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2023-04

Sandroni , C , Skrifvars , M B & Taccone , F S 2023 , ' Brain monitoring after cardiac arrest '
, Current opinion in critical care. , vol. 29 , no. 2 , pp. 68-74 . https://doi.org/10.1097/MCC.0000000000001023

http://hdl.handle.net/10138/356971
https://doi.org/10.1097/MCC.0000000000001023

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Brain monitoring after cardiac arrest

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Purpose of review
To describe the available neuromonitoring tools in patients who are comatose after resuscitation from cardiac arrest because of hypoxic–ischemic brain injury (HIBI).

Recent findings
Electroencephalogram (EEG) is useful for detecting seizures and guiding antiepileptic treatment. Moreover, specific EEG patterns accurately identify patients with irreversible HIBI. Cerebral blood flow (CBF) decreases in HIBI, and a greater decrease with no CBF recovery indicates poor outcome. The CBF autoregulation curve is narrowed and right-shifted in some HIBI patients, most of whom have poor outcome. Parameters derived from near-infrared spectroscopy (NIRS), intracranial pressure (ICP) and transcranial Doppler (TCD), together with brain tissue oxygenation, are under investigation as tools to optimize CBF in patients with HIBI and altered autoregulation. Blood levels of brain biomarkers and their trend over time are used to assess the severity of HIBI in both the research and clinical setting, and to predict the outcome of postcardiac arrest coma. Neuron-specific enolase (NSE) is recommended as a prognostic tool for HIBI in the current postresuscitation guidelines, but other potentially more accurate biomarkers, such as neurofilament light chain (NfL) are under investigation.

Summary
Neuromonitoring provides essential information to detect complications, individualize treatment and predict prognosis in patients with HIBI.

Keywords
brain tissue oxygenation, cardiac arrest, coma, electroencephalogram, hypoxic–ischemic brain injury, intracranial pressure, near-infrared spectroscopy, transcranial Doppler

INTRODUCTION

About two-thirds of patients admitted to an ICU after resuscitation from cardiac arrest die because of hypoxic–ischemic brain injury (HIBI) [1▪]. Limiting brain injury is a primary goal of postresuscitation care [2▪▪] and to this aim, neuromonitoring is paramount. Several neuromonitoring tools are currently available in patients with HIBI (Fig. 1).

MONITORING ELECTRICAL CEREBRAL ACTIVITY

The electroencephalogram (EEG) is widely used for neuromonitoring in HIBI [3▪▪]. However, its signal is complex and includes a variety of abnormal patterns [4▪]. These have been codified by the American Clinical Neurophysiology Society (ACNS) in standard terminology for use in intensive care [5▪▪]. Immediately after the return of spontaneous circulation (ROSC), the amplitude of EEG is often markedly depressed or discontinuous. Suppression (EEG amplitude below 10 μV) or burst-suppression (suppression for more than half of the recording, alternating with electrical bursts) [5▪▪] are markers of severe HIBI and, especially if they appear after 24 h from ROSC, are almost invariably associated with poor long-term disability or death [6].

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Curr Opin Crit Care 2023, 29:68–74

DOI:10.1097/MCC.0000000000001023

KEY POINTS

- Hypoxic–ischemic brain injury (HIBI) is the major cause of morbidity and mortality after cardiac arrest and evolves rapidly after resuscitation.
- HIBI may be associated with seizures, brain edema, intracranial hypertension, altered cerebral autoregulation, and brain tissue hypoxia that may further aggravate brain injury.
- EEG is useful in HIBI to detect seizures, to guide their treatment, and to assess the severity of HIBI for prognostic purposes.
- Monitoring of ICP, TCD, $PbtO_2$ and NIRS can provide useful information on brain oxygenation and perfusion, potentially guiding treatments aimed at reducing the severity of HIBI.
- Serial assessment of biomarkers of HIBI, such as NSE or NfL, is useful for predicting the outcome of patients who are comatose after cardiac arrest.

However, in patients who achieve neurological recovery, the EEG shows progressive background improvement towards continuous and normal-amplitude tracing [7▪].

The postarrest EEG background can also show superimposed epileptiform discharges. When isolated, discharges are of little significance in patients with HIBI. However, if discharges are abundant and/or appear repetitively in a regular fashion, they are called rhythmic or periodic patterns (RPPs) and deserve special attention. Seizures are RPPs lasting 10 s or more and having a frequency above 2.5 Hz or a spatiotemporal evolution [5▪▪]. Seizures or RPPs occur in about 30% of unconscious resuscitated patients. Still, because of sedation and/or muscular paralysis, these abnormalities often lack clinical manifestations and are only detectable on EEG. Seizures on EEG within 24–48 h from ROSC indicate severe HIBI and predict poor outcome. Conversely, later-appearing seizures do not exclude recovery [8].

EEG monitoring is commonly used to guide treatment with antiepileptic drugs (AEDs) after cardiac arrest. However, the benefits of AEDs in post-arrest seizures remain unclear. In the multicenter randomized open-label TELSTAR trial on 172 unconscious postcardiac arrest patients with RPPs, a stepwise treatment including AEDs, hypnotics and barbiturates did not improve the rates of good neurological survival at 6 months compared with no treatment [9▪▪]. However, a subgroup analysis showed a nonsignificant trend towards improvement with AEDs in patients with seizures as opposed to those with slower RPPs.

Full-montage routine EEG for 20–30 min is most commonly used after HIBI [10] and is available during office hours at most hospitals. Continuous EEG monitoring facilitates assessment of the EEG evolution after ROSC and increases sensitivity for seizure detection compared with routine EEG [11], but there is no evidence that it improves outcome prediction compared with intermittent EEG [12].

MONITORING ARTERIAL CEREBRAL BLOOD FLOW

Experimental evidence shows that after an initial transient post-ROSC hyperemia, cerebral blood flow (CBF) decreases significantly [13] in patients with HIBI. Although CBF cannot be directly assessed at the bedside, transcranial Doppler sonography (TCD) provides a noninvasive estimate of CBF velocities (CBFV). Changes in CBFV on TCD mirror changes in CBF if the arterial diameter remains unchanged. In two early studies [14,15], mean CBFV in the middle cerebral artery (MCA) decreased immediately after ROSC but returned to normal within 72 h with no difference between survivors and nonsurvivors. However, while in survivors, the cerebral oxygen extraction fraction (CEO_2) decreased slightly and returned towards normal values within 72 h, in nonsurvivors, the CEO_2 showed a significant decrease and remained low at 72 h. In line with these results, a recent study [16] showed supranormal levels (>75%) of jugular venous oxygen saturation in HIBI patients with poor neurological outcome and elevated brain injury biomarkers. Overall, these findings suggest that, following cardiac arrest, a reduction in CBF occurs, paralleled by a reduction in cerebral metabolism, which is more pronounced in patients with more severe HIBI. The GOODYEAR trial (NCT04000334) is investigating the feasibility of an early-goal-directed hemodynamic management guided by TCD during the first 12 h after ROSC.

MONITORING INTRACRANIAL PRESSURE

HIBI is often associated with neuronal swelling (cytotoxic edema) and severe neuroinflammation with disruption of the blood–brain barrier (BBB), leading to vasogenic edema. These may result in both increased intracranial pressure (ICP) [17] [i.e. intracranial hypertension (ICHT)] and reduced cerebral perfusion pressure (CPP). In one study on 84 comatose postcardiac arrest patients, more than one quarter experienced ICHT (ICP >25 mmHg) by their second day after ROSC and in more than half of them CPP dropped below 50 mmHg [18]. In a physiologic study ($n = 10$), ICP was monitored via an intraparenchymal probe at a median of 8.5 h after

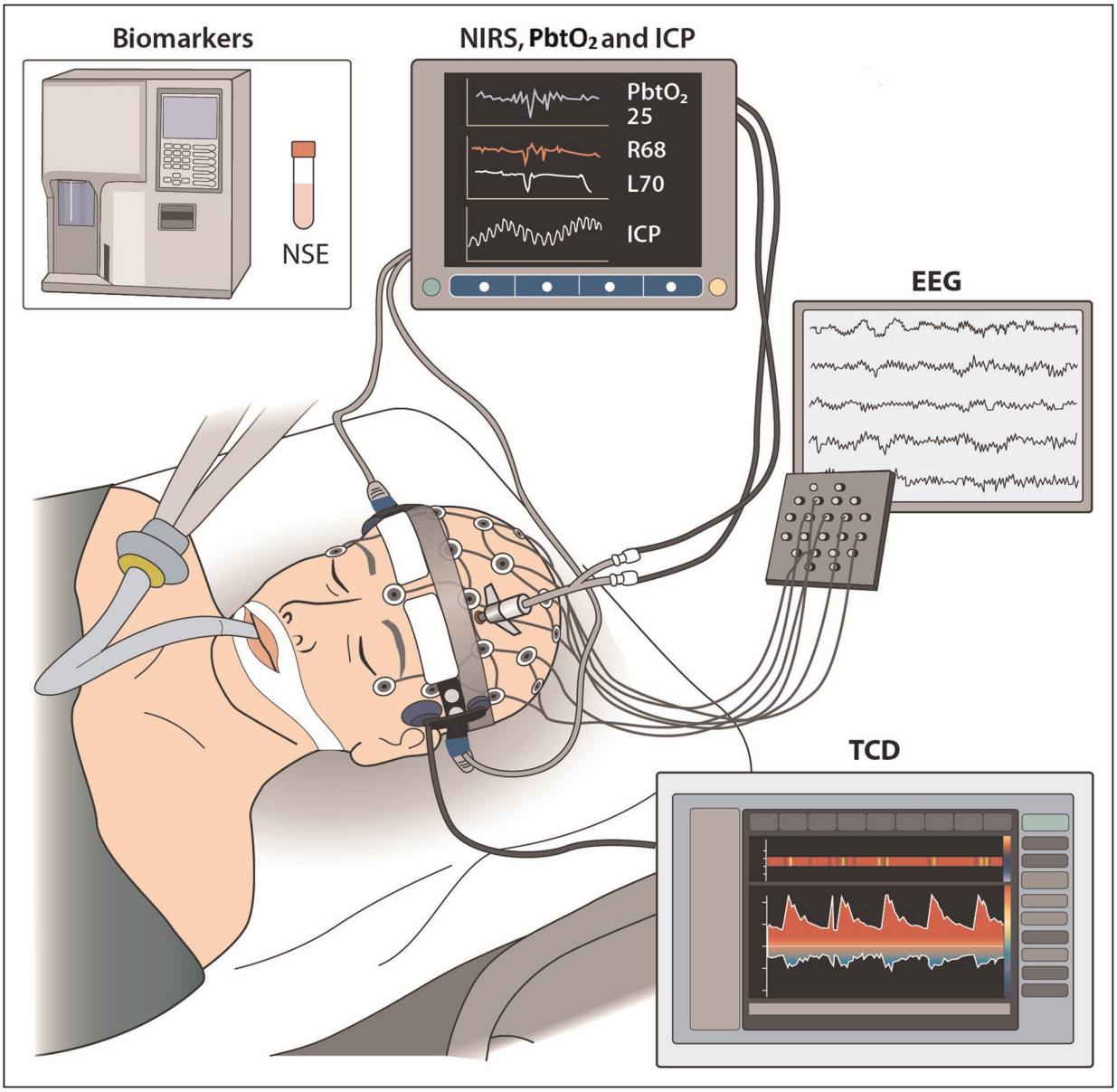

FIGURE 1. Overview of the major neuromonitoring tools after cardiac arrest. A schematic presentation of means of monitoring the brain in patients treated in the intensive care unit after cardiac arrest. EEG, electroencephalogram; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; $PbtO_2$, brain tissue oxygen pressure; TCD, transcranial Doppler.

ROSC and for a median duration of 40.5 h (interquartile range 24–51 h). Although the mean ICP was only 14 mmHg, ICHT (ICP >20 mmHg) occurred during 22% of the total neuromonitoring time. Two patients developed a lethal refractory ICHT despite maximal medical therapy. In addition, all patients exhibited decreased intracranial compliance, measured in real time as the correlation coefficient between the mean ICP and mean pulse amplitude pressure of the ICP waveform [19]. In another physiologic study ($n = 10$), ICP and lactate/pyruvate ratio (LPR) were measured hourly during the first 72 h after ROSC via an intraparenchymal catheter and a cerebral microdialysis membrane in 10 patients undergoing therapeutic hypothermia followed by gradual rewarming for 24–48 h. In patients with poor neurological outcome, ICP was consistently higher and further increased during rewarming. LPR was normal during hypothermia but increased significantly after rewarming in patients with poor neurological outcome, suggesting anaerobic cerebral metabolism [20].

Invasive ICP monitoring is not routinely used in resuscitated patients because of the limited clinical experience and the concomitant use of antiplatelet and/or anticoagulant therapy. TCD may provide an alternative noninvasive estimate of ICHT based on

the measurement of increased arterial vascular resistance from cerebral edema [21]. On TCD, vascular resistance is measured using pulsatility index, which is calculated as (systolic – diastolic CBFV)/mean CBFV. Pulsatility index values at least 1.20 indicate increased arterial resistance and suggest ICHT in this clinical scenario. In one study on 11 patients with HIBI, noninvasive ICP measured using pulsatility index showed a linear correlation ($R = 0.30$) with invasive ICP measured using an intraparenchymal probe and a good predictive value for ICHT [area under the receiver-operating characteristics (AUROC) curve = 0.91 (95% CI 0.83–1.00)] [22]. In a recent study ($n = 42$), while mean CBFV values at 6 h after ROSC were within normal range in most patients, pulsatility index was significantly increased (1.49 vs. 1.12, $P = 0.01$) in patients with poor neurological outcome, of whom six died of brain death [23].

The rationale for monitoring ICP after cardiac arrest is to treat ICHT from brain edema potentially exacerbating HIBI. There is still uncertainty on what is the best strategy for treating ICHT following cardiac arrest. Although hyperosmolar therapies mitigate cytotoxic brain edema, they may aggravate vasogenic edema [1▪,24] because of extravascular accumulation of osmotically active particles. Nevertheless, evidence of benefit from osmotherapy has been reported in brain edema following experimental cardiac arrest [25]. Moreover, a retrospective, single-center, matched observational cohort study ($n = 65$) showed that aggressive treatment of ICHT guided by neuromonitoring in patients with HIBI was associated with significantly higher rates of favorable neurological outcome vs. standard care [26▪]. To date, no clinical trial aimed at treating ICHT or mitigating brain edema in HIBI has been published.

MONITORING BRAIN OXYGENATION

Brain tissue oxygen pressure

Although studies on TCD and jugular venous bulb oxygen saturation suggest a possible normal coupling between cerebral blood flow and metabolism in patients with HIBI [13–15], they did not directly assess the oxygenation level of the brain tissue. This is achieved by measuring $PbtO_2$ at the interstitial level using an intraparenchymal probe. Brain oxygenation depends not only on oxygen delivery (i.e. cerebral blood flow and arterial oxygen content) but also on microcirculatory oxygen diffusion and cerebral metabolism [27]. A $PbtO_2$ less than 20 mmHg is considered as the threshold to identify tissue hypoxia and trigger-specific interventions.

Occurrence of brain tissue hypoxia is a potential mechanism of reperfusion injury in HIBI. A study on 18 HIBI patients showed that low $PbtO_2$ was associated with active release of brain injury biomarkers and cerebral release of interleukin-6, the latter suggesting a significant role for neuroinflammation in HIBI [28]. In another study ($n = 10$) from the same group, patients experienced a $PbtO_2$ less than 20 mmHg for 38% of the monitoring time (743/1944 10 min averaged periods) [29]. The authors described two pathophysiologic phenotypes in this cohort. The first was a 'diffusion-limited' phenotype with persistent tissue hypoxia despite optimizing oxygen delivery, probably because of BBB disruption with resultant perivascular edema or mitochondrial dysfunction; the second was a 'perfusion dependent' phenotype, with intact oxygen diffusion [30]. Therapies aimed at mitigating brain tissue hypoxia, such as osmotic therapy or MAP augmentation, would be more likely effective in this latter phenotype.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a noninvasive tool to monitor the regional cerebral oxygenation (rSO_2) using infrared light absorbance to calculate oxyhemoglobin and de-oxyhemoglobin [31]. In commercially available NIRS monitors, near infrared light is emitted from one diode and received by two diodes, all placed on the scalp above the frontal cortex [32]. The NIRS sampling volume is located about 2 cm underneath the skull. Since about 70% of the sampled blood is venous, normal rSO_2 is approximately 60–80%.

Several observational studies have investigated NIRS for assessing the severity of HIBI, with conflicting results. In 2012, a multicenter study in Japan enrolling 596 patients who were unconscious after resuscitation from out-of-hospital cardiac arrest showed that rSO_2 measured at hospital admission predicted 30-day neurological outcome more accurately than lactate (AUROC 0.91 vs. 0.77; $P = 0.0001$). However, subsequent studies did not confirm these findings [33–35]. A major problem with NIRS is contamination from extracerebral circulation [36]. In addition, NIRS is derived using proprietary algorithms that make it difficult to compare results obtained by different monitors [32]. At present, NIRS is not recommended for prognostication after cardiac arrest [2▪▪]. Like for other monitoring tools, rSO_2 trends are probably more informative than absolute values.

Monitoring cerebral autoregulation

Normally, cerebral circulation maintains a stable CBF within a range of mean arterial pressure

(MAP). This property is called cerebral autoregulation. However, in about one-third of patients with HIBI, the autoregulation plateau is narrowed and right-shifted [37]. Consequently, arterial hypotension after cardiac arrest may result in cerebral hypoperfusion, worsening HIBI. A pilot trial [38] and a larger clinical trial [39] showed that targeting high vs. low MAP after cardiac arrest does not change neurological outcome or the severity of HIBI measured with blood biomarkers. Alternatively, authors have advocated for individualized blood pressure targets aimed at maintaining MAP within the individual patient's range of intact autoregulation to optimize cerebral perfusion. To that aim, two derived parameters, cerebral oxygenation index (COx) and pressure reactivity index (PRx), have been investigated. These are the correlation coefficients between rSO_2 and ICP, respectively, and MAP. An increase in COx or PRx with MAP suggests dysfunctional autoregulation, whereas a near zero or negative value of COx or PRx suggests that autoregulation is maintained. On the basis of that model, the 'optimal MAP' is the range corresponding to the lowest values of COx or PRx.

In one observational pilot study [40], 18 of 51 postcardiac arrest comatose patients had dysfunctional autoregulation measured using COx, and the time spent below the optimal MAP was associated with a lower likelihood of survival [odds ratio (OR) 0.97 (0.96–0.99), $P = 0.02$]. In another pilot study ($n = 23$), a higher COx during days 1–3 after cardiac arrest was independently associated with mortality at 3 months [41]. A similar association between dysfunctional autoregulation and poor outcome in patients with HIBI has also been found using PRx [42,43]. Recently, cerebral autoregulation in normothermia and hypothermia after cardiac arrest has been assessed using TCD. In a study on 50 patients resuscitated from out-of-hospital cardiac arrest, Crippa *et al.* investigated cerebral autoregulation during therapeutic hypothermia and after rewarming by measuring mean flow index (Mxa), which is the Pearson correlation coefficient between mean CBFV in the MCA and arterial blood pressure. Mxa above 0.3 defined altered cerebral autoregulation. Although the rates of altered autoregulation were similar between outcome groups during hypothermia, Mxa greater than 0.3 was significantly more common in patients who died or had poor neurological outcome after rewarming [31/36 (86%) vs. 7/14 (50%); $P = 0.02$]. On multivariate analysis, high Mxa was associated with poor neurological outcome [44].

Although dysfunctional cerebral autoregulation measured by COx or PRx is associated with poor neurological outcome after cardiac arrest, it is not clear if this simply represents a marker of HIBI severity or a therapeutic target, and no controlled trials assessing if an autoregulation-targeted MAP mitigates HIBI severity have been published to date.

Biomarkers

Biomarkers of brain injury are cellular components released by the brain tissue in response to an insult. The rationale for their use for assessing HIBI is that their release is proportional to the severity of the cellular injury. The most studied biomarkers are neuron-specific enolase (NSE), S-100B, neurofilament light chain (NfL), Tau, GFAP and UCH-1. Of these, only NSE is widely used in clinical practice, and is the only recommended in postresuscitation care guidelines [2▪▪]. NSE, like UCH, originates from the neuronal body, while NfL and Tau are released from the axons, and S100B, GFAP from the glial cells [45].

Understanding the kinetics of biomarkers is important for their correct clinical use. NSE blood levels peak at 48–72 h after ROSC, when their accuracy for assessing HIBI severity is maximal [6,45]. NSE half-life is 24–30 h, so that significantly high levels of NSE can still be found at 4-5 days after ROSC and beyond in poor outcome patients [46,47]. Although NSE levels increase from 24 to 72 h in patients with severe HIBI, they decrease or remain stable in patients who recover. In one study, a 1.7 ratio between NSE values at 48 h and those at 24 h after ROSC, and a 1.3 ratio between values at 72 and 24 h was 100% specific for poor neurological outcome [48]. Similar results have been found in other studies [49,50]. The European Resuscitation Council and European Society of Intensive Care (ERC-ESICM) guidelines for postresuscitation care suggest measuring NSE serially between 24 and 72 h after ROSC [2▪▪] and recommend using a NSE threshold of 60 μg/l at 48–72 h for prediction of poor outcome in HIBI.

Among recently investigated biomarkers of HIBI, NfL is the most promising. In multicenter biobank studies [51,52] NfL was more accurate than NSE for predicting poor neurological outcome, and its accuracy was high as early as 24 h after ROSC [AUROC 0.94 (0.92–0.95)]. The major limitation of NfL is that, because of its limited diffusion through the blood–brain barrier, its plasmatic levels are very low and require specific ultrasensitive assays [53]. Moreover, the NfL cut-off levels for identifying irreversible HIBI vary widely across studies, and its optimal threshold has not yet been identified.

CONCLUSION

Cardiac arrest causes an extensive brain injury of variable degree whose outcomes vary from complete

recovery to severe disability or death. After the initial ischemia, reperfusion injury evolves over time and may result in neuronal membrane instability, brain edema, intracranial hypertension, brain hypoperfusion and reduced autoregulation. All these changes present an indication for neuromonitoring after cardiac arrest. Among the available tools, EEG is useful for prognostication and for seizure detection and treatment. ICP, TCD, $PbtO_2$ and NIRS may guide clinicians for optimizing CBF and brain oxygenation and perfusion. Serial assessment of biomarkers is useful for assessing the severity of brain injury and predict the likelihood of recovery from postanoxic coma. In addition to their potential clinical applications, all these neuromonitoring tools are undergoing active research aimed at increasing our understanding of the pathophysiology and optimal management of HIBI.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

C.S. is co-author of articles mentioned in this review. M. B.S. reports lecture fees and travel grants from BARD Medical. He is also co-author of articles mentioned in this review. F.S.T. is Scientific Advisor for Neuroptics and Nihon Khoden. He is also co-author of articles mentioned in this review.

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