (7.2 mm (IQR, 6.8–7.4) vs. 6.5 mm (IQR, 6.0–6.8); $p = 0.008$). On multivariate analysis, it was found that every millimeter increase in ONSD above 5.5 mm was associated with a significant risk of mortality (OR, 6.3 (95% CI, 1.05–40); $p = 0.03$). This was associated with adverse survival and neurological outcomes on discharge as well as brain edema on computed tomography [50•].

Monitoring Cerebral Metabolism

Cerebral Microdialysis

Cerebral microdialysis (CMD) consists of the insertion of two-channel semipermeable catheters into the brain parenchyma. When perfusate comes into contact with the immediate probe-surrounding area (PSA) in the extracellular fluid (ECF), substance exchange takes place through the semipermeable membrane, and the second catheter channel accumulates a liquid with a composition different from that of the original liquid. This is known as the microdialysate [51]. The levels of measured analytes can be impacted by changes in CBF, cellular metabolism (glucose, lactate, pyruvate, and lactate/pyruvate ratio), excitotoxicity (glutamate), and cellular membrane damage (glycerol). These analytes as well as a freely diffusible endogenous control (urea) and other substances of interest such as cytokines, nitric oxide (NO) metabolites (inflammation/injury), *N*-acetylaspartate (NAA; a neuron-specific analyte) can be measured. Critical threshold values for injury and ischemia damage have been established based on observational studies as follows: glucose (<0.2 mmol l^{-1}), lactate (>1.5 mmol l^{-1}), pyruvate (<25 μmol l^{-1}), lactate/pyruvate (*L*/*P*) ratio (>25), glycerol (>50 μmol l^{-1}), and glutamate (>5 μmol l^{-1}) [52].

There has been a small case series in which microdialysis has been studied in the post-resuscitation period. Nordmark et al. examined this technique within 6 h after ROSC in four patients undergoing hypothermia. Samples were collected hourly up to 36 h after ROSC. All four patients had a favorable neurological outcome [53]. They found that an initial *L*/*P* ratio was deranged in the first 6 h and even though clinical recovery was noted, the *L*/*P* ratio did not always return to baseline. In fact, in three of the four patients, normal values were never reached even though the patients had been extubated and were deemed neurologically intact. The authors attributed this to energy perturbation. In two of the four patients, hypothermia reversal was associated with an increase in the *L*/*P* ratio from around 20 to 30 followed by a return towards the previous value over the next day. Glutamate was high initially in all patients but reverted to normal in all. Glycerol showed a biphasic pattern with an early peak related to membrane disruption and a second peak after rewarming possibly related to a whole body rise in glycerol secondary to lipolysis and spillover into the brain from blood–brain barrier disruption which was thought to be related to the ischemic event. Overall, it was concluded that neurochemical changes indicating cerebral ischemia (increased lactate/pyruvate ratio) and excitotoxicity (increased glutamate) are found after CA, and signs of ischemia were also observed during the rewarming phase. These data suggest that CMD may play a significant role in monitoring the metabolic changes that occur during the post-resuscitation period.

Cerebral Oxygenation Monitoring

Direct Brain Tissue Oxygenation Monitoring

Cerebral oxygenation can be measured directly using a parenchymal brain tissue oxygen monitoring probe or indirectly based on the saturation of hemoglobin in the brain. However, it should be noted that brain tissue oxygen levels may vary in different parts of the brain during the post-resuscitation state, due in large part to differences in perfusion through the large vessels, the metabolic rate in different regions and different layers of the cortex, local blockages in macro- and microcirculation, and changes in ICP and CPP over time during the post-resuscitation period [54••, 55••].

Direct parenchymal brain tissue oxygen ($PbtO_2$) monitoring uses a thin, metallic electrode that measures free dissolved oxygen from the brain tissue. The oxygen diffuses across a semipermeable membrane to be reduced by a gold polarographic cathode generating a flow of electrical current proportional to the amount of oxygen. It is a highly localized measurement, with a sampling area of 7.1–15 mm^2. Normal $PbtO_2$ is 23–35 mmHg but can vary depending on probe depth and may be lower in deeper brain regions [56, 57]. Critical cerebral hypoxia ($PbtO_2$ <15 mmHg) is dependent on multiple factors including CBF, CPP, $PaCO_2$, PaO_2, as well as any systemic factors that increase cerebral metabolism ($CMRO_2$), e.g., fever and seizures [56, 58, 59]. The probe is typically placed in tissue that is considered to be "at risk" and can be combined with probes for temperature, ICP, and brain metabolism monitoring [54••].

There have not been any case series or human trials available, in which $PbtO_2$, has been studied in the post-resuscitation period. However, in a case report in which $PbtO_2$ monitoring was carried out during the post-resuscitation period, a reduction in $PbtO_2$ to 7 mmHg was accompanied by a surge in CBF and high lactate/pyruvate ratio compatible with increased metabolic demand which was deemed to be out of proportion to the increase in CBF. This was seen during seizures but resolved after treatment [60]. During the interictal periods, $PbtO_2$

returned to 22–25 mmHg and was accompanied by a cessation of surges in CBF, ICP, and brain temperature.

Indirect Brain Oxygen Monitoring Using Near-Infrared Spectroscopy

Cerebral oximetry relies on near-infrared spectroscopy (NIRS), which is based on the Beer-Lambert law. According to this law, the absorption of light through any medium is (1) proportional to the length the light has to travel, (2) the concentration of molecules with light-absorbing properties (*chromophores*) present in the medium, and (3) the molar extinction coefficient (i.e., the measure of how strongly the molecules (chromophores) absorb light at a given wavelength) [61]. NIRS determines the ratio of oxyhemoglobin to deoxyhemoglobin and calculates the cerebral hemoglobin oxygen saturation, thus providing an index of changes in regional brain hemoglobin oxygen saturation [62]. Since 70–80% of blood in the measured areas of brain tissue is venous, this data mainly represents cerebral venous saturation [63].

The Use of Cerebral Oximetry During Cardiac Arrest Resuscitation

There have been a number of studies examining the role of cerebral oximetry during cardiac arrest. It has been demonstrated that increases in rSO_2 are strongly associated with ROSC. It has also been shown that rSO_2 levels can be used for monitoring the quality of resuscitation and neurological prognostication [64••, 65, 66]. In a recently completed observational study of 183 in-hospital CA patients, a higher rSO_2 was independently associated with ROSC vs. no ROSC (mean ± SD, 51.8 ± 11.2 vs. 40.9 ± 12.3%; $p < 0.0001$). This effect was carried through to survival to discharge with favorable neurological outcomes vs. death or adverse neurological outcomes (56.1 ± 10.0 vs. 43.8 ± 12.8%; $p < 0.001$) [64••]. It was also demonstrated that rSO_2 can be used as a diagnostic test to accurately predict ROSC. Specifically, an rSO_2 of ≥25% provided 100% sensitivity (95% CI, 94–100%) for ROSC, while an rSO_2 ≥65% provided 99% specificity (95% CI, 95–100%) for ROSC [64••]. Furthermore, rSO_2 during mechanical CPR has been shown to lead to a significant relative rSO_2 increase, which suggests that this monitoring modality may be used as a dynamic rather than static marker of CPR quality [65].

Mean rSO_2 during CA has been found to be a better marker of ROSC than the initial rSO_2. In a recent meta-analysis of 20 observational studies encompassing 2436 patients, a stronger association between ROSC and mean NIRS values (SMD = 1.33; 95% CI = 0.92 to 1.74) than between ROSC and initial NIRS measurements (SMD = 0.51; 95% CI = 0.23 to 0.78) was shown. Overall, a mean cutoff rSO_2% of <30% was found to be largely incompatible with ROSC. Furthermore, survival to discharge with favorable neurological outcomes was also found to be associated with both higher initial and mean rSO_2% values [66].

The Use of Cerebral Oximetry During the Post-resuscitation Period

A number of small studies have examined the association between post-resuscitation rSO_2 levels and survival with favorable neurological outcomes. In one study of 60 post-resuscitation patients, survivors with favorable neurological outcomes had significantly higher rSO_2 levels compared with those who died or had severe brain injury (68 vs. 58%; $p < 0.01$) [67]. A similar result was also demonstrated in another study of 21 consecutive post-resuscitation patients admitted to an ICU. In this study, survivors achieved an rSO_2% of 68.2 (66.0–71.0) compared with non-survivors who had an rSO_2% of 62.9 (56.5–66.0) ($p = 0.01$) [68]. In both of these studies, the survivors exhibited rSO_2 levels that were within the normal range and close to 70%, reflecting a state of balanced oxygen delivery and uptake whereas the non-survivors exhibited rSO_2 values that were in the ischemic range. While these data are promising, many more studies are needed to study the association between post-resuscitation rSO_2 and post-resuscitation outcomes.

Indirect Brain Oxygen Monitoring Using Jugular Venous Bulb Oxygen Saturation

The jugular venous bulb oxygen saturation ($SjvO_2$) is measured by cannulating the internal jugular vein in a retrograde fashion to the jugular bulb and measuring the oxygen saturation of venous blood returning from the brain [69]. Traditionally, $SjvO_2$ has been used as a means for indirect assessment of global rather than regional cerebral oxygen balance. $SjvO_2$ is an invasive procedure, which limits its use during active cardiac arrest resuscitation; however, it has been utilized as a monitoring tool in the post-resuscitation period. Although oximetry by $SjvO_2$ provides a global measure of cerebral saturation, oximetry by NIRS provides a measure of regional cerebral saturation. Normal $SjvO_2$ is considered to be 55–75%. $SjvO_2$ values <55% are consistent with cerebral ischemia, while an elevation in $SjvO_2$ is consistent with impaired oxygen uptake by brain tissue. At least 13% of the brain volume needs to be ischemic for the $SjvO_2$ to be abnormal and thus the ability to detect regional ischemia is limited; however, this modality is better suited for the detection of global cerebral ischemia as what occurs after CA [56]. In a study of eight post-resuscitation patients, Takasu et al. found that the mean $SjvO_2$ of non-survivors (80%) was significantly higher than survivors (67%) at 24 h ($p < 0.001$), suggesting an impaired cerebral oxygen uptake in non-surviving patients [70]. In another

post-resuscitation study of 34 patients, it was found that having a mixed central venous oxygen saturation ($SmvO_2$) > $SjvO_2$ between 24 and 48 h after ROSC provided 95% sensitivity, 100% specificity, 100% positive predictive value, and 92% negative predictive value for predicting recovery of consciousness [71].

In a study of 30 comatose post-resuscitation patients (21 non-survivors and 9 survivors), Buunk et al. compared the $SmvO_2$ with $SjvO_2$ at 6, 12, and 24 h [72]. In survivors, the $SjvO_2$ did not change and remained lower than the $SmvO_2$ in eight of nine survivors. However, in the non-survivors, the $SjvO_2$ increased significantly and was higher than the $SmvO_2$ in 12 of 20 patients 24 h after cardiac arrest [72]. The investigators concluded their data indicated a decrease in cerebral oxygen consumption due to extensive loss of functional brain tissue in non-survivors. The positive predictive value of ($SmvO_2$–$SjvO_2$) ≤ 0 for predicting irreversible brain damage at 24 h after cardiac arrest was 93%, while the negative predictive value of ($SmvO_2$–$SjvO_2$) > 0 for this outcome was 53%, with a sensitivity of 65% and specificity of 89% [72].

Monitoring Cerebral Function

Electroencephalography

EEG Monitoring During Cardiac Arrest Resuscitation

There have only been a very limited number of case reports and case studies examining EEG changes in the brain after cardiac arrest and during resuscitation. During circulatory standstill, brain function ceases immediately, as there is an immediate drop in CBF to levels less than that required to maintain cellular metabolic activity before CBF ceases completely within a few seconds [73]. The initiation of CPR typically cannot meet the metabolic requirements of the brain, which is manifested as a loss of brain function and evidenced clinically by the immediate loss of brainstem reflexes as well as consciousness [74–77]. The loss of CBF initially manifests as slowing of the EEG that progresses to an isoelectric (flat) line within 2–20 s and remains flat in spite of attempts at CPR until at least after the resumption of the heartbeat [77].

EEG Monitoring During the Post-resuscitation Period

EEG activity mainly reflects cortical synaptic activity [78•]. As cortical synaptic activity is very sensitive to the effects of hypoxia-induced cerebral damage, the EEG is a very sensitive test for the detection of hypoxia-induced cerebral damage. During ischemia, the rhythms with higher frequency of electrical activity (beta, and alpha) which arise from layers IV and V of the cortex are the first to succumb to the effects of reduced CBF after a normal flow of 50 ml 100 g^{-1} min^{-1} drops to 25–35 ml 100 g^{-1} min^{-1} [79–82]. Thereafter, as ischemia reaches a critical ischemic threshold of approximately 17–18 ml 100 g^{-1} min^{-1}, the slower frequencies (theta and delta) generated from the thalamus and cells in layers II–VI of the cortex gradually increase [81].

Currently, observed EEG patterns during the post-resuscitation period after anoxic encephalography can be broadly classified into six categories: (i) isoelectric, (ii) low voltage (<20 μV), (iii) burst suppression, (iv) epileptiform (status epilepticus and generalized periodic discharges, (v) continuous activity with frequencies lower than 8 Hz (diffusely slowed EEG), and (vi) continuous activity with frequencies of ≥8 Hz (normal EEG) [78•]. The isoelectric, low voltage, and burst-suppression patterns are generally considered to be unfavorable patterns, while the presence of continuous activity (either diffusely slowed or normal) is considered to be favorable [83]. However, as the presence of unfavorable EEG patterns reflects ischemia rather than permanent cerebral damage, data suggests the presence of a given pattern alone may be insufficient for the purpose of determining adverse outcomes. Thus, timely improvement of EEG patterns may be the more critical determinant of outcomes. The longer unfavorable patterns persist, the higher the likelihood of adverse outcomes. Nonetheless, the exact time needed for a given unfavorable pattern to determine true adverse outcomes (death or severe neurological injury) is not known precisely, especially as the use of post-resuscitation therapeutic hypothermia (TH) and sedatives can impact EEG readings [84•, 85••]. In a recent meta-analysis and systematic review, the relationship between specific unfavorable EEG patterns and adverse outcomes were reviewed [84•, 85••]. It was concluded that the strongest predictors of adverse outcomes were the presence of burst suppression after rewarming and status epilepticus during TH and after rewarming. However, the authors acknowledged that the level of evidence upon which their conclusions were drawn was limited [85••]. The presence of burst suppression during the post-resuscitation period was found not to be invariably associated with an adverse outcome. However, in one study, the presence of burst suppression after rewarming at 48 h from CA was found to be 100% specific for death or severe neurological injury [86].

Larger studies are needed at this time to adequately determine the relationship between EEG patterns in the post-resuscitation period and favorable as well as unfavorable neurological outcomes.

Multimodal Monitoring

Secondary brain injury processes during the post-resuscitation period remain complex and involve multiple injurious pathways that result from secondary ischemia and reperfusion

injury. These include cerebral edema, inflammation, deranged CBF and cellular energy dysfunction and may be compounded by the presence of seizures and systemic insults such as disordered hemodynamics or glucose metabolism [87, 88].

Most of the monitoring modalities that have been discussed in this review are capable of monitoring a specific downstream manifestation of cellular injury pathways, e.g., changes in CBF, oxygenation, metabolism, etc. However, in any individual patient, different pathophysiological processes may occur sequentially or simultaneously, thus combinations of data may potentially allow better overall cerebral monitoring when combined together. Additionally, there may be interdependence with respect to the interpretation of data from different cerebral monitors. Some monitoring data may not be interpreted correctly without knowledge of the ICP [87]. Conversely, ICP data may often be correctly interpreted where data from other monitors are available. For example, raised ICP could be secondary to cerebral edema or transient hyperemia, both of which require different therapeutic approaches [89]. Additionally, as the use of intracranial probes increases, probe location and displacement becomes crucial and artefactual data becomes more common. Thus, the use of multimodality monitoring may help prevent misinterpretation of data.

Multimodality monitoring is an evolving area and has been used in other injury processes such as traumatic brain injury. This refers to the simultaneous recording of multiple parameters of brain function and provides integrative data to monitor pathophysiological processes, target therapies, as well as prognostication [90]. Currently, most monitors are standalone systems and integrative display in an ergonomically efficient easily interpretable output format is still a challenge. Although there have not been many studies in which this approach has been applied to post-resuscitation subjects, such a system would allow for high-resolution time synchronization so as to allow for logical interpretation of all waveforms in terms of patients pathophysiology and may represent the future of cardiac arrest brain monitoring.

Conclusions

Although larger studies are needed, a review of studies to date suggests that currently available invasive and non-invasive bedside systems can be utilized to aid emergency and critical care physicians in monitoring diverse aspects related to brain resuscitation. The use of these systems may potentially aid clinicians in delivering individualized and tailored brain resuscitation strategies that may prevent brain injury and lead to improved survival and neurological outcomes after cardiac arrest.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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